



Leak point pressures: how useful are they?

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Purpose of review

The present article reviews the literature from the last 12 months relevant to our understanding of leak point pressures.

Recent findings

Literature is reviewed regarding leak point pressures.

Summary

There remains a need for larger randomized trials, investigating urodynamic parameters with relation to effective surgical management of urinary stress incontinence.

Keywords

abdominal, detrusor, leak, point, pressure

INTRODUCTION

The present review aims to discuss literature over the last 12 months and will put this within the context of our current knowledge base of leak point pressures (LPP).

Urodynamic studies (UDS) involve the assessment of the function and dysfunction of the lower urinary tract (LUT) by any appropriate method [1]. UDS can be either noninvasive, such as flow tests, or invasive, the principle methods being filling cystometry and pressure flow (voiding) studies. They are performed to define LUT dysfunction (LUTD) in patients with bothersome LUT symptoms (LUTS), usually before an invasive intervention or as part of long-term surveillance, as in some groups of patients with neuro-urological LUTD, such as in meningocele (MMC) children and adults. The aim of UDS is to reproduce the patients' LUTS while taking objective measurements, to come to a urodynamic diagnosis and plan management accordingly. UDS are performed for a variety of indications, including assessment of urinary incontinence and neuro-urological disorders. UDS are normally performed in a standardized and reproducible manner, according to Good Urodynamic Practice [2], with a specific UDS question, or questions, in mind. For urinary incontinence, the questions are usually whether either urodynamic stress incontinence or detrusor overactivity incontinence can be demonstrated before interventions such as a mid-urethral sling or sacral nerve stimulation, respectively. NICE certainly recommends UDS in patients

before surgery for stress urinary incontinence (SUI), 'except for the small group who have pure SUI' [3].

Bladder storage function is assessed by filling cystometry, throughout which bladder pressure is measured. Storage ability is assessed by measuring bladder capacity, bladder compliance, bladder sensation, USI, and the presence/absence of detrusor overactivity.

Urethral storage function can be assessed by measuring urinary LPP. LPP is the pressure at which a urinary leak occurs during UDS. LPPs were first described by McGuire in an attempt to evaluate the effect of urethral function on upper urinary tract function (UUT) and in relation to urinary incontinence. There are two types of LPP measurement: detrusor LPP (DLPP) and abdominal LPP (ALLP). Both are measured during filling cystometry, but are used in very different contexts.

DETRUSOR LEAK POINT PRESSURE

DLPP is defined as the lowest detrusor pressure at which urinary leakage occurs in the absence of a detrusor contraction or an increase in abdominal pressure [1]. DLPP is performed during filling

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KEY POINTS

- Standardized urodynamics according to good urodynamic practice remain an essential element of investigation of urinary incontinence.
- Detrusor leak point pressure measurement is helpful to guide management in patients with neuro-urological conditions.
- There is as of yet no consensus as to how useful abdominal leak point pressure is in guiding operative management of SUI and its effectiveness.

cystometry, as the bladder is filled, the urethra is examined for leakage. At the point that leakage occurs, the detrusor pressure is recorded, this is the DLPP. The main determinant of a normal low detrusor pressure, during bladder filling, is the compliance of the bladder, which in turn is dependent on the visco elastic properties of the detrusor muscle, normal bladder wall composition, and normal neural mechanisms. However, if bladder compliance is abnormal then detrusor pressures are high during filling and may interfere with normal drainage of urine from the kidneys to the bladder.

DLPP was originally described by McGuire [4] in the evaluation of low-compliance bladders in children with MMC. McGuire found that MMC patients with a DLPP over 40 cmH₂O had a higher risk of UUT deterioration than patients with a DLPP less than 40 cmH₂O. This is because the higher pressures were being transferred to the UUT leading to hydronephrosis and impaired renal function, sometimes made worse by associated vesico-ureteric reflux. However, in these children, urethral function is often impaired, and this acts as a safety mechanism in children who, if they had good urethral function would be at risk of UUT deterioration because of their poor bladder compliance. However, if the outlet pressure is normal, then there will be a high detrusor pressure, and leakage will occur at higher pressures, and this is dangerous for kidney function.

Although UDS should be performed according to Good Urodynamic Practice, there is no standardization of the technique of measurement of DLPPs, such as how to record urine leakage, which can be recorded visually, via a flowmeter or seen radiologically. Measurement of detrusor pressure can either be by a urethral or suprapubic catheter, but the calibre of catheter has not been standardized. This is very important, particularly if small children are being investigated, as if a relatively large catheter is being used, the DLPP will be artefactually increased. Furthermore, the rate of bladder filling has not been

standardized and it is well known that artificially fast filling may reduce bladder compliance and raise the detrusor pressure. Therefore, in any comparison between studies, these factors must be borne in mind.

Neuropathic patients are at particular risk of UUT deterioration, either from poor compliance or from detrusor overactivity, either of which can, in the presence of reasonable urethral function, lead to a high DLPP. The ability to quantify the urethral resistance to leakage allows the risk of UUT damage to be assessed. In a patient with high LPP, the threshold for intervention will be lower. Wang *et al.* [5] calculated a urodynamic risk score including a DLPP more than 40 cmH₂O, bladder compliance of less than 9 mL/cmH₂O and evidence of an acontractile detrusor, in children with neurogenic LUTD. They found these three factors to be the main UDS risk factors for UUT dilatation, and suggested that a patient with these risk factors would need to be monitored more closely.

ABDOMINAL LEAK POINT PRESSURE

ALPP is defined as the intravesical pressure at which urine leakage occurs because of increased abdominal pressure in the absence of a detrusor contraction [1]. This is measured during the UDS assessment of women with bothersome SUI. ALPP can assess urethral dysfunction and forms part of the diagnosis for urodynamic SUI. Raised abdominal pressure does not cause leakage in a functionally and anatomically normal urethra. Leakage is caused by an increase in abdominal pressure when there is an incompetent urethra.

There are thought to be two types of SUI, either urethral hypermobility or intrinsic sphincter deficiency (ISD): urethral function can be assessed during video UDS and been classified according to the Blaivas criteria, with ISD being type three. ALPP can also help distinguish between these types.

ALPP was originally described by McGuire [4] and was based upon Valsalva LPP (VLPP). They noted that 75% of women with SUI and a VLPP less than 60 cmH₂O had ISD, whereas most patients with a VLPP more than 90 cmH₂O had urethral hypermobility. Following this, a VLPP of less than 60 cmH₂O is thought to represent ISD, VLPP of 60–90 cmH₂O is said to be equivocal and VLPP more than 90 cmH₂O suggests urethral hypermobility. An ALPP >150 cmH₂O suggests incontinence is unlikely to be because of the urethra not being able to contain urine.

As with DLPP there is no agreed standard way of performing ALPP. There is no consensus on how full the bladder should be at the point of carrying out

ALPP. To measure ALPP, filling is stopped and the patient is asked to increase their intra-abdominal pressure by coughing, or by blowing into a syringe (Valsalva manoeuvre), until the patient leaks and the lowest pressure at which this happens is recorded as the ALPP. Increasing the volume at which the Valsalva manoeuvre is carried out, does not appear to affect the ALPP result. However, underfilling may result in not enough volume for a satisfactory effect, and overfilling may induce detrusor overactivity thus giving a false reading. Filling to volumes of 250–300 mL appears to be the most accurate in distinguishing between hypermobility of the urethra and ISD [6].

The pressure can be measured from either the abdominal (rectal or vaginal) or bladder pressure line. In theory, the absence of a urethral catheter would allow a more meaningful measurement of ALPP, but would mean the bladder catheter being removed and reintroduced to allow filling cystometry to be completed. Hence, any urethral catheter present during ALPP measurement should have the smallest diameter possible, so as to minimize its effect on ALPP measurement. Weissbart *et al.* [7[■]] found that 32 of 169 men undergoing postprostatectomy urodynamics failed to leak whereas the 7fr catheter was in-situ, all 32 leaked without the catheter.

When comparing methods of inducing leakage, ALPP appears to be higher with a cough compared to Valsalva, possibly because of reflex contraction of the pelvic floor during coughing. Coughing is perhaps a more frequent cause in everyday life of SUI, however using cough ALPP measurement, the exact pressure at which leakage occurs can be difficult to determine because of the rapid changes of pressure, and the assumption that leakage is at the peak of the cough spike is often made (Fig. 1).

Another difficulty possibly encountered is the presence of an anterior wall prolapse. This may artificially elevate the ALPP by absorbing some of the force of the abdominal contraction, therefore the patient may not leak until pressures are higher. The ALPP measurement in patients with significant cystocele may need to be treated with caution. Furthermore, UDS are invasive investigations and patients are understandably anxious about having a clinician examining the perineal region for incontinence. This may lead to contraction of the pelvic floor, thereby not reproducing the normal circumstances in which the woman leaks. Factors such as catheter size, bladder volume, patient anatomy and the precise method of determining ALPP will all affect the result and should be interpreted cautiously.

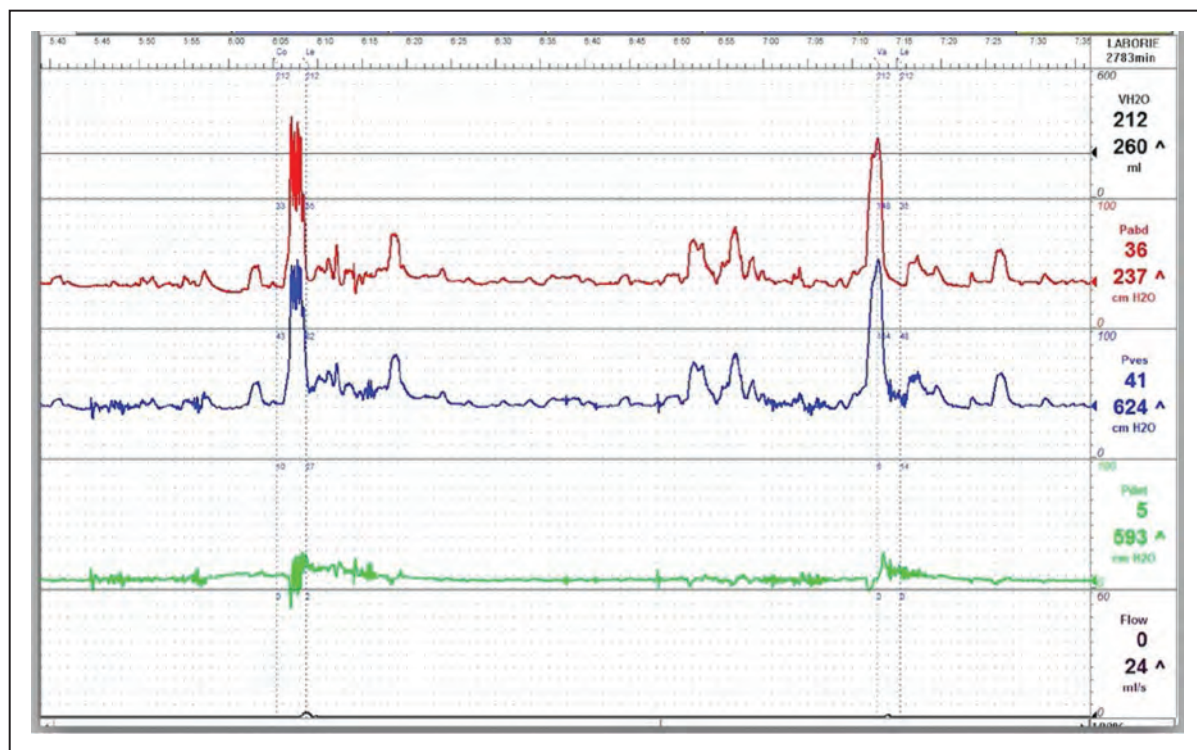


FIGURE 1. Demonstration of urodynamic trace showing cough and Valsalva leak during filling cystometry. It can be seen that it is difficult to ascertain the exact pressure at leakage with a series of three coughs as seen here.

ALPP can be used in conjunction with other urethral studies to differentiate between ISD and hypermobility. The urethra may be examined during coughing to look for mobility. The Q-tip test, now no longer in favour, was used to assess the degree of movement of the urethra during coughing or straining. This test was thought to be inaccurate and invasive. However, a paper in 2014 again examined this relationship, and found a significant correlation between Q-tip angle and grading of urodynamic SUI on video UDS [8[¶]]. The paper had several flaws; a small numbers retrospective review, in patients with pure SUI. Pure USI accounts for less than 5% of patients in whom we perform UDS for urinary incontinence [9], therefore it is difficult to determine if this would be applicable to our general population. However, clinical examination remains a key element in the UDS examination.

Urethral pressure profilometry is thought to be a more objective way of measuring urethral function. Urethral pressure is defined by the ICS as the fluid pressure needed to just open a closed urethra. The urethral pressure profile is a graph indicating changes in the intraluminal pressure along the length of the urethra. Although low maximum urethral closure pressures (MUCP) are associated with SUI, there is no absolute cutoff figure below which the urethra can be implicated as the cause of incontinence. There are many continent women with low MUCP and incontinent women with high MUCP readings. A combination of a low MUCP and a low ALPP may add weight to the diagnosis of ISD but cannot definitively prove it. Guerette *et al.* [10] found cutoff values of less than 60 cmH₂O ALPP and less than 40 cmH₂O MUCP were the most predictive factors of surgical success, showing high sensitivity and specificity.

NICE recommends that when conservative measures fail and surgery is being considered for the treatment of SUI, all surgical options should be discussed [3]. UDS should be considered in all patients other than those with pure SUI [3] (a small percentage of patients [9]), therefore most patients will have had UDS. Yet, there remain important urodynamic questions – does the diagnosis of urethral hypermobility versus ISD predict a successful surgical outcome? Can ALPP assist in decisions regarding type and relative success of surgery? There is evidence on the one hand to support its use, and on the other to dismiss it.

In the developed world, the most common operation for SUI is a mid-urethral sling (MUS). Despite this surgical procedure being less invasive, with a shorter hospital stay than other options, long-term follow-up data [11] still shows approximately 20%

recurrence of urinary incontinence. Therefore, any UDS parameters that may be useful in predicting operative failure are important.

Whether diagnosing ISD is helpful in predicting surgical outcome remains controversial, many papers have been written with varying results. A recent systematic review by Iancu and Peltecu [12^{¶¶}] found that a low preoperative VLPP was predictive for a higher risk of failure following a MUS. The studies involved only followed up patients for a maximum of 6 years with median follow-up being much lower. Nager *et al.* [13] used data from the TOMUS trial (Trial of MUS) for a multivariate analysis of surgical outcome and preoperative urodynamic findings. ALPP and MUCP were the only parameters consistently associated with objective failure, but there was no absolute cutoff value. Patients with ALPP and MUCP in the lowest quartile had a twofold increased risk of objective failure after 1 year of follow-up, and for every 10 cmH₂O increase in ALPP and MUCP, there was a 7 and 12% reduction in failure rate, respectively. Han *et al.* [14^{¶¶}] recently retrospectively reviewed 12-year follow-up data and preoperative UDS data in patients who underwent a TVT. They found a VLPP less than 60 cmH₂O was the only independent factor able to significantly predict recurrence of incontinence. Despite small numbers ($n=88$), this appears to be an important paper, as it is one of the few to look at long-term follow-up data.

Conversely, Ryu *et al.* [15[¶]] studied 204 patients before placement of MUS and found preoperative VLPP was not related to cure rate or quality of life. Rodriguez *et al.* [16] also found no difference in cure rate when grouping women into different levels of ALPP before MUS placement. Nager *et al.* [17] also found ALPP did not predict success after Burch or autologous sling placement after 24 months follow-up. Constantini *et al.* [18] studied 145 patients randomized to TVT versus TOT and found no significant differences in objective cure rates with ALPP or MUCP.

A newer use of ALPP is in the management of men with postprostatectomy incontinence. Barnard *et al.* [19[¶]] determine the VLPP threshold permitting success in the use of the male sling (AdVance). They questioned the use of pad weighing tests to determine severity of incontinence, using, as an example, a very active young man potentially have the same pad weights as a nonactive elderly man, but commenting that the severity of incontinence in this example would vary by exercise and activity and may not necessarily reflect the underlying severity of sphincter dysfunction. Some surgeons believe in using severity of incontinence as a decisive factor in selecting between the artificial urinary sphincter

and the male sling, with the milder incontinence group being usually offered a sling. The group investigated 46 patients with postprostatectomy incontinence with preoperative video UDS. They found a VLPP cutoff of less than 100 cmH₂O could predict treatment failure. Although this may be a potentially useful adjunct to assessing severity of sphincter dysfunction, we believe that the actual question remaining unanswered is whether we are correctly selecting an appropriate procedure for postprostatectomy incontinence based upon incontinence severity. We eagerly await the results of the MASTER trial, which is currently recruiting and is randomizing patients with postprostatectomy incontinence to either male sling surgery or an artificial urinary sphincter regardless of severity of incontinence.

DISCUSSION

So, how useful are LPPs? The answer appears to be that the evidence remains controversial. Questions continue to be asked as to whether there is value in acquiring an accurate diagnosis of either urethral hypermobility or ISD, and whether this alters clinical management or predicts surgical effectiveness. LPPs were one of the variables examined in a Cochrane review in 2002 and the suggestion was that a large definitive trial should be carried out to determine the place of UDS in patients with incontinence [20].

Although this question is as yet to be definitively answered, our opinion is that accurately performed UDS remain incredibly important before surgical management of SUI. Evidence appears to be continuing to emerge that ALPP is a useful adjunct, along with MUCP, in determining underlying anatomical causes of SUI, enabling an informed discussion with patients, and in particular choosing an operation from those available.

DLPP appears less controversial, but again has limited repeat validity of the originally suggested cutoff values. What is clear is that UDS remain a crucial part of the baseline study of neuro-urological conditions and its continued safe management in order to protect renal function long-term and manage continence in a holistic setting.

CONCLUSION

LPPs are widely used UDS parameters that remain a controversial area. There is evidence, particularly for ALPP, both for and against its use. What is clear is that standardized UDS remain an important part of the diagnostic pathway for urinary incontinence, particularly when considering interventions, to enable appropriate and informed patient management.

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Conflicts of interest

K.W. and H.B. declare no conflicts of interest. P.A. declares that he consults for Astellas, Ferring, Pfizer, Proctor and Gamble, and Chiltern: lectures for Astellas, Ferring, and Pfizer and is an investigator for Astellas and Ferring.

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**The Scottish Independent Review
of the Use, Safety and Efficacy of
Transvaginal Mesh Implants
in the Treatment of
Stress Urinary Incontinence and
Pelvic Organ Prolapse in Women**

Interim Report

2 October 2015

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*These documents have been provided separately due to their size and are available online

Preface

This Independent Review (IR) into the use of transvaginal mesh in surgery for incontinence and pelvic organ prolapse came about because of growing public concern about the number of women experiencing serious complications. This was linked with under-reporting of adverse events and a poor understanding as to why these complications have occurred. Women felt that their voice had not been heard as they raised concerns about the side effects a number of them had suffered. Many of them eventually felt that the only way to bring this to the attention of the “powers that be” was to lodge a petition bringing the issue to the attention of the Petitions Committee of the Scottish Parliament. At that Committee the then Cabinet Secretary for Health and Wellbeing, Alex Neil MSP, promised an Independent Review and asked NHS Scotland to suspend transvaginal mesh procedures pending the outcome of this review.

From the outset, we were charged with listening to and valuing the views of patients, both those with a good result and those with a poor result, including those living with significant impacts on their day to day life. We were asked to review the best available research evidence, statistics and both patient and expert opinion to find out the nature and scope of the problem.

We have tried to do this by involving women who have undergone such surgery; the local clinical experts in this surgery; clinical experts from around the UK; the Scottish Public Health Network for an objective review of the research literature; the Information Services Division of National Services Scotland, for an objective epidemiological review of the information from routine data; MHRA, the statutory regulatory body; the professional bodies, including the Royal College of Obstetricians and Gynaecologists (RCOG), the standard setting body for the profession; and input from the Chief Medical Officer’s office and the Division of the Scottish Government Health and Social Care Directorate which deals with medical devices. We have been very ably supported throughout by a member of that latter Division.

During this Independent Review we heard evidence from women who are disabled as a result of the surgery they had undergone. They also felt that they had not been listened to, or even believed which only increased their distress. We also heard of lives transformed and improved by the same surgery with statistical and research evidence showing poor outcomes to be in the minority of procedures done. We also acknowledged that adverse events could not be totally excluded from any surgery, as any surgery carries a risk. What we have tried to do is to take an objective view of both the results of the research and of the information review but also what they did not tell us, what was missing, what the patient stories can tell us and what the experience of clinicians in practice can tell us.

We found some concerning features about how new techniques are introduced into routine practice, how and for how long they are followed up, how women are informed of the risks and benefits so that they can give true informed consent and also how adverse events are reported and to what extent.

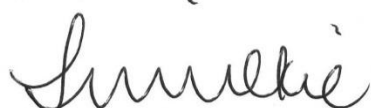
Our conclusions focus on the need for improved governance around both the introduction of new procedures or techniques and also of how women are assessed and treated, both initially and in the event of any side effects following surgery. Reporting of adverse events is another area where we feel that a tighter, more explicit practice is required and we suggest ways the government should consider to ensure this area is improved. We

differentiate between the use of mesh in the treatment of stress urinary incontinence and when it is used in the repair of pelvic organ prolapse. We see the need for an Expert Group to oversee the implementation of an improved way of working, and of organising services. We are aware that some of our conclusions have wider implications and see the need to embed this in the Patient Safety and Clinical Governance strands of the NHS.

As Chairman, I hope that this report goes some way towards ensuring above all that patient voices continue to be heard, believed and valued and that women with these conditions can be assured that the treatment which they receive within the NHS is evidence based, audited and likely to produce a good result while keeping to a minimum the possibility of an adverse effect.

The following report sets out what we did, how we did it, what we concluded and why and what we consider should be done as a result.

This Report was the work of many people and disciplines. I am extremely grateful for all their contributions. Readers of this report may notice differences in styles in the chapters arising from this collaborative process.

A handwritten signature in black ink, appearing to read 'Lesley Wilkie', with a stylized, cursive script.

Lesley Wilkie

Executive Summary

This report outlines the work of the Independent Review (IR) of the use, safety and efficacy of transvaginal mesh implants in the treatment of stress urinary incontinence (SUI) and pelvic organ prolapse (POP) in women. It is an interim report as the publication of further pieces of work are awaited, including: Opinion of the European Commission and its Scientific Committee on Emerging and Newly Identified Health Risks Opinion (SCENIHR) and PROSPECT (PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials). However as the main programme of work has been completed the IR has been able to draw conclusions and make recommendations.

The work has taken several months and is the product of individuals with a range of skills and interests including patients, clinicians, statisticians, public health experts, researchers, regulators, scientists and legal advisers.

The deliberations of the IR have been based on considering published evidence, patient stories and the opinion of clinical experts. In addition an epidemiological study has been conducted using routinely reported Scottish hospital inpatient data.

The IR meetings have also assessed verbal evidence from different experts, including patients, to reach consensus conclusions. It is expected that these will improve the quality of care in a field that crosses primary, secondary and specialist care and can have lifelong effects on women's quality of life.

Some conclusions are specific to improving care in the use of transvaginal mesh. Others are intended to benefit patients in general. All conclusions are described below:

Conclusion 1

Robust clinical governance must surround treatment, the decision to use mesh and the surgical approach used. To support decision making, management of the individual patient should take place in the context of multi-disciplinary team assessment, audit and review. The use of a comprehensive information system will underpin this. **The Expert Group should address this with NHS planners, including an assessment of any administrative support required for the clinical teams.**

Conclusion 2

Evidence of involvement in multi-disciplinary team working, engagement in audit activity and recording and reporting of adverse events should be an important part of consultant appraisal and thus statutory revalidation of medical staff. **The Expert Group should work with Medical Directors as Responsible Officers to include this in the conduct and supervision of appraisal. In addition the Scottish Government should consider the alternative methods for the capture of adverse events set out in chapter 8 to determine further the most effective way to ensure complete notification.**

Conclusion 3

Informed consent is a fundamental principle underlying all healthcare. There has been extensive work done by the Expert Group which preceded the establishment of the Independent Review, with leadership by both patients and clinicians. This has resulted in an SUI information leaflet and consent form. **Following on from this the Independent Review concludes that additional work is required to ensure that this work is extended to include POP procedures and that the SUI leaflet is reviewed in the light of this work and other recent developments. This should be addressed by the Expert Group as a matter of urgency. Other points highlighted by the Independent Review include the provision of adequate time for discussion and reflection. Patients should be provided with information enabling them to report adverse events if these occur.**

Conclusion 4

The Independent Review does not consider that current research studies on safety and effectiveness will provide evidence on long term impact of mesh surgery. The lack of extended long term follow up and related outcome data, including information on quality of life and activities of daily living, should be addressed. **The Independent Review recommends the Expert Group highlights this knowledge gap to funders of health research and the research community. Opportunities for routine audit should be explored by the Expert Group in conjunction with NHS Scotland.**

Conclusion 5

Good information, as stated before, is essential to good patient care. The experience of the Independent Review has been that there are many gaps although there is information both in a professionally led database (the BSUG database) and routine NHS information (SMR01 and SMR00). **It is recommended that the Expert Group works with ISD, BSUG and others to ensure that an information system is developed which is universal, robust, clinically sound and focused on fostering good patient outcomes. Work already underway on consistent coding by ISD will be vital to this endeavour.**

Conclusion 6

The Independent Review expressed serious concern that some women who had adverse events found they were not believed, adding to their distress and increasing the time before any remedial intervention could take place. Improving awareness of clinical teams of the possible symptoms of mesh complications together with good communication skills, (including good listening and empathy) is an essential part of good clinical care. **The Independent Review concluded that the Expert Group should review the training and information available to clinical teams and find ways of incorporating patient views in multi-disciplinary working. It should also continue oversight of the mesh Helpline.**

Conclusion 7

A review of the different sources of evidence available to and considered by the Independent Review (patient experience, clinical expert opinion, research evidence and epidemiological evidence from routine information) has led us to express concern in this Interim Report at the use of the transobturator rather than the retropubic approach for routine surgery for stress urinary incontinence using mesh. The clinical governance arrangements that we have recommended will allow an individual case to be considered in the context of a multi-disciplinary assessment, including patient views. **We await the final publication of key research reports but wish to register these concerns and to recommend that the Expert Group in the following months before the publication of the final report explore further appropriate pathways to ensure the techniques chosen take the differential patient and clinical experience, as well as research evidence into account.**

Conclusion 8

Similar concern is expressed, both for effectiveness and adverse events, at the use of transvaginal mesh in surgery for pelvic organ prolapse. The clinical governance arrangements that we have recommended will allow an individual case to be considered in the context of a multi-disciplinary assessment, including patient views. **We await the final publication of key research reports but wish to register these concerns and to recommend that the Expert Group in the following months before the publication of the final report explore further appropriate pathways to ensure the techniques chosen take the differential patient and clinical experience, as well as research evidence into account.**

Chapter 1: Introduction

1.1 Background

Stress urinary incontinence (SUI) and pelvic organ prolapse (POP) are conditions affecting a significant number of women and can result in a reduced quality of life for many. Synthetic polypropylene mesh is a permanent implantable medical device used in a number of operations to correct SUI and POP. Between 2000 and 2014, up to 1,500 women suffering from SUI and 350 suffering POP had synthetic mesh implant surgery each year in Scotland.

Concerns about the safety of mesh devices were raised by women experiencing complications. Some women adversely affected by these implants have experienced very serious complications, altering their lives forever.

The former Cabinet Secretary for Health and Wellbeing, Alex Neil MSP, first met with a group of women adversely affected by the use of mesh to treat these conditions in May 2013. Following this meeting, the Cabinet Secretary asked that a Working Group be set-up to address the issues affecting women who have undergone transvaginal mesh surgery.

The Transvaginal Meshes Working Group (TMWG) was initiated to develop a clearer understanding of the issues affecting women who had suffered complications from mesh surgery. A review of the remit of this working group led to greater clinical representation to review current clinical practice and make recommendations for change. The Expert Group was formed in December 2013.

The Expert Group was established to look at ways of improving clinical practice, including developing pathways of care for women experiencing complications and to improve the consent process to ensure women are better informed of the risks and benefits of all procedures available to treat these conditions.

1.1.1 Opinion on the Safety of Mesh Devices

It is clear that a number of women have suffered serious, life changing complications following transvaginal mesh implant surgery. It is also evident that many women have benefitted from these procedures. However, due to the way these procedures are coded, it is not possible to provide accurate data on the number of mesh procedures where complications have occurred. This lack of information, allied with the fact that adverse events have been under-reported, has led to opinion being divided on the safety of transvaginal mesh procedures.

Many women have experienced a positive outcome following a transvaginal mesh implant procedure. No procedure is without risk and therefore many people, including the broad clinical community consider that polypropylene mesh should continue to be used in these procedures as it presents an acceptable level of risk, supported by a number of studies, including research by the UK regulator for medical devices, the Medicines and Healthcare product Regulatory Agency (MHRA). Many women have experienced a positive outcome and because of this, combined with less successful outcomes associated with alternative surgical procedures, consider that they are the most effective way to treat these distressing conditions.

There is broad consensus that work to improve clinical governance of these procedures is required, including improving pathways of care and the informed consent process; work which has been taken forward by the Expert Working Group.

The Scottish Mesh Survivors Group (SMSG) brought together women affected by polypropylene mesh to campaign to have these procedures suspended until the six points of their petition had been met. This group campaigned to suspend these procedures as they consider the severity of the complications, which can occur years after the procedure, present an unacceptable level of risk. Similar campaigns exist elsewhere, including: US, Canada, Europe, New Zealand and Australia.

Some women experiencing complications reported that they were not believed, adding considerable distress to their situation. This fact, combined with the absence of accurate data on the number and severity of complications occurring, allied with under-reporting of these adverse events, has understandably led to many people concluding that these procedures should not continue.

1.1.2 The Public Petition Committee of the Scottish Parliament

On 1 May 2014, a public petition was lodged on behalf of the Scottish Mesh Survivors Group. The petition called on the Scottish Parliament to urge the Scottish Government to:

1. Suspend use of polypropylene Transvaginal Mesh (TVM) procedures;
2. Initiate a Public Inquiry and/or comprehensive independent research to evaluate the safety of mesh devices using all evidence available, including that from across the world;
3. Introduce mandatory reporting of all adverse incidents by health professionals;
4. Set up a Scottish Transvaginal Mesh implant register with view to linking this up with national and international registers;
5. Introduce fully Informed Consent with uniformity throughout Scotland's Health Boards; and
6. Write to the MHRA and ask that they reclassify TVM devices to heightened alert status to reflect ongoing concerns worldwide.

In the light of growing public concern about the number of women experiencing complications, linked with under-reporting of adverse events and a poor understanding as to why these complications have occurred, the Scottish Government considered that an Independent Review of transvaginal mesh surgery was necessary to establish the facts. The former Cabinet Secretary for Health and Wellbeing, Alex Neil MSP, announced the Independent Review on 17 June 2014 and the acting Chief Medical Officer, Dr Aileen Keel, wrote to all health boards requesting that they consider suspending routine use of synthetic mesh for these procedures until the Review has reported its findings.

1.2 Remit of the Independent Review

The published remit of the Independent Review is to evaluate both the efficacy and the extent and causes of adverse incidents and complication rates associated with stress urinary incontinence and for pelvic organ prolapse. The Independent Review recognises that these are different conditions, each managed by several different procedures and will take account of this.

The Independent Review includes members of both the clinical and patient community and has the means both of identifying and determining the causes of issues where this is possible, finding and implementing solutions.

1.2.1 Purpose

1. To determine the safety of vaginal mesh implants for both stress urinary incontinence and pelvic organ prolapse in Scotland and to compare it to international standards. Information on how many women are experiencing complications and possible reasons for these complications will be examined.
2. To determine the relative efficacy of surgery for stress urinary incontinence and pelvic organ prolapse with and without the use of mesh or tapes.

1.2.2 Scope

In determining the appropriate course of action on this issue, the Group is able to consider:

- The available data on procedures using mesh implants for pelvic floor surgery, including data on efficacy and complications compared to alternative surgical and non-surgical treatments.
- Identifying best practice standards in management of SUI and POP.
- Any issues that may lead to clinical practice not conforming to best practice standards.
- Reported safety issues with devices, including improvement in reporting adverse events.
- Barriers to regular prospective auditing of results of surgical procedures.
- Short, medium and long-term patient follow-up.
- Identification of best practice in managing both treatment failure and complications, and resources to do so.
- Whether the information provided to patients before undergoing these procedures should be updated.

The full remit and membership of the Independent Review is set out at Appendix A and B.

1.3 Remit of the Expert Group

The Scottish Government led Expert Group first met in February 2014 and has a remit to develop a clearer understanding of the issues affecting women who had suffered complications from mesh surgery. The working group includes clinical and patient representation to review current clinical practice and make recommendations for change. The following areas are currently being considered by the Expert Group:

Informed Consent – a minimum standard of information to be provided to women considering surgery.

New Care Pathways –specifically for women who may require complex surgery; and for those who have suffered complications.

The Group has produced a new Patient Information and Consent Booklet for stress urinary incontinence¹ which was published June 2014 on the Scottish Government website. This

¹ <http://www.gov.scot/Publications/2014/06/2806>

Booklet clearly demonstrates the risks associated with this procedure and the alternatives available before women make a decision on whether they wish to proceed.

Whilst overlapping with the Expert Group, the Independent Review has a distinct remit and constitution. The Expert Group suspended its activities during the period of the Independent Review's main work programme and re-formed in August 2015.

1.4 What are Medical Devices?

A medical device means: any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

Medical devices in the UK are regulated by the MHRA, an Executive Agency of the Department of Health.

MHRA regulates devices placed on the market by the manufacturer, but the healthcare services or clinical procedures they are used for is not within its remit.

CE marking

Apart from the very lowest risk products, medical devices are certified by independent conformity assessment organisations called Notified Bodies who are designated and monitored as competent to undertake conformity assessment activities this function by the member states competent authorities. Once Notified Body certification is obtained and their other obligations under the Medical Devices Regulations are being met the manufacturer can put the CE marking on the device and place it on the EU market.

The MHRA as the Competent Designating Authority in the UK oversees UK Notified Bodies, for example, the British Standards Institute a list of which may be obtained from the MHRA website at: <https://www.gov.uk/government/publications/medical-devices-uk-notified-bodies/uk-notified-bodies-for-medical-devices>.

The MHRA conduct regular audits of Notified Bodies quality assurance processes, monitor their certification and sample witness their compliance assessments of manufacturers to ensure that they operate to high standards:

The MHRA conduct regular audits of Notified Bodies including their quality assurance processes, certification activities and compliance with the medical device regulations.

MHRA also witness their assessor's competency during routine assessments of manufacturers to ensure that they operate to high standards.

<https://www.gov.uk/government/publications/notified-bodies-for-medical-devices/notified-bodies-for-medical-devices>

A CE Mark is applied by the manufacturer and means that the device meets the relevant regulatory requirements and when used as intended, works properly and is acceptably safe. In order to be in compliance with the requirements of the Medical Device Regulations and obtain Notified Body certification manufacturers should be able to support their safety and performance claims for the device. This involves appointing a Notified Body who oversees the process, to demonstrate verify that they the devices meet the relevant essential requirements laid down in the regulations for things such as including for example biocompatibility, toxicity, technical specifications, clinical data, sterilisation, right through to packaging and labelling and quality management systems.

Classification system

There are a vast range of products falling within the broad definition of medical devices; hence, the level of conformity assessment to which a device is subjected to varies according to the degree of its inherent risk.

The aim is to balance the burden of regulatory control relative to the perceived risk whilst at the same time protecting public safety. It is the stated intended purpose of the device, assigned by the manufacturer, which determines the class in which a device is categorised. The classification of devices is therefore a risk-based system. 'General' medical devices are grouped into four classes as follows:

- Class I - generally regarded as low risk;
- Class IIa - generally regarded as medium risk;
- Class IIb - generally regarded as medium to high risk; and
- Class III - generally regarded as high risk.

Medical devices are classified according to general specific criteria, which include duration of use, whether the device is invasive via a body orifice or surgically invasive, whether devices are implantable, whether or not they are considered to be active (i.e. have a power source), particularly invasiveness, duration of continuous contact, nature of the tissue contact, and distinction between non-active and active devices. For transvaginal use, Polypropylene mesh, used in urogynaecological surgery is a class IIb device, while meshes containing or which are entirely made of biological material (outside the remit of this Review) are Class III devices.

Classification of medical devices varies across the world and while there is some read across with the United States, there is not equivalence. Therefore a direct comparison between US and EU criteria is not possible. The FDA classifies mesh devices as Class II and this remains the case as of 21 Sep 2015.

<http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194438.htm>

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm?id=otn>

In Sept 2011 the [FDA's Obstetrics and Gynecology Devices Panel](#) recommended that surgical mesh for transvaginal POP be reclassified from class II to class III and require

premarket approval. In April 2014 the FDA issued two proposed orders to reclassify mesh devices and a decision on these orders is awaited.

From a European perspective the current position is that reclassifying these medical devices would not confer any material difference as they are already in the medium to high risk devices as non-active implantable devices.

1.5 Approach to the Independent Review: evidence, its limits and interpretation

The Independent Review's approach was set out in the first meeting in August 2014 – “to be conducted in an atmosphere of trust and openness, where transparency would underpin open discussion in the knowledge that participants may do so in confidence”.

The aim has been to discuss the scientific evidence from the literature, understand the data from Scottish information sources, hear patients' and clinicians' opinions, appreciate the work of bodies such as the Chief Scientist Office, the NHS Incident Reporting and Investigation Centre and NHS Central Legal Office, and base the conclusions on the best analysis of all the material.

As with any review of evidence and the deliberative work to gain an understanding of complex real world situations, there are limitations to this work. In part this is because the reports on some important research work have not yet been published and has led the Review to publish an Interim Report. Once other evidence strands become available, notably the Opinion of the European Commission and its Scientific Committee on Emerging and Newly Identified Health Risks Opinion (SCENIHR) and the results of the PROSPECT (PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials) study, the Independent Review will be able to conclude its final Report. In addition, it is expected the conclusions directed to the Expert Group and researchers will continue to improve our knowledge base. What is most important is listening to and working with patients and health professionals. In order to support understanding and transparency, this Report has included the full analysis and review of evidence so others can follow our interpretations.

Chapter 2: The clinical uses of mesh for stress urinary incontinence and pelvic organ prolapse

2.1 Clinical indications

2.1.2 Stress Urinary Incontinence

Stress urinary incontinence (SUI) is the condition where urine leaks with coughing, sneezing, laughing or with lifting and exercise. A woman's bladder and urethra (water pipe/outlet of urine) are supported by pelvic floor muscles and ligaments. If the support is weakened, for example by childbirth, then stress urinary incontinence may occur. The problems can be mild, moderate or severe and can lead to a considerable loss in quality of life. There are several non-surgical and surgical treatment options for women with SUI.

Non –surgical options include:

- Physiotherapy, including pelvic floor exercises;
- Diet;
- Stopping smoking;
- Pharmaceutical treatment;
- Continence pessaries;
- Absorbent products;
- Catheterisation; and
- No treatment.

Surgical options include:

- Colposuspension (otherwise known as bladder neck suspension);
- Urethral injection therapy;
- Suprapubic sling;
- Retropubic transvaginal mesh tapes;
- Transobturator transvaginal mesh tapes; and
- Single incision mini-slings.

There are two main types of vaginal mesh tape procedure for SUI. They are:

Retropubic mesh tape procedure

This was the first mid-urethral tape procedure introduced and the synthetic material is inserted through a small incision on the anterior vaginal wall, emerging through two small incisions in the lower abdomen above the pubic bone.

Transobturator mesh tape procedures

This procedure was developed to minimise the potential for bladder and bowel injuries associated with the retropubic mesh tape procedure. The synthetic material is inserted through a similar incision on the anterior vaginal wall, emerging through a small incision in each groin area.

Single incision mini-slings are miniature slings delivered via a single vaginal incision through the obturator muscles.

2.1.3 Pelvic Organ Prolapse

The pelvic organs (uterus, vagina, bladder and bowel) are supported by the pelvic floor muscles, fascia and ligaments. There is rarely a single cause for a prolapse, although the following are often involved: childbirth, menopause, ageing, other pelvic problems and / or surgery, long term coughing, constipation, repeated heavy lifting or manual work and being overweight. Prolapse may arise in the front wall of the vagina (cystocele), back wall of the vagina (rectocele and enterocele) or the uterus / top of the vagina (uterine prolapse or vault in women who have had prior hysterectomy). Many women have prolapse in more than one compartment at the same time, or may experience prolapse in different compartments over a period of time. The effects can be mild, moderate or severe. There may be local discomfort with the feeling of dragging, heaviness, or a need to push the prolapse back; or there may be effects on the urinary, bowel and sexual functions for a woman.

There are several non-surgical and surgical treatment options for women with POP.

Non –surgical options include:

- Physiotherapy, including pelvic floor exercises;
- Diet;
- Stopping smoking;
- Vaginal pessary; and
- No treatment.

Surgical options include:

- Anterior colporrhaphy: repair front wall without mesh;
- Posterior colporrhaphy without mesh; repair posterior wall without mesh
- Anterior colporrhaphy with implant; repair of ant wall prolapse with implant, usually mesh
- Posterior colporrhaphy with implant: repair of post wall prolapse with implant, usually mesh
- Vaginal hysterectomy;
- Vaginal colpopexy/hysteropexy; vaginal vault support without mesh

Vaginal colpopexy/hysteropexy with implant: approach suspension with mesh;

Sacrocolpopexy / Sacrohysteropexy: Abdominal approach suspension with mesh
(this procedure is outwith the remit of this Review)

2.2 Guidance for surgery (NICE and professional bodies)

As part of the surgical training for gynaecologists, urologists and urogynaecological sub-specialists there is a need to be familiar with the range of procedures to offer as treatment when discussing symptoms with patients. These procedures include the options noted above, some of which will be initially tried in General Practice before a referral to a specialist. The specialist will be aware of the range of professional advisory documents on the procedures to offer. In NHSScotland it is obligatory to use the guidance from the National Institute for Health and Care Excellence's (NICE) interventional procedures programme. This programme includes a range of procedures from 2005 – 2009 for both SUI and POP². In addition NICE published a detailed clinical guideline in 2013 on urinary

² <http://www.nice.org.uk/guidance/published?type=ipg>

incontinence management in women³ which can be used when arranging services in NHSScotland. The professional societies including British Society of Urogynaecology (BSUG⁴), the British Association of Urological Surgeons (BAUS⁵) and the Royal College of Obstetricians and Gynaecologists (RCOG⁶) provide specialist training and professional guidance, plus a method of recording activities and patient information and consent information.

2.3 Mesh products

Transvaginal mesh used can be one of a range of type: absorbable synthetic; biological (usually made from cow or pig tissue), non-absorbable synthetic or a combination of the different products. Non absorbable synthetic (permanent) mesh is usually made from polypropylene. There are a range of methods to use mesh, including:

- Mesh-inlay: the mesh is cut to the desired shape and size and placed through a single incision inside the vagina.
- Mesh-kit: pre-shaped mesh is placed using introduction needles or trocars that may require external skin incisions at several points.

The International Urogynaecological Association (IUGA) /International Continence Society (ICS) definitions list can be accessed at the following web address:

http://c.ymcdn.com/sites/www.iuga.org/resource/resmgr/iuga_documents/iugaics_terminologyprothese.pdf

³ <http://www.nice.org.uk/guidance/cg171>

⁴ <http://bsug.org.uk/>

⁵ <http://www.baus.org.uk/>

⁶ <https://www.rcog.org.uk/>

Chapter 3: Women's experiences

3.1 "Telling the Story"

In Scotland, the story of those women whose experiences of mesh implant surgery was poor was first told in newspaper reports. These stories were characterised by the histories of painful and debilitating complications; often experienced several years after the original SUI or POP; of being told by clinicians that their experiences were rare; not being believed when they sought help; of further surgery; of loss of quality of life; and even that it was no longer worth living. This review was put in place in the light of such personal experience by women for whom mesh surgery had not been a success.

However, these stories are not the only ones that came to be told. Other stories of good outcomes and everyday lives restored also came to light. Experiences of women for whom mesh surgery had been successful. It can be acknowledged that there are fewer of these, but that is perhaps not surprising when it is considered that for many women, successful surgery is not something that they feel the need to discuss, especially when it is about a delicate subject, or they simply want to move on.

Without detailed, qualitative research evidence, it is hard to fully understand these differing experiences from women who have had similar mesh surgery. Such research does not – as yet – exist and to undertake such research is beyond the scope of this review. However, some insight at least is possible into aspects of the experiences; though it does need to be understood that interpreting such data must be done with some care.

3.2 Evidence availability

As the UK MHRA safety review noted, what evidence exists from the personal experiences of women who have had SUI and POP surgery using mesh tends to be that which highlights the realities of long-term, life changing adverse outcomes [UK1]. Data on those women for whom their outcomes were successful, or where the surgery did not give a lasting cure are less easy to identify. In other words, what evidence does exist is presenting only one side of the overall picture.

We have been able to identify three sources of data relating to the personal experiences and reported outcomes amongst some of the Scottish women who have received mesh implants. These data are drawn from three sources: (1) from personal, written statements by women in regard of their mesh surgery, sent to the Cabinet Secretary for Health, Wellbeing and Sport; the collected experiences of those women who are associated with the Scottish Mesh Survivors Group (SMSG); and the experiences of women within the ongoing PROSPECT (PROlapse Surgery: Pragmatic Evaluation and randomised Controlled Trials) trial of POP surgery. Of these, only the third source of data have been collected as part of a formal research process and this means that drawing firm "scientific" conclusions from this evidence is difficult. For example, the evidence is such that we cannot be sure that we have not heard the same story more than once, captured in each of the three types of data. This is unavoidable. By not over-interpreting the evidence, such bias as could arise from this 'double-counting' should be limited.

In exploring this evidence we are not seeking to establish a rigorous set of scientific findings. Rather, we are seeking to throw some light on these patient experiences and draw out what insights it can offer.

3.3 Methods

The quality of the data available is such that a formal set of qualitative and quantitative statistical analyses would be unhelpful. Each source of data have its own limitations which have a bearing on how it can be interpreted.

Patient stories – all written responses to the Cabinet Secretary were reviewed and a sample of these, representing the balance of experiences were turned into anonymised patients stories. Whilst women were asked to provide such written responses, the specific content of them was very much left up to the women themselves. As a consequence it is not possible, for example, to know when the surgery occurred or the type of mesh used in all cases. All the women whose stories are included have given consent for this.

Analysis of SMSG data – All women who are in contact with the SMSG were asked to complete a questionnaire concerning their experiences. All completed questionnaires were made available to the Independent Review and the data they contained was transcribed to allow a descriptive analysis to be completed. For questions which provided either “yes/no” or categorical data a simple extraction scheme was used. For more qualitative data, a coding frame was developed by the data analyst and agreed by the author.

PROSPECT trial qualitative data – Personal experience data from women undergoing the PROSPECT trial has been collected at one year and two years post surgery. These data have only recently become available and only a very preliminary analysis is included in the review. This has simply calculated the number of positive versus negative comments at the two post-surgery time intervals.

3.4 Results

3.4.1 Patient stories

In total nine patient stories were developed from the written submissions to the Cabinet-secretary. Five of these describe adverse outcomes and four positive ones. These are contained in Table 3.1 at the end of this chapter.

These stories speak for themselves. However, it is clear that women have experienced both very positive outcomes as well as very negative ones. They also show a remarkable intensity associated with their experience. Irrespective of the outcome, women do feel passionately about the impact that mesh procedures have on their quality of life.

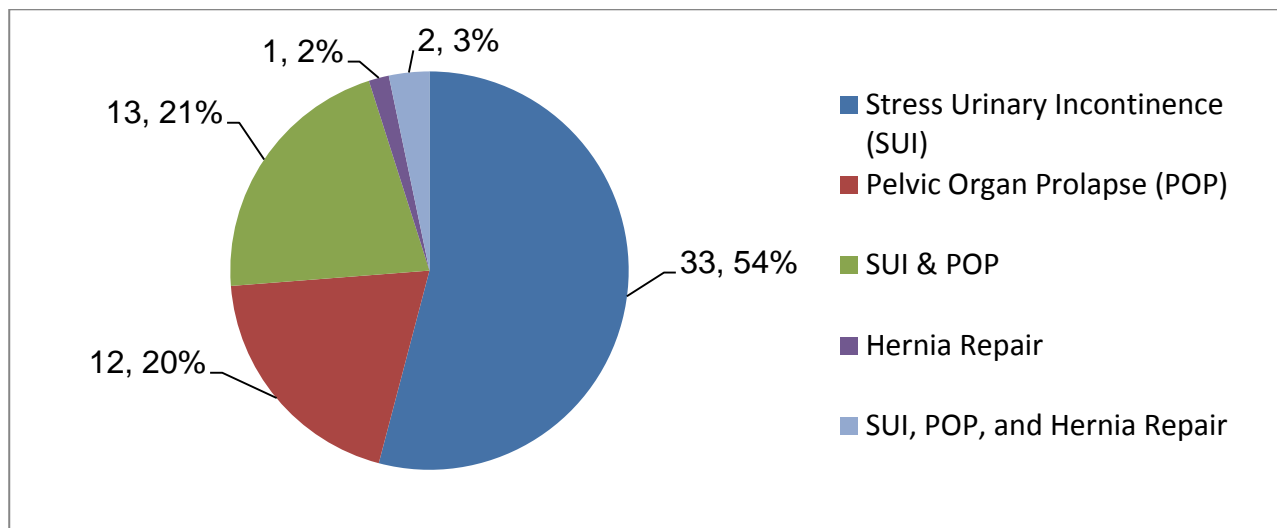
3.4.2 Analysis of Scottish Mesh Survivors Group data

The SMSG questionnaire was circulated to *approximately* 80 women, though no precise record was made of this. This provides an approximate response rate of 77.5% (95% CI: 67% - 85%) completed questionnaires. No demographic data were collected, which focussed on details of the mesh procedure and the women's subsequent experiences.

The dates of the mesh procedures ranged from 1999 to 2014, with two thirds (66%) taking place between 2008 and 2012. Some 10% of women had multiple mesh implants (n=5, two procedures, n=1, three procedures),

The questionnaire asked what was the reason for which the mesh was used. Data in answer to this question was provided by 61 (98%) of the responders. These data are shown in Figure 3.1 below.

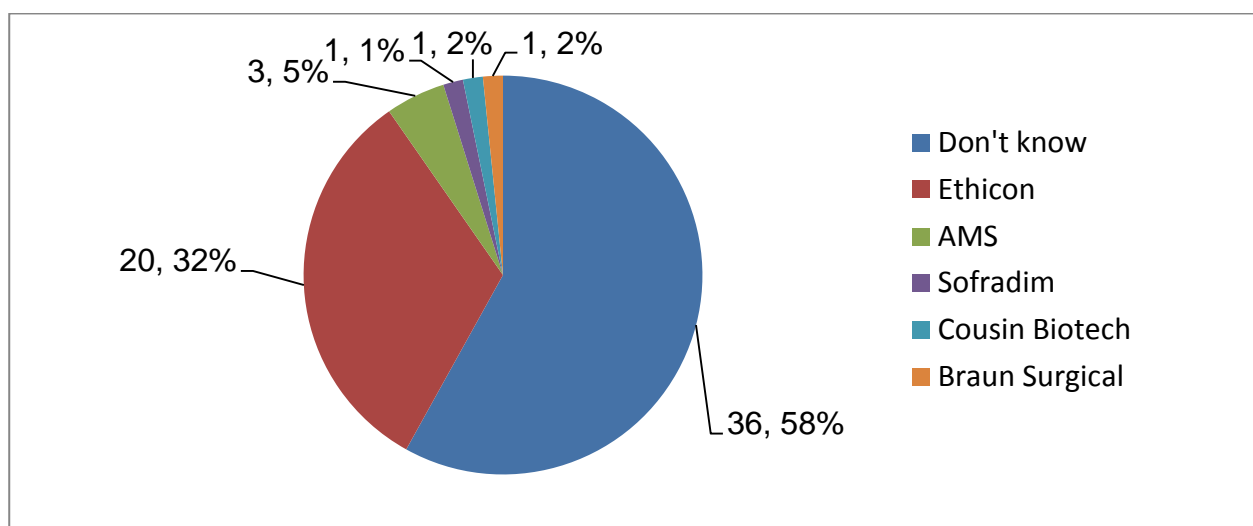
Figure 3.1 Reasons women reported for undergoing mesh procedures



(Data labels = n of reason, % of responders)

As Figure 3.1 highlights, the largest proportion of procedures were for SUI alone (54%), followed by SUI and POP procedures (21%). Single POP procedures accounted for 1 in 5 procedures (20%). Of the 62 responders, over half of them do not know what mesh product was fitted (58%) and just under one third aware that they had received the Ethicon™ product. This is shown in Figure 3.2.

Figure 3.2 Types of mesh product used in the procedure



(Data labels = n of reason, % of responders)

Before survey the women commented on the information they had received and about informed consent. Only 10 of responders answered the question about the information they were given, pre-operation about mesh (35% of the responders). Most (n=7) said that it was

inadequate and three women said they were given no information. Almost all of the women (n=61/62, 98%) said their consent to mesh surgery was not informed. One woman said she had been denied access to her patient records by the NHS Board responsible.

The questionnaire asked the women to describe how the mesh had affected them. From this it has been possible to identify the symptoms they experienced post mesh surgery. These self-reported health states, are shown in Table 3.2 below.

Table 3.2 Self-reported health state / symptoms experienced after mesh surgery

	Number of women reporting ever experiencing	Percentage of all women surveyed (n=62)
Pain	55	89%
Impaired Mobility	31	50%
Incontinence/Frequent Urination	24	39%
Relationship/Marriage Difficulties	21	34%
Sexual Difficulty	21	34%
Loneliness/ Social Withdrawal or Exclusion	19	31%
Depression	17	27%
Recurring infection	16	26%
Lethargy	15	24%

Overall, some 74% (n=46/62) of the women reported that their symptoms were still current. Only a small proportion of these reported that their symptoms had improved / resolved over time (7%). Symptom severity was reported to have been unchanged by 72% and over a fifth reported their symptoms were getting worse (22%).

The questionnaire also asked the women about their experiences of healthcare. This question provided an opportunity for a wide range of issues to be raised. These may be summarised as:

- 65% of women described their surgeon's aftercare. Of these 70% (n=28/40) indicated that their surgeon was not open to the idea that mesh was the cause of their symptoms;

- 77% of women reported that they had repeatedly told a clinician about their symptoms or asked for a referral, of these, 40% (n=19/48) indicated that their case had not been followed up;
- 82% of women reported on their current status, of these 33% (n=17/51) were not receiving ongoing care; and of the 66% who were ongoing care, some 38% (n=13/34) were critical of the treatment they were currently receiving; and
- 32% of respondents made a comment indicating they had lost faith in medical professionals or the healthcare system.

More widely smaller numbers of women mentioned issues such as: concerns over the processes of medical device manufacture and regulation; and the lack of financial support available from the public sector.

These women consider that there is no capacity in Scotland for full removal of mesh as no surgeons are trained. They also acknowledge that, for some of them, partial removal can leave some mesh and enhance erosion into organs.

3.4.3 PROSPECT Data

As part of the PROSPECT trial, women were asked at one and two years about their personal experiences. These data were collected using a questionnaire developed specifically for inclusion in the research. Only the additional comments have been made available to the Independent Review for preliminary analysis. No demographic detail was provided and it should be noted that this study includes experiences of women from other parts of the UK.

Table 3.3 Positive and negative patient comments at one and two years within the PROSPECT trial.

	One year follow up	Two year follow up
Positive comment	16	54
Negative comment	18	53

As can be seen, whilst there is an increase in the number of comments between follow up at year one and year two, the number of positive and negative comments are roughly equal. A simple Chi² test shows these differences are not significant ($p = 0.844$, ns).

Clearly, a more detailed analysis of these comments, notably seeking to understand the content of them more fully, will be undertaken by the PROSPECT trial team in due course.

3.5 Interpretation

The data we have regarding the experiences of women who have undergone mesh surgery is limited and needs to be handled in a manner which does not over analyse it. We also have to be careful in interpreting the data and in framing any conclusions from it.

Ideally, it would have been helpful to be able to undertake formal research into the experiences of these women, those with both positive and adverse outcomes. This did not prove to be appropriate in the context of the Independent Review and may have been

difficult to undertake. What data we have, whilst it has been considered in a scientific manner, is not without its potential sources of bias and this has been taken into account in the analyses underlying this chapter.

Long-term, adverse outcomes in mesh surgery for SUI and POP are real and can profoundly affect the everyday lives of some women. For many of the women who have been so affected, they report that they were not able to give informed consent, were unaware of the type of mesh device implanted, and have lost confidence in medical follow up, even though some are still experiencing unpleasant and debilitating symptoms that reduce their capacity for everyday life.

However, for other women, there are positive outcomes which have occurred. These have been experienced as strongly as have adverse outcomes. Where the data have captured something of the positive stories from women as well as those of adverse outcomes, they seem to be broadly equal in number.

Finally, it can be noted that the largest proportion of women who have had mesh surgery have not shared their personal experiences. Theirs are the silent voices, the absent evidence is the most difficult to interpret. For some, this silence is evidence for successful treatment and reflects that fact that these women have had positive outcomes. For others, it is a sign that – at best – the surgery has not worked, but these women have chosen not to seek further intervention as this was their “last, best hope”. Finally, there are some for whom this is evidence that there are women in Scotland who are still “suffering in silence”. In the absence of specific research to hear these stories, this must remain an absence of evidence for which no single interpretation is possible.

Table 3.1 Patient stories

Adverse experiences
<p>I watched and listened intently to <i>[the Scottish Parliament's]</i> Question Time this morning and heard you say that those of us who have approached our GP regarding the implant should tell what reaction we got. I would like to let you know what my experience has been.</p> <p>In June 2003 I received [a TVT] implant. By 2008 I was having some problems and must say that they were investigated, but was told that they did not know the cause. These problems have got worse but I never associated them with the implant until I read Marion Scott's article in Sunday Mail in April 2013.</p> <p>When I visited the GP to discuss her reaction was "You are just scaremongering like the mothers' who questioned the MMR Vaccine and did I not realize all the trouble we caused the Medical Profession". Reluctantly she referred me to the consultant who had performed my operation and I met with him on 8th August 2013. Only remark I took away from that appointment was "We don't know everything".</p> <p>On 23rd January 2014 I wrote the consultant to ask to be referred to X at Southern General in Glasgow. His reply said that he had forwarded my letter to my GP. At 3.10pm this afternoon I checked with Appointments Dept at Southern General and no request has been received.</p> <p>I have no way of ever finding out what, if any, damage the implant has done. If a record of how patients are treated is going to be set up I would like my experience to be added.</p>
<p>I am writing to inform you that I have read about your concerns surrounding the TVT mesh implant! I have had two attempts at this surgery and have been left with on-going complications. I am now in the process of being re-referred to my gynaecologist! This has led to 4 separate surgical procedures with no avail and now I have been left with severe problems. I had requested after the first tape erosion to have the procedure done the old fashioned way with skin graft but was refused point blank.</p> <p>I am pleased there is finally someone listening to us ladies on this matter. Let me know if I can do anything to help you with this matter or if I can do anything about it for myself. I'm only too happy to help.</p>
<p>I am a 51 year old female who until recently enjoyed a long career as a senior theatre nurse. That all changed, however, when in November 2013 I began to suffer pain in my groins and legs which was diagnosed as being mesh related.</p>

I had mesh inserted in 2010 and again in 2011. The reason for this email is to make you aware of the problems I am having at the moment with the DWP. I was assessed by ATOS on 25th November 2014 as I was receiving ESA and they sent report to DWP who then decided that I was fit to work. I was then taken off ESA and put on JSA. Having never signed on in my life I have found this extremely traumatic and upsetting.

I appealed the decision and have now got to the stage where my case should go in front of a tribunal. However, another decision maker at the DWP has reassessed my claim and again taken the evidence of the ATOS assessment, basically disregarding all the evidence I produced (and there was a ton of that!!) and has recommended that the tribunal not go ahead.

I feel as if I'm fighting a losing battle with this. According to the letter I was sent I "believe that I am unfit for work". This is not my decision to make. I would love to still be working but because of this material inside me I have been declared unfit to work by medical professionals, my GP consultant gynaecologist and an NHS Occupational Health consultant. THIS IS NOT MY FAULT !!

It also states that the report "does not indicate if the Health Care Professional is familiar with X's diagnosed condition" and that she "gave an opinion that her assessment does not indicate significant functional restriction".

As it is, I am in constant pain for which I now take regular analgesia and I cannot stand or sit for any length of time without having to change position regularly.

My home life has completely changed. I do not sleep well which means my husband doesn't sleep well before doing a full day's work. My two sons see me in constant pain. I have no income and my pay off from the NHS is now finished so I have no idea how I am going to pay my mortgage and household bills from next month.

This is just a very small insight into my life with this material inside me. This email was just really to let you know how hurt and disgusted this now makes me, being treated like a scrounger and all through no fault of my own.

I am one of many women left in pain daily through mesh implant and would like to know what help is being put in place for so many injured women. I have recently lost my home after 17 years paying mortgage had to quit my job after 25 years' service fight to receive benefits after being told to visit a food bank to feed my family. I have been told I'm not entitled to PIP. I have never had benefits in my life and am struggling on a daily basis due to this. I have had to double up dose of antidepressants due to having my life taken away from me I'm only 49 and feel my life is over due to this please put some help in place for those of us crippled through no fault of our own.

I am writing to you as I recover from my 5th surgery to repair the problems left in my body by Mesh. I am now 46 years old and the last 6 years of my life have been hell since being implanted with this device after the birth of my daughter. I won't go in to all the medical intricacies of my situation, as I frankly am an emotional wreck at present, as I try to recover from a removal that was unsuccessful. I am a working mum and always have been. I am a Faculty Head in Education, a job that I love and enjoy. However, once again I have been forced to take time off from my job for another surgery that I had to wait one year for - from referral to surgery.

This isn't good enough. I am losing valuable years of my child's life, and my own. If I am unable to return to work I risk losing the home that I have worked so hard to make. This has to be dealt with now, to allow women who have been injured and left in a disgusting state a better quality of life. I am urging you to ensure that the 'right thing' is done.

Positive experiences

Below is an email I sent supporting the continuing use of tape in urinary incontinence. He has encouraged me to copy you so that you are aware of the many lives that have been dramatically improved by this surgery.

“With so much adverse publicity I just want to say how much my life was changed following insertion of a TVT. I’m running twice a week (not that far!) and could never have undertaken this before. I have never felt fitter which is a real bonus in mid 50s! There is no way I would have contemplated a colposuspension.

“I am sure for everyone who feels their life has been adversely affected; there are hundreds whose lives have been transformed for the better”.

I have been advised by my Gynaecologist that fitting women with tapes to support their bladder has been suspended due to a tiny amount of problems. I would like to share my experience.

I was advised there was a small chance of the procedure not being a success. Before I had these tapes inserted, I was housebound. I was wetting myself up to 20 times a day. I couldn't bend over, kneel down, carry a bag, lean over anything.. it was so humiliating. Lifting or hugging my grandkids was impossible too. My life has been given back to me.. I AM 49 YEARS OLD and am far too young to have lost my dignity and freedom. I am now going to the gym, lifting weights let alone being able to carry shopping. It is the MOST AMAZING procedure. 7

I would ask you, for the sake of the many women looking in desperation for a cure to this awful problem, Please, please lift this suspension. I have been advised that 4 young women have been refused this simple procedure and that only from ONE surgeon. Any surgery has its risks. but we are warned beforehand. Any woman considering having this done is at her wits end and desperate for help.

You cannot deny them the chance of freedom from all the problems connected with having no bladder control.

I accompanied my friend to yet another appointment relating to incontinence issues, as a support. She is a young 66 years old, fit and active, takes care of herself well. She is absolutely shattered with her health situation. She has endured her incontinence for over 9 years. Was diagnosed with triple prolapse and operated on previously. Although prolapse now repaired, her incontinence continues. She was waiting for TVT surgery, but obviously this option is no longer available for time being. How long is this going to go on? What alternatives are being put in place? I can hardly believe that with the existing - and growing - number of women who are victims of this situation, there is so little help available. Her current option is to try (again) various medications. There may be some relief for her if she was able to use a newish product, some kind of tampon like insert ('vaginal rockets'- sound more exciting than they are!!) but these are not available on prescription, and are very expensive to buy privately.

First of all - Why?? If there is no surgery available currently, then why on earth are these products not being given on prescription? Second - why the terrible expense? although previously expensive enough, it seems that the producers, with an eye on the (lack of) surgery options, have latched on to the opportunity to make a few bucks, and are charging ridiculous prices for items that are desperately needed.

Thirdly - What is happening with TVS? I appreciate that some women have suffered as a result of these operations, but what is the % in comparison to the rest of the successful procedures? This situation is only going to grow and grow. You can just bet that the people making the decisions about both the surgery options, and the help available, are either men who obviously don't suffer from this, or women who don't suffer this condition at its 'full strength'. Well woe betide them!!! When they start to encounter this, I really hope it is as bad as my friend's situation. And I hope they think back and wish they had done more, fought harder! It absolutely scunnens me, that this - a situation brought on mainly because of childbirth, is being side-lined. Think of the expense if all women decide they are not going to 'push' and go for C-sections? And the number of hospital beds that will impact?? And yes - this IS written on behalf of my chum - but I am also thinking of the future and the possibility of similar situation for myself.

PLEASE get this back in focus and off the subs bench!

I refer to the letter recently sent to X (of which I received a copy) in response to the concerns I raised re Transvaginal Implant procedures.

On 13 January I received an email from Y, referring to my email about these procedures "particularly how these have been reported lately." In my original letter to X two thirds of that letter concerned the present coverage of the issue by the press. I was very disappointed to see that it gave no mention whatever to the issue of press coverage, far less to the nature of that coverage. In the articles that I read I could find no vestige of any form of balanced reporting. It's clear that there are patients who experienced very serious problems indeed. However, no mention was made of any successes.

One year ago I underwent one of these procedures because of a long standing and intractable problem. Despite the very best efforts of health professionals and myself my condition failed to respond to conservative treatments. In no way was surgery the first course of action.

I was provided with very comprehensive written and verbal information which was very straightforward and easy to understand. I was encouraged to discuss this with family and friends. My family practitioner was able to discuss the proposed surgery in detail and to study closely all the written information.

It was originally planned that I was to be a participant in the trial. My operation was carried out Z in a private hospital but because this hospital did not permit its premises to be used for research purposes I was no longer eligible to be part of that trial.

Media is the means by which information flows and the information that flows from certain press coverage makes no mention of any success. Certain aspects of the press continue to vilify in the most extreme terms the doctors who carry out these operations. I could imagine that these doctors may find themselves in a state of limbo, unable to respond to the allegations while their reputations and professionalism are savaged.

Confidence is a fragile commodity and in the wider medical world patient confidence in their surgeons and physicians is currently to an extent being undermined.

Chapter 4: Assessing the safety and effectiveness of vaginal mesh surgery for stress urinary incontinence and pelvic organ prolapse in Scotland

4.1 Operations provided in Scotland for stress urinary incontinence and pelvic organ prolapse

For this study, Information Services Division (ISD) used routine hospital discharge records to identify the different operations provided for stress urinary incontinence and pelvic organ prolapse in Scotland between 1997/98 and 2013/14. Specific types of operation that were provided in reasonably high numbers were included in the analysis.

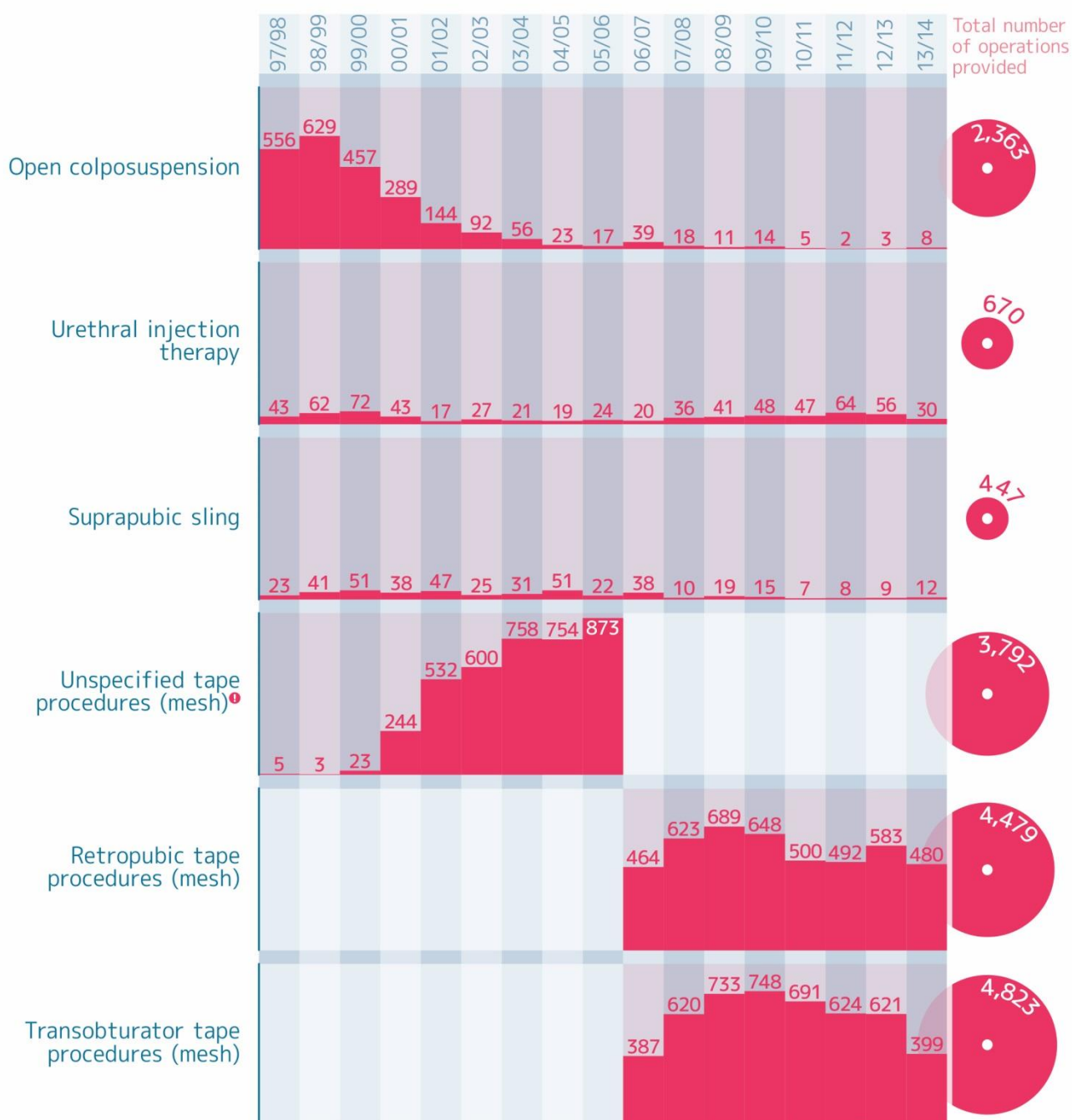
In general, only single operations were included in the analysis. 'Single' means that the woman did not have any additional/second operation for incontinence or prolapse at the same time as the operation being examined. It is quite common for women to have more than one operation at the same time. However if complications subsequently develop it can be difficult to know which operation caused the problem. Only single operations were included so that the study could focus on the risks of each particular operation separately.

In general, only first operations were included in the analysis. 'First' means that the woman had not had any other operation for incontinence or prolapse in the previous five years. Only first operations were included because the risk of complications may be quite different for a woman having a repeat operation, and it was important that the study did not mix operations with different levels of risk.

4.1.1 Operations provided for stress urinary incontinence

Open colposuspension was the main operation provided in Scotland for stress urinary incontinence in the late 1990s. Tape (mesh) procedures were introduced around 2000/01 and quickly became the most common operation type for this condition, however the number of tape procedures done fell substantially in the last year included in the analysis (2013/14). Urethral injection therapy and suprapubic sling operations have been provided in low numbers throughout the time period included in the analysis.

Numbers of first, single operations for stress urinary incontinence by year



¹ Operations provided during a patient's admission to hospital are recorded on routine hospital discharge records using OPCS Classification of Interventions and Procedures codes. Between 1997/98 and 2005/06, the codes available did not specify which kind of tape operation had been provided. After April 2006, new codes allowed the particular type of tape operation (retropubic or transobturator) to be recorded.

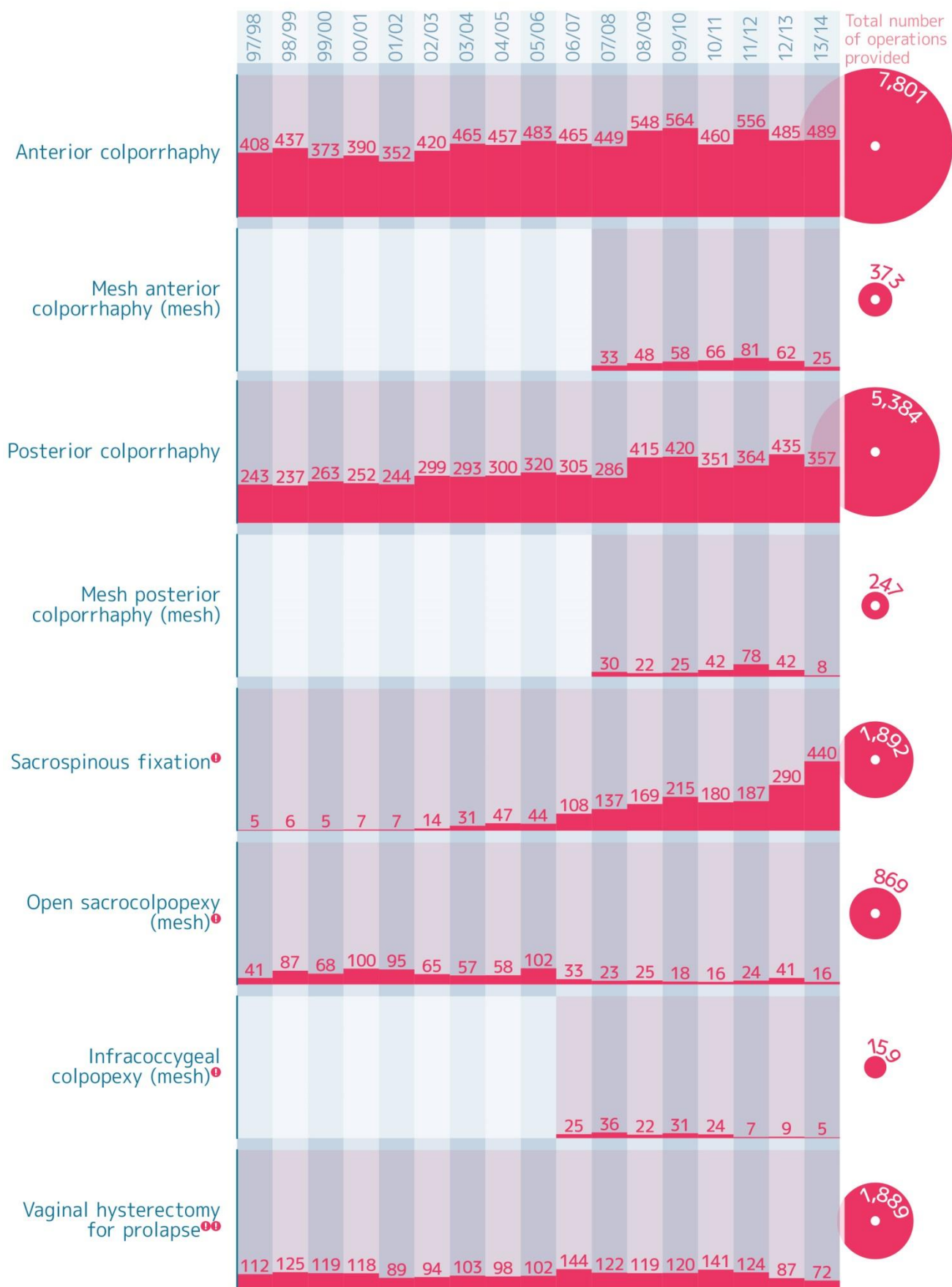
4.1.2 Operations provided for pelvic organ prolapse

Anterior and posterior colporrhaphies (first, single operations) have been provided in increasing numbers over the time period included in the analysis. Anterior and posterior mesh colporrhaphies can be identified in hospital discharge records from 2007/08 onwards. Relatively small numbers of mesh colporrhaphies have been provided in Scotland since then, and numbers provided have fallen in the most recent years.

Sacrospinous fixation operations have increased substantially over recent years. Mesh open sacrocolpopexies have been provided in moderate numbers over the time period included in the analysis. Mesh infracoccygeal colpopexies can be identified in hospital discharge records from 2006/07 onwards. Relatively small numbers have been provided since then, and numbers provided have fallen in the most recent years. Moderate numbers of (first, single) vaginal hysterectomies for pelvic organ prolapse have been provided over the time period included in the analysis.

- ❶ Sacrospinous fixation, sacrocolpopexy, and infracoccygeal colpopexy are usually provided for prolapse of the top of the vagina following a hysterectomy. These operations were therefore included if the woman had had a previous hysterectomy (but no other operation for incontinence or prolapse in the previous five years). In addition, these operations are rarely done as single operations so ISD included them if they were done at the same time as a traditional (non mesh) colporrhaphy (but no other incontinence or prolapse operation).
- ❶❶ Vaginal hysterectomy can be done for prolapse or other problems such as heavy periods. Only vaginal hysterectomies done for prolapse were included in the analysis.

Numbers of first single operations for pelvic organ prolapse by year



4.2 Problems after surgery for stress urinary incontinence or pelvic organ prolapse

4.2.1 Main problems

ISD looked at three main problems that can develop after an operation for stress urinary incontinence or pelvic organ prolapse. These were:

- immediate complications;
- later complications;
- further incontinence or prolapse surgery.

4.2.2 Immediate complications

‘Immediate complications’ means that at least one complication was recorded on the same hospital discharge record as the operation being examined; in other words the woman developed a complication when she was still in hospital following her first operation.

4.2.3 Later complications

‘Later complications’ means that at least one complication was recorded on a subsequent hospital discharge record; in other words the woman had been discharged home then readmitted for a complication at a later date. In general, readmissions for later complications were counted if they happened within five years of the operation being examined. Complications that would be expected to develop quickly after an operation were only counted if the readmission was within three months of the operation.

4.2.4 Further incontinence or prolapse surgery

‘Further incontinence or prolapse surgery’ means that at least one operation for either of these conditions was recorded on a subsequent hospital discharge record; in other words the woman had been discharged home after her first operation then readmitted for another stress urinary incontinence or pelvic organ prolapse operation at a later date. All readmissions for further surgery were counted if they happened within five years of the operation being examined.

4.2.5 What is a ‘complication’?

‘Complications’ included the following:

- problems directly related to the operation, such as damage to the bladder or difficulty passing urine;
- excessive bleeding;
- infection;
- pain;
- partial or total removal of mesh (later complications only).

Only complications that were treated in hospital were included in the analysis. Complications treated in outpatient clinics or in general practice were not included.

4.2.6 Additional problems

ISD also looked at the following additional problems that can develop after incontinence or prolapse surgery:

- readmissions for later complications or further incontinence or prolapse surgery;
- readmissions for any reason;
- referrals to an outpatient pain clinic;
- prescriptions for strong pain relief medication that contained an opiate such as codeine;
- death.

This report shows the results relating to the three main problems only. Full results, including those relating to the additional problems, are available at Annex A.

4.2.7 The risk of developing problems after an operation

The risk of developing problems after an operation for stress urinary incontinence or pelvic organ prolapse depends on the type of operation done and on a number of other factors such as:

- age of the woman;
- how many additional health problems she has;
- how experienced the surgeon doing the operation is.

To compare the risks specifically associated with different types of operation, it is important to take account of these other factors that may be influencing the number of problems seen.

For example, if older women with a lot of additional health problems tend to have mesh colporrhaphies rather than standard (non mesh) colporrhaphies, we would expect to see more problems after mesh operations even if mesh colporrhaphy was not in itself any more risky than standard colporrhaphy.

Statistical methods can be used to take account of all the other factors that may influence the number of problems seen after different types of operation and allow us to focus on the differences that are due specifically to the type of operation that was provided.

4.3 Problems following operations for stress urinary incontinence

The risk of developing problems after the different types of stress urinary incontinence operation included in the analysis is shown below.



¹ This is the total number of readmissions that would occur on average if 200 women were each monitored for five years after having their stress urinary incontinence operation.

The increase or decrease in risk of the various problems following each type of operation compared to that experienced by women undergoing open colposuspension, the commonest non mesh operation, is shown below.

These final results have used statistical methods to take account of various factors that may influence the level of problems seen after operations as discussed above. The factors that have been accounted for are a woman's age, deprivation level, and additional health problems; the experience of the surgeon; and the type of hospital providing the operation.

Taking these factors into account means that the remaining differences in risk are not due to those factors and are likely to reflect genuine differences in risk associated with the different types of operation.

To help interpret these figures, a 50% decrease in risk is the same as the risk being halved, and a 100% increase in risk is the same as the risk being doubled.



Green indicates significantly lower risk than that seen after open colposuspension

Red indicates significantly higher risk than that seen after open colposuspension

4.4 Summary of findings for stress urinary incontinence operations

Operations for stress urinary incontinence that involve operating through the abdomen (open colposuspension and suprapubic sling) carried the highest risk of immediate complications. Infections and problems directly related to the operation were the most common immediate complications following all types of stress urinary incontinence operations.

Each of the specific types of operation for stress urinary incontinence included in the analysis carried a somewhat higher risk of being readmitted for a later complication than open colposuspension. The higher risk of later complications seen for urethral injection therapy may be due to the very high risk of needing another incontinence operation after this type of surgery (see below), as every new operation carries new risk of complications. Longer term problems directly related to the operation, infections, and (for mesh operations) further surgery to remove the mesh, were the most common later complications seen after operations to treat stress urinary incontinence.

Urethral injection therapy carried a much higher risk of being readmitted for further incontinence or prolapse surgery over the five years following the initial operation than open colposuspension. Suprapubic sling operations carried a somewhat higher risk of needing another operation, and tape operations carried a somewhat lower risk. The type of further surgery needed was different for the different types of stress urinary incontinence operation. Almost all further operations following urethral injection therapy were for stress urinary incontinence, suggesting that the first operation did not completely cure the woman's incontinence. By contrast, around half of further operations following open colposuspension were for stress urinary incontinence and half were for pelvic organ prolapse, suggesting that prolapse problems developed after the colposuspension. After suprapubic slings and tape operations, around 75% of further operations were for incontinence and 25% for prolapse.

4.5 Problems following operations for pelvic organ prolapse

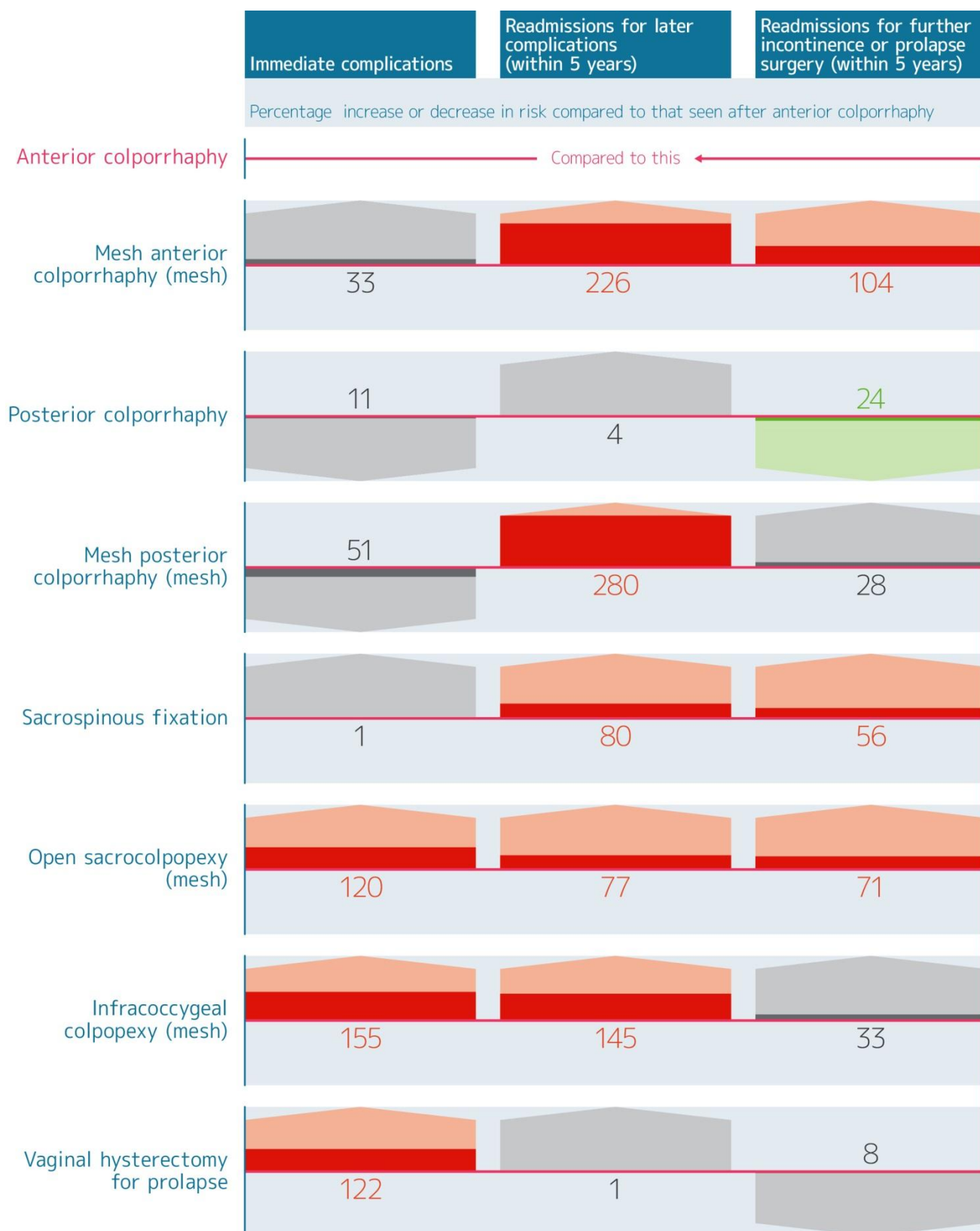
The risk of developing problems after the different types of pelvic organ prolapse operation included in the analysis is shown below.



¹ This is the total number of readmissions that would occur on average if 200 women were each monitored for five years after having their pelvic organ prolapse operation.

The increase or decrease in risk of the various problems following each type of operation compared to that experienced by women undergoing anterior colporrhaphy (the commonest non mesh operation) is shown on the right.

As described before, these final results have used statistical methods to take account of the various other factors that may influence the level of problems seen after these operations. The differences shown are therefore likely to reflect genuine differences in risk associated with the different types of operation.



Green indicates significantly lower risk than that seen after anterior colporrhaphy

Red indicates significantly higher risk than that seen after anterior colporrhaphy

4.6 Summary of findings for pelvic organ prolapse operations

Among the pelvic organ prolapse operations included in the analysis, open sacrocolpopexy, infracoccygeal colpopexy, and vaginal hysterectomy carried the highest risk of immediate complications. In general, infections and problems directly related to the operation were the most common immediate complications following prolapse operations. Excessive bleeding was also quite common after open sacrocolpopexy and vaginal hysterectomy.

Mesh colporrhaphies (anterior and posterior), sacrospinous fixation, open sacrocolpopexy, and infracoccygeal colpopexy all carried considerably higher risk of being readmitted for a complication over the five years following the initial operation than non mesh anterior colporrhaphy. Longer term problems directly related to the operation and (for mesh operations) further surgery to remove the mesh were the most common later complications seen after operations to treat pelvic organ prolapse.

Mesh anterior colporrhaphy, sacrospinous fixation and open sacrocolpopexy carried a higher risk of being readmitted for further incontinence or prolapse surgery over the five years following the initial operation than non mesh anterior colporrhaphy. Non mesh posterior colporrhaphy carried a somewhat lower risk of being readmitted for further surgery compared to non mesh anterior colporrhaphy. Around 80% of the further operations provided after each type of pelvic organ prolapse operation were for prolapse, and around 20% were for stress urinary incontinence.

4.7 What does all this mean for women and doctors?

This study has used routinely available health information to look at:

- the number of operations provided in Scotland for stress urinary incontinence and pelvic organ prolapse;
- how often women having the different types of operation develop problems after their surgery.

Some information on the risks associated with different types of operation for stress urinary incontinence and pelvic organ prolapse was available prior to this study.

For example, there have been a number of clinical trials directly comparing different types of incontinence or prolapse operations. Clinical trials are important to improving understanding of how well operations work however they tend to only include patients who are relatively healthy and only look for problems developing quite quickly after the surgery.

In addition, in the UK, if a patient develops a problem after surgery due to a medical device such as a mesh implant, the patient's doctor is required to notify the problem to the appropriate safety regulator such as the Medicines and Healthcare products Regulatory Agency. This is an important system but it is likely that not all problems, particularly less severe problems, are notified in this way.

This study adds to these other types of information by looking at operations provided as part of routine NHS care in Scotland and looking to see how many problems develop over the five years after the operation.

When thinking about the results of this study it is important to remember that in general only first, single operations for stress urinary incontinence or pelvic organ prolapse were included and that only later complications that were severe enough to require a readmission to hospital were included.

4.8 Key Messages

No operation is without risk. It is important for women and doctors to have clear information about the different risks associated with different types of operation. This will help them decide which operation will be best for any particular woman.

The risk of immediate complications, later complications, and needing further surgery for stress urinary incontinence or pelvic organ prolapse differs between the different types of operation examined. A specific type of operation can carry a relatively high risk of one of these problems (for example immediate complications) but a relatively low risk of a different problem (for example longer term complications).

More extensive operations, for example those involving operating through the abdomen or a hysterectomy, tend to carry the highest risk of immediate complications.

Compared to open colposuspension, tape (mesh) operations for stress urinary incontinence tend to carry a somewhat higher risk of later complications but a somewhat lower risk of needing further incontinence or prolapse surgery. This highlights the difficult choices facing women and doctors as it is difficult to decide if or when the higher risk of complications would outweigh the lower risk of further surgery.

Compared to open colposuspension, urinary injection therapy carries a much higher risk of needing further surgery and an associated higher risk of later complications.

Mesh colporrhaphies for the treatment of pelvic organ prolapse carry a substantially higher risk of later complications than non mesh colporrhaphies. Mesh colporrhaphies also carry a higher risk of needing further surgery for incontinence or prolapse than non mesh colporrhaphies.

Sacrospinous fixation, open sacrocolpopexy, and infracoccygeal colpopexy for prolapse of the top of the vagina all carry a higher risk of later complications than anterior colporrhaphy. Sacrospinous fixation and open sacrocolpopexy also carry a higher risk of needing further incontinence or prolapse surgery than anterior colporrhaphy.

Chapter 5: Review of the evidence from safety reviews and systematic reviews

5.1 Evidence availability

This section of the Independent Review (IR) was undertaken in line with a modified form of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline⁷.

This review considered systematic review evidence of two sorts. The first were the reviews of evidence undertaken by those agencies responsible for the safety of medical devices on an international and national basis. The second were the published, peer-reviewed Cochrane systematic reviews and health technology assessments undertaken in relation to mesh devices for SUI and POP.

Cochrane systematic reviews are produced by the Cochrane Collaboration. This is a global, independent network of researchers, professionals, patients, carers and people interested in health. It is formed as a not-for-profit organisation which spans contributors from more than 120 countries. Its work is always free from commercial sponsorship and other conflicts of interest. Cochrane Collaborators do this by producing reviews that summarise the best available evidence generated through research to inform decisions about health and health care. These Cochrane Reviews are systematic reviews of primary research in human health care and health policy. They are internationally accepted as providing evidence-based health care advice of the highest standard. Cochrane Reviews are updated as needed, ensuring that treatment decisions can be based on the most up-to-date and reliable evidence. The full text of every Cochrane systematic review and the Review Protocols for work in progress, are published online in the Cochrane Database of Systematic Reviews in the Cochrane Library⁸. In the UK Cochrane Reviews are used to inform the National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines, as well as informing policy and decision making in health care commissioning and development.

The following databases were searched for relevant reviews: Cochrane Library (2004 to 2015) and Medline (2004 to 2015). The search strategies used a range of key words and subject headings to identify information focussed on mesh implants for the treatment of stress urinary incontinence (SUI) or pelvic organ prolapse (POP), either alone or in comparison with other, alternative approaches to treatment. These two limits were applied to the identification of systematic reviews and safety reviews for inclusion in the review. Selected material was also limited to data reviews published in English, or where an English translation existed.

National and international websites of medical device safety organisations were also searched.

In total ten safety reviews were included⁹. These were:

- Australia – Therapeutic Goods Administration (2014) [AUS];
- Canada – Health Canada (2014) [CA];

⁷ <http://www.prisma-statement.org/>

⁸ <http://www.cochranelibrary.com/>

⁹ A full list of references in Chapter 5 can be found in the Reference section

- Denmark – Danish Health and Medicines Authority (2012) [DK];
- European Union (consultation draft) - Scientific Committee on Emerging and Newly Identified Health Risks (2015) [EU];
- Netherlands – Health Care Inspectorate (2013) [NL];
- New Zealand – Accident Compensation Corp. (2015) [NZ1];
- New Zealand – MedSafe (2014) [NZ2];
- UK – Medical Devices and Healthcare Regulatory Authority (2014) [UK1];
- UK – York Health Economics Consortium for the Medical Devices and Healthcare Regulatory Authority (2012) [UK2]; and
- USA – Food and Drug Administration (2011) [USA].

Of these, six were full, completed reviews [NL, NZ 1&2, UK 1&2 and USA], one [EU] was reviewed as a provisional draft report published for consultation and three were based on reported summaries on, or news alerts published on, official websites [AUS, CA and DK].

There were 12 pertinent Cochrane systematic reviews completed, of which nine related to mesh use and alternative management approaches for SUI:

- Glazener CMA & Cooper K. (2001). Anterior vaginal repair for urinary incontinence in women. [Glazener 1];
- Dean N et al (2006). Laparoscopic colposuspension for urinary incontinence in women. [Dean];
- Rehman H (2011). Traditional suburethral sling operations for urinary incontinence in women [Rehman];
- Lapitan MCM et al (2012). Open retropubic colposuspension for urinary incontinence in women. [Lapitan];
- Kirchin V (2012). Urethral injection therapy for urinary incontinence in women. [Kirchin];
- Bakali E et al (2013). Treatment of recurrent stress urinary incontinence after failed minimally invasive synthetic suburethral tape surgery in women [Bakali];
- Nambiar A (2014). Single-incision sling operations for urinary incontinence in women. [Nambiar];
- Glazener CMA & Cooper K (2014). Bladder neck needle suspension for urinary incontinence in women. [Glazener 2]; and
- Ford et al (2015). Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. [Ford]

In addition there was one health technology assessment completed in relation to SUI:

- Cody J et al. (2003). Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.¹⁰ [Cody].

Finally, there were three Cochrane systematic reviews were completed in relation to POP;

¹⁰ NICE CG 171 (2013). *“Urinary incontinence in women: the management of urinary incontinence in women”* provides an update to the first edition of the NICE guidance published in 2006. This was informed by the Cody *et al* systematic review undertaken by the UK HTA included here. The 2013 edition of the NICE guideline added material from RCTs not included in the Cody et al review, as well as drawing on the extant Cochrane Reviews available at that time. As four of these Cochrane Reviews were published in 2013 (and therefore drawing on the same additional RCT material as NICE) or post 2013 (and therefore drawing on material not available to NICE, the decision to remain with the original Systematic Review and the updated Cochrane Reviews was taken.

- Maher C et al (2013). Surgical management of pelvic organ prolapse in women. [Maher];
- Bugge C et al (2013). Pessaries (mechanical devices) for pelvic organ prolapse in women [Bugge]; and
- Hagen S & Stark D. (2011). Conservative prevention and management of pelvic organ prolapse in women. [Hagen].

5.2 Methods

Following discussions with both patients and clinicians, a number of key outcome areas were identified to provide a data extraction framework. These were:

- Effectiveness of SUI or POP procedure(s):
 - effectiveness in terms of objective SUI / POP cure at one year or more;
 - effectiveness in terms of subjective SUI / POP cure at one year or more;
 - need for repeat SUI or POP surgery; or
 - further conservative treatment for SUI.
- Reported safety issues with SUI or POP procedure;
 - mesh technology; or
 - proprietary brand of mesh;
- Patient-focussed outcomes: Quality of Life (QoL):
 - measurable QoL at one year or more post procedure, specific to SUI or POP;
- Patient-focussed outcomes: adverse outcomes:
 - short term/postoperative complications;
 - long term disability due to adverse effects;
 - surgical treatment for adverse effects.
- Relative efficacy of alternative therapy to mesh.
- Systems efficacy;
 - Surgical capacity and competency issues;
 - Service capacity and feasibility;
 - Other factors.

Data were extracted and tabulated for further interpretation. The overall quality of the evidence reviewed was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) on grades of evidence [SIGN 50 reference].

5.3 Safety reviews of mesh implants

5.3.1 Nature of the evidence

At its heart, any review of the safety of a medical device is seeking to determine if the device can continue to be used safely and how best to ensure that patient safety is maintained throughout the medical or surgical processes that implant or connect the device to the patient, without reducing the overall effectiveness of the device.

However, it is fair to say that the 10 safety reviews included in this IR differed in their specific focus, the content of the review, and in which actions were considered necessary. Some provided a comprehensive review of the evidence relating to adverse outcomes following mesh implantation; others considered the effectiveness of the original safety review process; whilst others simply provided health care systems with advice on how to proceed in the current set of circumstance.

In the context of the outcomes being considered, such safety reviews are most likely to focus mainly on the nature, severity and frequency of any surgical complications and adverse outcomes. They are also likely to consider aspects of efficiency and effectiveness in the delivery of care. Finally, they may consider whether there has been any failure in the regulatory system that was used to determine the original safety of the device as "safe" for health care use.

Different reviews may use varying methods. In most cases, the reviews can be classified as being "narrative reviews", reporting on available evidence. For the purposes of this review of safety reviews, the quality of this evidence has been assessed to be in a range from SIGN 1++ to SIGN 4 evidential levels. As such, they represent very good sources of evidence, within the context of the review's stated aim and focus. Four reviews specifically reviewed the safety of synthetic surgical mesh implants for SUI and POP [AUS, EU, NL, and UK 1&2], of which one specifically considered whether a withdrawal of mesh for POP [NL]. Three reviews were undertaken to provide updated advice to patients, health care providers and clinicians [CA, DK and USA]. Finally, the two reviews from New Zealand [NZ 1&2] only considered data on adverse outcomes following mesh surgery. It is noted that whilst seven of the reviews considered both SUI and POP procedures as being within scope [AUS, EU, NZ 1&2 & UK 1&2], three reviews only considered POP procedures [DK, NL and USA].

5.3.2 Results

The extracted data in relation to the safety reviews are summarised within two tables. Table 1a provides a detailed analysis of the data contained in each of the International Agency's Safety Reviews, whilst Table 1b gives general observations and findings from the International Agency Safety Reviews. In this section, the main findings are summarised across the reviews.

None of the safety reviews concludes that there is sufficient evidence to withdraw synthetic mesh from clinical use for either SUI or POP [AUS, CA, EU, DK, NL, NZ 1&2, UK 1&2, USA], though one review does recommend that women with mesh implants for POP are recalled to hospital for clinical assessment [DK].

In a similar way, none of the reviews under-estimate the reality that for some women, the use of mesh devices has been associated with long-term, adverse outcomes that have had severe effects which limit their everyday activities and reduce their quality of life. [AUS, CA, EU, DK, NL, NZ1&2, UK1&2, USA]

Mesh safety in treating SUI

The scientific rationale for the use of synthetic mesh is specifically considered in the safety review from the EU's Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) [EU].

They conclude in relation to SUI procedures that there is a robust evidence-base to support the use of Mid Urethral Slings (MUS) which they described as being *“the most extensively reviewed and evaluated procedure for female SUI now in use”* [EU]. This is the case for both retropubic and transobturator MUS procedures [EU]. It should be noted that the safety review by the Australian Therapeutic Goods Agency, as reported on their website described the evidence base for SUI as “adequate”. (AUS) The EU review notes that, as with any surgical procedure, there can be complications associated with MUS. Where these do occur, the surgical complication rates are low [AUS, EU, NZ1, UK 1&2]. Complications found to be associated with MUS procedures include bleeding, damage to the bladder and bowel, voiding difficulty, mesh tape exposure and pelvic pain. All these complications may require repeated surgery, but this is uncommon. [CA, EU, NZ1, UK 1&2] What evidence of longer term effectiveness that does exist suggests that treatment success decreases over five years for both retropubic and transobturator MUS procedures, though patient satisfaction with both types of slings remained high. [EU] New mesh erosions occurred in both types over time at a similar rate. [EU, NZ1, UK1&2]

Mesh safety in treating POP

For POP procedures the EU safety review concluded that there is convincing evidence in favour of the use of a synthetic mesh to repair a prolapsed anterior vaginal wall. The evidence suggests that mesh implants are both subjectively and objectively superior in terms of clinical outcomes to a native tissue repair, though the reported health-related QoL post-surgery is no different (EU). Complications are reported with the rate of new pelvic organ prolapse in the untreated vaginal compartment significantly higher when synthetic mesh is used, though there is no evidence that this leads to a need for subsequent operations for POP. A similar pattern is observed for post-procedure SUI where the use of mesh is associated with higher rates of reported SUI; again this is not reflected in the need for SUI surgery. [EU] Mesh exposure is reported frequently following anterior wall repair with mesh, though there are no differences in reported rates for new dyspareunia or sexual dysfunction. [EU]

For repairs to the posterior vaginal compartment, the review concluded that there is moderate evidence that the use of mesh results in higher rates of objective cure. This, however, is also associated with higher rates of new POP of the anterior vaginal compartment. Subjective cure or cases of new SUI are observed to be no different from native tissue repair. As with anterior vaginal wall repairs, mesh exposures are reported frequently. [EU, NZ1] This pattern is also broadly observed for mesh repairs in more than one vaginal compartment. Repairs using mesh were found to result in higher rates of subjective and objective cure, but also in significantly higher rates of new POP of the untreated vaginal compartments. No differences in other outcomes or surgical complications were found, though mesh exposures were frequently reported. [EU, NZ1]

Surgical approach to POP repair was considered in the Australian review. This concluded that whilst there was evidence of effective use of mesh in abdominal POP, there was insufficient evidence to support its use in transvaginal POP repairs. [AUS] This is consistent with the advice provided by both Health Canada and the Food and Drug Administration (FDA) in the United States which advised clinicians to note that transvaginal procedures may carry a higher risk of complications than abdominal POP or native tissue repairs. [CA, USA]

For all types of POP repair, reported mesh exposure, (symptomatic or asymptomatic), obviously differed from that in native tissue repair (observed complication rates 4-19%); however no differences in complication rates were observed for dyspareunia (post-surgical

or new), post-surgical pain, haemorrhage, bowel and/or rectal injury, urinary infection and postoperative urinary retention between mesh and native tissue surgery. [EU] Overall, complication rates for POP were reported to be low. [AUS, EU] However, it was noted that the follow-ups in papers in these meta-analyses were mainly short-term (up to 12 months); a few were medium-term (1-5 years). Long-term results (5-10 years) of RCT's are not yet published but are needed for the full appreciation of outcomes. [EU, UK 1&2, USA]

Risk factors for adverse outcomes

The EU review undertook a very detailed analysis to identify possible sources of risk associated with adverse outcomes in the use of mesh implants. This review has been used as the basis for this section of the report, augmented by other evidence from safety reviews where appropriate.

An analysis of adverse outcomes associated with the type of synthetic surgical meshes for treating SUI and POP was undertaken. At present, four major types of mesh are produced commercially. The data suggested that two types of mesh are “most appropriate” for mesh implants:

- synthetic mesh type 1 (polypropylene monofilament, macroporous >75µm):
 - synthetic mesh for vaginal use; and
 - synthetic mesh for insertion via the abdominal route; and
- synthetic mesh type 3 (polyester ,multifilament , microporous <10µm):
 - synthetic mesh for insertion via the abdominal route .[EU]

Synthetic mesh type 2 (mono and multifilament, microporous, and synthetic mesh type 4 (monofilament, nanoporous <1µm) were considered to be “not appropriate” for this clinical use. For all other forms of synthetic mesh materials, the EU review concluded that there was insufficient evidence on which to base an opinion. [EU] When considering factors which may be associated with mesh design, the review highlighted a number of factors that may be possible potential sources of risk. These included: overall surface area of mesh used, (which is greater for POP than for SUI); the composition of the mesh weave and its porosity; the physical character of the mesh and its durability within the context of long-term indwelling of the device in human tissue on a long-term basis. [EU]

Whilst the available evidence only allows for a two year follow up, specific surgical techniques were noted to be associated with a higher risk of adverse outcomes. At the most fundamental level, it was noted that mesh exposure is **only** seen with a non-absorbable material such as synthetic mesh, this is true of all synthetic materials. Generally, it was concluded that vaginal surgery is associated with a higher risk of mesh-related complications and morbidity than abdominal mesh procedures. [AUS, CA, EU, NZ1, UK 1&2, USA] Overall, the EU review was of the opinion that the risk assessment of the use of mesh needs to differentiate between its use in SUI and POP in that the evidence:

- on efficacy and use of implanted meshes for SUI suggested that the associated risk of complications was low (albeit that follow data were limited and there was an absence of long-term -up (5-10 years) follow up data;
- on vaginal insertion of non-absorbable synthetic mesh with a large surface area for POP suggests it is associated with the highest incidence of complications; and
- that vaginally implanted mesh for POP is associated with increased risks compared to mesh implantation for SUI. [AUS, CA, EU, NZ1, UK 1&2. USA]

In the light of these considerations, the EU review concluded that the use vaginally implanted mesh for POP should be restricted [EU]. This is, however, the only review to reach such a conclusion.

Surgeons' experience of the procedures in question was considered a risk factor for adverse outcomes in a number of the safety reviews. These can be summarised as:

- surgical experience in SUI and POP MUS procedures – the evidence suggests only surgeons with experience should perform these procedures, though there is not clarity on the definition of an “experienced surgeon”; [AUS, EU, UK1&2]
- level of surgical training and maintaining competence – the evidence suggests that successful learning may vary from one trainee to another and may be affected by factors such as: the trainee’s prior surgical experience; the difficulty of the procedures; and the level/quality of the clinical supervision; [CA, EU, UK1, USA] and
- adherence with clinical guidelines – the evidence suggests that there is a greater risk of adverse outcomes if surgeons do not follow appropriate clinical guidelines or the manufacturer’s instructions. [EU, NZ1, UK 1&2]

The potential to identify patient groups that were at a higher risk of complication was noted in four safety reviews [AUS, EU, UK1&2]. However, there is at present very little robust evidence available to inform patient selection when synthetic mesh is proposed for use in POP or SUI procedures. More research needs to be done on this, at present it is recognised that: smoking is statistically associated with an increased risk of mesh exposure; and factors such as obesity and age may also be important. In this latter regard, the EU review concluded that it was prudent to be “more reluctant” to use mesh devices for POP in younger age groups. [EU]

Patient Consent

The need to ensure that patient decisions to undergo a mesh procedure must be based on appropriately informed patient consent is noted in six safety reviews [AUS, CA, EU, NL, UK1, USA]. They note that gaining effective patient consent should be the result of a wide-ranging discussion regarding the patient’s specific situation and all the potential benefits and risks from the use of synthetic mesh for either SUI or POP procedures. Safety reviews providing specific guidance on what should be included in such patient consent discussions include those from Health Canada [CA], SCENIHR [EU], The Dutch Healthcare Inspectorate [NL], the UK Medicines and Healthcare products Regulatory Agency [UK1], and the US Food and Drug Administration. [USA]

Data gaps and long-term follow up

The need for more detailed data, or the relative lack of such data, was mentioned in some way by all the safety reviews. In general data identified as being lacking related to:

- research evidence on long-term follow up (greater than 5 years post-surgery) for patients receiving mesh procedures for SUI or POP; [EU, UK1&2, USA] ,
- the lack of traceability for individual mesh devices used in such procedures; [EU]
- the lack of data on the specific surgical approaches used in mesh procedures; [EU], and
- the lack of comprehensive adverse outcome reporting. [CA, EU, UK1&2, NL, USA]

Whilst there were differences in proposed approaches to deal with the evidential gaps identified, it is notable that these focused on the need for effective data capture and reporting.

Medical device regulatory systems

Finally, six safety reviews commented on aspects of the processes by which medical devices are assessed for their safety and what could be done to improve this. [AUS, CA, EU, NL, UK1, USA] Whilst the Therapeutic Goods Administration in Australia have indicated that they are reviewing the safety compliance of all mesh devices [AUS] and the US Food and Drug Administration has taken action to bring mesh devices for POP into a level of regulatory requirement more in line with that in Europe, [USA] the most comprehensive consideration of the overall system of assessing medical devices and safety was provided by the Dutch Healthcare Inspectorate. [NL]. They concluded that whilst the processes by which mesh devices had been assessed as being safe were in line with the Dutch regulatory framework, there were areas for improvement. The first of these was that the requirements for the evaluation process of devices should be made stricter, with more time taken to assess safety and judgements taken in the light of clear criteria for effectiveness and safety. The second improvement was that the formal Vigilance and Post-Marketing Surveillance stage of the evaluation process be strengthened in European legislation. This improvement, which was recommended in three other safety reviews [CA, UK1, USA], would allow for longer-term assessment of complications and adverse outcomes, especially when novel procedures were being used with devices deemed to already be safe. [CA]. Finally, the agency recommended the creation of a central, independent registry for implants, recording product information and patient information as a minimum. It was noted, however, that this was not specific to mesh devices and that the registry should include all implants, across all specialties. [NL] Clearly these recommendations are specific to the Dutch circumstances, though the revised EU Medical Devices Directive will address several of these requirements
[\[http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/index_en.htm\]](http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/index_en.htm)

5.3.3 Interpretation

The key messages from this analysis are:

- No safety review by an international agency has called for mesh devices used in SUI and POP procedures to be withdrawn from use.
- For some women, there are long-term, adverse outcomes associated with the use of mesh devices that have had severe effects on their everyday activities and quality of life.
- The use of mesh for MUS in treating SUI is generally considered effective with low complication rates, accepting that long-term follow up data are not presently available.
- The use of mesh for some forms of POP repair is considered effective, provided that it is used in abdominal rather than vaginal procedures. The risk of complications/adverse outcomes is higher following the use of mesh for POP than for SUI.
- Risk factors for adverse outcomes include: surgical approach, the experience of the surgeon and some patient characteristics. Factors which may influence risk include the physical characteristics of the mesh device used.
- Well-informed patient consent is essential.
- Data associated with long-term follow up of mesh procedures are not currently collected. This needs to be remedied.

- The systems used to assess the safety of medical devices could be improved, notably in the area of vigilance and post-marketing surveillance.

5.4 Systematic reviews of effectiveness of mesh in stress urinary incontinence and pelvic organ prolapse

5.4.1 Nature of the evidence

The systematic reviews included in this section of the report are either Cochrane systematic reviews (12 reviews) or Health Technology Assessment s (one review). In each case the methods adopted in creating these reviews mean that they fulfil the highest level of SIGN evidence grades in that they are based on evidence ranging from SIGN 1++ (High quality meta-analysis, systematic reviews of Randomised Controlled Trials (RCTs), or RCTs with a very low risk of bias) to SIGN 1+ (Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias).

Using such systematic reviews, allows the professional and patients within the Independent Review (IR), and those who will read this IR more widely, access to the most recent clinical knowledge in a more readily accessible form. In the context of this review, they can facilitate the process to evaluate clinical effectiveness data of treatments and services across a range of settings and circumstances.

However using such systematic reviews does have some drawbacks. For example, they are not good at summarising evidence “gaps” (you cannot summarise what is not there), at the same time the review system will still work with evidence which is of differing “robustness”. Though in this latter regard, the methods used do include ways of assessing the underlying strength or weakness of data included in the systematic review. Another limitation that should be noted is that systematic reviews tend to focus on the experiences of patient groups and not on individual patients. As such it is better at summarising research, than personal experiences.

Whilst such systematic reviews still require interpretation of the reviewed evidence, not least in how it relates to clinical effectiveness and public / patient experience, they are the best available evidence on which to base such assessments.

5.4.2 Results

As noted above (section 5.2 above) 12 systematic reviews were included in this analysis. Nine of these related to SUI procedures and three to POP procedures. The systematic reviews cover not only mesh procedures, but also comparisons with conventional treatment. This was to allow consideration of the effectiveness of mesh against other treatment approaches. The results of the analysis in relation to SUI procedures is shown in Table 2a, whilst that for POP procedures is shown in Table 2b.

In this section, the major conclusions from each of the systematic reviews in relation to effectiveness (clinical and patient outcomes and QoL measures) are presented.

Effectiveness of SUI Procedures

Anterior vaginal repair (without mesh) for urinary incontinence in women [Glazener1]

Open abdominal surgery (retropubic suspension) was more effective than anterior vaginal repair for the treatment of primary urodynamic stress incontinence. The effect was longer lasting, whether or not the women had associated prolapse. Marginal differences in QoL recorded.

No differences in effectiveness or QoL were observed between anterior vaginal repair and needle suspension. No comparative trials were found between anterior vaginal repair and mock operation, laparoscopic colposuspension, and suburethral sling procedures.

Overall the evidence was assessed as being of poor overall quality. Long term follow up data in trials included were limited.

Effectiveness of tension-free vaginal tape [Cody]

Laparoscopic colposuspension and traditional slings have broadly similar cure rates to Tension-free Vaginal Tape (TVT) and open colposuspension. The QoL of patients treated with TVT were significantly better in relation to their emotional state, social functioning, and mental health. However generally all QoL was shown to be better post-operatively compared to pre-operation levels.

Overall, the authors considered that there were “limited” data on which to base the review. The lack of long-term follow up data was specifically noted.

Laparoscopic colposuspension for urinary incontinence [Dean]

Laparoscopic colposuspension is reported to provide a lower objective cure rate for SUI over colposuspension by open surgery (in the shorter-term, less than 18 months). However, no significant differences were found in an 18 month to five year period. There were significantly fewer perioperative complications with Laparoscopic colposuspension and some evidence for less pain. The QoL data did not suggest any differences between the two.

In comparison with vaginal mesh slings (self-fixing slings), laparoscopic colposuspension was found to be less effective than mesh in objective cure rate for SUI, though there was no statistically significant difference in subjective cure rate between them. The data on QoL was not pooled, meaning a single analysis was not possible. Of five studies, only one suggested that mesh was associated with improved QoL

When differing approaches to laparoscopic colposuspension were compared it was reported that objective and subjective cure rates were higher when it was performed using sutures for the repair than when it was performed using mesh fixed with surgical staples. In a further comparison, suture repairs that used two sutures were more effective than those using a single suture. QoL was not assessed in these trials.

No research trials which compared laparoscopic colposuspension to mock operation, conservative management, needle suspension, traditional sling procedures, anterior vaginal repairs or peri-urethral injections were found.

The authors considered that the data was adequate in 13 trials and of uncertain quality in a further eight included in the systematic review. One trial was described as inadequate. The lack of long-term follow up data was noted as a specific omission which limited the analysis.

Traditional suburethral sling operations for urinary incontinence [Rehman]

The systematic review concluded that in trials which compared traditional slings with minimally invasive slings using synthetic mesh, there were no differences in the effectiveness of either type of sling on objective or subjective cure rate for SUI. Whilst QoL data were collected in some studies, no differences were found between types of sling procedure.

In comparisons with other surgical techniques – open abdominal retropubic colposuspension, abdominal and vaginal needle suspension and trials of different types of traditional sling materials – suggested that traditional slings may be equally as effective as other surgical approaches. Whilst not suitable for detailed analysis QoL data suggested that patients undergoing open abdominal retropubic colposuspension had better post-operative QoL than those with a traditional sling procedure.

Traditional slings may be more effective than either drugs or injectable agents, synthetic material. However, in comparisons with conservative management, anterior vaginal repair and laparoscopic procedures were not found to be more effective.

The authors considered that caution was needed in interpreting the results of the systematic review. The quality of evidence in the studies was variable; with only short-term follow-up and the lack of focus on primary outcome data (e.g. complication rates).

Open retropubic colposuspension for urinary incontinence [Lapitan]

Open retropubic colposuspension was found to be an effective treatment for stress urinary incontinence compared with other forms of surgery (anterior colporrhaphy (repair), needle suspension, and laparoscopic colposuspension). Long term data were analysed suggesting that it was effective in the long term with approximately 80% patients undergoing open retropubic colposuspension still continent at 5 years. QoL data in these trials were sparse and whilst post-operative improvements were observed, little evidence for differences between procedures was found.

Sling procedures, both traditional and minimally invasive mesh sling procedures, were found to be not significantly different from open retropubic colposuspension in objective or subjective SUI cure. QoL data also showed no significant differences.

More limited evidence in relation to open retropubic colposuspension compared with conservative management, pharmaceutical drug treatment, and injectable synthetic material suggested that surgical intervention may be more successful. No trial data was found for other possible comparisons.

Overall the authors considered the data quality to be classed as “unclear”, though the ability to analyse longer term data was welcomed.

Urethral injection therapy for urinary incontinence [Kirchin]

Injection therapy with synthetic particulate material shows a short-term advantage over home pelvic floor muscle training in reducing SUI and an increased QoL. However, as follow up was limited to three months, it is not clear if this advantage is maintained.

Injection therapy appears inferior to open surgery at 12 months, but has a better safety profile.

Out of 14 trials in the systematic review, risk of bias was assessed as either “low” or “unclear” in all but one trial. This one trial was assessed at “high” risk of bias. Only short-term follow data was considered.

Treatment of recurrent stress urinary incontinence after failed minimally invasive synthetic suburethral tape surgery [Bakali]

No trials were found suitable for inclusion.

Non RCT data suggest that repeat suburethral tape surgery is less effective than for primary surgery. There is some evidence that retropubic suburethral tapes are superior to transobturator tapes as secondary procedures.

Single-incision sling operations for urinary incontinence in women [Nambiar]

Single incision (mini) slings were found to be less effective than retropubic, minimally invasive slings in achieving objective or subjective cure. QoL was reported to be statistically significantly better in the retropubic group.

Twenty trials were included which comparison between single incision slings with obturator minimally invasive slings; either the medial-to-lateral ‘inside out’ surgical approach (TVT-O) or the lateral-to-medial ‘outside-in’ approach (TOT). Objective and subjective cure rates were found to be significantly better for both TVT-O and TVT-O/TOT combined than for single incision slings. No difference was found for TOT alone compared with the single incision sling. No QoL data was reported.

No trials were identified in which single-incision slings were compared with no treatment, conservative treatment, open colposuspension or laparoscopic procedures. Whilst trials comparing them to traditional sub-urethral slings were found, the authors did not consider the data of an appropriate quality on which to confidently identify any differences between any of the different types of single-incision sling.

The overall quality of the data included was assessed by the authors as variable. About half of the trials were considered to have used using adequate methods to reduce the risk of bias, while in the other half, the methods used were considered to be inadequate or were not described. Long term follow up data were noted as lacking.

Bladder neck needle suspension for urinary incontinence in women [Glazener2]

Needle suspension was compared with open abdominal retropubic suspension using different techniques. Subjective outcome at both under and at one year suggested that open abdominal retropubic suspension was the more effective treatment.

When compared with anterior vaginal repair, needle suspension was found to be similar in terms of subjective cure rates after 12 months and long-term problems with voiding dysfunction.

One small trial compared needle suspension with suburethral sling procedures. However it was too small to address differences in cure rates,

No statistically significant differences were found in the one trial that presented comparisons between types of NS. No trials were found which compared needle suspension with mock procedure, conservative management, laparoscopic colposuspension, periurethral injections, or pharmaceutical drug treatment.

Overall the authors considered the quality of the data low. Long term follow data was only available for three of the included trials.

Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women [Ford]

Mid-urethral slings using mesh implants were found to be a highly effective treatment for SUI. Robust short term data suggests no significant differences between the two insertion routes, transobturator; and retropubic, in subjective or objective cure of incontinence. . There is some evidence that the observed equivalence in subjective and objective cure rates in the medium (1 to 5 years) and longer term (over 5 years).

The trials that compared the retropubic, bottom-to-top approach with the retropubic, top-to-bottom one approach showed that inserting the mesh tape through the retropubic route from bottom to- top is the more effective than the top-to-bottom approaches.

Comparisons between the transobturator, medial-to-lateral approach with the transobturator, lateral-to-medial approach showed no evidence of any differences between the two approaches with respect to SUI outcomes. When a retropubic route is employed, a bottom-to-top approach is more effective in terms of subjective cure than a top-to-bottom approach. When traversing the transobturator route, the evidence suggested that medial-to-lateral ('inside-out') and lateral-to-medial ('outside-in') approaches have similar effects.

No significant differences in efficacy or surgical outcomes were observed in those studies which compared one method of mid-urethral tape insertion with another using the same insertion route.

Differences between monofilament tapes and multifilament tapes were assessed. No statistical differences in objective or subjective cure rates were found.

As a general finding, QoL was found to improve significantly post-operatively within treatment groups, whatever the comparison being undertaken. However, no statistically significant differences were found *between* groups in the comparisons.

The majority of the trials included in the systematic review were rated by the authors as being of unclear quality. Longer term data, particularly on the long-term effects of surgery, and how the different insertion routes affect long-term outcomes are lacking.

Effectiveness of POP Procedures

Surgical management of pelvic organ prolapse in women [Maher]

The findings in relation to POP surgery are complex. Overall, the authors conclude that the data they have reviewed does not provide sufficient evidence to guide clinical practice.

Abdominal sacral colpopexy was associated with a lower rate of recurrent vault prolapse and less dyspareunia than vaginal sacrospinous colpopexy.

The use of absorbable polyglactin mesh overlay, absorbable porcine dermis or polypropylene mesh at the time of anterior vaginal wall repair reduces the risk of recurrent cystocele on examination, however improved outcomes including patient satisfaction, quality of life and reduced operations for recurrences have not yet been demonstrated.

Posterior vaginal wall repair may have a better anatomical success rate than transanal repair in the management of posterior vaginal wall prolapse, but the clinical effects are uncertain. There is no evidence to support the use of graft materials in the posterior compartment.

The evidence at this stage does not support the use of transvaginal combined total, anterior or posterior mesh kits for multi-compartment prolapse. Whilst anatomical outcome may be improved (as compared to native tissue repair) no difference was found in symptoms or quality of life outcomes. The mesh exposure rate was nearly 1 in 5, with nearly 1 in 10 requiring surgical intervention.

Performing continence surgery at the time of prolapse surgery in women with stress urinary incontinence is likely to be beneficial. This benefit is also associated with women undergoing prolapse who have been found to have occult stress incontinence pre-operatively.

Generally, the quality of the trials was described as “variable” by the authors in almost all cases, they considered that it was “unclear” what risk of bias the included trials presented. Long-term outcomes were noted as being absent. They should be reported at least at two and five years after surgery, preferably longer.

Pessaries (mechanical devices) for pelvic organ prolapse in women [Bugge]

Formal comparison between the use of a mechanical device and the use of any surgery, with or without any form of mesh, were not considered in this review.

Conservative prevention and management of pelvic organ prolapse in women [Hagen]

In relation to this systematic review, only data relating to the comparison of physical and/or lifestyle interventions supplementing surgery with surgery alone was included. In three areas: physical intervention versus surgery; lifestyle intervention versus surgery; and combined physical and lifestyle intervention against surgery, no trials were identified.

The two trials identified in this systematic review provide contradictory findings. Whilst both compared pelvic floor muscle training (PFMT) following surgery with a control group who underwent surgery alone. In one trial the results indicate that despite the tendency towards improvement in the PFMT group over time, there were no significant differences in manometry scores between the controls and those in the PFMT arm. Change from baseline in the other objective measures (vaginal resting pressure, peak maximum vaginal squeeze pressure, and area maximum vaginal squeeze pressure) did not differ between groups. The second trial, however, reported that improvement in mean maximum pelvic floor muscle squeeze was significantly greater in the PFMT group than the control group. Both trials reported on urinary function. In one trial it was reported that there were no significant differences between the intervention and control groups in reported incontinence using validated instruments. The second trial reported a significant improvement in urine leakage for both the intervention and control groups, but no significant difference in improvement between the groups.

5.4.3 Interpretation

SUI Procedures

The key messages from these analyses are:

- Abdominal surgery (retropubic colposuspension) was more effective than anterior vaginal repair for the treatment of primary urodynamic stress incontinence.
- Mid-urethral sling procedures were found to be as effective as traditional surgical approaches for SUI. Marginal benefits in QoL were noted.
- Mid-urethral sling procedures were found to be objectively more effective than laparoscopic colposuspension, but not subjectively so. Laparoscopic colposuspension was found to be no more effective than open colposuspension in the medium term. The type of surgical approach to make repairs when undertaking laparoscopic colposuspension may be a factor in achieving successful outcomes. Findings from analysis of QoL data were limited.
- Traditional sling operations are as effective as either mid-urethral sling procedures for SUI or other surgical approaches.
- Whilst open retropubic colposuspension was found to be more effective than other surgical approaches, it was not found to be significantly different from mid-urethral tape procedures.
- What data there is suggests that treating SUI with injectable materials is better than conservative management, but less effective than open surgery.
- There is limited (non-RCT) evidence that retropubic suburethral mesh tapes are superior to transobturator mesh tapes when used in repeat procedures.
- Women were more likely to remain incontinent after surgery with single-incision (mini) slings than after use of inside-out transobturator (TVT-O) tapes.
- Open abdominal retropubic suspension was found to be more effective than needle suspension. Anterior vaginal repair and suburethral (mesh) slings were not significantly different.
- Mid-urethral slings using mesh implants were found to be a highly effective treatment for SUI.

POP Procedures

The key messages from these analyses are:

- The findings in relation to POP surgery are complex. Overall, the authors conclude that the data they have reviewed does not provide sufficient evidence to guide clinical practice.
- Whilst some trial findings to support the use of pelvic floor muscle training as a treatment for women with prolapse, the evidence remains complex and limited. There was insufficient evidence about other interventions or combinations of interventions to inform practice

5.5 Systematic Reviews of Adverse Outcomes in SUI and POP

5.5.1 Nature of the evidence

See section 5.4.1 above.

5.5.2 Results

As noted above (section 5.2 above) 12 systematic reviews were included in this analysis. Nine of these related to SUI procedures and three to POP procedures. The systematic reviews cover not only mesh procedures, but also comparisons with conventional treatment. This was to allow consideration of the effectiveness of mesh against other treatment approaches. The results of the analysis in relation to SUI procedures is shown in Table 2a, whilst that for POP procedures is shown in Table 2b.

In this section, the major conclusions from each of the systematic reviews in relation to adverse outcomes are presented.

Adverse Outcomes in SUI procedures

Anterior vaginal repair for urinary incontinence in women (Glazener1)

Clinically relevant post-operative complications were reported for both abdominal retropubic suspension and anterior vaginal repair, but the complication rates were not different. New or recurrent prolapse was found to be less likely after anterior vaginal repair, whilst repeat surgery for recurrent incontinence was higher after anterior vaginal repair. No other differences were found for any other adverse outcomes.

No long-term adverse outcomes were considered.

Adverse outcomes associated with tension-free vaginal tape [Cody]

There were no significant differences in adverse outcomes between TVT and comparative surgery reported.

Laparoscopic colposuspension for urinary incontinence [Dean]

Significantly fewer perioperative complications were reported for laparoscopic colposuspension compared with open colposuspension.

No robust, statistically significant differences were found in adverse outcome rates for any other comparisons included in the systematic review. This included the comparison between laparoscopic colposuspension and vaginal mid-urethral mesh tape procedures.

No long-term adverse outcomes were considered.

Traditional suburethral sling operations for urinary incontinence [Rehman]

When comparing traditional slings with mid-urethral mesh tape procedures, perioperative complication rates were found to be higher for the traditional sling. New cases of overactive bladder function were also noted, but no other adverse outcomes were found to be significantly different.

Significantly fewer perioperative complications were found amongst open colposuspension patients than traditional sling patients. Voiding dysfunction was also significantly higher after traditional sling surgery compared with open colposuspension. Significantly more women

who had traditional slings had post-operative complications compared with those who had needle suspension.

No long term adverse outcomes were considered.

Open retropubic colposuspension for urinary incontinence [Lapitan]

Perioperative complication rates for open retropubic colposuspension were lower than those observed for both needle suspension or anterior colporrhaphy. The procedure may also be associated with lower rates of bladder perforation when compared with laparoscopic colposuspension.

The long-term profile of adverse outcomes for sling procedures, in particular with the use of mid-urethral mesh tape procedures, is still unclear.

Urethral injection therapy for urinary incontinence [Kirchin]

Overall, the complication rate for injections was lower than for open surgery. However, the follow up periods were very short and as the approach is not efficacious, the adverse events are not clinically relevant.

Treatment of recurrent stress urinary incontinence after failed minimally invasive synthetic suburethral tape surgery [Bakali]

No trials were included in the systematic review.

Single-incision sling operations for urinary incontinence in women [Nambiar]

Both repeat stress incontinence surgery and new cases of urinary urgency were found to be associated with single incision (mini) slings compared to minimally invasive retropubic slings.

In the comparison between single incision slings and transobturator mid-urethral mesh tapes, a complex set of adverse outcomes were reported. These may be summarised as:

- Vaginal mesh exposure (erosion): TVT-O had a significantly lower risk of mesh erosion than single-incision slings. No statistically significant difference between the TOT and single incision sling treatment groups.
- Post-operative pain or discomfort: Both TVT-O and TOT patients had more post-operative pain and discomfort than single-incision sling patients.
- Long-term pain or discomfort: TOT was found to be associated with higher rates of long-term pain than single-incision. No differences were observed for TVT-O compared with single-incision slings. TOT and TVT-O are both obturator devices.
- Repeat stress incontinence surgery: women undergoing single-incision slings were nearly six times more likely to need further stress incontinence surgery after single-incision sling surgery than after TVT-O. There was no evidence of a difference between single-incision slings and TOT slings.
- Need for any other additional or new surgical procedure to treat complications: TVT-O was found to be associated with a statistically lower chance of needing surgery whilst no differences in risk was found for TOT compared with single-incision sling surgery.

No long term adverse outcome data were reported.

Bladder neck needle suspension for urinary incontinence in women [Glazener2]

No significant differences were found in complication rates for needle suspension when compared with either open abdominal retropubic suspension or anterior vaginal repair. Sling operations were associated with higher complication rates than needle suspension.

One small trial (n= 9 treatment v 10 controls) found that postoperative pain was significantly less at three months in women whose needle suspension used polytetrafluoroethylene sutures compared with polypropylene ones.

No long term data were considered.

Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women [Ford]

Overall perioperative complication rates for the transobturator route compared to the retropubic route were not statistically significant different.

Where individual adverse outcomes were reported, the transobturator route was associated with significantly fewer: major vascular injuries, bladder / urethral perforations, and post-operative voiding dysfunction. However the clinical importance of these adverse outcomes vary. Vascular and bladder perforation, for example, sound serious, but clinically they should always be detected by cystoscopy and remedied by re-positioning.

Pain rates were found to vary between groups as to which approach was associated with greater pain. Groin pain was higher for the transobturator route whilst suprapubic pain was lower. Most cases of pain resolved within six months. However, in at least one RCT (Teo et al (2011), the trial team decided to finish recruitment early, due to excess leg pain in the tension-free vaginal tape transobturator group¹¹. This highlights the clinical importance of adverse outcomes.

The need for repeat incontinence surgery was found to be not significantly different between groups under 12 months, though it was found to be more common for patients undergoing transobturator procedures over one year.

No statistically significant difference was seen in overall perioperative complications when comparing the retropubic bottom-to-top approach with the retropubic top-to-bottom approach. Significantly fewer women undergoing the retropubic bottom-to-top approach experienced bladder perforation, voiding dysfunction or vaginal tape erosion.

In the transobturator, medial-to-lateral approach compared with the transobturator, lateral-to-medial approach analysis, the former was found to be associated with fewer vaginal wall perforations, but higher levels of voiding dysfunction. There were no statistically significant differences between the two groups for: overall perioperative complication rate; major vascular / visceral injury; bladder perforation; de novo urgency symptoms; detrusor overactivity; vaginal tape erosions; and groin/thigh pain. No significant difference in the rates of repeat incontinence surgery in the medium term was found.

Whilst data greater than five years was included in these analyses, it was acknowledged that the long term effects of mesh sling insertion required further detailed research.

¹¹ Teo R1, Moran P, Mayne C, Tincello D. *Randomized trial of tension-free vaginal tape and tension-free vaginal tape-obturator for urodynamic stress incontinence in women.* J Urol. 2011 Apr; 185(4):1350-5. doi: 10.1016/j.juro.2010.11.064.

Adverse Outcomes in POP procedures

Surgical management of pelvic organ prolapse in women [Maher]

The data relating to adverse outcomes following POP surgery is of relatively low quality and few conclusions can be drawn from it.

Where adverse outcomes are reported, it is difficult to assess the clinical significance of these. In many cases the differences between groups within comparisons are reported as not significant. Of all possible complications, mesh erosion is one of the more commonly identified, adverse outcomes noted following the treatment of POP

Pessaries (mechanical devices) for pelvic organ prolapse in women [Bugge]

No adverse outcomes considered in the report.

Conservative prevention and management of pelvic organ prolapse in women [Hagen]

No data on adverse outcomes was reported in the systematic review.

5.5.3 Interpretation

SUI Procedures

The key messages from these analyses are:

- Anterior vaginal repair was found to increase likelihood of further SUI surgery, but reduce the risk of new or repeat prolapse when compared with abdominal retropubic surgery.
- No significant differences were found in the risk of adverse effects between retropubic and transobturator, mid-urethral mesh tape procedures.
- Mid-urethral mesh tape procedures were not found to be associated with greater risk of adverse outcomes than laparoscopic colposuspension, though long-term, data was not collected.
- Mid-urethral mesh tape procedures were associated with lower complication rates than traditional suburethral sling operations.
- The long-term profile of adverse outcomes associated with the use of TVT mesh, remains unclear due to the absence of adequate research.
- Adverse events are lower for treatment by injection than for open surgery, although efficacy is significantly lower.
- Treatment with single-incision slings is more likely to need further continence surgery and experience mesh exposure more often than those treated with transobturator (TVT-O) tapes.
- Minimally invasive sling procedures appear to have similar in their adverse outcome rates, though long term effects have not been adequately researched.

- The clinical importance of these adverse outcomes do differ: bladder perforation (more common in retropubic procedures) is of little or no clinical importance, whilst groin pain (more common for transobturator procedures) is of greater importance clinically.

POP Procedures

The key messages from these analyses are:

- The data relating to adverse outcomes following POP surgery is of relatively low quality and few conclusions can be drawn.
- Mesh erosion is one of the main adverse outcomes noted following the treatment of POP.
- No data on adverse outcomes were reported in the systematic review on conservative management of POP compared with surgery.

5.6 Conclusions

On the safety of mesh

The evidence from systematic reviews into the safety and effectiveness of SUI and POP mesh procedures and the adverse outcomes associated with them presents a complex picture.

Although the international safety reviews have differing emphasis and explore the issues in a variety of ways, all the international safety reviews recognise that, for some women, there are long-term, adverse outcomes associated with the use of mesh devices that have had severe effects on their everyday activities and quality of life.

At the same time, none of the international safety reviews conclude that this is a need for mesh devices used in SUI and POP procedures to be withdrawn from use.

In those safety reviews which directly addressed the effectiveness of mesh devices, the general conclusion is that mesh use in mid-urethral sling procedures to treat SUI is effective with low, short-term complication rates. The use of mesh for **some** forms of POP repair is considered effective, provided that it is used in abdominal rather than vaginal procedures. The risk of complications/adverse outcomes, notably mesh erosion is higher for POP than for SUI.

The reviews which have explored the possible risk factors associated with women who have had serious adverse outcomes have identified the following factors:

- the surgical approach adopted: transobturator versus retropubic in SUI procedures and vaginal versus abdominal in POP procedures;
- the experience of the surgeon undertaking the procedures;
- patient characteristics, including health risk behaviours; and
- the physical characteristics of the mesh device used.

It is accepted in several of the reviews that long-term follow up data are not presently available to capture late complications of mesh surgery. It is also recommended that this

gap in the data needs to be addressed and routinely collected. More widely the systems used to assess the safety of medical devices were identified as areas for further improvement, notably in the area of vigilance and post-marketing surveillance.

All the reviews note the essential need for well-informed patient consent.

On the effectiveness of mesh

The effectiveness of mesh was considered in the systematic reviews. This is also a complicated picture. The key messages sections try and draw out the specific findings, but even they can be complex and difficult to interpret.

The main thrust of the findings in relation to SUI suggest that mid-urethral slings using mesh implants were found to be a highly effective treatment for SUI. There is limited (non-RCT) evidence that retropubic suburethral mesh tapes are superior to transobturator mesh tapes when used in repeat procedures. In comparison with other surgical techniques traditional sling procedures could be as effective as mesh procedures, though this was not the case for other non-mesh surgery.

The findings in relation to POP surgery are complex. Overall, the reviews conclude that the data does not provide sufficient evidence on effectiveness to guide clinical practice regarding the use of mesh implants over other surgical and non-surgical interventions.

For both SUI and POP the absence of appropriate long term data and on patient focussed outcomes was a persistent issue. Long-term data on surgical effectiveness outcomes were simply not being collected in many RCTs. Where patient important outcomes were assessed, these suggested on marginal benefits in terms of improvement in formal Quality of Life measurements, these may not be suitable measure for the types of adverse outcomes experienced by some women.

On adverse outcomes associated with mesh

The data from the reviews on adverse outcomes associated with the use of mesh procedures for SUI procedures suggests that mid-urethral mesh tape procedures were associated with fewer adverse outcomes than traditional suburethral sling or Laparoscopic colposuspension operations, though long-term, data was not collected

There were no statistically significant differences found in the risk of adverse effects between retropubic and transobturator, mid-urethral mesh tape procedures. Though once again, possible long term effects have not been adequately researched.

The clinical importance of these adverse outcomes to mesh procedures for SUI do differ. For example, bladder perforation (more common in retropubic procedures) is of limited or no clinical importance, whilst groin pain (more common for transobturator procedures) is of greater importance clinically.

The reviews were consistent in finding that the data relating to adverse outcomes following POP surgery with mesh is of relatively low quality and few conclusions can be drawn. That aid, even with the limited data that does exist, mesh erosion is one of the main adverse outcomes noted following surgical treatment with mesh

No data on adverse outcomes were reported in the systematic review on conservative management of POP compared with either mesh or traditional POP surgery.

Chapter 6: The choice of surgical approach of mesh device implantation for the treatment of stress urinary incontinence in women: Clinicians' view

6.1 Clinicians' views

For best outcome of surgery, a well-informed patient is as important as a well-informed clinician. In 2014, the Scottish Government's Expert Group first published a comprehensive leaflet for patients considering surgery using synthetic mesh for stress urinary incontinence (SUI). This leaflet is currently being updated with current evidence and adapted for use by all four UK nations later this year¹².

In 2013, NICE published the document: **information to assist counselling** of women considering SUI surgery using mesh implants, mainly aimed at clinicians¹³. The document was largely based on the MHRA York report¹⁴. The following table represents updated level I evidence from the Cochrane Collaboration, building on the NICE and MHRA document, as interpreted by the Scottish Government's Independent Review. Where research evidence is lacking, expert opinion based on collective experience from the expert group of the clinicians is expressed (level III).

Clinicians counselling patients for such surgery may find the updated information useful during the shared-decision process, alongside the national patient information leaflet available on the Scottish Government website and the relevant full NICE guidance.

¹² <http://www.gov.scot/Resource/0045/00453999.pdf>

¹³ <https://www.nice.org.uk/guidance/cg171/chapter/recommendations#information-to-facilitate-discussion-of-risks-and-benefits-of-treatments-for-women-with-stress>

¹⁴ <http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con205383.pdf>

Table 6.1

Outcomes from the recent systematic review from the Cochrane Collaboration (Ford et al)	Retropubic mesh tape device (%)	Transobturator mesh tape device (%)	RR, 95%CI, number of studies and participants	Favours...	Notes on research evidence from the Cochrane Collaboration
Short term efficacy	Similar Subjective: 84.4% Objective: 87.2%	Similar 82.3% 85.7%	RR 0.98, 95% CI 0.96 to 1.00 36 trials, 5514 women. RR 0.98, 95% CI 0.96 to 1.00 40 trials, 6145 women	None	Research evidence favouring retropubic approach for both patient-reported and clinician-reported outcomes did not reach statistical significance.

Long term efficacy	Similar	Similar		None	Research evidence favouring retropubic approach for both patient-reported and clinician-reported outcomes did not reach statistical significance.
	Subjective: 70.7%	65.1%	RR 0.95, 95%CI 0.80 to 1.12. 4 trials, 714 women.		
	Objective: 85.5%	83%	RR 0.97, 95% CI 0.90 to 1.06; 3 trials, 400 women		
Need for repeat continence surgery after 1 year	Lower 1.1%	Higher 11.3%	RR 8.79, 95% CI 3.36 to 23.00; 4 trials, 695 women	Retropubic	Research evidence favours retropubic approach. Despite reaching statistical significance, the number of studies and participants are relatively smaller than those contributing to short-term efficacy.

Bladder injury	higher risk 4.5%	lower risk 0.6%	RR 0.13, 95% CI 0.08 to 0.20; 40 trials, 6372 women	Obturator	While risk of bladder injury is higher with retropubic approach, it is diagnosed intra-operatively in almost all cases, as cystoscopy is routinely employed. The tape is replaced in the correct position and no long-term problems are expected.
Voiding problems	higher risk 7.2%	lower risk 3.8%	RR 0.53, 95% CI 0.43 to 0.65; 37 trials, 6200 women	Obturator	Retropubic tapes appear to be more 'obstructive'. Patients at increased risk of voiding dysfunction following surgery (using an obturator or retropubic approach) may need to learn self-catheterisation beforehand.
groin, pelvic and thigh pain	lower risk 1.3%;	higher risk 6.4% v	RR 4.12, 95% CI 2.71 to 6.27; 18 trials, 3221 women	Retropubic	Chronic pain and dyspareunia appear to be the most common symptoms reported by mesh-injured women.

mesh exposure	Similar risk 2.1%	Similar risk 2.4%	RR 1.13, 95% CI 0.78 to 1.65; 31 trials, 4743 women	None	None
mesh erosion into bladder or urethra	Similar risk	Similar risk		None	None
Operative blood loss	Higher	Lower	MD 6.49 95%CI 12.33 to 0.65	Obturator	The 6.5-ml statistically-significant difference in favour of the obturator approach is clinically-insignificant.
Operation time	Longer	Shorter	MD 7.54 95%CI 9.31 to 5.77	Obturator	The 7.5-minute statistically significant difference in favour of the obturator approach is thought to be due to usage of cystoscopy to rule out bladder injury during the retropubic approach. The time is thought to be well-invested.

Feasibility and characteristics of complete surgical removal	Possible, regardless of duration of implantation.	Possible, only during the first few weeks of implantation. Removal is difficult afterwards.	Clinical Opinion (Level III)	Retropubic	In either condition, complete removal of the mesh device does not guarantee cure from pain.
	Removal usually requires an abdomino-perineal approach.	Removal usually requires only a perineal approach.			
	The surgical technique and anatomy of the retropubic space are well understood by most surgeons.	The surgical technique and anatomy of the upper thigh are poorly understood.			
	Removal is usually complete.	Removal is usually incomplete.			

6.2 Conclusion

In light of the above clinical interpretation of evidence, members of the Independent Review who perform surgery for SUI are of the view that

- The retropubic approach (with diagnostic cystoscopy) is preferred when offering routine surgery for women who choose a mesh tape procedure for treatment of stress urinary incontinence.
- The transobturator approach may be offered if a retropubic approach carries additional risks e.g. organ damage in women who had prior extensive abdominal surgery.
- Regardless of the approach employed, patients with persistent groin or pelvic pain for 4-8 weeks following mesh tape insertion should be considered for timely removal surgery. Patients should be aware that even complete removal of tape does not guarantee relief of pain. All patients should be discussed by the multi-disciplinary team and referral to a regional centre may be required.

Chapter 7: Legal Judgements

7.1 Evidence availability

Legal proceedings in relation to claims for personal injury, the safety of specific mesh and tape devices, and lack of appropriate information regarding possible complications have been launched in both the United States and in the UK.

In Scotland, the main focus of such litigation is twofold, firstly, in relation to the cases against the Health Boards, the claim is that there was a failure to adequately consent the patient by discussing material risks and alternatives. In relation to the case against the manufacturers, the Pursuer is seeking to establish that the manufacturers were negligent under common law by aggressively marketing products which had been inadequately tested and further, misrepresenting failure and complication rates.

The case against the manufacturers can also be brought under the Consumer Protection Act 1987 which requires the Pursuer to establish that a defective product has been manufactured. The statute describes a "defective product" as one in which the safety of the product does not meet the standard which consumers are entitled to expect. This can include the safety of materials and components within the product, any instructions and/or warnings needed in using the product, and what the expected use of the product might be. This is an objective test and all these factors must be taken into account. In order for a manufacturer to be held liable it must be established that:

- they manufactured the product;
- that the product was defective (as defined in statute); and
- the defect caused injury.

Once liability is established, it is not necessary to also establish that the manufacturer was negligent (although separate proceedings to show negligence under the common law may also be pursued).

7.2 Methods

Given that legal proceedings in relation to the use of mesh and tape are still ongoing in Scotland, it is not appropriate to discuss the detail of these extant cases at this time. Rather, the NHS Central Legal Office was asked to provide an overview of current legal proceedings in Scotland. In the results section that follows, any counts of cases which are fewer than five cases have been discounted to avoid any possible data protection breach. . All manufacturer and device names have also been removed for confidentiality reasons.

7.3 Results

7.3.1 Litigation in Scotland

At the end of July 2015, there were 368 claims in relation to the use of vaginal implants in women with SUI and POP. Of these, the largest number (258 cases) was being heard in the Court of Session.

Of the cases being considered by the Court of Session, there were 120 cases associated with mesh implants for SUI. Of these, 45 were related to transobturator mesh implants, with 33 of the cases considering medial-to-lateral procedures and the remaining 12 cases

lateral-to-medial procedures. There were six cases that arose from retropubic mesh implants, with both down-up procedures and up-down procedures represented (NB the specific number of these cases by type of procedure has not been published to protect patient confidentiality). The remaining 69 cases are awaiting categorisation as the mesh devices can be used for either surgical approaches. Of these, 55 cases are for a mesh device from a single manufacturer.

Vaginal mesh implants represents the largest proportion of POP procedures with 75 cases. Of these, 48 of the cases relate to a device which has now been withdrawn from the market. The remaining 27 cases relate to six devices, produced by four manufacturers. Of the other POP procedures, fewer than five cases relate to abdominal implants and 13 cases relate to devices which can be used either vaginally or abdominally. Overall, there were 96 POP mesh claims, though less than five relate to devices used for treatment of rectal prolapse or where the devices was not made of polypropylene.

Finally, there were a further 42 cases where the categorisation of procedures was not complete.

7.3.2 Litigation in the USA

Data from the US Judicial Panel of Multidistrict Litigation has been used to summarise the situation in the US, as at the end of July 2015. The number of US lawsuits in relation to the use of vaginal implants in women with stress urinary incontinence (SUI) and pelvic organ prolapse (POP) is estimated at 100,000. The majority are litigated in Federal Courts (Multidistrict Litigation, MDL).

So far, 18 trials (relating to 24 patients) have reached verdict or settlement during trial (see below). POP procedures related to 11 of the cases; ten of which related to vaginal mesh implants and one where the POP procedure was combined with an SUI mesh implant. In this combined case and in four of the solely POP procedures, a jury reached a verdict in favour of plaintiffs. No jury verdicts were in favour of the manufacturer and in the remaining six cases, the manufacturer reached a settlement during the trial.

For SUI procedures, one case related to retropubic mesh implants. The case did not reach trial, the Judge directed that the case found in favour of the manufacturer prior to trial commencement. Six cases related to transobturator mesh implants. Jury verdicts in favour of the plaintiffs were found for five cases and, in a single case, in favour of the manufacturer.

One manufacturer settled thousands of claims in an out of court settlement.

In presenting data from the US, it should be noted that the legal tests against which these cases were judged are not those described above. The legal tests assessed within Federal Courts in the US differ from those in Scotland.

7.4 Interpretation

- Legal cases relating to possible negligence or product liability are underway in Scotland and other countries.
- Whilst negligence or product liabilities may be established for specific cases, generalising from these in the context of this review is difficult given the evolving nature of the evidence.

Chapter 8: Adverse event reporting

8.1 Situation

Reporting adverse events in NHS Scotland occurs through a range of statutory and governance procedures. The reports can be initiated by a number of healthcare professionals and patients. The aim of reporting on medical devices is to improve patient safety and for two different functions: to aid local learning and to add to the information necessary for the regulation of medical devices. It is recognised that there is under reporting so there are a number of work programmes in development to improve the two functions. This chapter describes the background to adverse event reporting; the on-going work programmes and specific requirements for reporting incidents with respect to transvaginal mesh implants.

8.2 Background

What Every patient is an individual and as such may react to medical treatment in different ways. All interventions in healthcare carry a measureable risk. Reporting adverse events from clinical care is the responsibility of the individual team involved in the care. The learning must be managed locally but shared if there are generalisable lessons. As there is a diversity of systems and definitions in place in 2012, the Scottish Government tasked Healthcare Improvement Scotland (HIS) to develop a framework, examine current practice and support developments. The framework included a definition¹⁵, which must be clear and agreed with patients, and consider near misses.

http://www.healthcareimprovementscotland.org/our_work/governance_and_assurance/management_of_adverse_events1.aspx

For the purposes of this paper an adverse event should be considered as adverse signs and symptoms recorded by the patient or the clinician and considered as a consequence of the insertion of transvaginal mesh. To help identify what should be reported the British Society of Urogynaecology (BSUG) lists adverse events from the use of synthetic meshes for prolapse and incontinence at <http://bsug.org.uk/MHRA.php> i.e.

- Vaginal exposure
- Erosion into the urinary tract
- Erosion into the bowel or rectum
- Infection
- Pain
- Fistulae
- Mesh shrinkage
- Organ perforation
- Nerve or vascular injury
- Sexual difficulty

Why The main function of adverse event reporting is early detection of new, rare or serious problems with a device. Manufacturers have a statutory duty to conduct post market surveillance ie follow-up, via their sales, complaints, research and reports data. Clinicians and patients using the devices provide individual feedback. Reporting is however not universal. Research on the reporting of adverse drug reactions to spontaneous (ie not routinely collected) reporting systems such as the Yellow Card scheme suggest that around

¹⁵ An adverse event can be defined as an event that could have caused, or did result in, harm to people or groups of people.

20-25% of serious and severe reactions are commonly reported, with around 5% of less serious events¹⁶ officially reported. This research found that a number of clinicians did not report if the reaction was known at the time the drug was on the market.

When a problem occurs after surgery there are a range of reasons why including characteristics of the patient, expectations, pre-and post op care, the surgeon, the hospital, as well as the device.

Some events are very rare, for example the association of a type of breast cancer, and breast implants. The cancer accounts for less than 1% of all breast malignancies and is found in association with breast implants. This rare event (there were less than 150 cases worldwide and between 5-10 million breast implants used) needs the accumulation of lots of data on adverse events in association with a medical device.

In contrast, single cases of using a wrong connector to inject drugs into the spinal cord area as opposed to the vein led to immediate deaths and now is the rationale for a whole new production of small tube connectors for health services around the world, including in the NHS.

From the studies on adverse event reporting on devices and drugs¹⁶ mechanisms to improve reporting are:

- improved feedback – why the report mattered, what else has been reported
- peer acceptance and training in practice
- easy electronic methods of reporting
- greater range of notifiers, including patients
- Undergraduate and postgraduate training

These mechanisms are in variable practice in NHSScotland. Examples are professional groups working with data in quality assurance schemes, for instance in general surgery; the enhanced appraisal system all doctors must have for their revalidation to discuss their outcomes; Yellow Card promotion for reporting by patients; simple on line reporting to national bodies.

In addition a number of countries in Europe have voluntary 'bottom-up' reporting systems for orthopaedic adverse events, demonstrating good outcomes.

How Notification of adverse events is used for the trend analysis work of the regulator and investigators. There is a simple online process to MHRA (Yellow Card) and the Incident Reporting and Investigation Centre (IRIC) in NHSScotland. The Yellow Card is a reporting mechanism used for over 50 years for gathering adverse events associated with medicines and has been extended to medical device users <https://yellowcard.mhra.gov.uk/>.

MHRA has recently embraced media technology to improve functionality and reporting of medicines events <https://www.gov.uk/government/news/digital-evolution-for-ground-breaking-yellow-card-scheme>

In Scotland it is currently expected that professional groups will report to IRIC via this link (also on the MHRA webpage)

¹⁶ 2006 Drug Safety <http://www.ncbi.nlm.nih.gov/pubmed/16689555>

Once an event is notified it will be examined electronically for necessary information such as the device type and symptoms. If patients report they may not know which implant they received. This information needs to be shared and easily accessible. The track and trace element of medical devices is currently managed through details entered into the operation note. It is a legal duty to keep these records. Most commonly these are still kept in paper form and full details are not necessarily communicated to a patient or their GP. An improvement to the track and trace is the **unique device identifier (UDI)** work to store this information in a patient electronic record (either the hospital record, SMR01 or the GP record).

Where The long term aim is for one report on an adverse event to be made locally when it happens and fed into local learning systems and at the same time transmitted to all other necessary users (patient safety groups, IRIC and MHRA in terms of the medical device). Adverse events ideally should be reported through a local NHS Board's incident report form which feeds into all necessary databases but currently this is not the case due to IT and confidentiality issues.

Where reports are made to IRIC by professionals, these are shared on a regular basis with the MHRA as the UK regulator. Equally if MHRA is aware of a report from a resident in Scotland, they will inform IRIC so both systems have comparable and timely information.

When Reports can be made at any time in the life of an implant. Most patients who receive surgery are discharged to the care of their GP and are not routinely followed-up in hospital outpatient departments. Even new symptoms seen in patients in outpatient departments may not be recognised as adverse events. New symptoms will require primary and secondary care knowledge of adverse events that should be reported and the requirement to report. In future, once the unique device identifier (UDI) system is in use, a change to or removal of an implant will also be noted. Once an adverse event report has been fully reviewed, it is a legal duty of the regulator to share this with the manufacturers who will respond with a further range of questions, which can require extensive review of the notes. This additional work is unlikely to be accounted for in current consultant job plans.

8.3 Assessment

There are a range of current activities to support and improve adverse event reporting in NHSScotland and across the UK. They include:

- local system improvements
- electronic track and trace methods
- professional guidance
- mandatory systems of candour
- UK initiatives

8.4 Feedback to clinicians and patients

Research has shown that if those making a report gain feedback on the value and use of it, more reporting is encouraged. To get a response on the value of a report, as opposed to just an acknowledgement of the notification, requires additional systems to be in place to

give summary information. MHRA are taking forward work with manufacturers to release data to external bodies including those who send in reports.

Currently it is possible to get annual figures of events reported to IRIC but the detail is high level, dependent on the information received which may be incomplete and not useful for specific implant analysis. The feedback needs to be used at quality assurance meetings and shared among NHS Boards. The community of practice on adverse events developed by HIS <http://www.knowledge.scot.nhs.uk/adverse-events/sharing-learning.aspx> is gathering interest but it is not yet clear whether individual clinical groups receive feedback on a regular basis from a Board's incident reports.

The development of the NHS England patient safety incident management system has two relevant objectives:

- Improve efficiency by introduction of a single process for reporting patient safety incidents, capturing high quality, standardised data about safety and harm with reduced duplication and omission; and
- Improve the quality of support provided by the national patient safety function to enable more learning and improvement in all organisations at all levels.

<http://www.england.nhs.uk/wp-content/uploads/2014/12/nrls-dev-stakeholder-update-dec14.pptx>

The Scottish Government remains in dialogue with NHS England as to whether the development would fit our system.

8.5 Resources to report mesh adverse events – staff and follow-up

The NHSScotland is committed to improving the ease and knowledge on reporting so clinicians and patients report more often and have confidence in the system. For clinicians this may need:

- further training in addition to the letters already sent describing mesh adverse events,
- discussion on pathways and administrative support so longer term events are recorded,
- involvement of the multi-disciplinary teams in knowing what and when to report,
- additional guidance on how enhanced appraisals can use better indicators of work in this area for the revalidation assessments, and
- in the longer term, one reporting system (using all forms of communication including apps) that serves a number of purposes and provides regular feedback.

8.6 Legalisation

One of the key requirements from the public petition is a mandatory system of reporting adverse events. In considering a legislative route, we need to demonstrate that we have used all the levers at our disposal to try to affect change and assess to what extent these have been effective. We need to have regard to enforcement, and consider inspection, monitoring and evaluation regimes. As noted in discussions in the Independent Review there are pros and cons to this approach. The policy development process would assess the pros and issues, based on available evidence.

Pros

- The pros are there would be a statutory duty to report.

Issues

- Legislation requires development of the policy. All policies need to be tested against their impact and equality ensuring that one area does not disadvantage another. Policy development needs to take account of current legal frameworks and demonstrate additional benefit.
- Agreement on the rules to enforce the policy with penalties for not reporting.
- Parliamentary time
- Resources (which then would not be available for other services) to develop and to ensure the impact.

Routine data collection versus standalone system

The Independent Review has discussed whether there should be a new mesh database (registry) to collect all the implant data and/or improve the data capture for NHSScotland's routine data collection and analysis (SMR data).

Pros of routine data

Routine data collection on a range of health interventions for the population of Scotland is gathered by trained data collectors (in hospitals) and by electronic systems from primary care and analysed by the Information Services Division (ISD). This system has been in place for decades. The systems are regularly updated and funded. ISD is working on data for the Independent Review and this level of information could be provided on a regular basis to multi-disciplinary teams or the Expert Group. In addition new indicators for performance can be developed for specific topics, and are currently in use for certain cancers.

Cons of routine data

Routine data is not set-up to analyse all areas of interest to mesh implant patients. Routine data may not be 100% completed. Changing coding can take time and other resources.

Pros of a new mesh database / standalone data system

A new mesh database could concentrate on mesh implants and potentially collect more detailed information. The BSUG database is an example of a standalone system which collects a range of information and can be completed in theatre or outpatient departments. It also has the advantage of enabling comparison across Scotland and throughout the United Kingdom.

Cons of a new mesh database / standalone data system

Setting up a new single issue database takes substantial time and resources and therefore requires justification that it is covering an area that has no other support. Having a single issue database does not guarantee all the information of interest can be included, depending on the IT infrastructure used. Setting up a system and then ensuring coverage by clinicians and administrative staff, ensuring confidentiality, transparency and use for patient groups as well as independent analysts is complicated. Standalone data may not be 100% completed. The current BSUG database can only be accessed by members, is not available to general practice and some NHS Boards IT system do not currently allow access.

8.7 Summary

Adverse event reporting and analysis is important for mesh implants and together with adverse event reporting for clinical care in general, requires on-going improvement. There are a range of activities in NHSScotland and the UK to keep improving the current levels of reporting, including:

- Additional training led by the Expert Group
- Exploring quality indicators and additional data requests led by multi-disciplinary teams overseen by the Expert Group
- Implementation of the unique device identifier (UDI)/ implant systems including access to this information by patients
- Devising guidance for enhanced appraisal
- Improve the use of the current BSUG database
- Pathways guidance which must include job plan requirements
- Legislation for reporting
- Standalone data systems

Chapter 9: The Conclusions and recommendations of the Independent Review

No surgical intervention is without risk. This Independent Review has shown that mesh procedures for both SUI and POP carry a risk of complications which in some cases are life changing and cannot be corrected. However for the majority such serious complications do not occur. The aim of our conclusions and recommendations is to minimize and manage that potential risk. Input from clinicians and provision of adequate information will allow patients to make informed choices regarding their treatment.

In the process of coming to its conclusions, the Independent Review has considered evidence from a number of sources; this included patient stories, clinical expert opinion, published scientific evidence, legal reports and the rich epidemiological data provided by ISD. It also benefited from presentations from other bodies such as the Chief Scientist Office and the NHS Incident Reporting and Investigation Centre (IRIC). The following conclusions with recommendations (**in bold text**) are drawn from this evidence and discussion.

Conclusion 1

Robust clinical governance must surround treatment, the decision to use mesh and the surgical approach used. To support decision making, management of the individual patient should take place in the context of multi-disciplinary team assessment, audit and review. The use of a comprehensive information system will underpin this. **The Expert Group should address this with NHS planners, including an assessment of any administrative support required for the clinical teams.**

Conclusion 2

Evidence of involvement in multi-disciplinary team working, engagement in audit activity and recording and reporting of adverse events should be an important part of consultant appraisal and thus statutory revalidation of medical staff. **The Expert Group should work with Medical Directors as Responsible Officers to include this in the conduct and supervision of appraisal. In addition the Scottish Government should consider the alternative methods for the capture of adverse events set out in chapter 8 to determine further the most effective way to ensure complete notification.**

Conclusion 3

Informed consent is a fundamental principle underlying all healthcare. There has been extensive work done by the Expert Group which preceded the establishment of the Independent Review, with leadership by both patients and clinicians. This has resulted in an SUI information leaflet and consent form. **Following on from this the Independent Review concludes that additional work is required to ensure that this work is extended to include POP procedures and that the SUI leaflet is reviewed in the light of this work and other recent developments. This should be addressed by the Expert Group as a matter of urgency. Other points highlighted by the Independent Review include the provision of adequate time for discussion and reflection. Patients should be provided with information enabling them to report adverse events if these occur.**

Conclusion 4

The Independent Review does not consider that current research studies on safety and effectiveness will provide evidence on long term impact of mesh surgery. The lack of extended long term follow up and related outcome data, including information on quality of life and activities of daily living, should be addressed. **The Independent Review recommends the Expert Group highlights this knowledge gap to funders of health research and the research community. Opportunities for routine audit should be explored by the Expert Group in conjunction with NHS Scotland.**

Conclusion 5

Good information, as stated before, is essential to good patient care. The experience of the Independent Review has been that there are many gaps although there is information both in a professionally led database (the BSUG database) and routine NHS information (SMR01 and SMR00). **It is recommended that the Expert Group works with ISD, BSUG and others to ensure that an information system is developed which is universal, robust, clinically sound and focused on fostering good patient outcomes. Work already underway on consistent coding by ISD will be vital to this endeavour.**

Conclusion 6

The Independent Review expressed serious concern that some women who had adverse events found they were not believed, adding to their distress and increasing the time before any remedial intervention could take place. Improving awareness of clinical teams of the possible symptoms of mesh complications together with good communication skills, (including good listening and empathy) is an essential part of good clinical care. **The Independent Review concluded that the Expert Group should review the training and information available to clinical teams and find ways of incorporating patient views in multi-disciplinary working. It should also continue oversight of the mesh Helpline.**

Conclusion 7

A review of the different sources of evidence available to and considered by the Independent Review (patient experience, clinical expert opinion, research evidence and epidemiological evidence from routine information) has led us to express concern in this Interim Report at the use of the transobturator rather than the retropubic approach for routine surgery for stress urinary incontinence using mesh. The clinical governance arrangements that we have recommended will allow an individual case to be considered in the context of a multi-disciplinary assessment, including patient views. **We await the final publication of key research reports but wish to register these concerns and to recommend that the Expert Group in the following months before the publication of the final report explore further appropriate pathways to ensure the techniques chosen take the differential patient and clinical experience, as well as research evidence into account.**

Conclusion 8

Similar concern is expressed, both for effectiveness and adverse events, at the use of transvaginal mesh in surgery for pelvic organ prolapse. The clinical governance arrangements that we have recommended will allow an individual case to be considered in the context of a multi-disciplinary assessment, including patient views. **We await the final publication of key research reports but wish to register these concerns and to recommend that the Expert Group in the following months before the publication of the final report explore further appropriate pathways to ensure the techniques chosen take the differential patient and clinical experience, as well as research evidence into account.**

Chapter 10: Chairman's concluding remarks

Stress urinary incontinence and pelvic organ prolapse are conditions which, while not life threatening, cause considerable distress to many women, with disruption of their normal lives. The hope of a treatment which can reduce that distress and return their lives to normal is understandably sought eagerly. Similarly the gynaecologists and urologists who see these symptoms and the distress they cause to their patients seek to test and find new and better ways of producing good outcomes for their patients. The use of mesh in this clinical area came about because of that desire and many women have had a good outcome from these operations. However no surgery is without complications and a number of women have had both minor and major complications due to the surgery itself and some have found their lives transformed completely for the worse, unable to pursue a normal family, personal and working life.

Balancing this knowledge of both good outcomes and very bad experiences has been one of the difficult tasks faced by this review. We have taken an approach of both seeking and sifting the best available research information on both safety and effectiveness as well as the epidemiological information provided by the routine NHS linked information which is so rich in Scotland. While extensive, that left us with many gaps which has formed the basis of our conclusions and recommendations. In addition we decided to listen and reflect on what our patient members and our clinical members tell us as they add their expertise and experience to that research and epidemiology. This led us to the specific recommendation we make on the use of mesh tape in particular circumstances and to ask for work on the clinical pathways to take this concern into account.

We can now see a way by which surgery can again take place but it will require a number of actions to ensure lessons are learnt and good and safe patient care is ensured. These are outlined in our recommendations but include:

- informed consent is obtained using approved processes and information;
- an approved clinical pathway is followed;
- information, including adverse events, is recorded in a universal and robust way;
- patient treatment and audit is considered as part of a clinical network involving all practitioners;
- the Expert Group develops a pathway for the retropubic approach in SUI as the routine mesh procedure with any variation considered as part of the multi-disciplinary team; and
- the Expert Group develops a pathway for the treatment of POP where transvaginal mesh is not used routinely. Any variation in the future is considered in light of the awaited results of the PROSPECT study and follows discussion within the multi-disciplinary team.

I also want to acknowledge the opinion of the Scottish Mesh Survivors Group, who consider that the report recommendations should be actioned and able to be monitored before any transvaginal mesh implant procedures take place.

Further research which is currently awaited, information and opinion will be considered as part of the preparation of the Final Report which will also be informed by the discussions and actions following the publication of the Interim Report.

Finally, listening is a key part of good and compassionate healthcare. The many women who began the process leading to this review together with the women who valued this surgery and wanted that benefit to continue I hope will feel that they have been listened to and that patient care will benefit as a result.

Appendix A - Remit of the Independent Review of transvaginal mesh implants

The remit of the Review is to evaluate both the efficacy and the extent and causes of adverse incidents and complication rates associated with stress urinary incontinence and for pelvic organ prolapse. The Review Group recognises that these are two very different procedures and will take account of this.

It will involve the clinical and patient community and will have the means both of identifying and determining the causes of issues where this is possible, finding and implementing solutions.

Purpose

3. To determine the safety of vaginal mesh implants for both stress urinary incontinence and pelvic organ prolapse in Scotland and to compare it to international standards. Information on how many women are experiencing complications and possible reasons for these complications will be examined.
4. To determine the relative efficacy of surgery for stress urinary incontinence and pelvic organ prolapse with and without the use of mesh or tapes.

The Review will take account the Opinion of the Scientific Committee on Emerging and Newly Identified Health Risks of the European Commission, the MHRA report on Safety/Adverse Effects of Vaginal Tapes/Slings/Meshes for Stress Urinary Incontinence and Prolapse and the output from the UK Working Group on surgery using vaginal mesh.

This will involve:

- Putting the needs of patients first (both need for effective treatment and protection from harm).
- Appraising the current research evidence for the efficacy of these tapes and meshes relative to alternative surgical and non-surgical treatments from unbiased sources, such as Cochrane reviews and randomised controlled trials (RCTs) along with verified alternative sources.
- Reviewing the information on adverse incidents and complications for mesh used for stress urinary incontinence and pelvic organ prolapse in Scotland and elsewhere.
- Understanding, with the clinical and patient communities, possible reasons for any complications.
- Identifying where possible which complications arise from the device itself, the insertion technique or the procedure as a whole.
- Identify where possible improvements which could improve efficacy, safety or decrease complications.
- Fostering clinical consensus to recommend appropriate clinical pathways for mandatory reporting of any complications or adverse incidents, making recommendations to the Cabinet Secretary of changes that may be required to improve quality, safety or efficacy.

Scope

In determining the appropriate course of action on this issue, the Group is able to consider:

- The available data on procedures using mesh implants for pelvic floor surgery, including data on efficacy and complications compared to alternative surgical and non-surgical treatments.
- Identifying best practice standards in management of SUI and POP.
- Any issues that may lead to clinical practice not conforming to best practice standards.
- Reported safety issues with devices, including improvement in reporting adverse events.
- Barriers to regular prospective auditing of results of surgical procedures.
- Short, medium and long-term patient follow-up.
- Identification of best practice in managing both treatment failure and complications, and resources to do so.
- Whether the information provided to patients before undergoing these procedures should be updated.

Appendix B – Independent Review group members

Lesley Wilkie, Chair of Independent Review, retired Director of Public Health, NHS Grampian

Terry O'Kelly, Colorectal Surgeon, NHS Grampian, Scottish Government Senior Medical Officer

Sara Davies, Scottish Government Consultant in Public Health Medicine

Catherine Calderwood, former Scottish Government Senior Medical Officer

Frances Elliot, former Deputy Chief Medical Officer

Patient Representatives

Elaine Holmes - Scottish Mesh Survivors Group

Olive McIlroy - Scottish Mesh Survivors Group

Isobel Montgomery – Patient representative

Researcher

Charis Glazener - Professor of Health Services Research. Chief Investigator, PROSPECT, VUE, MAPS, ProLong. Co-ordinating Editor, Cochrane Incontinence Review Group, University of Aberdeen

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Paul Hilton – Retired Consultant Gynaecologist and Urogynaecologist

Karen Guerrero - Sub-specialist Urogynaecologist, NHS Greater Glasgow and Clyde

Voula Granitsiotis - Consultant Urologist, NHS Greater Glasgow and Clyde

Elizabeth Crothers, Physiotherapist, Chartered Society of Physiotherapists

Medicines and Healthcare products Regulatory Agency

Neil McGuire - Medical Director

Professional Bodies

David Richmond - President of Royal College of Obstetricians and Gynaecologists

Ash Monga - Chairman of British Society of Urogynaecology

Roland Morley - Chairman of The British Association of Urological Surgeons Section of Female, Neurological and Urodynamic Urology

Scottish Public Health Network

Phil Mackie - Lead Consultant in Public Health, Scottish Public Health Network

Information Services Division

Rachael Wood - Consultant in Public Health Medicine

Jo Morling - Speciality Registrar in Public Health

Gillian McCallum, Scottish Government, Secretary to the Independent Review

Acronyms

AUS	Australia (research reference)
BAUS	British Association of Urological Surgeons
BSUG	British Society of Urogynaecology
CA	Canada (research reference)
CE	Conformité Européenne
CLO	Central Legal Office
CMO	Chief Medical Officer
DK	Denmark (research reference)
EU	European Union (research reference)
FDA	Food and Drugs Administration
IRIC	Incident Reporting and Investigation Centre
ISD	Information and Services Division
IUGA	International Urogynaecological Association
MDL	Multidistrict Litigation
MHRA	Medicines and Healthcare products Regulatory Agency
MUS	Mid-Urethral Slings
NICE	National Institute for Health and Care Excellence
NL	The Netherlands (research reference)
NZ1	New Zealand 1 (research reference)
NZ2	New Zealand 2 (research reference)
PFMT	Pelvic Floor Muscle Training
POP	Pelvic Organ Prolapse
PROSPECT	PROLapse Surgery: Pragmatic Evaluation and randomised Controlled Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of Life
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
ScotPHN	Scottish Public Health Network
SIGN	Scottish Intercollegiate Guidelines Network
SMR00	Scottish Morbidity Record – outpatients
SMR01	Scottish Morbidity Record – hospital inpatient
SMSG	Scottish Mesh Survivors Group
SUI	Stress Urinary Incontinence
TMWG	Transvaginal Mesh Working Group
TVT-O™	Transobturator Tape
TVT™	Tension-free Vaginal Tape
UDI	Unique Device Identifier
UK1	United Kingdom 1 (research reference)
UK2	United Kingdom 2 (research reference)
USA	United States of America (research reference)

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Autologous Muscle Derived Cell Therapy for Stress Urinary Incontinence: A Prospective, Dose Ranging Study

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Purpose: In this feasibility study we assessed the 12-month safety and potential efficacy of autologous muscle derived cells (Cook MyoSite Incorporated, Pittsburgh, Pennsylvania) as therapy for stress urinary incontinence.

Materials and Methods: A total of 38 women in whom stress urinary incontinence had not improved with conservative therapy for 12 or more months underwent intrasphincter injection of low doses (1, 2, 4, 8 or 16×10^6) or high doses (32, 64 or 128×10^6) of autologous muscle derived cells, which were derived from biopsies of their quadriceps femoris. All patients could elect a second treatment of the same dose after 3-month followup. Assessments were made at 1, 3, 6 and 12 months after the last treatment. The primary end point was the incidence and severity of adverse events. In addition, changes in stress urinary incontinence severity were evaluated by pad test, diary of incontinence episodes and quality of life surveys.

Results: Of the 38 patients 33 completed the study. Treatment related complications were limited to minor events such as pain/bruising at the biopsy and injection sites. Of patients who received 2 treatments of autologous muscle derived cells who were eligible for analysis, a higher percentage of those in the high dose vs the low dose group experienced a 50% or greater reduction in pad weight (88.9%, 8 of 9 vs 61.5%, 8 of 13), had a 50% or greater reduction in diary reported stress leaks (77.8%, 7 of 9 vs 53.3%, 8 of 15) and had 0 to 1 leaks during 3 days (88.9%, 8 of 9 vs 33.3%, 5 of 15) at final followup.

Conclusions: Injection of autologous muscle derived cells in a wide range of doses appears safe with no major treatment related adverse events reported. In addition, treatment with autologous muscle derived cells shows promise for relieving stress urinary incontinence symptoms and improving quality of life.

Key Words: transplantation, autologous; urinary incontinence, stress; myoblasts

Abbreviations and Acronyms

AMDC = autologous muscle derived cells

SUI = stress urinary incontinence

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Study received institutional review board approval.

Supported by Cook MyoSite Incorporated, Pittsburgh, Pennsylvania.

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† Financial interest and/or other relationship with Cook-MyoSite.

‡ Financial interest and/or other relationship with MED Institute, a Cook Group Company.

§ Financial interest and/or other relationship with Cook, Allergan, Astellas and Pfizer.

URINARY incontinence is estimated to affect 25% to 45% of women.¹ Stress urinary incontinence, the involuntary leakage of urine on effort or exertion (eg sneezing, coughing, laughing), is the most common type of urinary incontinence, and is caused by loss of appropriate anatomical support (eg

pelvic floor weakness or bladder neck hypermobility) and/or sphincter dysfunction.

Patients with SUI resistant to behavioral therapies such as pelvic floor exercises may require interventional treatment for symptom relief. Tension-free vaginal tape and transobturator

rator tape procedures, 2 of the most common surgical procedures for SUI,² have long-term cure rates ranging from 84% to 92%, but complications of vaginal or urethral erosion, urinary retention, persisting pelvic or groin pain, infection, hemorrhage, worsening urge incontinence and bowel perforation have been reported.³ Injection of urethral bulking agents is a less invasive alternate therapy. However, these agents fail to maintain effectiveness over time, and issues with degradation, migration, reabsorption, overbulking, bladder outlet obstruction and hypersensitivity have occurred.⁴

Since augmenting sphincter function may benefit patients with SUI, autologous muscle cells have been investigated as a potential therapy. Autologous muscle cells are isolated from skeletal muscle biopsies, expanded *ex vivo* and injected into the urethral sphincter. In several animal studies of SUI, muscle derived cells have successfully integrated in tissue and improved sphincter function.^{5–11}

Although limited data supporting the clinical safety and performance of this potential therapy are currently available,^{12–15} there are several potential advantages to the use of autologous muscle cells. The biopsy and injection procedures are minimally invasive, and may be performed with local anesthetics. Since this is an autologous therapy, immunological reactions are unlikely to occur. In animal studies muscle derived cells fuse to form post-mitotic multinucleated myotubes, which suggests that cellular expansion is limited and the risk of urinary tract obstruction from cell overgrowth is low.¹⁶ In addition, animal studies suggest that the newly formed myotubes and myofibers may become innervated within the native muscle, thereby improving sphincter function.⁶

This feasibility study was designed to provide evidence of safety of AMDC for the treatment of SUI in women. This study extends previously published work by treating a larger number of patients and expanding the range of cellular doses tested for safety, with the maximum dose nearly 6 times greater than in the previous pilot study.¹² The potential efficacy of the therapy was assessed using quantitative and qualitative measures of SUI severity.

MATERIALS AND METHODS

This study was performed in accordance with the Declaration of Helsinki. The study protocol was approved by Health Canada and by the institutional review board at each study center before study initiation. Written informed consent was obtained from all patients before study procedures were performed.

Between September 2006 and June 2008, 38 women with primary symptoms of SUI were enrolled at the Sunnybrook Health Sciences Centre or the University of

Calgary. Prior noninvasive treatments had failed in all patients and there had been no improvement in incontinence symptoms for at least 12 months. Patients with known vesicoureteral reflux, abnormal detrusor activity, other significant pelvic floor abnormalities, or a history of treatment with injectable urethral bulking agents or surgical treatment for SUI were excluded from study (see Appendix). No selection criteria for baseline frequency of stress leaks or pad weight were used. However, all patients had leakage with cough or Valsalva maneuver during baseline testing.

Each patient underwent a needle biopsy of the quadriceps femoris with local anesthesia. The biopsy tissue was shipped to the cell processing facility at Cook MyoSite Incorporated (Pittsburgh, Pennsylvania) where a proprietary method was used to preferentially extract and expand desirable muscle derived cells from the biopsy. The AMDC product, which was enriched in myogenic cell content, was returned frozen to the investigator. The product was thawed and diluted with 0.9% NaCl solution for injection. Using a cystoscope assisted periurethral approach, at least 2 areas of the external urethral sphincter were injected to distribute AMDC into the muscle tissue.

In phase 1, 20 patients were randomized into 5 equal groups to receive 1, 2, 4, 8 or 16×10^6 AMDC. Patients and physicians were blinded to dose allocation. Phase 2 sequentially enrolled 9 patients, 3 per group, to receive 32, 64 or 128×10^6 AMDC. In phase 3, 9 patients (3 per group) were treated with 16, 32 or 64×10^6 AMDC and transvaginal ultrasound guidance was used to assure placement within the sphincter muscle. During phases 2 and 3 only patients were blinded to dose allocation. Patients could elect to receive a second treatment of the same dose after 3-month followup. Followup occurred at 1, 3, 6 and 12 months after the final treatment, or for patients receiving 2 treatments, at 1, 3, 7, 9, 12 and 18 months after the initial AMDC treatment.

Assessment of safety, the primary outcome of the study, was based on the incidence and severity of adverse events. Rates of events were based on the number of patients who experienced the event divided by the total number of patients enrolled in the study.

The potential efficacy of the therapy was evaluated secondarily by comparing the amount of leakage during a 1-hour standardized International Continence Society pad test, the frequency of diary reported stress leaks during 3 days, and quality of life scores from the IIQ-7 (Incontinence Impact Questionnaire short form) and UDI-6 (Urogenital Distress Inventory short form) at baseline and followup points. Pad tests with less than 1 gm weight increase were considered negative.¹⁷ Patients with negative pad tests at baseline were excluded from the analysis of pad test data and patients with no stress leaks during 3 days at baseline were excluded from the analysis of stress leak data since improvement could not be detected with these measures. The percentage of patients with 50% or greater improvement, the percentage with negative pad tests and the percentage with 0 to 1 stress leaks were based on the number who met the criterion divided by the number evaluated at each point. If no outcome data were available for a patient at a given point, the patient was

Table 1. Baseline patient characteristics

	All Pts	Low Dose, Single Treatment	High Dose, Single Treatment	Low Dose, 2 Treatments	High Dose, 2 Treatments
No. pts	38	3	3	20	12
Mean \pm SE pt age (range)	50 \pm 2 (30–73)	55 \pm 9 (44–73)	61 \pm 7 (46–70)	50 \pm 2 (41–65)	45 \pm 3 (30–63)
Mean \pm SE kg/m ² body mass index (range)	25.9 \pm 0.6 (19.0–34.4)	24.1 \pm 1.5 (21.8–27.0)	28.3 \pm 3.1 (24.2–34.4)	26.1 \pm 0.9 (19.0–33.0)	25.5 \pm 1.1 (19.9–34.2)
% History (No./total No.):					
Mild vaginal prolapse	10.5 (4/38)	33.3 (1/3)	33.3 (1/3)	5.0 (1/20)	8.3 (1/12)
Hysterectomy	18.4 (7/38)	33.3 (1/3)	66.7 (2/3)	10.0 (2/20)	16.7 (2/12)

excluded from the calculation of that particular outcome measure and point.

To assess potential dosing effects and to simplify analyses, patients were grouped based on dose and number of treatments received. Doses of 16×10^6 AMDC or less per treatment were classified as low dose, while doses of 32×10^6 AMDC or greater per treatment were classified as high dose. Patient data are presented independent of guidance method since ultrasound guidance did not appear to affect outcomes. This study was designed to provide evidence of safety for a range of AMDC doses. The sample size was not powered to conclusively demonstrate safety or efficacy by individual dose or number of treatments.

Data were analyzed using SAS® version 9.1. Continuous variables were summarized with means and standard error, and dichotomous variables were summarized as percentages and counts. As appropriate, p values were calculated using the paired t test, Z-test from a generalized estimation equation model or Fisher's exact test.

RESULTS

A total of 38 women (35 of 38 white, mean age 50.0 ± 1.6 years) were enrolled in the study and equally distributed between 2 sites (table 1). Prior behavioral therapy (eg Kegel exercises, biofeedback) had failed in all patients and drug therapy had failed in 15.8% (6 of 38). Thirty-two patients (84.2%) elected to receive a second AMDC treatment after their initial 3-month followup (table 2). In all, 33 patients (4 with 1 treatment, 29 with 2 treatments) completed the study, 4 withdrew and 1 was lost to followup.

Table 2. Patient followup status

	No. Low Dose	No. High Dose	Totals
Received 2nd treatment:	23	15	38
Completed 18-mo followup	19	10	29
Withdrew	1	2*	3
Only received single treatment:			
Completed 12-mo followup	2	2	4
Withdrew	1	1	2

Reasons for withdrawal included decision to undergo surgery for treatment of incontinence (1), history of prolapse surgery (1), personal reasons (1) and frustration with study (1).

* One patient was lost to followup.

No serious adverse events or major complications related to treatment were reported. Pain and/or bruising at the biopsy site (7.9%, 3 of 38) and pain at the injection site (10.5%, 4 of 38) were the most commonly reported procedure related events (table 3). Symptomatic lower urinary tract infection, mild self-limiting urinary retention, dysuria or increased frequency, pelvic/abdominal pain or cramping, and worsening incontinence each affected 2 patients (5.3%) within 30 days of AMDC treatment. Two patients experienced dizziness, shortness of breath,

Table 3. Complications

	% (No./total No.)
Biopsy related complications:	
Pain and/or bruising at biopsy site	7.9 (3/38)
Vasovagal syncope during biopsy	2.6 (1/38)
Adverse events occurring 30 or fewer days after AMDC injection:	
Significant bleeding requiring intervention	0
Gross hematuria	0
Symptomatic lower urinary tract infection, no sepsis*	5.3 (2/38)
Mild self-limiting urinary retention	5.3 (2/38)
Dysuria or increased frequency	5.3 (2/38)
Worsening incontinence	5.3 (2/38)
Pelvic/abdominal pain or cramping	5.3 (2/38)
Allergic reaction†	5.3 (2/38)
Pain at injection site	10.5 (4/38)
Other‡	18.4 (7/38)
Genitourinary events occurring more than 30 days after AMDC injection:	
Slight thickening of mid urethra with complaint of pain	2.6 (1/38)
Worsening incontinence	2.6 (1/38)
Dysuria	2.6 (1/38)
Increased urgency	5.3 (2/38)
Difficulty voiding	7.9 (3/38)
Symptomatic lower urinary tract infection, no sepsis*	7.9 (3/38)
Other§	21.1 (8/38)

* Urinary tract infections detected with a positive culture, ie 100,000 CFU/ml or greater in a clean catch specimen or 50,000 CFU/ml or greater in a catheterized specimen.

† Two patients experienced transient systemic allergic reactions not requiring intervention. These patients experienced dizziness, shortness of breath, pruritis and/or periorbital edema after injection.

‡ Includes kidney pain, increased blood pressure/heart rate at injection, vulvar irritation, vaginal itching or discomfort, migraine, perineal itching and swelling, and self-diagnosed hives.

§ Includes cervical polyps, ovarian cyst, fibroids, small protrusion at bladder neck with squamous metaplasia, vaginal yeast infection and tight vaginal introitus.

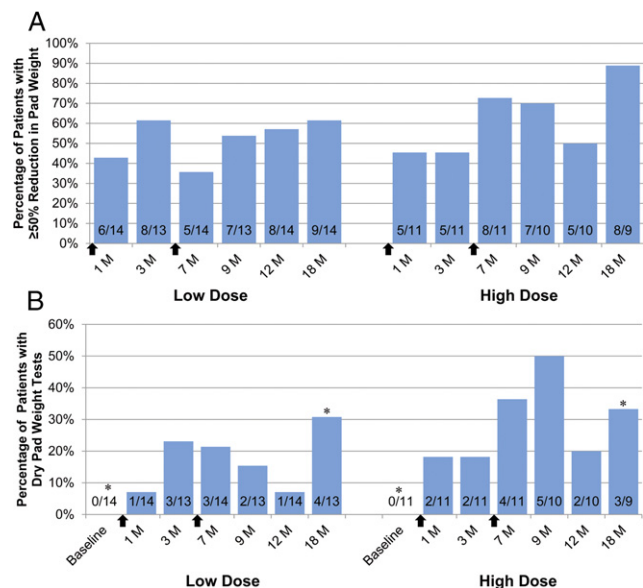


Figure 1. Improvement in 1-hour weighted pad test for patients who received 2 AMDC treatments. *A*, percentage of patients with 50% or greater reduction in pad weight. *B*, percentage of patients with negative pad tests (ie less than 1 gm pad weight). Vertical arrows indicate timing of AMDC treatments. Ratio at base of each bar is number of patients who met criterion-to-number evaluated at each point. Seven patients with less than 1 gm increase in pad weight at baseline were excluded from analysis. Low and high dose groups had significantly higher percentage of dry patients at 18 months than at baseline (asterisk indicates $p < 0.01$).

pruritus and/or periorbital edema after injection. However, these effects were transient and did not require intervention. The genitourinary events reported more than 30 days after treatment were not considered unusual for this patient population.

From baseline to 18-month followup, patients in the low and high dose groups who underwent 2 AMDC treatments had a statistically significant reduction in mean pad weight (low dose 15.5 ± 7.7 vs 12.8 ± 5.9 gm and high dose 15.7 ± 5.5 vs 2.0 ± 1.0 gm, $p < 0.01$ for both groups) and mean stress leak frequency (low dose 7.0 ± 1.3 vs 2.9 ± 0.7 leaks and high dose 3.9 ± 0.9 vs 0.4 ± 0.2 leaks, $p < 0.01$ for both groups). Additionally, 61.5% (8 of 13) of the low dose and 88.9% (8 of 9) of the high dose group had a 50% or greater reduction from baseline pad weight (fig. 1), and 53.3% (8 of 15) of the low dose and 77.8% (7 of 9) of the high dose group reported a 50% or greater reduction in stress leaks (fig. 2) at 18 months. Treatment also significantly increased the number of patients with negative pad tests. Approximately 30% of the low dose (4 of 13) and high dose (3 of 9) groups had less than 1 gm increase in pad weight at 18 months (baseline to 18 months, $p < 0.01$ for both groups, fig. 1). The treatment effect may be dose dependent since a significantly higher propor-

tion of the high dose group reported 0 to 1 leaks during 3 days at 18 months than the low dose group ($p < 0.01$, fig. 2).

Patient quality of life was assessed using the validated surveys IIQ-7 and UDI-6 at baseline and at each followup visit (fig. 3).¹⁸ Mean IIQ-7 scores significantly improved from baseline to 18 months for patients in the high dose group receiving 2 AMDC treatments (38.5 ± 4.4 vs 17.5 ± 6.2 , $p = 0.04$). A statistically significant change in mean IIQ-7 scores was not observed for the low dose group during the same period. However, mean UDI-6 scores significantly improved from baseline to 18-month followup for both dose groups (high dose 51.0 ± 5.2 vs 23.3 ± 5.9 , $p = 0.02$; low dose 45.8 ± 3.8 vs 34.2 ± 3.8 , $p = 0.03$). At 18-month followup 4 patients (2 low dose, 2 high dose) reported no longer experiencing leakage related to activity, coughing or sneezing (question 3, UDI-6). An additional 6 patients (4 low dose, 2 high dose) reported less bothersome stress induced leakage at 18-month followup than at baseline.

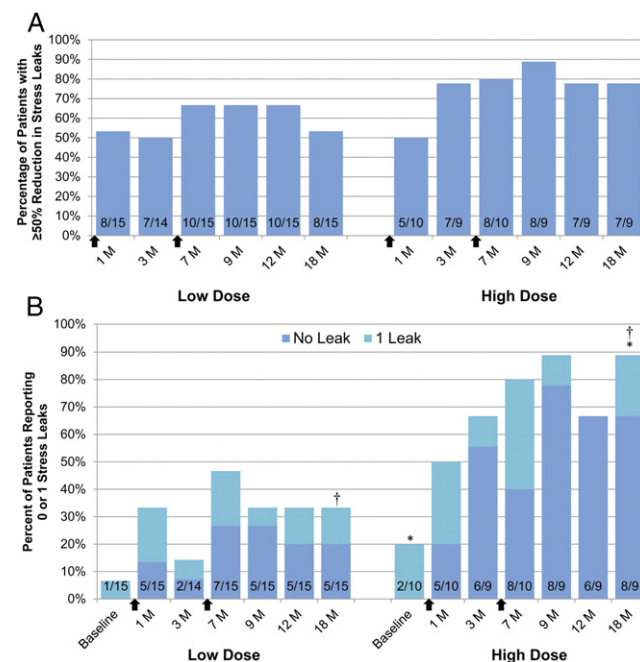


Figure 2. Improvement in diary reported stress leaks for patients who received 2 AMDC treatments. *A*, percentage of patients with 50% or greater reduction in number of stress leaks. *B*, percentage of patients with 0 or 1 stress leaks. Vertical arrows indicate timing of AMDC treatments. Ratio at base of each bar is number of patients who met criterion-to-number evaluated at each point. Seven patients with 0 stress leaks at baseline were excluded from analysis. Based on Fisher's exact test, percentage of patients in high dose group with 0 or 1 stress leaks at 18 months was significantly higher than at baseline (asterisk indicates $p < 0.01$). At 18 months percentage of patients in high dose group with 0 or 1 stress leaks was significantly higher compared to low dose group (dagger indicates $p < 0.01$).

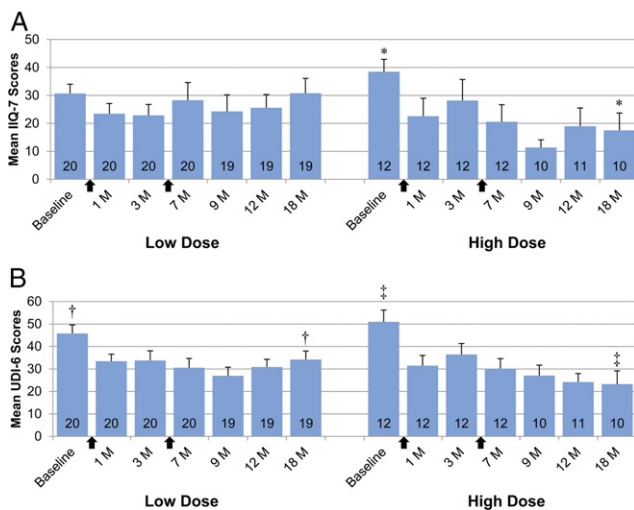


Figure 3. Mean quality of life scores for patients who received 2 AMDC treatments. *A*, mean IIQ-7 scores. *B*, mean UDI-6 scores. IIQ-7 and UDI-6 were scored 0 to 100 with lower scores indicating higher quality of life. Vertical arrows indicate timing of AMDC treatments. Number of patients who completed survey at each point is listed at base of each bar. Error bars represent standard error of mean. Compared to baseline, mean IIQ-7 scores were significantly lower for patients in high dose group at 18 months (asterisk indicates $p = 0.04$) but mean IIQ-7 scores were not significantly different for patients in low dose group at 18 months ($p = 0.98$). Mean IIQ-7 scores for low and high dose groups did not differ significantly at baseline or 18 months. Mean UDI-6 scores for patients in low and high dose groups differed significantly from baseline to 18 months (double dagger indicates high dose, $p = 0.02$; single dagger indicates low dose, $p = 0.03$).

Four patients (2 from each dose group) who received only a single AMDC treatment completed the 12-month study. At 12 months 1 patient experienced a dramatic reduction in pad weight (43.0 gm at baseline vs 0.0 gm at 12 months), while 3 patients reported a 50% or greater reduction in the incidence of stress leakage at 12 months.

DISCUSSION

Four other clinical feasibility studies describing autologous muscle cell treatment of SUI have been published.^{12–15} However, it is difficult to compare results across studies since limited information describing cell selection and culturing techniques is provided in published reports, and studies vary in patient enrollment criteria, procedural methods and outcome measures. Nonetheless, all studies published to date report low rates of operative morbidity for intrasphincter injection of autologous muscle cells.

The pilot study previously conducted¹² and the study described here share many similarities. Both

studies excluded patients who had undergone prior surgical treatment for SUI and limited enrollment to women in whom prior noninvasive treatments had failed. All patients underwent muscle biopsy and subsequent intrasphincter injection as outpatient procedures with local anesthetics. In addition, all patients were treated with AMDC prepared by Cook MyoSite Incorporated. In the pilot study 8 patients were treated with doses of 18 to 22×10^6 AMDC.¹² All patients completed the study without experiencing any serious adverse events or any unexpected safety issues. In addition, improvement in SUI was observed in 5 of the 8 women and 1 patient achieved total continence.

This report extends the pilot study by treating a larger number of patients with AMDC (38), and increasing the range of cellular doses (1, 2, 4, 8, 16, 32, 64 and 128×10^6 AMDC, maximum dose nearly 6 times greater than in the pilot study) tested for safety and potential efficacy. Additionally, since patients could elect to receive 1 or 2 treatments, the safety of 2 sequential treatments administered approximately 6 months apart was also assessed.

As in the pilot study the results of this study support the safety of AMDC treatment for SUI. During study followup no major treatment related complications were reported, and all minor complications associated with AMDC treatment occurred at a relatively low rate and generally self-resolved or were easily treated.

The data also suggest that AMDC may be able to improve SUI symptoms and quality of life. Additionally, improvement may be related to cell dose since a greater percentage of patients in the high dose group (32×10^6 AMDC or greater per treatment) than in the low dose group (16×10^6 AMDC or less per treatment) experienced a 50% or greater reduction in pad weight (88.9% vs 61.5%), had a 50% or greater reduction in diary reported stress leaks (77.8% vs 53.3%) and had 0 to 1 leaks during 3 days (88.9% vs 33.3%) at 18-month followup. A similar trend was observed with quality of life measures (fig. 3).

Although these data are promising, a number of study limitations exist. This small feasibility study was not powered to assess dose dependent safety or efficacy. Although all patients had a history of SUI and leaked with cough or Valsalva maneuver during baseline testing, 11 of the 38 enrolled patients were excluded from parts of the efficacy analysis since they reported no baseline stress leaks and/or had less than 1 gm baseline pad weight (4 reported no stress leaks, 4 had less than 1 gm pad weight, and 3 had no stress leaks and less than 1 gm pad weight). Since most patients elected to receive 2 treatments,

limited data are available for single treatments. Future studies should include a placebo control, be powered to assess efficacy, include selection criteria that exclude patients whose improvement cannot be easily assessed by voiding diary or pad test, and assess the efficacy of a single AMDC treatment.

To date, 2 feasibility studies evaluating AMDC injection for the treatment of SUI in women have been completed. Importantly, these initial investigations suggest that all doses of AMDC that have been tested are safe. Preliminary efficacy data also suggest that AMDC injection may reduce SUI severity and improve quality of life. A potential dose dependent treatment effect was observed with a trend toward greater efficacy in patients who received AMDC doses of 32×10^6 or greater per treatment. However, the most effective dose of cells has yet to be determined and a placebo controlled study powered to determine treatment efficacy is necessary. Two ongoing studies (ClinicalTrials.gov Identifiers NCT01008943 and NCT01382602) have been designed to address these issues.

APPENDIX

Selected study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ● Patient has provided written informed consent ● Patient is at least 18 years of age ● Patient has primary symptoms of SUI with normal detrusor activity demonstrated on filling cystogram ● Patient has bladder capacity greater than 200 ml ● Patient's incontinence has not shown any improvement for at least 12 months ● Patient has failed prior noninvasive treatments (eg behavior modification, bladder exercises, biofeedback, electrical stimulation and/or drug therapy) ● Patient has a viable mucosal lining along the urinary tract and in the bladder 	<ul style="list-style-type: none"> ● Patient has known vesicoureteral reflux, abnormal detrusor activity, or other significant pelvic floor abnormalities with high pressure instability ● Patient has a history of prior treatment with injectable urethral bulking agents or other urogynecologic reconstruction or corrective surgery ● Patient cannot be maintained on a stable dose of any medication known to affect lower urinary tract function, including, but not limited to, anticholinergics, tricyclic antidepressants or alpha-adrenergic blockers, throughout the treatment and followup period ● Patient has urinary incontinence of neurogenic etiology ● Patient has a neuromuscular disorder (eg muscular dystrophy, multiple sclerosis) ● Patient has fibrosis of the tissue at the likely injection sites ● Patient has any condition which could lead to significant postoperative complications, including current infection, or elevated residual urine from bladder outlet obstruction (ie repeated post-void residual greater than 150 ml) ● Patient is morbidly obese (defined as 100 pounds over ideal body weight, or body mass index greater than 40 kg/m^2) and would not be expected to benefit from treatment ● Patient has current or acute conditions involving bladder or urethra

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CONCLUSIONS

Intrasphincter injection of AMDC in doses ranging from 1×10^6 to 128×10^6 cells appears safe for the treatment of patients with SUI. Additionally, preliminary efficacy data suggest that AMDC treatment may relieve SUI symptoms and improve quality of life, with a trend toward greater efficacy with doses of 32×10^6 AMDC or greater.

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Stress Incontinence in the Era of Regenerative Medicine: Reviewing the Importance of the Pudendal Nerve

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Abbreviations and Acronyms

BDNF = brain-derived neurotrophic factor
EMG = electromyography
ENG = electroneurography
EUS = external urethral sphincter
LPP = leak point pressure
NMJ = neuromuscular junction
PN = pudendal nerve
SUI = stress urinary incontinence
trkB = type-B tyrosine kinase
VD = vaginal distention

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Purpose: Regenerative medicine will likely facilitate improved stress urinary incontinence treatment via the restoration of its neurogenic, myogenic and structural etiologies. Understanding these pathophysiologies and how each can optimally benefit from cellular, molecular and minimally invasive therapies will become necessary. While stem cells in sphincteric deficiency dominate the regenerative urology literature, little has been published on pudendal nerve regeneration or other regenerative targets. We discuss regenerative therapies for pudendal nerve injury in stress urinary incontinence.

Materials and Methods: A PubMed® search for pudendal nerve combined individually with regeneration, injury, electrophysiology, measurement and activity produced a combined but nonindependent 621 results. English language articles were reviewed by title for relevance, which identified a combined but nonindependent 68 articles. A subsequent Google Scholar™ search and a review of the references of the articles obtained aided in broadening the discussion.

Results: Electrophysiological studies have associated pudendal nerve dysfunction with stress urinary incontinence clinically and assessed pudendal nerve regeneration functionally, while animal models have provided physiological insight. Stem cell treatment has improved continence clinically, and ex vivo sphincteric bulk and muscle function gains have been noted in the laboratory. Stem cells, neurotrophic factors and electrical stimulation have benefited pudendal nerve regeneration in animal models.

Conclusions: Most regenerative studies to date have focused on stem cells restoring sphincteric function and bulk but whether a sphincter denervated by pudendal nerve injury will benefit is unclear. Pudendal nerve regeneration appears possible through minimally invasive therapies that show significant clinical potential. Treating poor central control and coordination of the neuromuscular continence mechanism remains another challenge.

Key Words: urethra; urinary incontinence, stress; regenerative medicine; stem cells; pudendal nerve

BACKGROUND

MANY incontinence treatments exist but none targets the underlying pathophysiology of failure of the neuromuscular continence mechanism or its coordination. As the era of regenerative

medicine dawns, gaining understanding of the etiologies of SUI will likely become beneficial, if not necessary, to maximize regenerative treatment efficacy. Structural changes to the pelvic floor, PN injury and EUS damage may

necessitate unique therapeutic approaches, while central nervous system etiologies, such as impaired coordination of continence reflexes or storage and voiding, may warrant alternative interventions.

Current treatments, which are largely mechanical, aim to recreate the suburethral vaginal hammock, cause dynamic kinking, reduce hypermobility and/or mechanically obstruct the urethra. Conservative treatments, including physiotherapy and medication, necessitate an intact, coordinated neuromuscular continence mechanism. Regardless of the treatment pursued, sphincteric deficiency, whether intrinsic and from muscular injury or due to denervation from nerve injury, challenges the attainment of successful clinical outcomes. Thus, restoring function to the neuromuscular continence mechanism will likely augment current surgical interventions and provide a potential means of preventing incontinence.

To date, investigations of urological regenerative therapy have demonstrated increased EUS muscle in the laboratory and improved continence clinically. However, it is uncertain whether success or failure was associated with a functional EUS gain or simply a bulking effect. Furthermore, whether EUS function was intact or deficient before clinical treatment was unclear. Therefore, more precisely identifying dysfunction of the neuromuscular continence mechanism, whether central or peripheral, may prove crucial to maximize regenerative treatment efficacy, improving not only muscle size but also the ability to use the muscle.

STRESS URINARY INCONTINENCE

Urinary incontinence is a common problem in women that causes significant quality of life and economic burdens. Long anecdotally related to childbirth, vaginal delivery is associated with pelvic floor injury and confers at least a 2.5 times greater risk of SUI.¹ A strong association between peripartum and postpartum SUI in primiparae supports this. Women in whom SUI develops during pregnancy were 5.79 times more likely to have SUI 1 year postpartum, while women with SUI 3 months postpartum were significantly more likely to be incontinent 5 years after delivery.^{2,3}

Conceptually, urinary continence is provided by a mechanism with 2 major components. One is structural and one is functional, with central and peripheral nervous system modulation and coordination of the functional components. The structural element comprises the pelvic floor musculature and connective tissue, while the functional component is the neuromuscular system of the PN and the EUS, which the PN innervates. With vaginal delivery SUI likely results from injury to structural and neuromuscular components. Damage to pelvic floor struc-

tures, such as connective tissue and the levator ani, can occur during vaginal delivery and is associated with SUI.⁴ Likewise, PN injury can occur during vaginal delivery according to prepartum and postpartum neurophysiological recordings.^{5,6} Direct urethral injury has also been observed after vaginal delivery.⁷ Thus, injury to the structural and neuromuscular components of urinary continence occurs with vaginal delivery.

Failure of the structural components that maintain continence is well addressed by contemporary treatments. However, failure of the functional, neuromuscular component of continence is not currently attended to clinically, whether it is of peripheral or central etiology. Persistent PN damage associated with SUI has been noted up to 7 years after delivery.^{8,9} Thus, neuroregeneration and recovery of childbirth mediated PN injury must be insufficient to adequately restore the neuromuscular function necessary to maintain continence. This concept is alluded to in the colorectal literature, highlighting improved surgical outcomes with intact PN function.¹⁰ Basic science studies confirmed this and identified antagonistic responses between muscle and nerve injury, which are likely implicated in their poor recovery and persistent dysfunction.¹¹

SUI is generally treated initially with symptom management, behavioral intervention and physiotherapy, and occasionally with medication. Minimally invasive treatments, used when conservative attempts fail, focus on restoring the structural integrity of pertinent tissues and obstructing or bulking the urethra to coaptation. None of these treatments regenerate the neuromuscular continence mechanism. In contrast, Kegel exercises target and strengthen the neuromuscular continence mechanism but rely on its intactness for success. Thus, using regenerative treatments to facilitate neuromuscular continence mechanism recovery addresses a gap in SUI treatment.

BASIC SCIENCE INSIGHTS INTO NEUROMUSCULAR CONTINENCE MECHANISM INJURY

Pudendal Nerve Injury

Crush injury to the PN induces a recoverable model of postpartum SUI in female rats with an LPP nadir after 4 days and recovery to almost normal levels after 2 weeks.¹¹ Molecular evidence of PN regeneration supports this. β_{II} -tubulin, a cytoskeletal protein indicative of neuronal growth and regeneration, is upregulated significantly in motoneuron cell bodies 7 days after injury and normalizes by 2 weeks.¹² Furthermore, levels of BDNF and other regenerative stimuli increase acutely in the EUS after PN injury to facilitate neuroregeneration.^{13,14}

The degree of PN injury determines the severity and duration of functional impairment.¹¹ While it may be challenging to translate these findings clinically, electrophysiological studies of the PN reflex loops and EUS in women provide valuable insight into the role of the neuromuscular continence mechanism. Associations between abnormal neurophysiological function and SUI in such studies implicate PN damage as a likely etiologic factor.^{15,16}

Direct electrophysiological studies of the isolated PN-EUS system in rats support functional continence outcomes, as measured by LPP. Overall muscle activity assessed by EMG nadirs 4 days after PN crush demonstrated persistent functional impairment with some recovery by 3 weeks.¹⁷ This echoes the results of other studies, in which LPP recovered 2 weeks after less intense PN crush.¹¹ Direct PN electrical activity on ENG revealed similar findings with impaired function 4 days after crush, requiring 3 weeks to recover, while PN transection took longer.¹⁷ Thus, changes in PN activity are linked to those in the EUS and injury severity determines the magnitude of dysfunction of the neuromuscular continence mechanism.

EUS Injury

VD simulates the second phase of labor and damages the EUS and distal PN branches as well as sympathetic nerves and smooth muscle in the urethra.^{11,18–21} Greater VD duration and extent, as controlled by balloon volume, are associated with worse EUS tissue damage, larger and more prolonged LPP deficits, and increased EUS nerve loss.¹⁸ This parallels a prolonged second stage of labor and macrosomia, which are each associated with postpartum SUI.^{7,16} Thus, EUS injury and PN damage are likely etiologic factors in SUI along with an element of decreased urethral sympathetic signaling and smooth muscle tone.

Functional studies differentiate VD induced SUI from that caused by PN injury. Although EUS EMG is reduced 4 days after VD or PN crush, VD produces no ENG deficit.¹⁷ Likewise, LPP required up to 10 days to recover after VD compared to 21 days after PN crush.^{13,17} Thus, VD induces SUI without proximal PN injury via direct sphincteric injury and distal nerve disruption, including adrenergic denervation of urethral smooth muscle.^{20,21} This highlights the possibility that birth induced EUS injury may occur independent of global PN dysfunction, making it a SUI etiology without a demonstrable PN deficit.

Decreased blood flow to the bladder, urethra and vagina during VD induces hypoxia in urethral smooth and striated muscle.¹⁸ Thus, the urethra and EUS are susceptible to hypoxic injury and trauma during delivery. These insults impair not

only EUS function but also its ability to stimulate PN recovery after VD, as evidenced by sphincteric BDNF down-regulation.¹³ Such molecular responses to hypoxia and tissue damage are potential targets for regenerative therapies.²²

Combined Vaginal

Distention and Pudendal Nerve Crush

Combined VD and PN crush is considered a more clinically relevant SUI model. Based on PN crush severity with VD, LPP deficits can persist beyond 3 weeks.^{13,17} Neuroregeneration appeared impaired on EUS EMG and PN ENG after combined VD and PN crush compared to either injury alone with the largest and longest lasting electrophysiological deficit on PN ENG requiring more than 3 weeks to recover.¹⁷ This highlights that impaired recovery occurred when nerve and muscle were injured, suggesting that EUS and PN childbirth injuries have a similar role clinically in SUI by preventing recovery of the neuromuscular continence mechanism.

NEUROMUSCULAR SYSTEM REGENERATION

Mechanisms

Neurotrophins are cytokines that maintain innervation and neural function, and stimulate axonal regeneration and neuronal growth.²³ A major neurotrophin is BDNF, which activates JAK/STAT signaling via trkB receptors to mediate neurite outgrowth, an essential component of neuroregeneration. Evidence of its importance comes from mice carrying a null trkB allele, which regenerate only 50% of motoneurons after nerve transection.²⁴

Spinal motoneuron terminals contain trkB receptors, while their supporting Schwann cells and innervated skeletal muscles express BDNF, suggesting that retrograde signaling occurs.²³ Sciatic nerve injury increases gastrocnemius BDNF expression, which peaks 7 to 14 days after injury.²⁵ EUS BDNF is up-regulated within 1 day of PN crush.¹³ While BDNF is required for neuroregeneration, it further reduces motoneuron death when given therapeutically at injury sites.^{26,27} The necessity of BDNF is also shown by anti-BDNF antibody treatment, which significantly impaired nerve regeneration after injury.²⁸ Likewise, anti-trkB antibody infusion decreased motoneuron conduction velocity, illustrating the necessity of BDNF-trkB signaling for maintaining neuromuscular function.²⁷

While BDNF is beneficial to neurons, it is inhibitory to and decreases during neuromuscular junction formation and restoration, and myogenic myoblast differentiation.^{29,30} BDNF expression is decreased in the EUS after VD induced injury.¹³ Thus, despite its neural benefits, BDNF decreases with muscle injury to likely lessen its negative effects on EUS neuromuscu-

lar junction and muscular recovery. As such, concurrent PN and EUS injury likely impairs PN neuroregeneration via the down-regulation of EUS BDNF to facilitate EUS muscle repair.

Competing Injuries

The more severe functional loss and the prolonged recovery of LPP, EUS EMG and PN ENG due to combined PN and EUS injury compared to either injury alone likely results from the opposing effects of PN crush and VD on EUS BDNF expression.^{13,17,23,24,26} Specifically, VD reduces EUS BDNF and PN crush increases it, although the down-regulation induced by EUS injury overcomes the up-regulation from PN crush when the injuries are combined.¹³ This likely impairs neuromuscular continence mechanism recovery by impeding PN neuroregeneration due to lower EUS BDNF.

Another possibility is that muscular and NMJ recovery is impaired. BDNF expression remains unchanged after NMJ damage.³¹ However, since VD causes EUS and NMJ disruption, myocyte loss and NMJ integrity may possibly not recover if BDNF is up-regulated in the EUS due to PN injury after a combined insult in childbirth.^{18,19} Agrin, a proteoglycan that facilitates NMJ restoration by clustering acetylcholine receptors and inhibiting neuronal sprouting, is inhibited by BDNF up-regulation.²⁹ Likewise, increased EUS BDNF may impair muscle recovery since decreased BDNF levels are necessary for the myogenic differentiation of progenitor cells, a phenomenon that can be enhanced by siRNA induced BDNF suppression.³⁰ As such, it is likely that EUS injury leads to EUS BDNF down-regulation to facilitate myocyte and NMJ recovery at the expense of PN regeneration in combined childbirth injury. Therefore, targeting not only the EUS but also the PN with regenerative therapies may be beneficial.

Assessment

The cytoskeletal protein β _{II}-tubulin, a marker of neuroregeneration, undergoes increased synthesis and antegrade transport from nerve cell bodies to neuronal sprouts at axonal injury sites, and its quantification approximates the peripheral nerve regenerative response.³² Levels of β _{II}-tubulin in the PN correlated with functional recovery after PN injury with increased expression 7 days after PN crush, which normalized by 14 days, echoing temporal trends in LPP after PN crush.^{12,13,17} Electrophysiologic data further support this, showing gradual PN recovery through 21 days.¹⁷ Thus, it appears that the neuroregenerative response precedes and likely facilitates functional recovery of the PN and EUS neuromuscular continence mechanism.

NEUROREGENERATIVE THERAPY

BDNF administration to nerve transection sites enhances functional recovery and decreases neuronal death *in vivo*.^{23,28} Various BDNF treatment methods improve cholinergic motoneuron activity, as evidenced by increased choline acetyltransferase.³³ However, neither a single injury site injection nor repeat subcutaneous injections improved nerve recovery, although continuous local administration to injury sites was successful.^{23,26,34}

A tibial nerve injury model revealed no acute response to BDNF therapy but showed up to an 83% dose dependent increase in regenerated motoneurons 2 months later with a 0.5 μ g per day, 4-week treatment being most effective.²⁶ Cavernous nerve injury models of erectile dysfunction have also proved the efficacy of BDNF and other neurotrophin treatments, as have studies showing increased sympathetic pelvic ganglion cell sprouting.^{35,36} Prolonged release calcium alginate hydrogels impregnated with BDNF facilitated 4-week experimental treatments and may exemplify a clinically relevant drug delivery approach.³⁴ While a depot approach may be most easily adapted for clinical use, other means of supplying BDNF to PN injury warrant further investigation, such as adipose derived BDNF secreting stem cells and electrical stimulation.^{37,38}

REGENERATIVE TREATMENTS FOR SUI

Stem Cell Therapy

Stem cells have been used to restore structural integrity in the urogenital organs and bulk the urethral sphincter.^{39,40} While this has been successful in small initial clinical trials, little is known about the actual mechanism of action and the durability of the therapeutic effect.^{41,42} Laboratory studies of periurethral stem cell injections revealed newly formed striated muscle, which was associated with improved continence.⁴⁰ However, functional proof of stronger muscle contraction was obtained *ex vivo*, leaving unanswered whether improved continence was due to a functional gain or to bulking a denervated sphincter.³⁹

A major uncertainty regarding stem cell therapy results from using *ex vivo* testing to demonstrate improved muscle function rather than *in vivo* electrophysiologic or manometric testing.³⁹ Nonetheless, when injected periurethrally, muscle derived cells were associated with increased EUS innervation and new striated muscle, although the model used urethral rather than proximal PN injury to induce EUS denervation.⁴³ Thus, while stem cells target the EUS and provide additional bulk through differentiation, the benefit this could provide to a denervated sphincter remains unclear.^{40,41} As such, using stem cells manipulated to produce BDNF, while

they still differentiate into myocytes, may facilitate the repair of a denervated EUS and provide a durable therapeutic benefit to sphincter deficiency. A potential alternative treatment with stem cells delivered intravenously also showed promise for urological sphincteric and neural injuries with the stem cells homing to nerve and muscle to facilitate electrophysiological and functional recovery.^{22,44}

Cell Signaling Interventions

Like stem cells, certain growth factors improve continence and can lead to improved EUS function. Administering bFGF after sphincteric denervation with botulinum-A toxin increased LPP and thickened smooth and striated EUS muscle.⁴⁵ However, similar to stem cells, gains in continence were potentially due to bulking and not necessarily functional since the EUS was denervated.⁴⁵ Multipotent lipoaspirate cells provided a measurable benefit to continence that was thought to be paracrine in nature, although this similarly relied on injection and likewise exerted a probable bulking effect.^{42,46} A study using intramuscular EUS stem cells supplemented with nerve growth factor impregnated poly(lactide-co-glycolide) microspheres showed improved continence gains with the growth factor compared to stem cells alone, possibly due to improved neuroregeneration since bulking was considered in control groups.⁴⁷ Lastly, a study of anal sphincter denervation revealed improved histological PN regeneration with sphincteric insulin-like growth factor-I injection.⁴⁸ Despite the beneficial effects of various cytokines, it is unclear whether the improved continence achieved by injecting them is due to gains of innervated functional muscle or to a transient bulking effect.

BDNF Therapy

Considering the limitations and uncertainties of cellular and molecular regenerative treatments, understanding the neuromuscular continence system and its dysfunction provides insight into optimizing SUI treatment. Decreased EUS BDNF after VD and EUS muscle damage are the dominant effects in a combined nerve and muscle injury model. This likely impairs PN recovery due to insufficient BDNF up-regulation in the EUS.^{13,23,26} Thus, treating the PN with BDNF is a logical intervention.

Targeted PN treatment with BDNF after PN crush and VD improved LPP and EUS EMG, and was associated with more robust EUS muscle on histological analysis.⁴⁹ Unlike EUS intramuscular or periurethral injection therapies, no potential existed for bulking. Furthermore, EUS function was

assessed in vivo with LPP and EUS EMG, which revealed recovery and indicated a regenerated, intact neuromuscular circuit. Since PN and EUS injury likely occurs in women, treatments aimed at regenerating the PN nerve may facilitate SUI recovery and even serve as a prophylactic peripartum therapy to prevent its development. Furthermore, treating the PN with BDNF benefits the sphincter since it is associated with lower EUS BDNF levels, which are detrimental to myocyte and neuromuscular junction recovery.^{18,19,29,30,49} Lastly, BDNF also increases sympathetic nerve sprouting and enhances sympathetic signaling, which may improve urethral smooth muscle tone.^{21,36,50} As such, targeted BDNF treatment can overcome EUS BDNF down-regulation to facilitate PN recovery. It may also further improve EUS musculature and reinnervation by reducing EUS BDNF and maintaining innervation to limit sphincter atrophy.

FUTURE DIRECTIONS

The field of regenerative medicine holds numerous possibilities for incontinence and voiding dysfunction. With the growing focus on regenerative and preventive medicine, a means of treating SUI, repairing the neuromuscular continence mechanism and also preventing SUI is attractive. Treatment aimed at PN neuroregeneration, such as supplemental neurotrophins, may accomplish this. As such, clinically pinpointing the origin of neuromuscular dysfunction, whether central or peripheral and due to nerve and/or muscle injury, may become increasingly crucial in SUI evaluation as the use of regenerative therapy begins.

Direct continuous neurotrophin treatment to the injured PN facilitates improved functional recovery.⁴⁹ In the clinical arena using degradable materials or formulations such as depot injections for delivery is attractive since they have already shown promise in the laboratory.³⁴ Similarly, PN electrical stimulation, which could be accomplished transvaginally in the office or at home, increases neurotrophin levels and stimulates PN neuroregeneration according to animal models.³⁸ Otherwise, stem cells engineered to secrete BDNF could provide supplemental neurotrophins to specific regions and can be harvested from various sites, including adipose tissue.^{37,42} With these possibilities and a likely number of undiscovered approaches, an exciting challenge for ongoing and future research is to explore PN regeneration and its role in reviving a dysfunctional neuromuscular continence mechanism.

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Surgery for postprostatectomy incontinence: which procedure for which patient?

Craig Comiter

Abstract | Surgery remains the most effective treatment for postprostatectomy incontinence. Over the past two decades, this surgery has evolved with respect to both operative technique and sling design, and various devices are now available that have different mechanisms of action, such as the artificial urinary sphincter, retroluminal sling or quadratic sling. The choice of device, however, should be individualized according to the circumstances of each patient. The optimal surgical treatment depends on a variety of patient-related factors, including the degree of urine leakage as assessed by incontinence pad weight test results, bladder contractility, urethral compliance, history of radiation exposure or prior incontinence surgery, and patient preference—given the choice, most patients opt for a sling procedure over an artificial sphincter to avoid implantation of a mechanical device. Athorough urodynamic evaluation is, therefore, necessary for the majority of patients. An artificial urinary sphincter, retroluminal sling or quadratic sling might be the most appropriate choice for a particular patient, depending on their specific urodynamic findings. Progress in this field continues, and several new devices are in development.

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Introduction

Each year, approximately 120,000 men with prostate cancer undergo radical prostatectomy in the USA alone.¹ Moreover, approximately 4% of men who undergo radical prostatectomy will require surgery within the subsequent 3 years to treat iatrogenic postprostatectomy incontinence (PPI).² Until the late 1990s, the two most common surgical treatments for PPI were transurethral injection of bulking agents (which achieved meaningful improvements in continence in only a minority of patients³) and implantation of an artificial urinary sphincter (AUS). AUS implantation has been regarded as the most effective treatment for PPI over the past 30 years. However, AUS implantation carries a well-known risk of revision surgery secondary to infection, erosion, urethral atrophy and mechanical failure. Sling procedures in men arose out of necessity for a lower-risk and less-invasive approach, especially in men who wish to avoid using a mechanical device.⁴

Innovations in device design and surgical technique have resulted in an increased interest in sling surgery. The original Kaufman prosthesis, which used a silicone-gel filled hemispherical prosthesis and polyurethane straps to create urethral compression, was replaced by the pubourethral sling,⁵ which was replaced by the bone-anchored male sling (BAMS) and the retroluminal sling. The BAMS is based upon a 4 × 7 cm sling that compresses the perineal portion of the urethra, secured to the pelvis by titanium bone screws.⁶ The retroluminal sling, which

is implanted under the proximal part of the urethral bulb is thought to provide continence by relocating the proximal urethra in a noncompressive manner.⁷ The latest product of sling evolution and development is the quadratic sling, a four-armed polypropylene mesh that provides both proximal urethral relocation via a transobturator component, and perineal urethral compression via a prepubic component.⁸ Each of these approaches substantially improves continence in men with mild to moderate PPI. Regardless of the particular device, the primary goals of sling surgery in men remain the same: tensioning the sling to adequately compress the bulbous urethra and/or relocate the proximal urethra, balancing sling tension and detrusor contractility to avoid urinary retention and maintaining sling tension to prevent recurrent leakage.

Several devices for treating men with PPI are available, although it is not clear which device should be offered to which patient. This Review will examine the efficacy of different surgical treatments for ISD (intrinsic sphincter deficiency) following prostate cancer surgery, and the risk factors for surgical failure. Patients and surgeons must decide, based on available data, who is a better candidate for implantation of one device versus another, aiming to balance surgical success and operative morbidity.

Urodynamic evaluation

PPI can be a result of either bladder dysfunction or intrinsic sphincter deficiency (ISD). A man presenting with leakage on straining that stops at cessation of the straining manoeuvre can be diagnosed as having ISD without

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Competing interests

The author declares that he has acted as a consultant for Coloplast.

Key points

- Intrinsic sphincter dysfunction (which can be confirmed using urodynamics) is the most common cause of postprostatectomy incontinence
- Quantifying the degree of urine leakage using incontinence pad weight or pad use is important for determining the optimal surgical treatment
- Implanted slings are generally effective in men with mild-to-moderate postprostatectomy incontinence
- Adequate sling tensioning during surgery and postprocedural maintenance of sling tension are necessary for sustained device performance
- Different sling designs suit different patients, and device selection should be based on the degree of leakage, residual sphincter function and bladder contractility
- Sling effectiveness is lowest in men with severe incontinence and a history of radiation exposure; implantation of an artificial urinary sphincter remains the procedure of choice in this group

further testing. A voiding diary is generally an effective way to confirm sufficient bladder capacity, and a bladder scan can be used to evaluate the patient's ability to adequately empty his bladder. However, bladder contractility can only be ascertained by a detailed urodynamic evaluation. Thus, the urologist must determine the precise pathophysiology of PPI before proceeding with surgery. The presence of an obstructive or anastomotic urethral stricture (which occurs in 2.7–20.5% of men after radical prostatectomy)^{9,10} should be ruled out, as this might alter the treatment plan. Furthermore, since adequate detrusor contractility is necessary to overcome the fixed resistance of a compressive urethral device,¹¹ patients with detrusor underactivity might have an increased risk of urinary retention following surgery. Compressive slings are, therefore, designed to prevent leakage on straining, and therefore are likely to interfere with voiding via straining. In men with an underactive bladder, I recommend that an AUS or a noncompressive retroluminal sling should be used, and that only men with adequate detrusor contractility should be considered candidates for implantation of a compressive quadratic sling.

Measurement of leak-point pressure (LPP) might not be necessary in men with demonstrable stress urinary incontinence (SUI), as LPP values neither correlate with incontinence pad weight nor do they typically alter the treatment plan.¹² By contrast, pad use correlates well with actual urine loss, which justifies reported daily pad use as a determinant of incontinence severity.¹³ Pad weight and pad use, therefore, remain the best methods for quantifying the degree of incontinence.

The finding of bladder dysfunction as detected by filling cystometry, in patients with severe incontinence must be interpreted cautiously. Although *de novo* reduced bladder compliance might be demonstrated in >25% of patients with PPI, even up to 3 years postoperatively,¹⁴ in my experience, reduced compliance does not usually worsen surgical outcome. In patients with severe ISD, urodynamic demonstration of diminished compliance, early sensation of fullness and even detrusor overactivity do not typically affect the outcome of AUS surgery.^{15,16} This discordance between urodynamic findings and clinical outcomes represents simple artefacts owing to supraphysiological filling rates in patients

whose bladders are chronically under-filled as a result of leakage. The finding of urodynamic bladder dysfunction in a patient with SUI should not, therefore, be considered an absolute contraindication to surgical treatment. Moreover, as also occurs after AUS surgery, normal storage will typically become re-established after successful sling surgery.

Detrusor underactivity (as determined by the bladder contractility index or measurement of isovolumetric detrusor contraction pressure on pressure-flow studies) can occur in 25–40% of patients >1 year after prostatectomy,^{14,17} and can occur *de novo* in up to 10% of such patients.^{18,19} However, no universally agreed measure of normal detrusor contractility following prostatectomy currently exists. Success rates of AUS surgery do not substantially differ in patients with normal bladder contractility compared to those with detrusor hypocontractility,^{20,21} as the cuff is deflated during voiding, which permits efficient bladder evacuation via abdominal straining if necessary. By contrast, adequate detrusor contractility is necessary to expel urine past a compressive sling.¹¹ Thus, placing a potentially obstructive sling in a patient with detrusor hypocontractility might be associated with an increased risk of urinary retention.

Unlike assessment of bladder storage and LPP measurement, the methods for evaluating bladder contractility have not been standardized. Nomograms based on populations of men with prostate enlargement (such as the bladder contractility index) provide inaccurate estimates of bladder contractile strength in men after prostatectomy,¹⁷ because voiding pressure is an unreliable determinant of detrusor strength in patients with low urethral resistance, as the contractile pressure required to maintain axial flow can approach zero. The isometric detrusor contraction pressure (P_{iso}) is probably the most accurate and direct measure of detrusor contractility, since this parameter is highly correlated with the Watts factor,²² which is generally recognized as a reliable approximation of bladder contractile strength. During voiding, P_{iso} can be determined using the mechanical stop test, a simple and validated measure of detrusor contractility.^{23,24} The examiner gently manually occludes the penile urethra during voiding, preventing urinary flow, but without causing a pelvic floor contraction, which could otherwise abort the detrusor contraction. P_{iso} is the maximum isovolumetric detrusor pressure reached during this manoeuvre (Figure 1). In addition to measuring the strength of the bladder contraction, the ability to sustain this contraction is also necessary for adequate evacuation of urine. Since urethral slings are typically tensioned to a resistance of 60 cm H₂O, we recommend that candidates for such devices have a minimum P_{iso} of 60 cm H₂O to be able to overcome the fixed resistance of the device.

Assessment of urethral mobility

The mechanism of action of the retroluminal sling is hypothesized to rely more on repositioning of the descended posterior and sphincteric urethra than on direct compression of the bulbar urethra.²⁵ Assessment

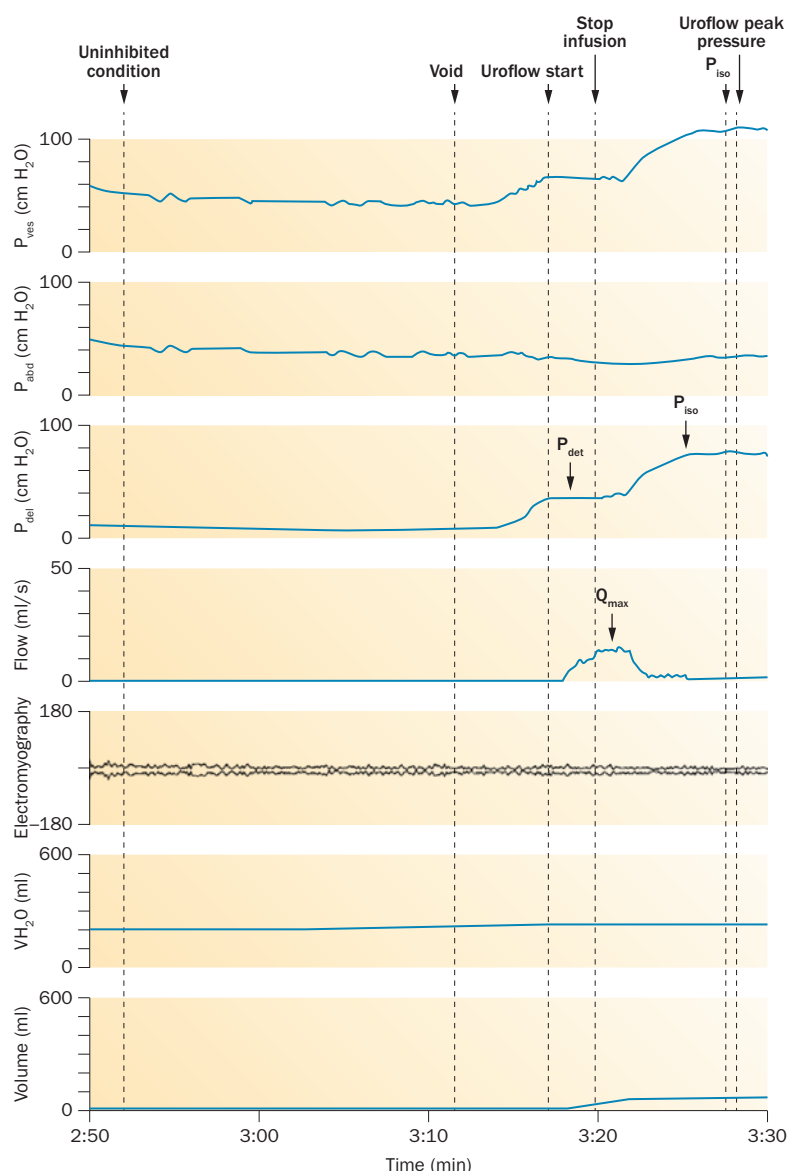


Figure 1 | Urodynamic measurements of detrusor contractility during the mechanical stop test. Upon gentle manual occlusion of the penile urethra during normal voiding, urine flow is stopped, but the isovolumetric contraction pressure continues to rise, signifying normal bladder contractility. Abbreviations: P_{iso} , isovolumetric contraction pressure; P_{det} , detrusor pressure at maximum flow; Q_{max} , maximum flow rate.

of proximal urethral mobility is, therefore, important in order to gauge the degree to which the posterior urethra might be repositioned by a retroluminal sling. Abdominal LPP increases on gently pressing the preanal midperineum towards a cephalad direction (while avoiding direct compression of the urethral bulb).²⁷ A favourable result on this 'repositioning' test—with visual closure of the external sphincter and concomitant increase in the LPP—has been advocated as a predictor of retroluminal sling success.²⁶ Moreover, upon perineal elevation, men with sufficient residual sphincter function (that is, mild ISD) demonstrate cystoscopically visible passive sphincter closure.²⁸ This concentric coaptive sphincter response during perineal elevation is also predictive of a successful outcome with the retroluminal sling.^{7,26,27}

Fluoroscopy is an effective method for determining the degree of proximal urethral and bladder neck mobility. As an alternative to the repositioning test, fluoroscopic assessment during straining can be used to demonstrate the degree of bladder neck and proximal urethral descent. My research group used videourodynamics to monitor bladder neck and proximal urethral mobility in a cohort of men with PPI.²⁹ Men who developed PPI following radical prostatectomy alone had significantly more proximal urethral descent on straining than men treated with adjuvant radiation or primary radiotherapy (Figure 2).²⁹ In my opinion, therefore, only men with adequate bladder neck and proximal urethral mobility should be offered retroluminal sling surgery, whereas those with an immobile proximal urethra would be more appropriately treated with a compressive quadratic sling or AUS.

Devices for surgical treatment of PPI

For more than three decades, implantation of an AUS has been regarded as the most reliable surgical approach for treating PPI owing to success rates typically above 80%. However, infection rates of 5–6%, erosion rates of 6–8% and mechanical failure rates of 6–23% have been reported over 7–13 years of follow-up in two large contemporary series.^{20,30} Patients and urologists alike realize the necessity for a lower-risk surgical alternative to AUS implantation.

The BAMS increased in popularity during the first decade of the 21st century. This device improves continence through direct compression of the distal bulbar and perineal urethra against the genitourinary diaphragm. The BAMS consists of a permanent synthetic sling fixed using a combination of titanium bone screws and polypropylene sutures, which gives high rates of operative success. Several large prospective studies demonstrated sustained effectiveness of the BAMS over 3–5 years of follow-up, with complete (pad-free) continence rates generally in the 50–65% range, and treatment success (defined as use of <1 pad daily) rates of 65–80%.^{31–34} Complication rates were generally low, with an overall infection rate of 3%, an erosion rate <2% and perineal pain (which occurred in 16–19% of patients) typically lasting up to 3 months postoperatively.^{31–34} However, the high cost of bone screws and the risk of osseous complications inspired the search for an anchorless perineal sling.

The retroluminal sling, which is implanted via a minimally invasive transobturator approach, was introduced in 2005. The principal mechanism of action of this device is proximal urethral relocation, since it provides only nominal bulbar urethral compression. Laxity of posterior urethral support and reduced functional length of the membranous urethra,³⁵ are hypothesized to contribute to ineffective coaptation of the urethral sphincter complex, secondary to relative misalignment (prolapse) of the proximal urethra.²⁷ This prolapse of the proximal urethra, which can follow prostatectomy, might be remedied by implantation of a retroluminal sling. This supportive device restores the preprostatectomy

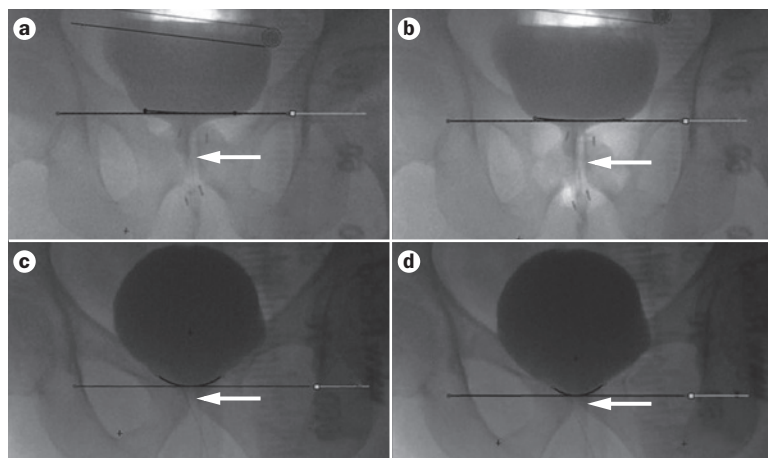


Figure 2 | Fluoroscopic determination of proximal urethral mobility. Relaxed **a** | and straining **b** | patient without previous radiation exposure. Relaxed **c** | and straining **d** | patient with previous radiation exposure. Note the increased descent of the proximal urethra, which indicates increased mobility observed in the patient without previous radiation exposure during straining compared with the patient with previous radiation exposure.

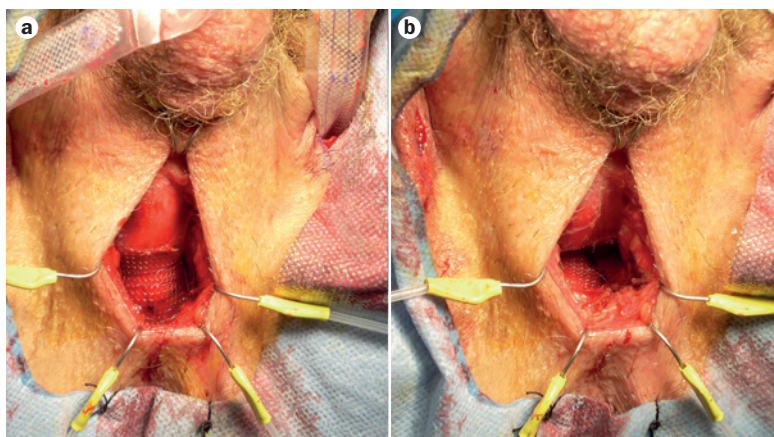


Figure 3 | Implantation of a retroluminal sling. **a** | Implanted retroluminal sling before tensioning. **b** | Implanted retroluminal sling after tensioning; the urethra has moved proximally by 2.5 cm.

urethral configuration by realigning the mobile sphincter complex. Once the sling is appropriately tensioned, the bulb of the urethra is relocated proximally into the pelvic outlet by a distance of 2–3 cm (Figure 3).³⁵ The additional support provided by the sling can also function as a ‘backstop’ during transient increases in straining (such as during coughing).³⁵

Success rates in prospective series of patients range from 54% to 80%.³⁶ In one study, a cure rate of 54% and success rate of 77% were achieved in 156 patients after 1 year of follow-up, which was maintained (cure and success rates of 53% and 77%) at 3 years.³⁷ However, in other reports of long-term outcomes of patients with a retroluminal sling, success rates progressively declined from 74% at 1 year, to 63% at 2 years and 62% at an average 3 years follow-up duration. Durable cure (no pad use) was achieved in 40% of patients at 3 years.³⁸

Reported rates of transient urinary retention range from 3% to 23%, but this complication typically resolves by 12 weeks.⁶ Rates of perineal pain vary widely (from 0% to >20% of patients, but typically <10%), probably owing to differences in the definition of postoperative pain.^{39–41} Pain usually resolves by 3 months postoperatively. Serious complications requiring sling explantation are rare (<1%).⁶

By combining the mechanisms of action of the BAMS and retroluminal sling, the quadratic sling (Figure 4) can increase urethral resistance to a greater degree than either purely perineal or solely transobturator devices. The additive nature of this effect was confirmed in a cohort of 22 men with PPI undergoing quadratic sling placement.⁴² Sequential and cumulative increases in retrograde leak-point pressure (RLPP) followed tightening of the transobturator and pubic extensions.⁸

In a multinational clinical trial, a quadratic sling with permanent suture-fixation achieved an objective success rate (defined as a >50% improvement in 24 h pad weight) of 79%, a subjective success rate (patient-reported very much improved or much improved continence) of 71%, and a median reduction in 24 h pad weight of 88% after 1 year follow-up duration. Cure (defined as <1.3 g detected using the 24 h pad weight test) was achieved in 46% of patients after 1 year.⁴³ Of note, the majority of patients in this cohort had moderate (100–400 g daily) or severe (>400 g daily) incontinence at baseline. All complications were mild (Clavien grade 1), and similar to those observed with other sling types: 19.4% of patients had mild genital paraesthesia and 12.0% experienced mild perineal pain. All paraesthesias resolved within 6 months, and all but two cases of pain resolved; both these patients reported only mild perineal discomfort (Table 1).⁴³

Sling tensioning

Appropriate tensioning of the retroluminal sling might be achieved by observing adequate proximal relocation of the bulbar urethra, or by cystoscopic observation of luminal coaptation. However, for a compressive perineal sling, neither urethral closure pressure nor urethral resistance can be visually quantified with a high degree of accuracy. A more precise method of sling tensioning involves measuring urethral resistance to flow. RLPP measurement has become an accepted and validated test of urethral sphincter competence in men with ISD,^{44–46} and this parameter correlates well with other accepted measures of urethral sphincter function, including abdominal LPP and maximal urethral closure pressure.⁴⁶ Abdominal LPP cannot be measured during surgery with the patient under general anaesthesia, but RLPP can be measured via perfusion sphincterometry, and is a useful quantification of urethral resistance during male anti-incontinence surgery.^{33,47,48}

Long-term efficacy

Long-term success requires that sufficient sling tension is maintained postoperatively. Use of allograft or xeno-graft (bioabsorbable) bone-anchored slings has been

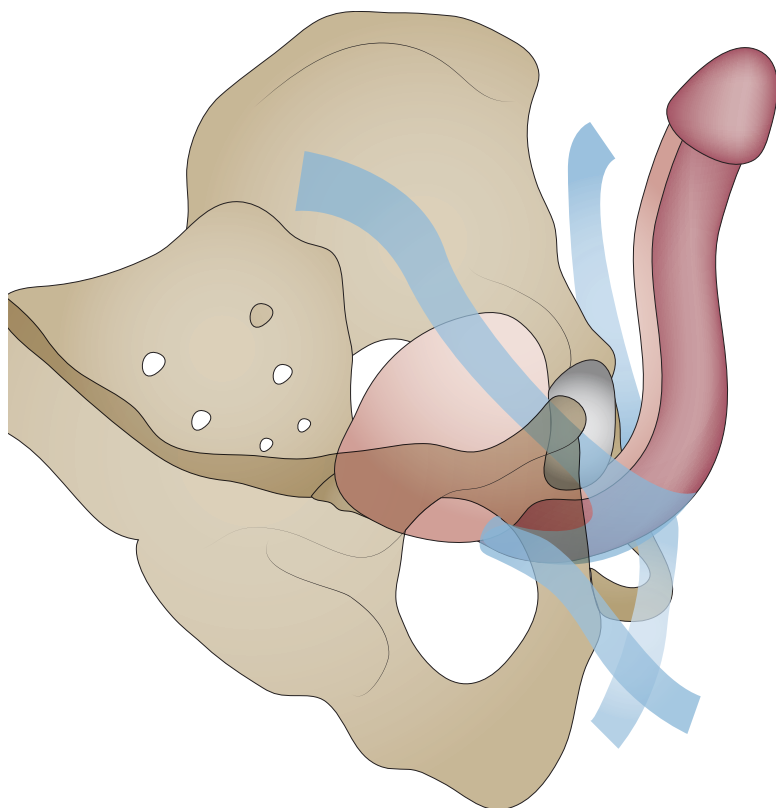


Figure 4 | The quadratic sling. The quadratic sling has transobturator and prepubic arms, which enable both proximal urethral repositioning and perineal urethral compression.

associated with loss of anti-incontinence function, with failure rates >90% after 6 months follow-up duration.⁴⁹ By contrast, efficacy rates do not substantially diminish over the 3 years or more following implantation with use of (nonabsorbable) polypropylene slings.^{31,33,34} Urodynamic evidence highlighting the importance of maintaining sling tension is provided by my group's prospective study of 22 patients with perineal slings, which demonstrated maintenance of urethral resistance 2 years postoperatively.⁴⁸ Thus, with a reliable fixation method and use of a permanent sling, tension and continence can be maintained.

Similarly, some early studies of the retroluminal sling reported loss of sling function over time. In a cohort study from the Cleveland Clinic, patient-determined success rates decreased from 87.3% to 62.5% in patients with a retroluminal sling, and average daily pad use more than doubled over the first 2 years after implantation.⁵⁰ Specific risk factors predisposing to retroluminal sling failure included the use of absorbable fixation sutures, fewer than four fixation sutures and absence of subcutaneous sling tunnelling.²⁸ However, further experience and improved fixation of retroluminal slings has led to substantially improved medium-term results, and a 76.8% success rate after 3 years of follow-up.³⁸ Novel types of tissue-anchoring mechanisms have been introduced to facilitate sling fixation,⁵¹ but are not necessarily available in all regions.

Patients implanted with an unfixed quadratic sling also generally experienced a progressive reduction in sling performance over the subsequent 12 months. Following initial subjective and objective success rates of 56% and 61% respectively, only 42% of patients who received an unfixed quadratic sling reported subjective and objective success by the end of the first post-operative year.⁴³ Thus, the original (unfixed) sling placement was revised to include fixation of the transobturator and prepubic arms, with subsequent avoidance of early loss of sling tension. Effectiveness was improved and maintained with the elimination of early sling slippage.⁴³

Factors affecting treatment choice

Patient preference

In spite of the track record of success achieved with AUS implantation over several decades, men with PPI overwhelmingly prefer sling implantation. When given a choice between AUS and sling implantation, 22 of 24 men (92%) chose the sling.⁴ In a group of 46 patients for whom the surgeon recommended sling implantation, all consented to the proposed treatment, whereas in 63 men for whom AUS implantation was recommended by the surgeon, 16 (25%) still opted for sling surgery.⁴ Avoidance of a mechanical device was the most common reason to disregard the surgeon's recommendation.

Clinical phenotype

Degree of incontinence

The degree of baseline urine leakage, as measured by pad weight, can affect the outcome of sling surgery (Table 2). The retroluminal sling has been associated with reduced success rates in men with severe incontinence (>200 g leakage daily) in two independent studies.^{52,53} In one of these studies, for each 1 g increase in baseline 24 h pad weight, the cure rate decreased by 0.4%.⁵¹ In patients with a baseline pad weight of 400 g daily, success was only 40% compared to a success rate of 86% in those with <100 g daily.⁵¹ Similarly, high baseline pad weights are associated with postoperative loss of efficacy of the BAMS, with a 24 h pad weight of approximately 450 g representing the cutoff for recommending AUS implantation over sling implantation.⁵⁴ Initial studies of the fixed quadratic sling did not detect a difference in success rates between patients with varying degrees of incontinence (namely leakage of <100 g, 100–400 g, and >400 g daily). However, with only a 1-year follow-up period and small numbers of patients, this study was not powered for such subgroup analysis.⁴³

Prior radiation exposure

A history of radiotherapy is associated with an increased risk of sling failure in multiple series of patients.^{53,55,56} Adequate tissue compliance is necessary for successful proximal urethral relocation as well as urethral compression. In a retrospective cohort study of men treated with retroluminal sling surgery, 63% of patients without prior radiation exposure were cured and 27% had improved symptoms after 1.5 years follow-up duration,

Table 1 | Effectiveness and complications of implantation procedures

Device	Success rate* (%)	Common complications
Artificial urinary sphincter ^{20,30}	>80	Infection or erosion 5–8% Urinary retention 0% Mechanical failure 6–23%
Bone anchored male sling ^{31–34}	65–80	Infection or erosion 2–3% Urinary retention 1–2% Pelvic pain 16–19%
Retroluminal sling ^{6,36,37}	63–80	Infection or erosion <1% Urinary retention 3–23% Pelvic pain 0–10%
Quadratic sling with fixation ⁴³	70–79	Infection or erosions 0% Urinary retention 0% Pelvic pain 12–19%

*Defined as either cure or substantial improvement of continence.

Table 2 | Indications and contraindications for surgical treatment of PPI

Device	Indications	Contraindications
Artificial urinary sphincter	Any degree of leakage Can be used effectively in patients with a history of radiation exposure, prior AUS implantation, ^{58–62} or prior sling implantation ^{66–69}	Patient's aversion to implantation of a mechanical device ⁴
Retroluminal sling	Mild to moderate leakage ^{52–54}	Less effective in patients with a history of radiation exposure, ⁵⁷ poor residual sphincter function ^{26,27} or prior AUS implantation ^{31,33}
Quadratic sling	Moderate to severe leakage ⁴³	Has not been evaluated in men with detrusor hypocontractility or prior AUS implantation

Abbreviations: AUS, artificial urinary sphincter; PPI, postprostatectomy incontinence.

versus 0% cured and 29% with improved symptoms in those who had received radiotherapy before sling placement.⁵⁷ In 24 patients with previous radiation exposure who received a retroluminal sling, only 25% were cured and a further 25% had some improvement after a median of 18 months follow-up duration. By contrast, the same procedure had a success rate of almost 80% in patients with no history of radiation exposure.⁵³ Radiation exposure also adversely affected the treatment success rate of the original pubourethral sling⁵⁶ and the BAMS.⁵⁵ Thus, the AUS remains the treatment of choice for men with urinary incontinence who have had prior radiotherapy.

Prior AUS surgery

In patients with AUS failure, revision surgery to replace one or more device components is the preferred surgical approach. Explantation of a failed AUS often results in a poorly compliant and relatively noncompressible, fibrotic urethra, which is associated with diminished efficacy of (noncircumferential) sling surgery.^{31,33} However, AUS reimplantation is associated with a predictably high success rate. In one study, patients undergoing AUS revision surgery were three times more likely to achieve adequate continence than those who underwent sling placement as a salvage treatment subsequent to AUS erosion.⁵⁸ Salvage treatment for urethral

atrophy in patients with an AUS might be addressed by replacement (and increasing the pressure) of the balloon reservoir, or urethral cuff revision surgery—including the use of two urethral cuffs, incorporation of the tunica albuginea of the corpora cavernosum within the cuff, or buttressing the urethra with bulking material.^{59–61} These approaches are highly effective.⁶²

Prior sling surgery

Rates of recurrence of incontinence after sling surgery in men range from 20% to 35% (usually within the first year postoperatively). When evaluating a patient with recurrent or persistent PPI, the urologist must verify the diagnosis of ISD and determine whether new-onset or previously unrecognized bladder dysfunction is present. In patients with persistent or recurrent leakage following sling surgery where repeat sling implantation is considered, the examiner should quantify the degree of incontinence (using a pad weight test) and perform a repositioning test to assess proximal urethral mobility.

In a cohort of 40 men who underwent transobturator sling placement, 15 experienced subsequent sling failure (all of whom had severe leakage preoperatively).⁶³ However, salvage treatment, using either an AUS or a periurethral balloon device, was successful in all 15 patients.⁶³ In 29 men with failure of primary retroluminal sling surgery, 10 (34%) were cured and 12 (41%) substantially improved—defined as use of only 1 pad daily at a mean of 16.6 months following implantation of a replacement sling. Of note, only patients with a positive repositioning test were offered revision sling surgery,⁶⁴ whereas those with substantial ISD were not offered sling revision, but were instead offered AUS implantation.

The results of a registry analysis of 16,348 men who underwent radical prostatectomy show that 13% of men who undergo sling surgery will ultimately require implantation of an AUS.⁶⁵ Although no prospective trials have compared the efficacy of an AUS with that of sling replacement in men with persistent PPI after prior sling failure, a number of small case series have shown that AUS implantation after sling failure has a high success rate (80–90%), and is not associated with an increase in the expected complication rate.^{66–69}

Following an unsuccessful retroluminal sling or BAMS, the mesh can be left *in situ*, and the surgeon may elect to place the AUS cuff trans-scrotally. The previous sling procedure neither renders AUS implantation more difficult nor decreases its postprocedural efficacy.⁷⁰ Indeed, the proximal sling device can act as a 'pseudo double cuff', and the potential for morbidity associated with sling explantation is avoided by leaving the device in place. By contrast, in men with an unsuccessful quadratic sling, the polypropylene mesh must be partially explanted. Only the mesh over the bulbous urethra needs to be incised, to allow for cuff placement. The mesh is readily identified over the perineal and bulbar urethra, and can be dissected from the underlying muscle quite easily (Figure 5). The bulbospongiosus is then divided, exposing the underlying spongy urethra, enabling AUS placement in routine fashion.

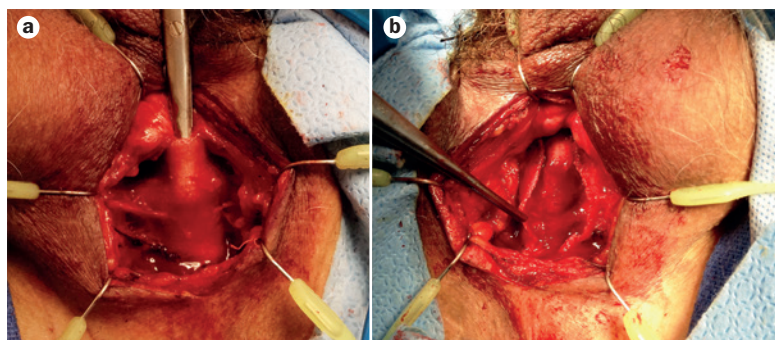


Figure 5 | Partial explantation of the quadratic sling before artificial urethral sphincter placement. **a** | The quadratic sling can be easily identified and dissected from the urethra. **b** | The sling is incised, exposing the bulbospongiosus, enabling straightforward artificial sphincter placement.

Retroluminal sling placement is sufficient to provide satisfactory continence in the majority of men with SUI who have adequate residual sphincter function, a positive repositioning test and preoperative leakage of <200 g daily. However, its efficacy is suboptimal in other groups of patients. The quadratic sling, which adds a component of urethral compression, provides satisfactory continence to men with substantial SUI (leakage of up to 400 g daily). In those with the most severe leakage, circumferential urethral compression with an AUS is preferred; this procedure offers the most predictable and reliable success rate, but also has a predictable complication rate.

Devices in development

AUS devices have undergone only minor changes over the past 30 years, such as the incorporation of a narrow-backed cuff in 1985,⁷¹ the addition of a minocycline and rifampin antibiotic coating in 2008,⁷² and the introduction of a 3.5 cm urethral cuff in 2010.⁷³ Accordingly, interest in the development of novel circumferential urethral occlusive devices is increasing.

The FlowSecure® (Sphinx Medical, Bellshill, UK) AUS is a four-part preassembled device consisting of a prefilled, pressure-regulating balloon, a stress-release balloon, a control pump and a circular occluding urethral cuff.⁷⁴ The pressure-regulating balloon can be adjusted to increase basal pressure by further filling, up to a pressure of 80 cm H₂O. The stress-relief balloon enables conditional occlusion during transient increases in intra-abdominal pressure to above the basal occlusive pressure. Early continence data published for this device were encouraging, but in a follow-up publication, high rates of infection (5%), mechanical failure (6%) and pump perforation (9%) have been reported.⁷⁵

The ZSI 375 (ZSI ZEPHYR Surgical Implants®, Villeurbanne, France) is a preassembled device consisting of a urethral cuff connected to a scrotal pressure-regulating tank.⁷⁶ The pressure-regulating tank contains an adjustable compensation pouch, hydraulic circuit and an activation button. Following activation (which initiates cuff inflation), the device pressure can be adjusted by either injecting or removing fluid from the compensation pouch, and by *in situ* activation of the pressure-regulating tank.

The periurethral constrictor continence device (Silimed®, Rio de Janeiro, Brazil) was originally designed for treatment of paediatric patients with SUI.⁷⁷ This hydraulic device relies on a constrictor cuff coupled to a self-sealing port. In this 'always on' device, relief of pressure, which is hypothesized to reduce the risk of urethral atrophy, is accomplished by removing fluid via the port for 2 months per year, which results in temporary return of leakage. A success rate of 73% was reported in the initial publication, but high rates of infection, erosion and device leakage, as well as the need for port-mediated volume adjustments, limit the utility of this device.⁷⁸

Human trials of the Tape Mechanical Occlusive Device (GT Urological Minneapolis, MN, USA) have not yet commenced. This is a single-piece, nonhydraulic device, based upon a circumferential urethral tape filled with a small volume of fluid, to create an efficient urethral seal. A switch regulates the tape tension, thereby allowing episodic deactivation to permit voiding.⁷⁹ The ARTUS® (MyoPowers, Lausanne, Switzerland) modular device is composed of two shape-memory alloy wire cuffs, operated via a battery-powered remote control. The two cuffs function either synchronously or metachronously to achieve urethral occlusion.^{80,81} This device has not yet been used in humans.

Conclusions

The evaluation and management of PPI has improved dramatically over the past two decades. Slings have evolved with respect to both device design and surgical technique during this period, and further innovations are likely as this field continues to progress. However, no single device should be exclusively considered the gold-standard option for treatment of PPI. Rather, individual devices are likely to be best suited to different groups of patients, depending on their clinical characteristics and history.

In men without prior radiation exposure or incontinence surgery, factors such as the degree of urine leakage, proximal urethral mobility and detrusor contractility can help determine the preferred surgical approach. In those with <200 g daily leakage and adequate urethral mobility (indicated by a positive repositioning test or videourodynamics), implantation of either a retroluminal or quadratic sling is the preferred approach. These devices are associated with lower complication rates than AUSs, and neither sling prevents or hinders future AUS implantation. For those with 200–400 g daily leakage, the quadratic sling might be preferred, owing to the compressive nature of this surgical device (which provides superior resistance compared to purely transobturator devices that require adequate residual sphincter function).⁸ However, adequate detrusor contractility is necessary to overcome the resistance of compressive devices. In men with detrusor underactivity and <200 g daily leakage, the retroluminal sling might be preferred, given its noncompressive mechanism of action, whereas in men with detrusor underactivity and moderate incontinence (200–400 g daily leakage), an AUS is the preferred option. In patients with leakage >400 g daily, AUS implantation

is the recommended option, but for patients who do not consent to use of a mechanical device, a compressive sling is recommended over a noncompressive sling.

Adequate urethral tissue compliance is necessary for successful compression and/or proximal repositioning of the urethra with a sling. Radiation exposure and previous AUS explantation, both of which might result in a relatively noncompressible urethra, are consequently associated with diminished sling effectiveness. With the exception of the occasional patient with persistent mild to moderate SUI following prior sling implantation and a positive repositioning test, who can successfully be treated with a repeat sling procedure, AUS implantation is the treatment of choice for patients with persistent PPI despite prior incontinence surgery. AUS implantation remains the optimal procedure for patients with persistent PPI because an AUS can provide the circumferential

urethral compression necessary for adequate coaptation even in the setting of diminished urethral compliance. With the expansion of therapeutic options for treating SUI in men, therefore, a thorough evaluation should include pad weight testing and urodynamic studies to best direct specific surgical therapy.

Review criteria

The PubMed database was searched for items published between 1970–2014 predominantly in the English language, using the search terms “post-prostatectomy incontinence”, “male stress incontinence”, “intrinsic sphincter deficiency”, “urodynamics”, “leak point pressure”, “artificial urinary sphincter”, and “male sling”. A combination of abstracts and peer-reviewed publications were cited in this manuscript.

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Brief Correspondence

The Underactive Bladder: A New Clinical Concept?

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Abstract

Detrusor underactivity (DU) is an increasingly recognised cause of lower urinary tract symptoms in both men and women. There has been a lack of research into all aspects of this dysfunction, and as yet, no effective treatments exist. DU can be diagnosed at present only on the basis of an invasive urodynamic study. An international consensus group met at the International Consultation on Incontinence–Research Society and International Continence Society annual meetings in 2014 to consider the feasibility of developing a working definition of a symptom complex associated with DU. Drawing an analogy to detrusor overactivity (urodynamic diagnosis) and overactive bladder (symptom complex), the aim of this process is to help identify affected patients and facilitate further clinical and epidemiological research.

Patient summary: Bladder underactivity is an underresearched but important cause of urinary symptoms in men and women. In this paper, an international expert group presents a working definition for the symptoms that characterise bladder underactivity, with the aim of facilitating further research in this area.

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In recent years, there has been a rise in interest in detrusor underactivity (DU) [1–3], a bladder dysfunction that affects both sexes and causes bothersome symptoms. DU is defined by the International Continence Society (ICS) as “a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or failure to achieve complete bladder emptying within a normal time span” [4].

As much as 48% of older men and 45% of older women undergoing evaluation for lower urinary tract symptoms (LUTS) show evidence of DU [5,6]. These patients may be affected by symptoms or require catheterisation for bladder

drainage. Despite this apparent frequency, DU is largely underresearched in comparison to other lower urinary tract dysfunctions, such as detrusor overactivity (DO) or bladder outlet obstruction (BOO). Moreover, there is no simple, effective treatment.

At present, it is widely thought that the LUTS experienced by patients with DU overlap significantly with the LUTS associated with BOO and that it is not possible to reliably differentiate the two without an invasive urodynamic study. This has hampered the acquisition of epidemiological data and, in turn, has led to a lack of comprehensive evaluation of

the true scale of the problem, its natural history, and its effects in terms of symptoms, symptom bother, and complications (eg, urinary retention, impairment of renal function).

Clinical experience and evidence from available urodynamic case series suggest that DU occurs in diverse patient groups, pointing towards the existence of multiple aetiological factors. These factors are likely to manifest in DU by disrupting the processes involved in the generation of an effective coordinated voiding contraction [2,7]. Interruption to efferent neural pathways secondary to traumatic injury or disease and intrinsic myogenic dysfunction due to fibrosis are well-recognised mechanisms. More recently, the potential importance of the urothelium and the afferent system has been suggested [8,9].

There is currently a remarkable lack of consensus on many aspects pertaining to DU as a diagnosis. A plethora of terms are used to refer to DU and/or its associated symptoms, despite the ICS terminology having been published more than a decade ago. Moreover, no accepted diagnostic criteria exist. Furthermore, the ICS report falls short in specifying parameters for *reduced contraction strength*, *prolonged bladder emptying*, or *normal time span*. Most current criteria focus on strength, either applying specific cut-offs for maximum flow rate (Q_{\max}) and maximum detrusor pressure Q_{\max} or using indices and calculations such as the bladder contractility index [10] or the Watt factor, which estimate isovolumetric contraction strength [11]. The application of these criteria to DU is limited for several reasons:

- The criteria do not consider definitional aspects, such as contraction speed or how effectively the bladder empties, mostly related to the duration of the contraction.
- Assumptions regarding bladder volumes and energetics are contained within these calculations, which likely are not applicable to some or all instances of DU.
- The rise in detrusor contraction strength with increasing BOO grade in elderly men suggests that it is difficult or impossible to define single threshold values for DU [12].
- Normative data in highly affected populations (eg, the aged) are not available.

There is a need for further research on all aspects of DU. In contrast, DO is well researched, and it is worth revisiting the development of the OAB symptom complex as a concept. This was based on recognition that patients present with symptoms that may not always correlate with an underlying urodynamic abnormality (ie, DO). This has proved to be an effective means of categorising patients in clinical practice to guide the instigation of therapy, particularly at the primary-care level. Consequently, an expansion of research followed that has contributed to our understanding of bladder storage function and pathophysiology and that allowed the development of novel therapies.

In terms of DU, a definition currently exists but is fairly nonspecific due to the extremely limited evidence base from which it was derived. Nevertheless, the urodynamic abnormality is clearly related to a group of recognised

symptoms (eg, slow flow, hesitancy). In addition, there are some associated, poorly defined, clinical presentations (eg, impaired or absent bladder sensation) and sequelae (eg, raised postvoid residual and urinary retention). A variety of patient groups are affected, both with and without neurologic disease or injury. In this context, it is easy to recognise some parallels to the example of DO and OAB. Categorisation of the symptoms and/or signs of DU seems like a logical initial step to facilitate standardisation and further research in this area.

A consensus group met at the International Consultation on Incontinence–Research Society and ICS annual meetings in September and October 2014 to review the available evidence base and consider the feasibility of developing a working definition of a symptom complex for underactive bladder (UAB). It was agreed that although patients with DU can present with a variety of storage, voiding, and postmicturition LUTS, the voiding symptoms often predominate. These symptoms appear to be variably associated with the symptoms and signs of incomplete bladder emptying and impaired bladder sensation.

It was clearly recognised that the clinical features of DU may show significant overlap with those of BOO. Despite this, it was felt that a definition of a symptom complex for UAB would be of potential clinical value and could form the basis of a definition on which further qualitative and quantitative epidemiological studies could be conducted.

We propose the following working definition: *The underactive bladder is a symptom complex suggestive of detrusor underactivity and is usually characterised by prolonged urination time with or without a sensation of incomplete bladder emptying, usually with hesitancy, reduced sensation on filling, and a slow stream.*

Associated factors that need to be considered include sex, age, and any known neurologic pathology. It should be pointed out that the underactive bladder symptom complex is not synonymous with DU, which can be confirmed only by urodynamic testing. The definition and the role of impaired detrusor contractility in DU and UAB also remain to be elucidated.

It must be emphasised that the proposed definition has been developed on the basis of expert opinion and discussion rather than the results of prospective studies. Such studies are now in progress, as are efforts to obtain qualitative data from focus groups. These efforts should help refine this working definition further. Nevertheless, we feel that the development of the definition presented in this paper represents a significant step in the right direction and will help raise the profile of this much-neglected problem and facilitate further research.

In summary, DU is a common but poorly understood lower urinary tract dysfunction that occurs in a heterogeneous group of men and women and that arises due to multifactorial aetiologies. Currently, it can be confirmed only after urodynamic testing. We propose a working definition for a complex of symptoms that we suggest are known as *underactive bladder* and associated with DU. We feel UAB could prove useful as a means of identifying affected patients, rather analogous to the relationship between DO and OAB,

and could provide a basis for further definitive qualitative and quantitative research on the subject.

Author contributions: Christopher R. Chapple had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chapple, Osman, Birder, van Koeveringe, Oelke, Nitti, Drake, Yamaguchi, Abrams, Smith.

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Voiding Dysfunction

Signs and Symptoms of Detrusor Underactivity: An Analysis of Clinical Presentation and Urodynamic Tests From a Large Group of Patients Undergoing Pressure Flow Studies

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Abstract

Background: The clinical diagnosis of detrusor underactivity (DU) is hampered by the need for invasive pressure flow studies (PFS) in combination with a lack of knowledge of the associated signs and symptoms. This has contributed to a lack of awareness of DU and underactive bladder, and to the assumption that symptoms are always due to bladder outlet obstruction (BOO).

Objective: To investigate the signs and symptoms recorded in a large urodynamic database of patients who met the diagnoses of DU, BOO, and normal, to identify the clinical features associated with DU.

Design, setting, and participants: From the database of 28 282 adult PFS records, 1788 patients were classified into: (1) those with DU without BOO; (2) those with BOO without DU; and (3) those with normal PFS.

Results: Patients with DU reported a statistically significantly higher occurrence of decreased and/or interrupted urinary stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, and absent and/or decreased sensation compared with patients with normal PFS. Other differences were found between men with DU and BOO, and between women with DU and normal PFS.

Conclusions: There are signs and symptoms that can distinguish DU patients from patients with normal PFS and further distinguish between DU and BOO, which is traditionally invasively diagnosed. This is a first step to better understand the clinical presentation of DU patients, is consistent with the recent underactive bladder working definition, and justifies further exploration of the signs and symptoms of DU.

Patient summary: The clinical diagnosis of detrusor underactivity is hampered by the need for invasive urodynamics in combination with a lack of knowledge of the associated signs and symptoms. This study has shown that there are signs and symptoms that can distinguish men and women patients with DU from patients with either normal urodynamic studies or with BOO.

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1. Introduction

The clinical diagnosis of detrusor underactivity (DU) is hampered by the need for invasive pressure flow studies (PFS) and a lack of knowledge of the associated signs and

symptoms. This has contributed to a lack of awareness of DU and its clinical correlate, underactive bladder (UAB) [1]. In consequence, this condition has been neglected compared with other causes of lower urinary tract symptoms. A recent review [2] concluded that DU “is

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surrounded by ambiguity” and recognises the limitations of the current definition. The International Continence Society defines DU as “a contraction of reduced strength and/or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span” [3]. This, however, does not define “prolonged bladder emptying” or “normal time span”. Various methods have been proposed to determine contraction strength [2]; however, none of these take into account the duration of contraction – a key factor in the definition [3].

Despite this imprecision, estimates suggest that DU is a prevalent condition, ranging from 9% to 23% in men <50 yr, increasing to as much as 48% in men >70 yr [2]. Elderly women show a DU prevalence ranging from 12% to 45% [2]. An analysis of the signs and symptoms associated with DU could potentially facilitate the diagnosis of patients with UAB, improve our knowledge of the epidemiology, indicate possible noninvasive diagnostic approaches, and facilitate the development and evaluation of treatment outcomes of new therapies for UAB [4].

The aim of this study was to investigate the signs and symptoms recorded in a large database of patients referred for urological evaluation who met strictly defined PFS criteria for DU, bladder outlet obstruction (BOO) or normal, in order to identify the clinical features associated with DU.

2. Materials and methods

Data from patients who underwent PFS, studied in a single specialist centre between 1985 and 2012, were recorded in a database that used the same variable fields throughout the 28-yr period.

Data gathering included patient interview to obtain symptoms and medical history, bladder diary data, physical examination, urodynamic studies, and diagnostic conclusions. PFS were carried out according to International Continence Society guidelines current at the time of testing. Free flow uroflowmetry was performed before each PFS. Postvoid residual urine volume was based on the volume obtained with catheterisation before filling commenced. The data from each PFS were screened for artefacts and manually entered into the database, thus avoiding automated data extraction errors. Prior to analysing the data, impossible values were removed in order to reduce corruption of data by manual entry errors. Several categorical (yes/no) variables used in the analysis were derived from a combination of database entry fields. For example,

additional variables for straining and for decreased sensation were derived by combining the number of patients who reported these as symptoms with the number of patients for whom these were noted during PFS.

Patients without full voiding data, with neurological diseases affecting the lower urinary tract such as multiple sclerosis, paraplegia, or Parkinson's disease, and/or with a urodynamic diagnosis of detrusor overactivity were excluded as these require special consideration [5]. This resulted in 9928 eligible patient records (men: 1639; women: 8289) without confounding causes of vesico-urethral dysfunction (Fig. 1).

In order to classify patients with pure DU, BOO, or normal PFS, very strict criteria were used to avoid overlap. The criterion values were based on expert opinion and are shown in Table 1, which are in line with other studies cited by Osman et al [2]. A normal group was composed of patients with PFS judged to be normal, taking no medication related to bladder or urethra, and (for women) no clinical obstruction. Men who had both a low bladder contractility index and a high BOO index, suggesting simultaneous DU and BOO, were excluded from the analysis. Women patients with clinical obstruction, defined as urethral/bladder neck obstruction and/or large cystocele or prolapse through the introitus, were also excluded from the DU and normal groups. Using these criteria, 1788 patient records (men: 507; women: 1281) were classified to DU, BOO, or normal PFS groups and used in the analysis (Fig. 1).

2.1. Statistical analysis

For all variables, the primary question was whether there was a difference in the reported values (numerical variables) or percentage of patients who reported a variable (categorical variables) for patients with DU compared with those with BOO or normal PFS.

For categorical variables, descriptive statistics for the number and percentage of patient records in each category were tabulated by patient group. Logistic regression models including patient group and age as factors were used for each binary variable. A *p* value for the hypothesis test that the odds ratio for each pair-wise comparison (DU vs BOO; DU vs normal PFS) was equal to 1 are provided with 95% confidence intervals. For example, a variable with an odds ratio for DU/BOO of 4.5 suggests that, after adjusting for age, the odds of a DU patient reporting the symptom are 4.5 times higher than for a patient with BOO. For cases where zero patients reported a variable outcome (ie, yes or no) in at least one group, estimates were obtained using exact logistic regression.

For numerical variables, descriptive statistics for the number of patients, median, and interquartile range (Q1–Q3) were summarised. PFS variables that were used to classify patients into groups (Table 1) were excluded from the analysis. Due to several variables appearing to be not normally distributed, a separate rank analysis of covariance model using patient group as factor and age as covariate was used for each pair-wise comparison (DU vs BOO; DU vs normal PFS). The rank analysis of

Table 1 – Inclusion criteria used for patient grouping

Group	Men			Women			
	BCI	BOOI	BVE %	P _{detQmax}	Q _{max}	BVE %	Excluding CO ^b
DU	<100	<20	<90	<20	<15	<90	X
BOO	≥100	≥40	≥90	≥40	<12	≥90	
Normal PFS ^a	≥100	<20	100	≥20	≥20	100	X

BCI = bladder contractility index; BVE = bladder voiding efficiency; BOO = bladder outlet obstruction; BOOI = Bladder Outlet Obstruction Index; CO = clinical obstruction; DU = detrusor underactivity; P_{detQmax} = detrusor pressure at maximum flow rate; Q_{max} = maximum flow rate; PFS = pressure flow studies.

^a A normal pressure flow study is a test with no abnormal pressure flow study findings and no present medication use related to bladder or urethra, in addition to the criteria listed.

^b Clinical obstruction for women patients was considered as the clinician recording either a urethral or bladder neck obstruction during a video urodynamic test or a large cystocele or prolapse through the introitus on examination.

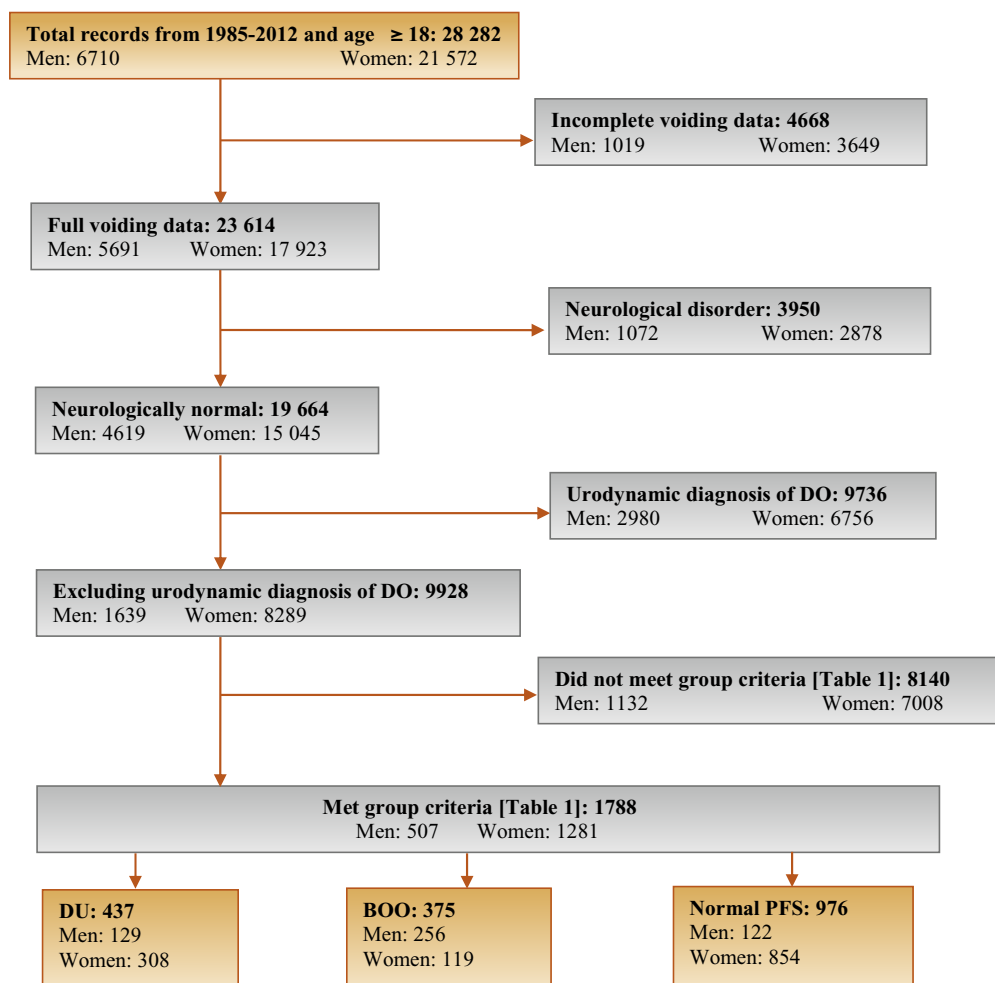


Fig. 1 – Selection process of patients with detrusor underactivity, bladder outlet obstruction, and normal pressure flow studies tests using criteria in Table 1. BOO = bladder outlet obstruction; DO = detrusor overactivity; DU = detrusor underactivity; PFS = pressure flow studies.

covariance was utilised for hypothesis testing and *p* values were calculated from a mean score test comparing the groups using the values of the residuals as scores. No multiplicity adjustments were performed in this exploratory analysis which aimed to generate rather than confirm hypotheses. Future studies aimed at confirming hypotheses would, however, make these adjustments.

3. Results

Age for men and women DU patients was statistically significantly higher compared with patients with normal PFS (median values: men 63 yr vs 55 yr; women 59 yr vs

Table 2 – Men: odds ratios and 95% confidence intervals for categorical variables of detrusor underactivity compared with bladder outlet obstruction and normal pressure flow studies, using logistic regression model with patient group and age as factors

Variable	Males, <i>n</i> (%)				
	DU (<i>n</i> = 129)	BOO (<i>n</i> = 256)	Normal (<i>n</i> = 122)	OR (CI) for DU/BOO	OR (CI) for DU/Normal
Signs and symptoms					
Urinary stream decreased	55 (56%)	150 (82%)	28 (30%)	0.31 ^{***} (0.18, 0.54)	3.02 ^{**} (1.65, 5.56)
Hesitancy	47 (51%)	126 (69%)	25 (26%)	0.47 ^{**} (0.28, 0.80)	3.27 ^{***} (1.74, 6.15)
Abnormal sexual function	30 (41%)	34 (26%)	21 (29%)	2.32 [*] (1.20, 4.48)	1.20 (0.55, 2.58)
Feeling of incomplete bladder emptying	37 (36%)	55 (29%)	22 (22%)	1.29 (0.77, 2.16)	2.16 [*] (1.14, 4.08)

Table 2 (Continued)

Variable	Males, n (%)				
	DU (n = 129)	BOO (n = 256)	Normal (n = 122)	OR (CI) for DU/BOO	OR (CI) for DU/Normal
Urgency, fear of leakage	31 (30%)	83 (45%)	35 (35%)	0.54 [*] (0.32, 0.90)	0.76 (0.42, 1.38)
Stress incontinence	17 (25%)	4 (3.7%)	16 (22%)	9.14 ^{**} (2.91, 28.7)	1.05 (0.48, 2.33)
Enuresis	15 (21%)	2 (1.8%)	15 (21%)	13.7 ^{**} (3.02, 62.3)	1.12 (0.46, 2.55)
Urinary stream interrupted	19 (19%)	20 (11%)	9 (9.2%)	1.88 (0.95, 3.72)	2.42 [*] (1.02, 5.73)
Palpable bladder	13 (14%)	1 (0.6%)	1 (1.1%)	28.0 ^{**} (3.60, 218.1)	13.5 [*] (1.71, 106.5)
Absent or decreased sensation	13 (13%)	0	3 (3.0%)	36.0 ^{***, a} (7.47, ∞)	4.57 [*] (1.24, 16.9)
Bowel function – strains	9 (11%)	4 (2.4%)	5 (5.6%)	4.98 [*] (1.48, 16.8)	1.73 (0.54, 5.51)
Feeling of incomplete bowel emptying	7 (8.6%)	1 (0.6%)	0	15.2 [*] (1.83, 126.2)	10.2 ^{*, a} (1.93, ∞)
Always strains to void	8 (8.0%)	1 (0.5%)	0	13.5 [*] (1.63, 111.8)	15.6 ^{*, a} (2.95, ∞)
Bowel function: poor control or urgency	5 (5.4%)	1 (0.6%)	5 (5.4%)	9.84 [*] (1.13, 85.8)	1.08 (0.29, 4.02)
Medical history					
TURP surgery ^b	36 (72%)	2 (5.9%)	28 (60%)	75.3 ^{***} (13.8, 410.4)	1.38 (0.48, 3.93)
Bladder outlet obstruction surgery ^b	52 (51%)	4 (2.3%)	35 (36%)	63.1 ^{***} (20.9, 189.9)	1.26 (0.65, 2.43)
Any retention ^c	39 (39%)	9 (4.9%)	13 (14%)	13.0 ^{***} (5.92, 28.4)	3.63 ^{**} (1.76, 7.47)
Surgery with possible denervation	11 (30%)	2 (5.7%)	1 (3.2%)	4.91 (0.95, 25.5)	20.4 ^{**} (2.17, 191.5)
Reported history of ≥1 UTI	29 (28%)	25 (14%)	21 (21%)	2.52 ^{**} (1.38, 4.61)	1.50 (0.78, 2.89)
Spontaneous retention ^c	21 (20%)	4 (2.2%)	9 (9.4%)	11.6 ^{***} (3.87, 35.0)	2.34 (1.00, 5.48)
Chronic retention ^c	14 (14%)	1 (0.5%)	0	29.2 ^{**} (3.78, 226.0)	17.5 ^{*, a} (3.60, ∞)
Present drug use – antibiotics	8 (8.3%)	4 (2.4%)	1 (1.1%)	3.56 [*] (1.03, 12.3)	10.2 [*] (1.20, 86.8)
Present drug use – antidepressants	6 (6.2%)	6 (3.5%)	0	1.65 (0.51, 5.38)	10.8 ^{*, a} (1.92, ∞)
Invasive measurements – pressure flow studies					
Reduced filling phase sensation	34 (28%)	2 (0.9%)	3 (2.5%)	44.5 ^{***} (10.5, 189.4)	17.3 ^{***} (5.05, 59.4)
Voids by straining	20 (16%)	0	0	64.8 ^{***, a} (13.9, ∞)	31.8 ^{***, a} (6.79, ∞)
Detrusor contraction with strain	12 (9.8%)	2 (0.8%)	1 (0.8%)	12.8 ^{**} (2.80, 58.0)	12.6 [*] (1.60, 99.7)
Combined variables (symptoms reported by patient and/or noted during invasive measurement)					
Decreased sensation	42 (40%)	2 (1.1%)	6 (6.2%)	59.6 ^{***} (14.0, 253.5)	10.9 ^{***} (4.28, 27.8)
Straining	37 (37%)	3 (1.6%)	1 (1.0%)	35.5 ^{***} (10.6, 119.2)	54.5 ^{***} (7.25, 409.3)

BOO = bladder outlet obstruction; CI = confidence interval; DU = detrusor underactivity; OR = odds ratio; PFS = pressure flow studies; UTI = urinary tract infection.

Only variables with a statistically significant result for any group versus detrusor underactivity are included, for economy of space.

An odds ratio, for example, of 4.5 for detrusor underactivity/bladder outlet obstruction suggests that after adjusting for age, the odds of a detrusor underactivity patient reporting the symptom are 4.5 times higher than for a patient with BOO. Table 2 presents variables in descending order of frequency for the detrusor underactivity group. Percentages of patients reporting a symptom are based on total number of patients with non-missing data to derive a yes or no response. For economy of space, only the % of patients who reported 'yes' are displayed.

^{*} indicates that the difference from the detrusor underactivity group was significant for $p < 0.05$.

^{**} indicates that the difference from the detrusor underactivity group was significant for $p < 0.01$.

^{***} indicates that the difference from the detrusor underactivity group was significant for $p < 0.0001$.

^a For cases where zero patients reported a variable outcome in at least one group, estimates were obtained using exact logistic regression which provides median unbiased estimates for odds ratios and sets upper 95% confidence interval values equal to infinity (∞).

^b Patients could report up to two types of surgery. Bladder outlet obstruction surgery for men counts the number of patients who reported at least one of the following: transurethral resection of the prostate, radical perineal prostatectomy, bladder neck incision, or urethral dilatation.

^c History of retention: patients could report up to two types of retention. Any retention counts the number of men who reported at least one of the following: acute retention after operation, chronic retention, or spontaneous retention.

Table 3 – Women: odds ratios and 95% confidence intervals for categorical variables of detrusor underactivity compared with bladder outlet obstruction and normal pressure flow studies, using logistic regression model with patient group and age as factors

Variable	Women, n (%)				
	DU (n = 308)	BOO (n = 119)	Normal (n = 854)	OR (CI) for DU/BOO	OR (CI) for DU/Normal
Signs and symptoms					
Stress incontinence	203 (79%)	61 (66%)	656 (81%)	1.91 [*] (1.11, 3.28)	0.87 (0.60, 1.28)
Urinary stream decreased	75 (29%)	21 (20%)	32 (4.0%)	1.81 [*] (1.00, 3.25)	10.8 ^{***} (6.56, 17.7)
Hesitancy	78 (28%)	29 (27%)	75 (9.1%)	1.01 (0.59, 1.71)	3.71 ^{***} (2.49, 5.52)
Feeling of incomplete bladder emptying	78 (28%)	39 (36%)	160 (20%)	0.70 (0.43, 1.15)	1.62 ^{**} (1.14, 2.29)
Mobility impaired	32 (13%)	4 (4.3%)	19 (2.8%)	1.51 (0.49, 4.62)	1.98 [*] (1.00, 3.91)
Enuresis	31 (12%)	5 (5.3%)	68 (8.4%)	3.21 [*] (1.18, 8.75)	1.98 ^{**} (1.19, 3.28)
Urinary stream interrupted	32 (12%)	10 (9.2%)	9 (1.1%)	1.22 (0.55, 2.73)	10.9 ^{***} (4.81, 24.6)
Absent or decreased sensation	12 (4.3%)	0	7 (0.8%)	8.56 ^{*, a} (1.64, ∞)	5.80 ^{***} (1.99, 16.8)
Palpable bladder	8 (3.3%)	0	11 (1.5%)	5.04 ^a (0.89, ∞)	3.34 [*] (1.16, 9.60)
Medical history					
Reported history of ≥1 UTI	112 (40%)	41 (38%)	242 (29%)	1.24 (0.77, 2.01)	1.83 ^{**} (1.33, 2.50)
Any retention ^b	50 (19%)	8 (7.5%)	55 (6.8%)	2.94 ^{**} (1.30, 6.64)	3.27 ^{***} (2.05, 5.22)
Acute retention after operation or childbirth ^b	35 (13%)	7 (6.6%)	52 (6.4%)	2.02 (0.84, 4.86)	2.08 ^{**} (1.24, 3.47)
Present drug use – diuretics	33 (12%)	3 (2.8%)	25 (3.1%)	2.40 (0.70, 8.31)	1.99 [*] (1.07, 3.71)
Present drug use – antidepressants	31 (11%)	3 (2.8%)	0	4.34 [*] (1.23, 15.4)	149.0 ^{***, a} (31.7, ∞)
Present drug use – antibiotics	13 (4.8%)	3 (2.8%)	15 (1.8%)	2.03 (0.53, 7.72)	3.13 ^{**} (1.33, 7.34)
Spontaneous retention ^b	11 (4.0%)	1 (0.9%)	3 (0.4%)	6.01 (0.71, 50.9)	15.2 ^{**} (3.80, 60.9)
Surgery with possible denervation	8 (3.3%)	1 (1.0%)	5 (0.6%)	2.72 (0.31, 23.8)	4.28 [*] (1.18, 15.4)
Present drug use – oral contraceptives	2 (0.7%)	16 (15%)	59 (7.3%)	0.20 [*] (0.04, 0.97)	0.44 (0.10, 1.92)
Invasive measurements – Pressure flow studies					
Voids by straining	55 (18%)	1 (0.8%)	3 (0.3%)	24.7 ^{**} (3.31, 183.5)	59.2 ^{***} (17.7, 198.1)
Detrusor contraction with strain	39 (13%)	13 (11%)	25 (2.9%)	1.21 (0.60, 2.46)	4.98 ^{***} (2.79, 8.90)
Reduced filling phase sensation	35 (12%)	3 (2.7%)	15 (2.0%)	4.87 [*] (1.42, 16.7)	6.67 ^{***} (3.33, 13.4)
After contraction	4 (1.4%)	19 (17%)	191 (24%)	0.09 ^{***} (0.03, 0.27)	0.06 ^{***} (0.02, 0.16)
Combined variables (symptom reported by patient and/or noted during invasive measurement)					
Straining	95 (34%)	15 (14%)	29 (3.5%)	3.13 ^{**} (1.67, 5.87)	13.7 ^{***} (8.35, 22.3)
Decreased sensation	42 (16%)	3 (3.0%)	22 (3.0%)	5.40 ^{**} (1.58, 18.4)	5.28 ^{***} (2.88, 9.69)

BOO = bladder outlet obstruction; CI = confidence interval; DU = detrusor underactivity; OR = odds ratio; PFS = pressure flow studies; UTI = urinary tract infection. Only variables with a statistically significant result for any group versus detrusor underactivity are included, for economy of space. An odds ratio, for example, of 4.5 for detrusor underactivity/bladder outlet obstruction suggests that after adjusting for age, the odds of a detrusor underactivity patient reporting the symptom are 4.5 times higher than for a patient with bladder outlet obstruction. Table 3 presents variables in descending order of frequency for the detrusor underactivity group. Percentages of patients reporting a symptom are based on total number of patients with non-missing data to derive a yes or no response. For economy of space, only the % of patients who reported 'yes' are displayed.

^{*} indicates that the difference from the detrusor underactivity group was significant for $p < 0.05$.

^{**} indicates that the difference from the detrusor underactivity group was significant for $p < 0.01$.

^{***} indicates that the difference from the detrusor underactivity group was significant for $p < 0.0001$.

^a For cases where zero patients reported a variable outcome in at least one group, estimates were obtained using exact logistic regression which provides median unbiased estimates for odds ratios and sets upper 95% confidence interval values equal to infinity (∞).

^b History of retention: patients could report up to two types of retention. Any retention counts the number of women who reported at least 1 of the following: acute retention after operation or childbirth, chronic or spontaneous retention.

44 yr). Age for women with DU was statistically significantly higher compared with women with BOO (median, 59 yr vs 44 yr). There were no significant differences in height, weight, or body mass index between the groups.

Tables 2 and 3 show the odds ratios and corresponding 95% confidence intervals for categorical variables that showed a statistically significant difference between DU patients and at least one other group ($p < 0.05$). Table 4 gives a summary of medians and interquartile ranges for numerical variables that had statistically significant differences between DU patients and at least one other group.

Supplementary Table 6 details all variables included in the analysis, so it may be deduced which variables were not statistically significantly different between groups by their absence from other tables.

The primary group comparisons of interest were DU versus BOO in men (the most difficult clinical differential diagnosis) and DU versus normal PFS in women. These comparisons are therefore described below and are all adjusted for age.

Refer to Supplementary Figure 2 (men) and Figure 3 (women) of forest plots and Table 5 showing symptoms

Table 4 – Medians and interquartile ranges of numerical variables for detrusor underactivity compared with bladder outlet obstruction and normal pressure flow studies

Variable	Statistic	Men			Women		
		DU (n = 129)	BOO (n = 256)	Normal (n = 122)	DU (n = 308)	BOO (n = 119)	Normal (n = 854)
Medical History							
Age at visit (yr)	n	129	256	122	308	119	854
	Median	63.0	63.0	55.5**	59.0	44.0***	44.0***
	Q1–Q3	(49.0–72.0)	(56.0–69.0)	(40.0–68.0)	(49.0–71.0)	(37.0–56.0)	(36.0–52.0)
Noninvasive measurements – bladder diary							
Daytime micturitions	n	86	167	84	247	100	758
	Median	6.0	8.0**	7.0	8.0	8.0	7.0**
	Q1 – Q3	(5.0–8.0)	(6.0–9.0)	(5.0–9.5)	(7.0–10.0)	(6.0–10.0)	(6.0–9.0)
Total nocturia episodes/24 h	n	85	169	85	249	101	754
	Median	1.0	2.0	1.0	1.5	1.0	0.5***
	Q1–Q3	(0.0–3.0)	(1.0–2.0)	(0.1–2.0)	(1.0–2.0)	(0.2–2.0)	(0.0–1.0)
Max time (h) between daytime voids	n	70	156	70	218	90	661
	Median	4.0	3.0**	4.0	3.0	3.0	3.5**
	Q1–Q3	(3.0–5.0)	(2.5–4.0)	(2.5–5.0)	(2.0–4.0)	(2.0–4.0)	(3.0–4.5)
Pads used in daytime	n	17	3	10	150	32	335
	Median	3.0	1.0	2.5	3.0	2.0	2.0**
	Q1–Q3	(1.0–3.0)	(0.0–4.0)	(2.0–3.0)	(2.0–4.0)	(1.0–3.5)	(1.0–3.0)
Pads used at night	n	16	2	9	118	30	278
	Median	1.0	1.0	0.0	1.0	0.0	0.0†
	Q1–Q3	(1.0–1.0)	(1.0–1.0)	(0.0–1.0)	(0.0–1.0)	(0.0–1.0)	(0.0–1.0)
Invasive measurements – pressure flow studies							
Bladder volume at first desire (ml)	n	114	230	120	282	115	812
	Median	350	180***	280**	230	200*	280***
	Q1–Q3	(200–500)	(130–240)	(190–360)	(160–330)	(140–270)	(210–370)
Volume at urgent desire (ml)	N	19	66	33	57	33	202
	Median	380	260**	400	260	280	400***
	Q1–Q3	(220–610)	(200–310)	(250–440)	(180–340)	(190–330)	(310–500)
Volume when leakage occurs (ml)	N	16	2	10	171	23	309
	Median	240	30**	250	330	310	440***
	Q1–Q3	(180–290)	(20–50)	(200–350)	(250–400)	(260–390)	(350–540)
Cystometric capacity (ml)	N	129	256	122	308	119	854
	Median	500	300***	440**	360	320**	450***
	Q1–Q3	(320–690)	(240–360)	(350–520)	(290–460)	(260–400)	(370–540)
Compliance (ml/cmH ₂ O)	N	119	213	115	275	113	823
	Median	125	89	157*	205	154	258**
	Q1–Q3	(50–287)	(49–254)	(75–426)	(86–310)	(68–252)	(99–390)
Abdominal pressure at Q _{max} (cmH ₂ O)	N	127	256	122	307	119	850
	Median	55	40***	40***	36	22***	25***
	Q1–Q3	(40–75)	(32–46)	(32–45)	(25–51)	(15–35)	(17–32)
Volume voided (ml)	N	129	256	122	308	119	854
	Median	230	290***	440***	200	310***	450***
	Q1–Q3	(130–360)	(250–360)	(340–520)	(130–290)	(260–390)	(370–540)

Q1 = 25th percentile; Q3 = 75th percentile; BOO = bladder outlet obstruction; DU = detrusor underactivity; PFS = pressure flow studies.

The p -values were derived using mean score test on residuals from rank analysis of covariance model with patient group as factor and age as covariate. A p -value for age at visit is taken from Wilcoxon rank sum test, as analysis of covariance cannot include age as both response variable and covariate.

* indicates difference from detrusor underactivity group was significant for $p < 0.05$.

** indicates difference from detrusor underactivity group was significant for $p < 0.01$.

*** indicates difference from detrusor underactivity group was significant for $p < 0.0001$.

Table 5 – Summary of symptoms with statistically significant differences reported for patients with detrusor underactivity compared with those with normal pressure flow studies or with bladder outlet obstruction

Men		Women	
Higher occurrence for DU vs normal PFS	Higher occurrence for DU vs BOO	Higher occurrence for DU vs normal PFS	Higher occurrence for DU vs BOO
Decreased urinary stream	Abnormal sexual function	Decreased urinary stream	Decreased urinary stream
Interrupted urinary stream	Stress incontinence	Interrupted urinary stream	Stress incontinence
Hesitancy	Enuresis	Hesitancy	Enuresis
Incomplete bladder emptying	Palpable bladder	Incomplete bladder emptying	Absent and/or decreased sensation
Palpable bladder	Absent and/or decreased sensation	Palpable bladder	
Absent and/or decreased sensation	Always strain to void	Absent and/or decreased sensation	
Always strain to void	Bowel strain	Enuresis	
Incomplete bowel emptying	Incomplete bowel emptying	Impaired mobility	
	Poor bowel control		
Lower occurrence for DU vs normal PFS	Lower occurrence for DU vs BOO	Lower occurrence for DU vs normal PFS	Lower occurrence for DU vs BOO
None	Decreased urinary stream	None	None
	Hesitancy		
	Urgency		

BOO = bladder outlet obstruction; DU = detrusor underactivity; PFS = pressure flow studies.

with statistically significant differences for patients with DU compared with those with normal PFS or BOO.

3.1. Symptoms

Men with DU reported a statistically significantly higher occurrence of decreased and/or interrupted urinary stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, feeling of incomplete bowel emptying, absent and/or decreased sensation, and always straining to void compared with men with normal PFS. Men with DU reported a statistically significantly higher occurrence of abnormal sexual function, stress incontinence, enuresis, palpable bladder, absent and/or decreased sensation, always straining to void, bowel straining, feeling of incomplete bowel emptying, and poor bowel control compared with men with BOO. A statistically significant lower occurrence of decreased urinary stream, hesitancy, and urgency was reported for men with DU compared with men with BOO.

Women with DU reported a statistically significantly higher occurrence of decreased and/or interrupted urinary stream, hesitancy, feeling of incomplete bladder emptying, palpable bladder, absent and/or decreased sensation, enuresis, and impaired mobility compared with women with normal PFS.

3.2. Medical history

Men with DU reported a statistically significantly higher occurrence of retention, surgery with possible denervation of bladder and/or bowel, and use of antibiotics and/or antidepressants compared with men with normal PFS. Men with DU reported a statistically significantly higher occurrence of BOO surgery, retention, one or more urinary tract infections, and use of antibiotics compared with men with BOO.

Women with DU reported a statistically significantly higher occurrence of retention, surgery with possible denervation of bladder and/or bowel, one or more urinary tract infections, and use of antidepressants, antibiotics, and/or diuretics compared with women with normal PFS.

3.3. Invasive PFS measurements

Men with DU reported a statistically significantly higher occurrence of reduced filling phase sensation, detrusor contraction with strain, and voiding by straining compared with men with normal PFS or BOO.

Men with DU reported statistically significantly higher values for bladder volume at first desire to void, cystometric capacity, and abdominal pressure at Q_{\max} compared with men with normal PFS, but statistically significantly lower values for bladder compliance and volume voided. Men with DU reported statistically significantly higher values for bladder volumes at first and urgent desire to void, when leakage occurred, and at cystometric capacity, and abdominal pressure at Q_{\max} compared with men with BOO, but statistically significantly lower values for volume voided.

Women with DU reported a statistically significantly higher occurrence of reduced filling phase sensation, detrusor contraction with strain, and voiding by straining compared with women with normal PFS, but a statistically significantly lower occurrence of after contraction.

Women with DU reported a statistically significantly higher value for abdominal pressure at Q_{\max} compared with women with normal PFS, but statistically significantly lower values for bladder volumes at first and urgent desire to void, when leakage occurred, and at cystometric capacity, for volume voided, and for bladder compliance.

3.4. Combined variables for straining and decreased sensation

Men and women with DU reported a statistically significantly higher occurrence of both decreased sensation and straining compared with patients with normal PFS or BOO.

3.5. Bladder diary measurements

Men with DU reported a statistically significantly higher value for maximum time between voids and a statistically significantly lower value for number of daytime micturitions compared with BOO patients.

Women with DU reported a statistically significantly higher value for daytime micturitions, nocturia episodes, and day and night time pad use compared with women with normal PFS, but a statistically significantly lower value for maximum time between voids.

4. Discussion

This study shows that cross-sectional data can be used to associate signs and symptoms with urodynamically-defined DU.

Two earlier studies failed to detect clear differences in clinical presentation of DU patients compared with other patients, and concluded that few symptoms were helpful [6,7], whereas this study and another recent report in women by Rademakers et al [8] used strict criteria and a wide range of symptoms.

The present study corroborated Rademakers et al's [8] findings of an increased prevalence of incomplete bladder emptying, hesitancy, and a weak stream in women with DU compared with women with normal PFS. Some variables from the medical history that were significantly associated with DU may reflect some patients' natural history. For example, previous surgery could affect pelvic innervation and decrease bladder function and sensation. Also, the association of DU with prior BOO surgery may be due to preoperatively present DU, contributing to the overall clinical picture. Any retrospective look at such patients would find some patients with persisting symptoms due to unmasked DU.

The strengths of this analysis are that the urodynamic technique and structure of the interview were similar throughout the period and that data covering a large number of patients were used. A limitation is that the database is not a reflection of the general urological patient population, nor of the normal population in general, since all patients were referred for specialist evaluation of functional urological problems and many had received prior diagnosis and/or intervention. This was a retrospective, *post hoc* analysis of an existing database. A non-validated, although constant, set of questions were used and many data points were derived from clinician recording of patient responses to questions, and the potential for bias in the reported rates of underlying symptoms within each group cannot be discounted. The percentage of patients showing certain derived variables (see Materials and

methods section) may have differed if patients had been directly asked if they experienced the symptom. Additionally, there are inherent limitations caused by the testing of multiple groups and endpoints. Notwithstanding these limitations, the analysis shows that there appears to be differences in signs and symptoms between DU patients in comparison with BOO patients and patients with normal PFS, which can be used to create instruments used to evaluate the results of treatments for UAB/DU.

Whilst patients in the normal PFS group were required to have a bladder voiding efficiency ($BVE = \text{volume voided} / [\text{volume voided} + \text{post void residual volume}] \times 100\%$) of 100%, a cut-off of 90% was used to distinguish between DU and BOO. Some studies have used $BVE < 60\%$ as indicative of DU. The results did not differ greatly when comparing the symptom patterns of DU patients using cut-offs of 60%, 70%, 80%, and 90%. We therefore feel that it is legitimate to use $BVE < 90\%$ as the criterion for DU, and $BVE \geq 90\%$ for BOO patients in order to clearly differentiate the groups. Although there would be obstructed patients with a $BVE < 90\%$, to have incorporated these patients in the analysis would potentially have masked true differences in symptom patterns due to patients with both DU and BOO.

The observations in this study suggest that further work to develop a specific symptom questionnaire to assess DU severity, possibly coupled with noninvasive tests, could be useful for diagnosis, assessment, and evaluation of treatment outcomes. The importance of the development of noninvasive methods to characterise DU has been highlighted by several authors [2,4,8–10]. Further analyses of this database, including flow and voiding parameters that may be relevant to the definition of DU [3], are planned.

5. Conclusions

The present study has demonstrated the utility of database analysis to aid the development of a symptom-based definition of a traditionally invasively diagnosed urological condition. The identification and diagnosis of UAB patients has currently been hampered by a poor understanding of the clinical presentation of DU and the necessity of invasive PFS. The present study has shown that there are signs and symptoms that can distinguish men and women DU patients from patients with normal PFS, and further distinguish between DU and BOO. This analysis is a first step to better understand the clinical presentation of DU patients, is consistent with the recently published UAB working definition [1], and justifies developing and testing a diagnostic algorithm based on the signs and symptoms of DU.

Author contributions: Andrew Gammie had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gammie, Kaper, Dorrepaal, Kos, Abrams.
Acquisition of data: Gammie.

Analysis and interpretation of data: Gammie, Kaper, Dorrepaal, Kos, Abrams.

Drafting of the manuscript: Gammie, Abrams.

Critical revision of the manuscript for important intellectual content: Gammie, Kaper, Dorrepaal, Kos, Abrams.

Statistical analysis: Kaper.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2015.08.014>.

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Neural reconstruction methods of restoring bladder function

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Abstract | During the past century, diverse studies have focused on the development of surgical strategies to restore function of a decentralized bladder after spinal cord or spinal root injury via repair of the original roots or by transferring new axonal sources. The techniques included end-to-end sacral root repairs, transfer of roots from other spinal segments to sacral roots, transfer of intercostal nerves to sacral roots, transfer of various somatic nerves to the pelvic or pudendal nerve, direct reinnervation of the detrusor muscle, or creation of an artificial reflex pathway between the skin and the bladder via the central nervous system. All of these surgical techniques have demonstrated specific strengths and limitations. The findings made to date already indicate appropriate patient populations for each procedure, but a comprehensive assessment of the effectiveness of each technique to restore urinary function after bladder decentralization is required to guide future research and potential clinical application.

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Introduction

Lower urinary tract dysfunction can occur after severe spinal cord injury (SCI), sacral root injury as occurs with cauda equina syndrome, or traumatic injury to the pelvic plexus as can occur with hip or pelvic fracture. Such injuries can disrupt the urinary bladder's main functions of storing urine (urinary continence) and emptying (micturition). Survey studies demonstrate that urological problems due to neurogenic bladder dysfunction (NBD) after SCI have a high prevalence and long-term consequences for the wellbeing of these patients, such as detrusor muscle hyperactivity and detrusor–external sphincter dyssynergia,^{1–4} resulting in impairment of urine storage and voiding. The current management of these urologic problems can entail simple techniques, such as the Credé manoeuvre, intermittent bladder catheterization, and pharmacological management.⁵ Other surgical management methods include sacral rhizotomy to decrease detrusor muscle contractions, sphincterotomy or pudendal nerve section to decrease sphincter tone,⁴ and vesicostomy to maintain an empty bladder.⁶ Each technique is intended to improve the efficiency of bladder emptying as well as decrease the risk of secondary urinary tract infections (UTIs) and damage to the upper urinary tract that could threaten the patient's life.

In patients with spinal cord and cauda equina injuries, the public focus has generally centred on the need to regain the ability to stand and walk. However, in a survey study performed in 2004, restoration of bladder function was rated by patients as having greater importance, listed as the second priority after sexual function

in paraplegic patients, and as the third priority after hand function and sexual function in quadriplegic patients.¹ Regaining bladder continence not only aids reintegration into the community, but also helps to prevent clinical complications, because it enables low-pressure storage and efficient bladder emptying at low detrusor pressure, avoids stretch injury to the bladder from repeated overdistension, and prevents hydronephrosis.⁷ Loss of one or more of these functions is the major urological complication in patients with NBD that is caused by upper or lower motor neuron lesions in the spinal cord.^{8–14} Before 1977, epidemiological studies identified renal disease as a complication of lower urinary tract dysfunction as the major cause of death in patients with SCI.^{8,9} Although the level of morbidity from urinary tract related complications has been considerably reduced, owing to modern techniques as described above, patient quality of life remains remarkably low. However, patient wellbeing could be markedly improved if restoration of urinary bladder function were accomplished. Thus, effective methods for improved management of the NBD and restoration of urinary functions after SCI are needed.

Restoration of urinary bladder control using surgical methods of reinnervation was first attempted more than 100 years ago in dog models by suturing the proximal end of lower extremity nerves to the distal end of the nerves innervating the bladder and rectum.^{15–17} Although these original experiments were not completely successful, variations of this strategy have been used numerous times in animal models and in patients, with variable success. In the past three decades, several reports of successful nerve transfer methods in animal models and patients for restoration of bladder function have been published.^{15–47}

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Competing interests

The authors declare no competing interests.

Key points

- Neurogenic bladder dysfunction, such as detrusor muscle hyperactivity and dyssynergia with the external urethral sphincter (EUS), are common long-term consequences affecting the wellbeing of patients with spinal cord injury (SCI)
- Various studies have investigated surgical strategies to restore function of a decentralized bladder after SCI via repair of the original roots or by transferring new axonal sources
- The Finetech-Brindley stimulation device is effective in triggering bladder contraction in patients with neurogenic bladder dysfunction caused by upper motor neuron lesion
- Surgical techniques for restoring bladder volume, without also inducing a high increase in bladder pressure, are needed to promote efficient storage and continence
- Development of surgical techniques to reinnervate both the detrusor muscle and the EUS are needed to promote coordinated detrusor–EUS function
- Comprehensive assessment of the effectiveness of surgical procedures can guide future research and potential clinical application

This Review describes the different nerve transfer strategies performed in the past century, discusses their strengths and limitations, and defines the optimal target populations for each procedure, when possible.

Bladder innervation

In this Review, the classic terminology for spinal cord neuroanatomy is used and matched to terms used in the cited publications. Of note, the term ‘roots’ does not refer to the mixed spinal nerve origins of brachial plexus trunks, but instead refers to dorsal spinal roots, which carry sensory axons only, and ventral spinal roots, which carry motor axons only. Sensory dorsal roots enter the dorsal root entry zone of the spinal cord and motor ventral roots exit the ventral root entry zone of the spinal cord (Figure 1). The dorsal and ventral roots then join into a mixed spinal nerve (also called radicular nerves), which is located within the intervertebral foramen. After exiting the intervertebral foramen, the spinal nerve immediately divides into four parts: a dorsal ramus which carries axons that innervate dorsal somatic structures, for example, back muscles and skin; a ventral ramus which carries axons that innervate ventral somatic structures, for example, trunk and leg musculature and skin, and the external urethral sphincter (EUS); connections to sympathetic ganglia from spinal nerves located in thoracic and lumbar regions (via the grey and white rami communicantes); splanchnic nerves in thoracolumbar and sacral regions that carry preganglionic sympathetic or parasympathetic axons, respectively, to ganglia located on the abdominal aorta or on or near the end organs. In these latter ganglia, preganglionic axons synapse on postganglionic neuronal cell bodies.

Sympathetic bladder innervation consists of preganglionic axons that project from thoracic level 10 (T10) to lumbar level 2 (L2) spinal cord segments through splanchnic nerves to the inferior mesenteric ganglion on the aorta (Figure 1). Within these ganglia, axons synapse on postganglionic neurons that then project axons to the bladder on one or more nerve branches that are collectively termed the hypogastric nerve. Other preganglionic sympathetic axons descend within the sympathetic chain

to upper sacral ganglia, where they synapse on neurons that project axons to the bladder.

Parasympathetic innervation of the bladder via pelvic splanchnic nerves consists of preganglionic axon projections from upper sacral spinal cord segments (S2–S4 in most mammalian species) to ganglia located near the bladder wall. The exact sacral segments from which parasympathetic innervation arises vary between mammalian species. Visceral and somatic structures send sensory feedback to the spinal cord. These sensory afferents ‘hitchhike’ on the various autonomic and somatic motor nerves innervating end organs. From the bladder, sensory afferents project back to both thoracic and sacral spinal cord regions, as well as to lumbar spinal cord regions.^{48,49} Lastly, the pelvic plexus comprises parasympathetic and sympathetic motor nerve branches to the bladder, and visceral sensory nerve branches from the bladder to the spinal cord (Figure 1).

Strategies for bladder reinnervation**Sacral root repair***Homotopic repair*

In the late 1960s, Carlsson and Sundin²³ explored homotopic intradural reconstruction of severed sacral ventral roots S1 and S2 in a cat model, using direct repair combined with a (then) novel tubulation technique (Figure 2a, Table 1). S1, S2 and S3 ventral roots were transected bilaterally, while dorsal sacral roots were preserved. Proximal ends of the severed S1 ventral roots were then sutured intradurally and homotopically to the distal ends of the S1 ventral roots in two cats, whereas a bilateral S2 to S2 repair was performed in two other cats. Severed ends were not sutured, but realigned end-on-end, encircled by a stainless steel mesh cylinder impregnated with filter material, and secured by circular silk ligatures or silver clips (Figure 2a).^{50–52} Between 4–6 months after surgery, bladder contractions were observed after direct stimulation of both S1 and S2 ventral roots, indicating that functional recovery of the micturition reflex could be achieved by homotopic reconnection of transected S1 and S2 ventral roots. In addition, histological analysis of the repaired roots showed axonal regrowth across the repair site in all animals.

Similar studies were performed by Sollmann and colleagues between 1977 and 1982.^{25,53,54} They explored microsurgical repair of sacral roots immediately after transection in a porcine model, using intradural root reconstruction after homotopic end-on-end alignment. In two studies, the researchers transected and repaired L5 or S1 dorsal and ventral roots in 18 pigs (Table 1).^{53,54} The roots were collected 3 months after surgery and examined using electron microscopy. Axonal regeneration was evident across all dorsal and ventral repair sites, although regrowth was more advanced in repaired ventral motor roots than in dorsal sensory roots. Unfortunately, longer survival times would have been required to enable full assessment of axonal regrowth, and recovery of bladder function was not examined in these two studies. Thus, the importance of the integrity of L5 or S1 signalling on bladder function remained unclear.

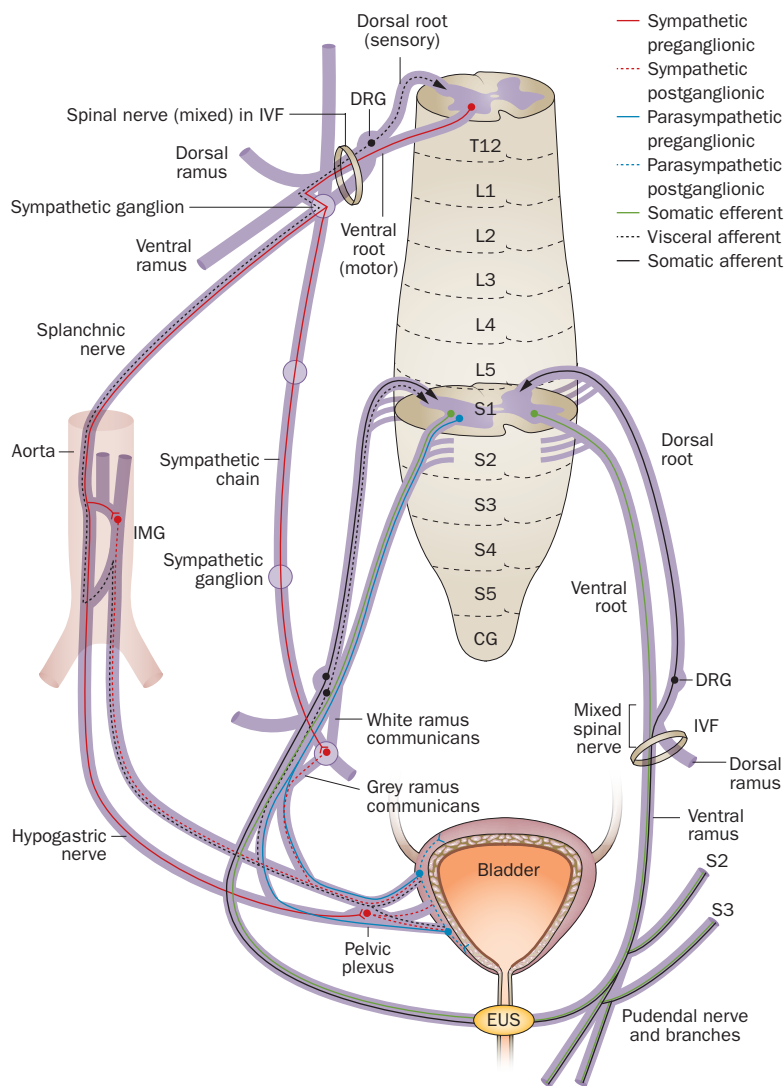


Figure 1 | Spinal cord neuroanatomy and bladder innervation in humans and other mammals. After exiting the spinal cord, dorsal and ventral roots (which consist of small rootlets that unite to form the large root) join into a mixed spinal nerve that divides into a dorsal ramus, a ventral ramus, the sympathetic chain, and splanchnic nerves. The bladder is innervated via sympathetic axons that project from T10 to L2 (exemplified for T12) through either splanchnic nerves to the inferior mesenteric ganglion on the aorta or descend within the sympathetic chain to upper sacral ganglia, where they synapse on neurons that project to the bladder. Parasympathetic bladder innervation from pelvic splanchnic nerves consists of preganglionic axon projections from S2 to S4 (exemplified for S2) in most mammalian species to ganglia located near the bladder wall. Sensory feedback travels to the spinal cord from visceral and somatic structures by ‘hitchhiking’ on autonomic and somatic motor nerves. Abbreviations: CG, coccygeal segment; DRG, dorsal root ganglion; EUS, external urethral sphincter; IMG, inferior or caudal mesenteric ganglion; IVF, intervertebral foramen; L, lumbar; S, sacral; T, thoracic.

In 1982, Conzen and Sollmann²⁵ extended these studies by examining the effects of immediate bilateral versus unilateral reconstruction of a mix of sacral roots (Table 1). One pig underwent transection (de-efferentation) followed by immediate reconstruction of S2, S3 and S4 ventral roots only, bilaterally. In this animal, the lost micturition reflex returned after 4 months, in contrast to another animal that underwent similar transection of S2, S3 and S4 ventral roots, but no reconstruction. Five additional pigs

underwent complete sacral decentralization via bilateral transection of the S2, S3 and S4 ventral and dorsal roots. In each animal, the micturition reflex disappeared after these transections. In two of the five pigs, bilateral or unilateral reconstruction of the S2 and S3 ventral and dorsal roots resulted in a return of the micturition reflex by 4.5 months or 7 months, respectively, but bladder capacity remained increased at 7 months in the pig with unilateral reconstruction. In another pig, in which only S2 roots were reconstructed bilaterally, return of micturition without increased bladder capacity was observed after 5 months. However, in one animal, in which the S2 roots were reconstructed unilaterally only, the micturition reflex did not recover. In the remaining animal, complete initial decentralization could not be determined. Although the authors reported histological evidence of axonal regrowth across the repair site, the histology was not shown in their report.

Overall, these results indicate that integrity of signaling across S2—and perhaps also S3—ventral roots, even if only unilateral, is important for preservation or recovery of the micturition reflex. Over the course of these studies, the researchers observed that spared thoracic and lumbar sympathetic input to the bladder was still present in the hypogastric nerve after sacral de-efferentation (that is, after bilateral transection of S2 to S4 ventral roots) and that this input does not produce detrusor muscle contractions in pigs,²⁵ similar to humans but different from rats.²⁹

In 2006, we assessed the feasibility of functional bladder reinnervation in 11 dogs after bilateral transection and immediate extradural homotopic reconstruction of S1 and S2 ventral and dorsal roots, which induced urinary bladder contraction as confirmed by intraoperative electrical stimulation (Figure 2b; Table 1).³⁶ Bladder decentralization was achieved in all animals by bilateral transection. In 10 dogs, roots were then repaired in the extradural space using end-on-end realignment and suturing of the epineurium. The remaining dog served as a denervated control. One repair site in each animal was surrounded by a silicone sheath connected to an osmotic pump (Figure 2b) and brain-derived neurotrophic factor (BDNF; 2.5 µg/h) given for 14 days to determine effects on neuronal regeneration. Bilaterally and immediately proximal to the repair site, a nerve cuff electrode (NCE) was placed around the sutured root bundles. In around 60-day intervals, the electrodes were stimulated to assess whether neurally evoked bladder emptying had been achieved. Fluid flow from the urethra was observed in five dogs during functional electrical stimulation (FES) of repaired roots located contralateral to the BDNF delivery side. In 10 dogs, retrograde nerve tracing and histological examination at 1 year after surgery showed axonal regrowth from the spinal cord to the bladder, although only contralateral to the BDNF delivery side. By contrast, the BDNF delivery site showed circuitous axonal outgrowth into the delivery sheath and surrounding connective tissue, suggesting neuroma formation rather than improved growth of axons across the repair site.

Based on the results of the contralateral side, we concluded that transected and repaired S1 and S2 ventral roots are capable of functional reinnervation of the bladder, and that FES could be used to stimulate bladder emptying.

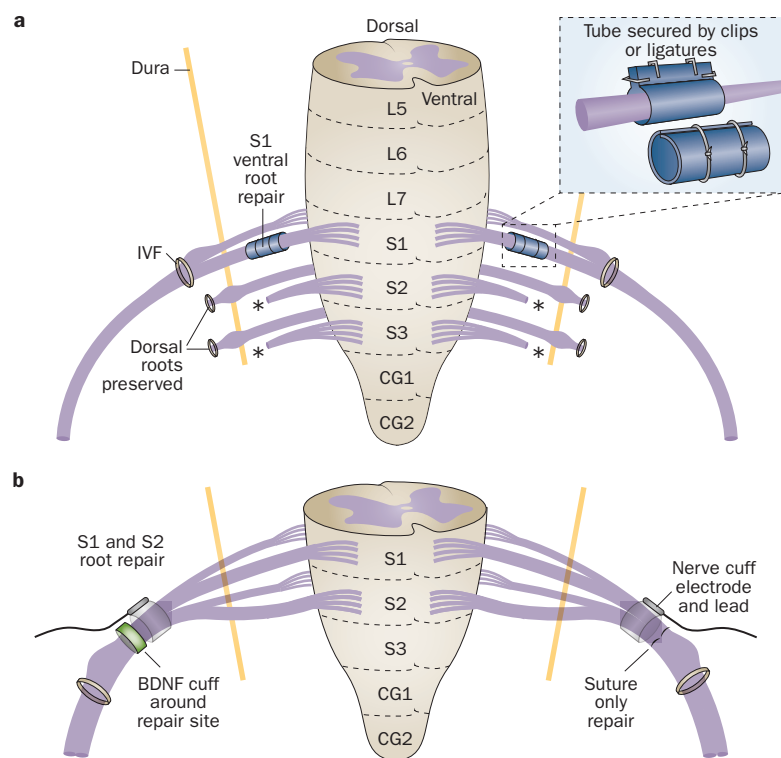


Figure 2 | Homotopic root repair.^{23,25,26,36} **a** | Intradural repair of ventral roots S1 and S2 in a cat model using a tubulation technique (exemplified for S1). The cylinder consists of mesh sheets and filter material, rolled into a tube around nerves and secured by ligatures or silver clips. **b** | Extradural bilateral repair of S1 and S2 ventral and dorsal roots in a canine model using end-on-end realignment and suturing. One site is surrounded by a silicone sheath to enable delivery of BDNF. Bilaterally, a nerve cuff electrode is placed immediately proximal to the repair site to assess neurally evoked bladder emptying via FES. Abbreviations: *, sectioned; BDNF, brain-derived neurotrophic factor; CG, coccygeal; FES, functional electrical stimulation; IVF, intervertebral foramen; L, lumbar; S, sacral.

Heterotopic repair

In 1907, one of the pioneers of peripheral nerve repair methods, Kilvington, performed a study in three dogs to determine whether dorsal or ventral spinal roots could regenerate after transfer to heterotopic dorsal or ventral roots (Table 2).¹⁵ In the first dog, the left S1 dorsal and ventral roots were isolated intradurally and sectioned. In the second dog, the left L7 ventral root was sectioned. Then, the proximal ends of each were sutured to the distal ends of ipsilateral S2 and S3 dorsal and ventral roots. In the third dog, the left L7 dorsal and ventral roots were sectioned and sutured to ipsilateral S2 and S3 dorsal and ventral roots (Figure 3a). At 4–6 months after repair, the spinal canal, but not the dura, was reopened and the repaired roots were isolated extradurally. In the first dog, faradic stimulation of the left S1 repaired roots, but not the contralateral severed S1 nerve, elicited strong tail movement, contraction of the pelvic diaphragm, and expulsion of bladder contents. In the second dog, after transection of the spinal cord at L6, faradic stimulation of the transferred L7 roots elicited contraction of pelvic muscles, contraction of the anal sphincter with defecation, and partial expulsion of bladder contents. In the

third dog, similar results, and additionally, leg contractions, were observed when faradic current was applied to the transferred L7 roots after detachment from the spinal cord. As a control, stimulation of contralateral S2 and S3 roots produced slightly more forceful bladder contractions. Thus, an intradural transfer of L7 or S1 dorsal roots to S2 and S3 mixed dorsal and ventral roots can provide at least partial return of bladder emptying, although forceful bladder contractions were not observed in any of the three dogs.

These results encouraged Kilvington to attempt the same surgical strategy in a human cadaver and then in a patient with a spinal cord lesion as high as the T12 dorsal root on one side and the T11 dorsal root on the other side, and extending for three vertebral levels (Figure 3b, Table 2).¹⁵ Kilvington attempted to reinnervate the bladder by intradural transfer of T12 or L1 roots to combined dorsal and ventral roots at S2 to S4. In the first operation, he identified the level of the SCI and dissected out feasible spinal roots near to the intervertebral foramen with enough length to transfer to sacral roots.¹⁵ Unfortunately, 10 days later in the second surgery, the root transfer could not be completed owing to scar tissue formation around the previously dissected roots. Kilvington concluded that this kind of surgical technique should be performed as a single procedure to avoid complications from scar tissue formation.

In 1968, Carlsson and Sundin²³ also explored heterotopic reconstruction of severed sacral ventral roots in six adult female cats by intradural transfer of L6 or L7 ventral roots to S1 or S2 ventral roots, bilaterally (L6 or L7 to S1, or L7 to S2), using their tubulation technique (Table 2). At 5 months after surgery, bladder contractions were observed after direct stimulation of either the L6 or the L7 ventral roots, indicating that functional recovery of the micturition reflex could be achieved by transferring L6 or L7 to S1 and S2 ventral roots. Histological analysis showed axonal regrowth across the repair site in all animals, further supporting the evidence for regeneration of transected and repaired sacral ventral roots.

In 2008, we examined whether bladder reinnervation could be achieved by extradural (yet still within the vertebral column) transfer of coccygeal roots to severed sacral roots in a dog model (Figure 3c, Table 2).³⁵ First, ventral roots of S1 and S2 segments shown to trigger bladder contractions were severed bilaterally to decentralize the bladder, which involved severing the dorsal roots because ventral and dorsal roots join together before exiting the dura. Then, in three dogs, ventral roots that induced only tail movement during intraoperative FES (that is, coccygeal (CG) 1 and CG2 roots) were transected and their proximal ends sutured to the distal ends of transected S1 and S2 roots using bilateral end-on-end repair. Last, an NCE was placed around the root bundles, immediately proximal to the repair site. Abdominal vesicostomies enabled bladder emptying during the recovery period.⁶ In one dog, FES on day 178 after surgery induced increased bladder pressure and urethral fluid flow.³⁵ Stimulation of the anterior vesical branch of the pelvic nerve also resulted in a substantial increase in

Table 1 | Homotopic root repair surgeries

Study	Procedure	Functional recovery (time)	Evidence	Limitations	Possible application
Carlsson <i>et al.</i> (1968) ²³	S1 or S2 v, bilateral Intradural, secured by tubulation Feline model	Yes (4–6 months)	Recovery of micturition reflex and axonal regrowth across repair site	Small study (n=2 per type of repair); limited utility of tubulation	S root or cauda equina injuries
Meier <i>et al.</i> (1977, 1978) ^{53,54}	L5 or S1 dv, bilateral Intradural Porcine model	Not tested (3 months)	Axonal regrowth across repair site (v>d)	Bladder function not assessed	S root or cauda equina injuries
Conzen <i>et al.</i> (1982) ²⁵	S2–S4 v, bilateral S2 and S3 dv, unilateral or bilateral S2, dv, unilateral or bilateral Intradural Porcine model	Yes (4–7 months)	Recovery of micturition reflex after complete decentralization or sacral de-efferentation and bilateral dv repair; axonal regrowth across repair site	Function assessed in 1 animal per type of repair; unilateral repair less effective than bilateral	S root or cauda equina injuries
Ruggieri <i>et al.</i> (2006) ³⁶	S1 and S2 dv, bilateral Extradural; bilateral FES, unilateral BDNF Canine model	Yes (5–12 months)	Increased bladder pressure and/or flow of saline out of urethra after FES; axonal regrowth from spinal cord across repair site to bladder	NCE failure in several dogs; BDNF induced neuroma formation at repair site	S root or cauda equina injuries

Abbreviations: BDNF, brain-derived neurotrophic factor; d, dorsal; dv, dorsal and ventral; FES, functional electrical stimulation; L, lumbar; NCE, nerve cuff electrode; S, sacral; v, ventral.

bladder pressure with urethral fluid flow in three dogs on day 373, day 426 or day 450 after surgery, respectively. Retrograde dye tracing showed labelled neuronal cell bodies in ventral coccygeal cord segments, demonstrating growth of motor axons from the coccygeal cord segment to the bladder across the repair site. These results indicate that bladder reinnervation can be achieved by heterotopic transfer of somatic motor roots that usually innervate skeletal muscle to sacral roots subserving bladder function. However, transfer of coccygeal roots to sacral roots is not suitable for humans owing to the presence of only vestigial coccygeal segments in humans.

In summary, homotopic and heterotopic end-to-end root repair seems most suitable for patients with sacral vertebrae fracture in which the sacral roots and maybe the cauda equina are injured, but the spinal cord remains intact.

Transfer of peripheral nerves to sacral roots

Several groups have examined the feasibility of using intercostal and spinal nerves as donors in nerve coaptation surgeries in animal models, cadavers, and in patients with injuries to caudal spinal cord segments or to the cauda equina (Figure 4, Table 3).^{22,24,27,30,39}

In 1912, Frazier and Mills²⁷ attempted to relieve urinary and faecal incontinence in a patient with SCI at lower lumbar and sacral levels and performed an extradural-to-intradural transfer of L1 spinal nerves to S3 and S4 dorsal and ventral sacral roots (Figure 4a, Table 3). After laminectomy, initially the T12 ventral root was transected extradurally, but this root was not long enough to reach the conus medullaris. Thus, the surgeons transected one L1 nerve extradurally within its intervertebral foramen, moved it back into the dural sac through a transverse incision, and sutured its distal end to the proximal ends of S3 and S4 dorsal and ventral roots intradurally. At 8 months after the operation, the patient was able to partially empty

the bladder using suprapubic mechanical pressure.²⁷ Findings from this study are limited by the small sample size and the absence of specific evaluation of detrusor function, and its success is weakened by the requirement of a Valsalva manoeuvre for bladder emptying; yet, these data held promise for future surgeons.

In 1980, Carlsson and Sundin²⁴ performed similar nerve transfer surgeries in two patients with traumatic lesions to their caudal vertebral column (Figure 4b, Table 3). The patients underwent laminectomy from T11–L2 at 10–14 days after vertebral fracture injury. During surgical exploration, there were signs of inflammation in the caudae equinae and residual small haemorrhages and lacerations in cauda equina nerves up to the entrance of the L1 roots. During surgery, the T12 intercostal nerves were extradurally bilaterally transected at 2–3 cm distal to their dorsal root ganglion (DRG), and moved intradurally and downwards to transected S2 and S3 ventral and dorsal roots emerging from the injured cord area. The T12 nerves were then anastomosed end-to-end to the sacral roots without sutures, using a silicone elastomer filter formed into a tube and secured with silver clips.

One patient had repeated UTIs between 3 months and 8 months after surgery and by 8 months the patient had hypersensitivity at the base of the penis on the left side, but also detrusor–sphincter dyssynergia during cystometry. By 12 months, the patient had sensitivity to touch and pain at the base of the penis on the left side, and felt urgency to void. When his bladder was full the patient could initiate micturition voluntarily and the residual urine was 35 ml. Reinnervation of the urethral sphincter was detected using electromyography, and detrusor contractions were detected by cystometry. Between 18 months to 30 months, the patient was able to achieve erection on local stimulation and voluntary voiding with a residual volume between 40 ml and 70 ml.²⁴

Table 2 | Heterotopic root repair surgeries

Study	Procedure	Functional recovery (time)	Evidence	Limitations	Possible application
Kilvington (1907) ¹⁵	S1 dv → S2 and S3 dv L7 v → S2 and S3 dv L7 dv → S2 and S3 dv Intradural, unilateral Canine model	Yes (4–6 months)	Partial or complete expulsion of bladder contents after faradic stimulation	Small study (n = 3); weak bladder contractions	S SCI, S root or cauda equina injuries
Kilvington (1907) ¹⁵	T12 or L1 → S2 and S3 dv Intradural, unilateral, 2-stage surgery Patient with SCI and cadaver	Surgery abandoned	NA	Scar tissue formation between surgeries prevented repair	Not recommended owing to scar formation
Carlsson <i>et al.</i> (1968) ²³	L7 v → S1 or S2 v L6 v → S1 v Intradural, bilateral, secured by tubulation Feline model	Yes (5 months)	Recovery of micturition reflex after L7 → S1 and L6 → S1 repair; axonal regrowth across repair site	Limited utility of tubulation	S root or cauda equina injuries
Ruggieri <i>et al.</i> (2008) ³⁵	CG1 and CG2 v → S1 and S2 dv Extradural, bilateral Canine model	Yes (6 months)	Increased bladder pressure under FES	Not suitable for humans due to vestigial coccyx	NA
Abbreviations: →, transfer to; CG, coccygeal; dv, dorsal and ventral; FES, functional electrical stimulation; L, lumbar; NA, not applicable; S, sacral; SCI, spinal cord injury; v, ventral.					

In the second patient, the neurological status was unchanged between 2 months and 8 months after surgery, and the patient had persistent UTIs. By 11 months, the patient was able to initiate voiding voluntarily by abdominal straining. We hypothesize that, as T12 innervates abdominal musculature, contracting these muscles should be the appropriate trigger to activate the newly innervated detrusor muscle. Between 12 months to 30 months after surgery, residual volume ranged from 20 ml to 120 ml and UTIs occurred frequently, although the patient was still able to initiate the micturition reflex by abdominal straining using the Valsalva manoeuvre. At 30 months, he underwent a transurethral external sphincterotomy to alleviate the UTIs attributed to large residual urine volumes. At 32 months and 36 months, the patient felt the desire to void and could initiate voiding voluntarily, although by 36 months an external catheter was needed owing to slight incontinence. In conclusion, by about 32 months after surgery, both patients could feel the urge to void, initiate micturition voluntarily, and empty their bladders satisfactorily. These results indicate restoration of bladder function is possible by transferring mixed extradural suprasacral nerves to intradural dorsal and ventral sacral roots that innervate the bladder. However, an improved surgical method was needed to avoid sphincter dyssynergia.

To meet this need, Vorstman *et al.*⁴² explored different approaches for this method in four human cadavers (Table 3). After a laminectomy to expose the dura and spinal nerves from T8 to S4, intercostal nerves were traced extradurally from the posterior axillary line to their origin to estimate the length of nerve available for a transfer to the ventral root of S3. A more limited approach was also investigated, with a T-shaped incision at the T9 vertebral body and extending caudally for five vertebral segments. The intervertebral foramen was enlarged to enable transfer of the T10 spinal nerve from an extradural position into the spinal canal to a position

proximal to the DRG of the ipsilateral S3 ventral root.⁴² The T10 intercostal nerve was long enough for this transfer. Upon assessment whether transfer of the T12 nerve to the S3 ventral root was possible, they determined that a nerve graft, such as 3 cm of the sural nerve, was needed to bridge the gap between the T12 nerve and the S3 ventral root.

Livshits and colleagues³⁰ also coapted intercostal nerves in eleven patients with chronic SCI at the L1 level (Figure 4c, Table 3). Patients underwent surgery 1–3 years after SCI (mean 2 years). Neurolysis of T11 and T12 intercostal nerves was carried out at a distance of 20–21 cm from the costal angle where the nerves divide into small-diameter branches. The nerves were then transferred into the vertebral canal intradurally at the upper sacral level, and sutured to the ventral roots of S2 and S3, which were identified by intraoperative FES as evoking increased intravesical pressure. The nerve roots were secured using a tube created from polymeric film secured with biological glue. At 10–12 months after surgery, all patients showed signs of restoration of the voiding reflex and improved urodynamics (voiding pressure was restored to $30.5 \text{ cmH}_2\text{O} \pm 4.9 \text{ cmH}_2\text{O}$). Eight patients had reappearance of their bulbocavernous, cremasteric and anal reflexes, and improved urodynamic parameters, although paraesthesias in the groin and scrotum also developed. Livshits *et al.*³⁰ concluded that decentralized bladders can be recentralized and voiding recovered if input is provided via transfer of lower thoracic intercostal nerves to sacral ventral roots that innervate the bladder, and that this procedure would be most suitable for patients with SCI in lumbar regions and children with spina bifida (Table 3).

Thus, it is possible to restore bladder function by transferring intercostal or lumbar nerves within the vertebral canal and dura to sacral ventral roots innervating the bladder. However, such procedures have limitations: patients might need to use Valsalva

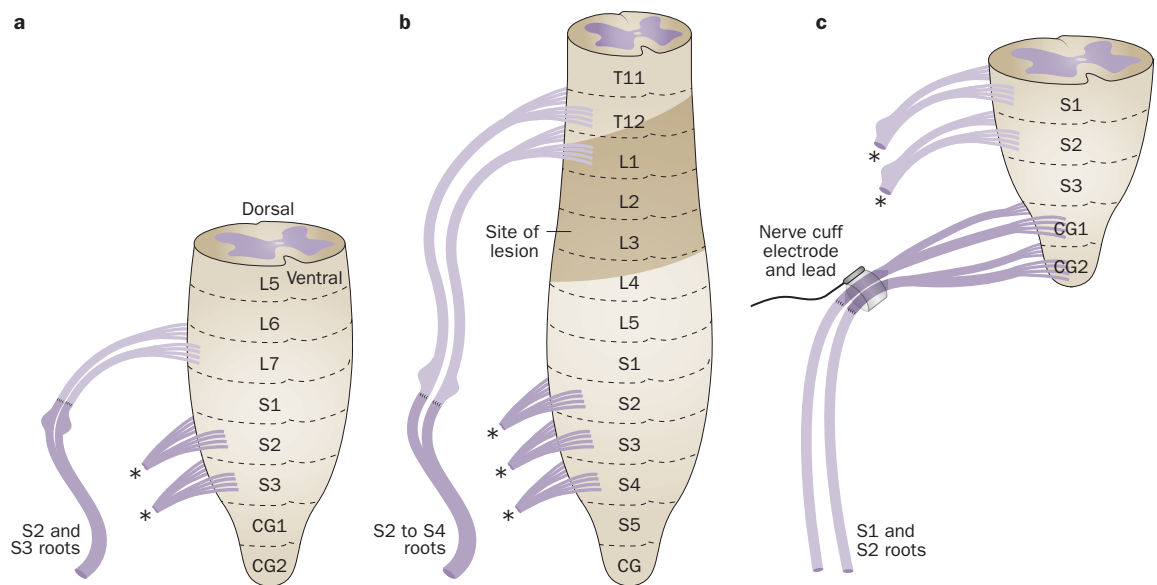


Figure 3 | Heterotopic root repair.^{15,35} **a** | Unilateral transfer of the L7 dorsal and ventral roots to ipsilateral S2 and S3 dorsal and ventral roots in a dog. **b** | Unilateral intradural transfer of T12 or L1 roots to combined dorsal and ventral roots at S2 to S4 in a patient with an SCI extending from T12 to L4. **c** | Bladder decentralization by severing S1 and S2 ventral and dorsal roots intradurally and bilaterally in a dog, followed by extradural end-on-end repair, using proximal ends of transected CG1 and CG2 ventral roots, and placement of an NCE around the root bundles. Abbreviations: *, sectioned; CG, coccygeal; L, lumbar; NCE, nerve cuff electrode; S, sacral; SCI, spinal cord lesion; T, thoracic.

straining to empty the bladder; an intervening nerve graft might be needed when transferring T12 nerves to sacral roots; patients might develop paraesthesias and detrusor-sphincter dyssynergia.

Transfer of roots to sacral spinal nerves

Sundin and Carlsson^{37,38} explored afferent fibre regeneration for functional recovery of bladder reflexes in a cat model (Figure 5a, Table 4). They transferred L7 or S1 dorsal sensory roots to S1 or S2 mixed (dorsal and ventral) spinal nerves, using their tubulation method (specifically, L7 to S1 in five cats and S1 to S2 in four cats). L7 or S1 dorsal roots were transected immediately distal to their DRG, sparing the ventral motor roots. The remaining dorsal sacral roots were transected intradurally for deafferentation of the pelvic and pudendal nerves. In addition, only the efferent fibres of the recipient S1 or S2 roots were transected, leaving the remaining sacral efferent fibres intact. At 8–11 months after surgery, the micturition reflex returned in cystometrograms in five of nine cats, which was a lower proportion than they had previously found after ventral root repair.²³ They concluded that in the L7 to S1 anastomosis group, the presence of a micturition reflex indicates that L7 dorsal root afferents had synaptic connections with the efferent limb of this reflex in the S1 spinal segment. However, it is unclear whether the efferent limb was carried by new, reinnervated motor fibres in the S1 spinal nerve or through the other remaining ventral sacral roots that were not transected. Polysynaptic multisegmental reflex circuits are probably involved in the micturition reflex, similar to other reflexes.

With regard to the storage reflex, the average bladder capacity increased twofold to fourfold from 34 ml pre-operatively during the first 2 months after nerve transection and reconstructive surgery. At 8–11 months after surgery, the average bladder capacity rose to 92 ml. Notably, the capacity further increased after transection of the previously reconstructed dorsal roots, indicating that reinnervation had occurred. In addition, intravesical pressure elevation or bladder volume decrease could be elicited in half of the reconstructed animals after FES of their pelvic and pudendal nerves. The researchers also observed propagated axon potentials in the L7 or S1 dorsal roots after stimulation of the pudendal and pelvic nerves. After transection of the reconstructed roots, the storage reflex and propagated axon potentials were no longer observed. FES of the spared hypogastric nerve (which arises from low thoracic segments; Figure 1) resulted in bladder relaxation. Transection of the hypogastric nerve abolished this response. Although this could indicate utilization of existing afferent pathways in the hypogastric nerves for the storage reflex, other studies in cats have shown that the afferent limb of this reflex is in sacral dorsal roots, and that the efferent limb is in the hypogastric nerve.^{48,49,55–57} Thus, adaptive reorganization of circuitry after heterogeneous root repair reconstruction might occur, in which both micturition and storage reflexes show functional recovery.^{23,38}

Vorstman and colleagues^{40,41} examined the feasibility of transferring dorsal and ventral roots of lumbar segments to sacral mixed spinal nerves for reinnervation of unilaterally decentralized bladders in cats (Figure 5b, Table 5). In one study, 11 adult female cats underwent unilateral transection of L7–S3 roots at an extradural site

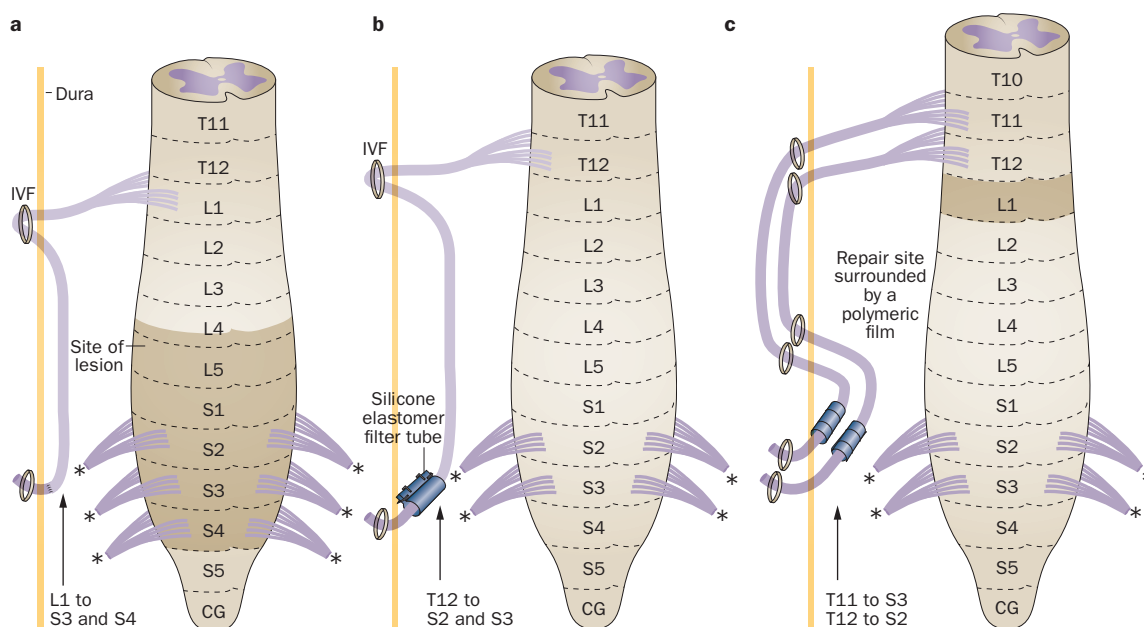


Figure 4 | Extradural-to-intradural transfer of spinal nerves to sacral roots.^{24,27,30} **a** | After extradural transection of the L1 nerve in its IVF, the nerve is moved back into the dural sac and sutured to the proximal ends of S3 and S4 dorsal and ventral roots. **b** | T12 nerves are extradurally transected, moved intradurally and anastomosed end-to-end to S2 and S3 ventral and dorsal roots, using a silicone elastomer filter tube formed into a tube and secured with silver clips. **c** | Extradurally neurolysed T11 and T12 nerves are reintroduced into the vertebral canal at the upper sacral level and aligned to S2 and S3 ventral roots using a polymeric film secured with biological glue. Abbreviations: *, sectioned; CG, coccygeal; IVF, intervertebral foramen; L, lumbar; S, sacral; T, thoracic.

distal to the DRG, followed by immediate transfer of L7 dorsal and ventral roots to the S1 spinal nerve.⁴¹ In six animals, a 4–6 mm portion of the ipsilateral S2 root was interposed into the repair site as a bridge. Each repair site was secured by microsutures. At 7 months after surgery, the repair sites were surgically exposed to evaluate if the bladder had regained function, using cystometric and electrophysiological methods. Detrusor contractions were observed in seven cats during maximum FES of the isolated roots, demonstrating that suprasacral mixed axons (specifically, L7 sensory and motor roots) transferred to a mixed sacral nerve (S1) can recentralize a unilaterally decentralized bladder in cats. No significant differences were observed between cats with and without the intervening nerve graft.⁴¹

In a second study, the researchers reported that the average bladder response to FES of the transferred root was 40% lower than that of a normal (nonoperated) S1 cystometric response.⁴² Similar to the results of Sundin and Carlsson,³⁸ these data also support a return of the micturition and storage reflexes after heterogeneous sensory and motor root transfers to sacral spinal nerves innervating the bladder—at least in cats. This type of procedure could be used in patients with NBD as a consequence of SCI or spina bifida, provided detrusor muscle viability is preserved.^{40,41}

Based on these studies, intradural root cross-over or nerve-to-root cross-over techniques for root repair are more suitable for patients with spinal cord or cauda equina injury, as they enable the surgeon to bypass the injured spinal cord segments. The use of intercostal

nerves or lumbar nerves for cross-over surgeries seems to be limited to patients with lower lumbar or upper sacral SCI or spina bifida.

Peripheral nerve transfer

Peripheral nerves to pelvic nerves

Nerve transfer as a method for bypassing an injured spinal cord region and reinnervation of bladders was first conceptualized in three dogs in 1907,¹⁵ and experimental results in five dogs were reported by Trumble in 1935 (Table 5).¹⁷ A study in 1907 by Elliott⁵⁸ in a variety of animal species demonstrated that FES of pelvic parasympathetic splanchnic nerves induced strong and sustained contractions of the detrusor muscle causing voiding. FES of the hypogastric nerve, which originates from thoracic spinal segments and the sympathetic splanchnic nerve to the bladder, induced a slight transitory increase of intravesical pressure, before relaxation of the detrusor muscle and a decrease in intravesical pressure.⁵⁸ These latter results were confirmed in subsequent studies.^{59–62}

Based on Elliott's findings, Trumble¹⁷ performed a two-stage surgical procedure as a possible means of restoration of the micturition and storage reflexes. Using a canine model, he first sectioned the hypogastric and pelvic splanchnic nerves unilaterally (between the spinal cord and the pelvic plexus) and transferred the proximal end of the hypogastric nerve to the distal end of the transected pelvic nerve on that side. Then, after several months of recovery, he transferred the obturator nerve to the distal end of the freshly transected pelvic nerve on

Table 3 | Extradural-to-intradural transfer of nerves to spinal roots

Study	Procedure	Functional recovery (time)	Evidence	Limitations	Possible application
Frazier <i>et al.</i> (1912) ²⁷	T12 or L1 nerves → S3 and S4 dv roots Unilateral 1 patient with SCI	Only with mechanical pressure (8 months after L1 transfer)	Partial recovery of bladder emptying	T12 nerve too short to reach sacral roots; Valsalva manoeuvre required for bladder emptying	SCI in lower L and S segments
Carlsson <i>et al.</i> (1980) ²⁴	T12 nerves → S2 and S3 dv roots Bilateral, secured with silicone elastomer filter and silver clips 2 patients with SCI	Yes (8–12 months; improved further by 30–36 months)	Recovery of penile sensation; with full bladder, one patient able to initiate micturition, the other able to empty with abdominal straining	Nerve graft needed to link T12 to sacral roots; possibility of developing detrusor–EUS dyssynergia	SCI in lower L and upper S segments
Vorstman <i>et al.</i> (1987) ⁴²	T10 or T12 nerves → S3 v roots Cadavers	NA	NA	Nerve graft needed to link T12 to S3 roots	SCI in lower L and upper S segments
Livshits <i>et al.</i> (2004) ³⁰	T1 and T12 nerves → S2 and S3 v roots Unilateral, secured with polymeric film tube and biological glue 11 patients with chronic SCI	Yes (10–12 months)	Recovery of reflex voiding in all patients; re-established bulbocavernosus, cremasteric and anal reflexes in 8 patients	Paraesthesias in the groin and scrotum; 3 patients needed Valsalva manoeuvre to empty bladder	SCI in lower L and S segments, spina bifida and S root injury

Abbreviations: →, transfer to; dv, dorsal and ventral; EUS, external urethral sphincter; L, lumbar; NA, not applicable; S, sacral; SCI, spinal cord injury; T, thoracic; v, ventral.

the contralateral side (Figure 6a). After 6–12 months, FES of the transferred obturator nerve induced bladder contractions, documented using a manometer, whereas stimulation of the hypogastric nerve that was transferred in the first operation produced only weak bladder contraction.

Trumble¹⁷ hypothesized that transfer of the hypogastric nerve led to more limited recovery owing to its reduced numbers of motor axons, compared with transfer of the obturator nerve—a somatic nerve with numerous myelinated motor axons. These results suggest that nerve transfer is suitable for patients with a lesion in the cauda equina. However, limitations of this procedure include that coaptation of the obturator nerve might cause paralysis of thigh abductor muscles, and coaptation of the hypogastric nerve might only produce weak contractions that are not under voluntary control.

In 1966, Kimmel²⁹ extended Trumble's idea by performing three variations of this nerve coaptation method in rats. First, the right pelvic splanchnic nerve was transected in all animals in all three experimental groups (Figure 6a). Then, in the first group, the proximal end of both hypogastric nerves were transferred to the distal end of the right pelvic nerve; in the second group, the proximal end of the right obturator nerve was transferred to the distal end of the right pelvic nerve; and in the third group, the transected pelvic nerve ends were repaired. Results were compared to three control groups that had undergone one of the following procedures: severance of right and left pelvic splanchnic nerves; severance of right and left pelvic splanchnic nerves, as well as the superior hypogastric nerve plexus; severance of right and left pelvic splanchnic nerves, superior hypogastric plexus, and all nerves supplying the ventrolateral abdominal wall. In the experimental groups, an arterial sleeve method was used for repair.⁶³

At 12 weeks after surgery, Kimmel performed a second procedure in the experimental groups to transect the—until then intact—left pelvic splanchnic nerve.²⁹ Most animals died of UTIs and, overall, survival

ranged from 7 weeks to 35 weeks. In the control groups, rats with both pelvic nerves severed were incontinent, whereas rats with one intact pelvic splanchnic nerve maintained good urinary function, based on palpated bladder emptiness and absence of incontinence. Rats with a transfer of hypogastric nerve to pelvic nerve showed nerve regeneration in histological analysis, but did not regain bladder function and developed atonic bladders. Rats with transfer of obturator nerve to pelvic nerve also showed nerve regeneration and recovered urinary function close to normal levels. However, animals in this group that had died of UTIs only had limited nerve regeneration. Finally, rats with pelvic nerve repair regained more robust urinary function than animals with obturator nerve to pelvic nerve transfer.²⁹

These results indicate that it is possible to retain bladder function in rats with just one intact pelvic parasympathetic splanchnic nerve, or by transfer of somatic motor nerves, such as the obturator nerve, to the distal ends of transected pelvic nerves. However, severing both pelvic nerves resulted in not only incontinence and urine retention, but also severe UTIs and consequential death of most animals.

We explored transfer of somatic nerves to the vesical branch of the pelvic nerve in a series of studies in a canine model (Table 5).^{19,34,35} In an initial study using intercostal nerves as donor nerves in one dog,³⁵ the immediate postoperative recovery was poor. We next examined the feasibility of transferring the ilioinguinal or iliohypogastric nerves, but each was too short to reach the bladder base. Thus, we decided to transfer the genitofemoral nerve, a mixed sensory and motor nerve, to the anterior vesical branch of the pelvic nerve (transected between the pelvic plexus and the bladder dome) in two intra-abdominal surgical conditions (Figure 6b): transection of the dorsal and ventral sacral roots within the spine followed by immediate transfer of the genitofemoral nerve versus transection followed by a 1-month or 3-month delay before transfer.³⁴ NCEs were implanted bilaterally in two of the four dogs with

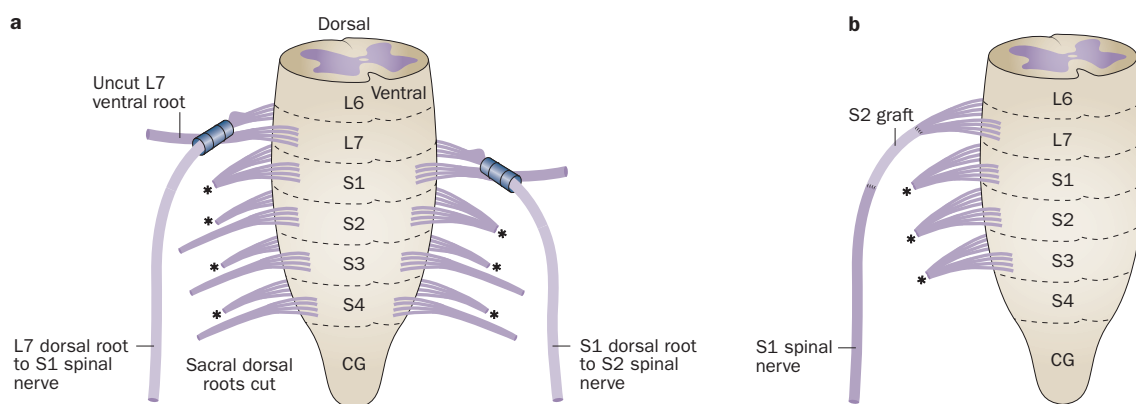


Figure 5 | Intradural-to-extradural transfer of lumbar or sacral roots to sacral spinal nerves.^{37,38,40,41} **a** | Transfer of L7 or S1 dorsal sensory roots to S1 or S2 spinal nerves, respectively, in a cat model, using a tubulation method. Ventral motor roots and sacral efferent fibres other than indicated S1 and S2 roots are left intact. **b** | Transfer of L7 dorsal and ventral roots to the S1 spinal nerve, after extradural unilateral transection of L7 to S3 roots, in a cat model, using a bridging S2 root graft in some animals. Abbreviations: *, sectioned; CG, coccygeal; L, lumbar; S, sacral.

immediate transfer and in all the dogs with 1-month ($n=4$) and 3-months ($n=6$) delay before transfer. At 32–138 days after surgery (mean 66 days), evidence of reinnervation included increased bladder pressure and urethral fluid flow after FES of the implanted NCEs on the immediately transferred nerves, and of four out of 20 NCEs implanted on the nerves that were transferred after a delay. At the time of the terminal surgery, direct FES of the transferred nerve immediately proximal to the repair site induced bladder pressure and urethral fluid flow in three of four animals with immediate transfer, in three of four animals with a 1-month delay before transfer, and in five of six animals with a 3-month delay before transfer. Three weeks after injection of fluorogold into the bladders for retrograde dye tracing, abundant retrograde transport of fluorogold to motor neurons in the upper lumbar cord was observed in three of four dogs with immediate transfer, and in all 10 animals that underwent delayed transfer, except unilaterally in one animal. Histochemical evidence of nerve regrowth across the repair site,^{34,35} and antero-grade axonal tracing,¹⁹ further confirmed regrowth of axons from the transferred genitofemoral nerve into the bladder detrusor muscle, resulting in successful bladder reinnervation in the majority of animals in all groups.

This surgical procedure, in which somatic nerves are transferred to pelvic nerves, might enable restoration of bladder function (specifically emptying) in a subset of patients who can still control their lower abdominal musculature (for example, patients with caudal SCI or isolated injury to bladder nerves). Following the transfer procedure, prolonged activation of the lower abdominal muscles could be used to stimulate initiation of a micturition reflex, supplying the sustained input signal required by the detrusor. The patient could be trained to activate this reflex; however, it might be activated unintentionally in some circumstances in which the intra-abdominal pressure is increased (such as coughing fits or sneezing).

To address neurogenic sphincter incontinence, we performed pilot studies in cadavers and then in dogs to determine the feasibility of transferring femoral nerve motor branches to the pudendal nerve for re-establishment of EUS and anal sphincter function after sacral spinal cord or root injury (Table 5).^{18,33} In the cadavers, we exposed branches of the femoral nerve to the vastus medialis and intermedialis muscles using an anterior thigh approach. Then, the pudendal nerve was exposed in the Alcock (pudendal) canal using a perineal approach, before transferring the femoral nerve branches medially and superiorly to the pudendal nerve.¹⁸

This study was then repeated in two canine cadavers, and in three live dogs.³³ Sacral ventral roots were selected using intraoperative FES to demonstrate their ability to stimulate bladder, EUS and anal sphincter contraction. These roots were then transected to decentralize the end organs. Motor branches of the femoral nerve were identified bilaterally using an anterior thigh approach, then tunnelled to the perineum and sutured end-on-end to transected pudendal nerve branches located in the Alcock canal. The proximal portion of the transferred nerve was enclosed in NCEs. After surgery, FES was performed at monthly intervals. At 72 days, 120 days or 187 days, nerve stimulation induced increased anal and urethral sphincter pressures in five of six transferred nerves in three dogs. Retrograde neurotracing from the external urethral and anal sphincter resulted in labelled neurons in the ventral horns of L2–L4 cord segments (but not S1–S3), consistent with reinnervation of these structures by the transferred femoral nerve motor branches. By contrast, a nonoperated control dog had labelled neurons only in S1–S3 spinal cord segments. Post-mortem neurotracing studies further confirmed axonal regrowth across the nerve repair site. Combined, these results indicate that return of EUS and anal sphincter function is possible using this femoral-nerve-to-pudendal-nerve approach.

Table 4 | Transfer of spinal roots to spinal nerves

Study	Procedure	Functional recovery (time)	Evidence	Limitations	Possible application
Sundin <i>et al.</i> (1972) ³⁸	L7 d roots → S1 nerves S1 d roots → S2 nerves Secured by tubulation Feline model	Yes (8–11 months)	Recovery of micturition and storage reflexes; propagated axon potentials during FES of pudendal and pelvic nerves	Functional recovery after afferent fibre regeneration is less than in study of efferent fibre regeneration ²³	S SCI; S root or cauda equina injuries
Vorstman <i>et al.</i> (1986) ^{40,41}	L7 dv roots → S1 nerves Feline model	Yes (7 months)	Observed recovered micturition reflex during FES	Nerve graft might be needed; detrusor muscle should be intact	SCI in L segments, spina bifida

Abbreviations: →, transfer to; d, dorsal; dv, dorsal and ventral; FES, functional electrical stimulation; L, lumbar; S, sacral; SCI, spinal cord injury.

We also explored the feasibility of translating similar somatic-nerve-to-pelvic-nerve transfer methods to human patients (Table 5).^{20,21} In pilot studies in 20 cadavers (female or male), the intercostal, ilioinguinal, iliohypogastric, and femoral nerves were exposed, carefully dissected to obtain the longest possible length, and then transected. These nerves, rather than the genitofemoral nerve, were chosen for transfer owing to their greater content of motor axons. The main branches of the vesical branches of the pelvic nerve were exposed in the pelvic cavity, and transected. The vesical branches of the pelvic nerve were detected as one or two main trunks at the base of the bladder, inferior to the ureter, and accompanied by inferior vesical vessels in all examined cadavers.^{20,21}

We first examined feasibility of transferring the eleventh and twelfth intercostal nerve directly to the vesical branch of the pelvic nerve, but both intercostal nerves were too short for this type of transfer. Thus, use of a femoral cutaneous nerve branch as a nerve graft was suggested.²⁰ Next, the use of ilioinguinal and iliohypogastric nerves for transfer to pelvic nerves was explored in 11 cadavers. Each could be dissected from the abdominal wall with enough length to reach the bladder, before branching extensively to the abdominal muscles. They were transferred using an intra-abdominal and retroperitoneal approach to the main vesical branches of the pelvic nerve.²⁰ Last, in 20 cadavers, a motor branch of the femoral nerve (which originates in L2–L4 ventral rami) was dissected using an anterior thigh approach. Two nerve branches to the vastus medialis and intermedialis muscles were split from the main trunk of the femoral nerve. They were transected with enough length to reach the interior of the pelvic cavity, and then moved superiorly and tunneled inferior to the inguinal ligament, before moving one branch to the ipsilateral vesical pelvic nerve at the base of the bladder and one branch to the contralateral vesical pelvic nerve.²¹ In all studies, the cross-sectional areas of each nerve were of sufficient and similar size for surgical coaptation.

These cadaveric studies show that the ilioinguinal, iliohypogastric and motor branches of the femoral nerve are candidates for transfer to the dominant (vesical) nerve branch of the pelvic nerve that innervates the bladder. However, further studies in animals, which are currently underway in our laboratories, or patients are required for confirmation.

Zhang and colleagues have published a summary of suggested procedures for bladder reinnervation using peripheral nerve rerouting. Specifically, they suggest isolating and rerouting intercostal nerves to sural nerves, and then connecting the intercostal–sural combination to the pudendal nerve.⁶⁴ Unfortunately, no histological or functional outcome data showing evidence of recovery was included in this or other reports.^{64,65}

Direct detrusor muscle reinnervation

In 1971, Rao and colleagues³² investigated the feasibility of direct reinnervation of the decentralized urinary bladder by transfer of suprasacral nerves (femoral and obturator nerve) to the detrusor muscle wall in animals (Figure 7, Table 5). Bladder decentralization was accomplished by bilateral pelvic nerve neurectomy in three of 15 dogs, intradural sacral rhizotomy of S2 and S3 roots in 12 dogs, and pelvic neurectomy in 80 rats. At 10 days after surgery, decentralization was confirmed using cystometrograms with bethanechol injections, and then either the obturator or femoral nerve was sectioned. The distal ends of these sectioned nerves were implanted directly into the detrusor muscle through a 1-cm-long intramuscular tunnel close to the ureterovesical junction. All dogs and 22 rats survived until the end of the study; the high mortality in the rats was due to severe UTIs. In six dogs at 8 weeks of recovery, the implanted nerves were still fixed to the bladder and had a normal appearance, although no bladder contractions were observed in response to stimulation of the implanted nerves. After an additional 12 weeks, the same six dogs were retested, but again no bladder contractions could be induced. The remaining nine dogs were tested at 30 weeks and 40 weeks after nerve transfer. Action potentials were detectable in the regenerated nerve proximal to its entry into the bladder, although no increase in bladder pressure was observed. The results in the surviving 22 rats were similar to those seen in the latter nine dogs. In both dogs and rats, although neuromas had formed at the implantation site, there was little histological evidence that the growing axons entered the smooth muscle bundles of the bladder and no structures resembling myoneural junctions were visible.³² These results suggest that direct transfer and implantation of nerves into the bladder wall can result in nerve regeneration, but not restoration of bladder function.

Table 5 | Coaptation of peripheral nerves to pelvic or pudendal nerves

Study	Procedure	Functional recovery (time)	Evidence	Limitations	Possible application
Transfer of peripheral nerves to pelvic nerves					
Trumble (1935) ¹⁷	Hypogastric nerve → pelvic nerve on one side Obturator nerve → pelvic nerve on other side Canine model	No (hypogastric nerve) Yes (obturator nerve) (6–12 months)	FES of obturator nerve induced bladder contractions	Limited motor nerve regeneration (hypogastric nerve)	Lesion of cauda equina
Kimmel (1966) ²⁹	Hypogastric nerve → pelvic nerve Obturator nerve → pelvic nerve Pelvic nerve repair Arterial sleeve method Rat model	No (hypogastric nerve) Yes (obturator nerve) Yes (repair) (2–8 months)	Recovery of bladder function after obturator nerve transfer and pelvic nerve transfer	Atonic bladder (hypogastric nerve → pelvic nerve)	Lesion of cauda equina
Transfer of peripheral nerves to pudendal or pelvic nerves					
Ruggieri et al. (2008) ^{34,35} and Barbe et al. (2011) ¹⁹	Genitofemoral nerve → anterior ventral branch of pelvic nerve Vesicostomy Canine model	Yes (4–6 months)	Axon regrowth from cord to bladder	Sustained abdominal contraction could result in unintentional voiding; indwelling FES electrodes need improved design	SCI in lower L and S segments, and cauda equina; patient needs control of abdominal muscles if FES not used
Ruggieri et al. (2011) ³³ and Barbe et al. (2011) ¹⁸	Motor branches of femoral nerve → pudendal nerve Cadavers or canine model	Yes (dogs) (3–6 months)	Reinnervation of EUS and anal sphincter	Not yet tested in patients	SCI in lower L and S segments; lesion of cauda equina
Brown et al. (2012, 2013) ^{20,21}	Ilioinguinal and iliohypogastric nerve → pelvic nerve Femoral nerve → pelvic nerve Cadavers	NA	NA	Not yet tested in patients	SCI in lower L and S segments; lesion of cauda equina
Direct detrusor muscle reinnervation by somatic nerve transfer					
Rao et al. (1971) ³²	Obturator or femoral nerves implanted directly into detrusor muscle Intramuscular tunnel (arterial sleeve) Canine and rat model	No (7.5–10 months)	NA	Neuroma formation; no regeneration of motor end plate; increased frequency of UTIs	Lesion of cauda equina

Abbreviations: →, transfer to; EUS, external urethral sphincter; FES, functional electrical stimulation; L, lumbar; NA, not applicable; S, sacral; SCI, spinal cord injury.

In summary, somatic nerves within the abdomen can also be coapted to the pelvic nerve in nerve transfer surgeries. However, use of the hypogastric nerve, a sympathetic autonomic nerve, has not proved successful in this type of surgery. The somatic nerve cross-over surgeries using genitofemoral nerve, motor branches of the femoral nerve, ilioinguinal and iliohypogastric nerves would be limited to patients with a very caudal SCI or isolated injury to the nerves subserving bladder function unless FES is utilized, because the patient must have retained active control over lower abdominal musculature so that successful bladder emptying can be triggered by sustained activation of the abdominal musculature. Somatic nerves in the thigh region can also be coapted to the pudendal nerve, although further studies in animals or patients are required.

Artificial somatic-to-autonomic reflex pathway

Xiao et al. performed a series of studies with the goal of restoring the micturition reflex after SCI without the need for FES by creating an artificial reflex pathway via the central nervous system (CNS) (Figure 8, Table 6).^{43–47,65} These investigators hypothesized that a skin–CNS–bladder pathway could be created by rerouting the efferent portion of a normal somatic reflex, for example, the patellar or Achilles⁶⁶ reflex arcs. They believed a reflex

circuit could be created that would enable bladder emptying in response to somatic sensory stimuli, by intradurally transferring the ventral root containing the somatic motor portion of the reflex arc to the ventral root that controls bladder emptying, while keeping the sensory portion of the somatic reflex arc intact (that is, the dorsal root). The success of this hypothetical model hinged on the ability of somatic motor nerve fibres to regenerate within an autonomic nerve.

To test their hypothesis, they first explored this surgical method in 24 rats.⁴⁴ First, all rats received a left hemilaminectomy to expose the spinal cord from L4 to S1, followed by transection of the ventral roots of these segments. Then, the proximal end of the L4 ventral root was transferred to the distal end of the L6 ventral root, while the L4 dorsal root was kept intact. At 3 months and 1 year after surgery, a strong bladder contraction could be initiated by FES of the left L4 ventral roots. In addition, at 1 year after surgery, bladder contractions were also observed after FES of the left sciatic nerves and by scratching the skin of the rats' left legs (the dermatome related to L4). Neural tract tracing studies 3 months after nerve transfer indicated successful regeneration of the L4 ventral root axons into the ventral root of L6. The researchers concluded that this procedure was practical in rats and might have potential clinical application.⁴⁴

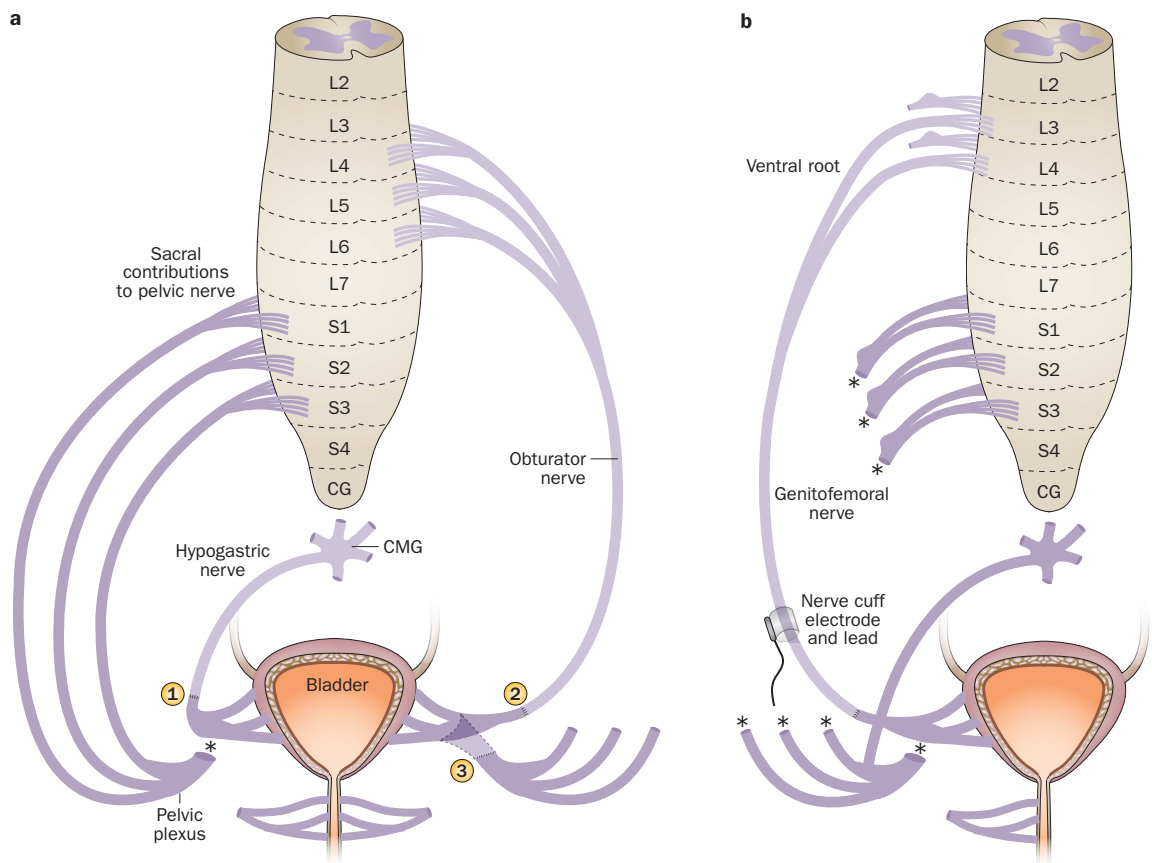


Figure 6 | Transfer of peripheral nerves to pelvic nerves.^{17,29,33–35} **a** | Transfer of the hypogastric (1) or obturator (2) nerves to the pelvic splanchnic nerves (transected between the spinal cord and the pelvic plexus), or repair of the transected pelvic nerve ends (3). **b** | Transfer of the genitofemoral nerve to the anterior vesical branch of the pelvic nerve after bilateral transection of the dorsal and ventral sacral roots to the bladder (exemplified unilaterally). Abbreviations: *, sectioned; CG, coccygeal; CMG, caudal mesenteric ganglion; L, lumbar; S, sacral.

In a subsequent study, the team tested a similar method in cats (Table 6).⁴³ In six animals, the left L7 ventral root was intradurally transferred and sutured to the left S1 ventral root. For triggering the micturition reflex, the left L7 dorsal root was left intact to conduct afferent signals from the skin innervated by L7. At 11 weeks after operation, detrusor contractions of short latency could be induced after scratching or percutaneous electrical stimulation of the dermatome related to L7. FES of the L7 nerve also increased bladder pressure. Urodynamic studies demonstrated that voiding could be stimulated without generating detrusor–EUS dyssynergia. Skin-stimulated bladder contractions were reduced after administration of the antimuscarinic agent atropine or the ganglion-blocking agent trimethaphan. Thus, the researchers could demonstrate that the skin–CNS–bladder reflex arc of L7 to S1 could effectively induce detrusor muscle contractions after bladder decentralization, that the new pathway was mediated by cholinergic transmission involving both muscarinic and ganglionic nicotinic receptors, and that somatic motor axons could innervate bladder parasympathetic ganglion cells and thereby transfer somatic reflex activity to the bladder smooth muscle, resulting in bladder contractions.⁴³

In 2003, Xiao and colleagues⁴⁵ published the results of the first clinical study of the skin–CNS–bladder procedure (Figure 8, Table 6). 15 male patients with hyperreflexic NBD caused by complete suprasacral SCI volunteered for this study. Bladder function was evaluated preoperatively using urodynamic methods, which showed that each subject had hyperreflexic bladders with detrusor–sphincter dyssynergia. All patients underwent a limited hemilaminectomy from L4 to S3. The dura was opened to expose the dorsal and ventral roots from L5 to S3. The ventral roots of L5, S2 and S3 were identified, separated from their respective dorsal roots by microdissection, and their function tested by FES before sectioning. Then, the proximal end of the L5 ventral root was sutured to the distal end of the S2 ventral root. The technique was modified as needed based on the length and function of the roots, and extent of cord damage (for example, transfer of the L5 ventral root to S2 and S3 ventral roots, or L4 or S1 ventral roots to S2 or S3 ventral roots). At 12–18 months after surgery, 10 patients (66%) recovered bladder storage and emptying functions. After 1 year, they were able to initiate voiding using the skin–CNS–bladder reflex pathway of L5 to S2. Their average residual urine was

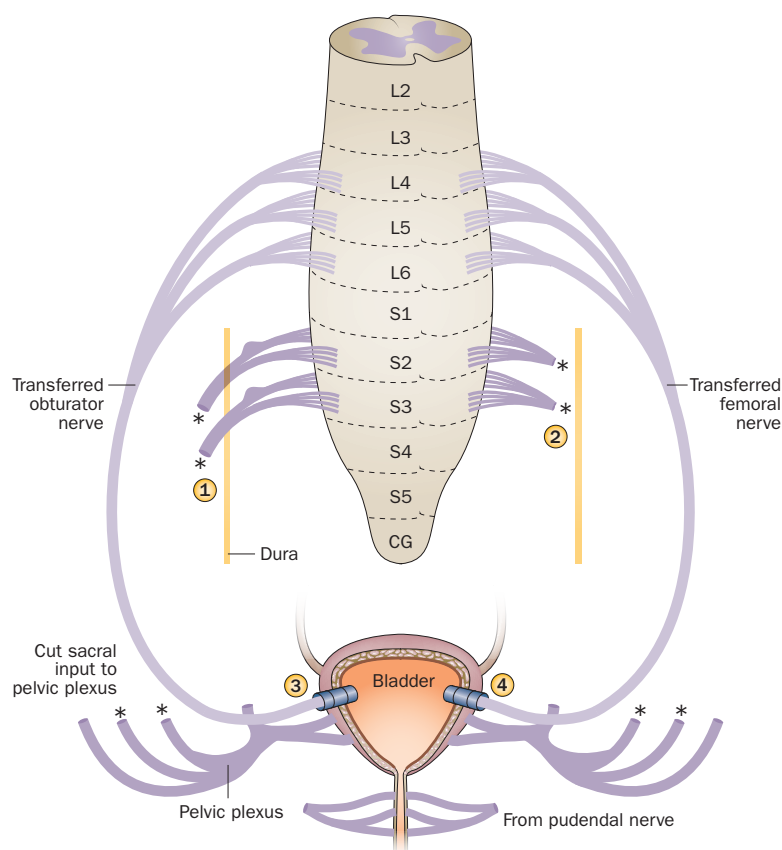


Figure 7 | Direct detrusor muscle reinnervation by somatic nerve transfer.³² In a canine model, the bladder is decentralized by bilateral pelvic nerve neurectomy (1) or intradural sacral rhizotomy of S2 and S3 roots (2). 10 days later, either the obturator nerve (3) or femoral nerve (4) is sectioned and their distal ends implanted directly into the detrusor muscle close to the ureterovesical junction using an arterial sleeve. Abbreviations: *, sectioned; CG, coccygeal; L, lumbar; S, sacral.

markedly decreased (from 332 ml to 31 ml), and UTIs and overflow incontinence ceased. Two patients had no improvement with surgery, one was lost to follow-up and two only had a partial reflex, which required them to electrically stimulate the sensory dermatome to initiate voiding.⁴⁵

These findings suggest that a somatic to autonomic reflex arc can be established via an intradural nerve transfer procedure, resulting in voluntary voiding, improvement of detrusor–sphincter dyssynergia, and increased bladder capacity. Xiao and colleagues proposed this method as an effective technique for restoring bladder function in patients with suprasacral SCI.

In 2009, Lin and colleagues⁶⁶ published the results of a confirmatory clinical study, using a slight variation on the Xiao procedure. 12 paraplegic patients with hyperreflexic NBD and detrusor–EUS dyssynergia caused by complete suprasacral SCI underwent an intradural transfer of S1 to S2 ventral roots, leaving the S1 dorsal root intact. The investigators chose the S1 nerve root instead of the L5 root to enable initiation of the somatic–CNS–autonomic reflex by tapping on the Achilles tendon in addition to skin stimulation, creating an

Achilles-tendon-to-bladder reflex pathway. Nine patients (75%) regained bladder control within 6–12 months after surgery. Urodynamic testing of these nine patients around 1 year after operation showed elimination of detrusor–sphincter dyssynergia, increased bladder capacity (258 ml to 350 ml) and decreased residual urine (214 ml to 45 ml). The remaining three patients showed no improvement after surgery.

Tuite and colleagues⁶⁷ performed the Xiao procedure in a 10-year-old boy with chronic T10–T11 paraplegia under the direct supervision of C. G. Xiao, but failed to reproduce previously reported results (Table 6). The L5 ventral root was transferred intradurally to the S2 and S3 nerve roots, leaving the L5 dorsal root intact. At 6–12 months after surgery, the patient reported improvement in his ability to control his voiding. However, by 24 months, he felt that he had no improvement in bladder or bowel control compared to his condition before surgery. During urodynamic testing, voiding and bladder contractions could not be consistently initiated after stimulating the L5 dermatome. When a separate lumbosacral intradural procedure was performed 3 years later, the previously performed L5 to S2–S3 transfer was found to be anatomically intact. However, FES proximal and distal to the repair site produced no bladder contractions, and nerve action potentials could not be demonstrated across the repair site. Histological analysis showed neuroma formation with very little nerve growth across the repair site. As reinnervation was not evident, the patient's transient improvements in bladder control were not related to a functional skin–CNS–bladder reflex.

Xiao and colleagues⁴⁶ also used the Xiao procedure as a treatment for neurogenic voiding dysfunction in 20 children with spina bifida and documented NBD (Table 6). In each child, the spinal defect had been surgically closed within the first 48 h after birth. Preoperative urodynamic studies showed two types of bladder dysfunction. 14 patients had an areflexic detrusor with small bladder capacity and incontinence—findings typical of a lower motor neuron lesion. The other six patients had hyperreflexic bladders with detrusor–EUS dyssynergia and overflow incontinence—findings typical of an upper motor neuron lesion. A limited laminectomy was performed between L4 and S2 vertebrae, followed by exposure of the dorsal and ventral roots of L4 and L5 and all sacral segments. The ventral roots of L4, L5, S2 and S3 segments were microdissected from their respective dorsal nerve roots, and the proximal end of the L5 ventral root was sutured to the distal end of the S3 ventral root, leaving the L5 dorsal root intact. As early as 6 months after surgery, 17 patients were able to initiate voiding and had regained continence, but the three remaining patients failed to show any improvement.

All 14 patients that had initially presented with urological signs of a lower motor neuron lesion showed increased bladder capacity and decreased residual urine in urodynamic studies at 1 year after operation. Five of the six patients that presented with urological signs of an upper motor neuron lesion were able to void voluntarily,

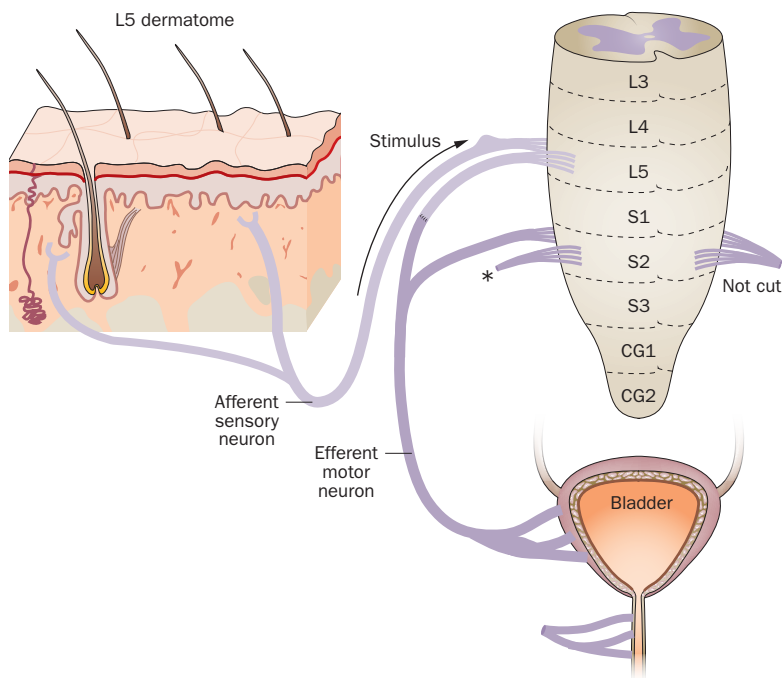


Figure 8 | Artificial skin–CNS–bladder reflex pathway methods.^{43–47} In patients with complete suprasacral SCI, after hemilaminectomy from L4–S3, the dorsal and ventral roots from L5–S3 are exposed, the ventral roots of L5 and S2 separated from their respective dorsal roots and sectioned. Then, the proximal end of the L5 ventral root is sutured to the distal end of the S2 ventral root. Variations included transfer of the L5 ventral root to S2 and S3 ventral roots, or L4 or S1 ventral roots to S2 or S3 ventral roots. Abbreviations: *, sectioned; CG, coccygeal; CNS, central nervous system; L, lumbar; S, sacral; SCI, spinal cord injury.

had decreased detrusor pressure and residual urine, and increased bladder capacity by 9 months after surgery.⁴⁶ These results provide clinical evidence that somatic motor axons can grow into autonomic nerves, and that an artificial skin-to-bladder reflex pathway can be established in patients with SCI and spina bifida.

In 2010, Peters and colleagues⁶⁸ reported the results of a similar study in children with spina bifida (Table 6). Nine patients with NBD related to spina bifida underwent the Xiao procedure, with Xiao directly participating in the surgeries. By 1 year after surgery, seven patients (78%) had a reproducible increase in bladder pressure during urodynamic testing with stimulation of the dermatome related to the nerve root used for coaptation. No patient was completely continent of urine, but the majority reported improved bowel function. As a result of the operation, one patient had a persistent foot drop at 1 year after surgery. Because these 1-year results⁶⁸ were not as encouraging as those reported by others,^{45,46,66} more studies and longer follow-up periods were recommended by the authors.⁶⁸

In summary, the Xiao procedure, in which efferent portions of a normal somatic reflex (such as the patellar or Achilles reflex arcs) are rerouted to motor nerves involved in autonomic bladder function, was successful in some studies,^{45,46,66} but disappointing in others,⁶⁸ particularly when success was evaluated after >2 years after surgery.⁶⁷

Of note, the study in the neurally intact cat⁴³ should be repeated in both neurally intact and spinal-transected cats to mimic the clinical state of human patients for which this surgery is intended. It is well known that, following spinal cord transection, spinal reflexes below the transection become hyperactive. Thus, control groups of spinal-transected animals with sham nerve transfer need to be studied to determine whether these hyperactive reflexes initiate micturition following dermatome scratching or FES even in the absence of nerve transfer. Ideally, the researchers performing the urodynamic examination of the cats following the surgery should be unaware of the type of surgery the cats had received.

Alternative management of NBD

Application of FES

FES describes the use of electrical current in excitable tissue to supplement or replace functions that have been lost in neurological injuries and assist or substitute an individual's voluntary ability. In general, activation of neuromuscular tissue requires at least two electrodes, placed near the peripheral nerve to be stimulated, to enable current flow. A localized electric field is established, which depolarizes the cell membranes of adjacent nerves, followed by an increased influx of extracellular sodium ions into the intracellular space generating action potentials.⁶⁹

To generate muscle contraction, the stimulus has to be applied along the length of the peripheral nerve, but not to the muscle itself. The number of nerve fibres that become activated and the force of the muscle contraction is determined by the strength of the electrical stimulus (amplitude and duration). In addition, the pulse frequency and waveform are important. To activate small-diameter, high-threshold autonomic nerves and generate contraction of a smooth muscle, the pulse amplitude has to be considerably higher than the amplitude required for activation of large-diameter, low-threshold motor axons that innervate striated muscle. The pulse height needs to be enough to generate a smooth muscle contraction. The stimulus itself can be monophasic or biphasic, but in the clinical setting, a balanced biphasic stimulus usually enables better control of the force of the muscle contraction and is less likely to cause tissue damage.⁷⁰ A balanced biphasic stimulus consists of a cathodic phase, in which the action potentials are initiated and the neural reaction is elicited, followed by an anodic phase that cancels the accumulated charge on the electrode and prevents electrolysis with dissolution of the electrode and tissue damage.⁷¹

Finetech-Brindley FES system

Spinal cord stimulation for NBD treatment is based on unexpected observations following spinal cord stimulation to control pain in patients with multiple sclerosis.⁷² Stimulation of the cord region that contains the micturition centre generated not only contraction of the detrusor muscle, but also contraction of the urethral sphincter, increasing outflow resistance and inhibiting

Table 6 | Creation of an artificial skin–CNS–bladder pathway

Study	Procedure	Functional recovery (time)	Evidence	Limitations	Possible application
Xiao <i>et al.</i> (1994) ⁶⁵	L4 v → L6 v (L4 d intact) Intradural, unilateral Rat model	Yes (3–12 months)	Dorsal rhizotomy not required; ipsilaterally, FES of sciatic nerve or scratching skin of legs induced bladder contraction	Less promising results in patients in other studies ^{67,68}	SCI in upper S segments and spina bifida
Xiao <i>et al.</i> (1999) ⁴³	L7 v → S1 v (L7 d intact) Intradural, unilateral Feline model	Yes (3–7 months)	Detrusor contractions induced by FES or scratching of the L7 dermatome; voiding stimulated without detrusor–EUS dyssynergia	Less promising results in patients in other studies ^{67,68}	SCI in upper S segments and spina bifida
Xiao <i>et al.</i> (2013) ⁴⁵ and Tuite <i>et al.</i> (2013) ⁶⁷	L5 v → S2 and S3 v L4 v → S2 v S1 v → S3 v Depending on level of injury; d roots intact Patients with SCI	Yes (Xiao) (12–18 months) Not long-term (Tuite)	Recovery of bladder storage and emptying	Neuroma formation; little nerve growth across suture site and recovery not long-term ⁶⁷	SCI in upper S segments
Lin <i>et al.</i> (2009) ⁶⁶	S1 v → S2 v (S1 d intact) Patients with SCI	Yes (12 months)	Elimination of detrusor–EUS dyssynergia; increased bladder capacity; decreased residual urine	Recovery not long-term	SCI in S segments below S1, or cauda equina
Xiao <i>et al.</i> (2005) ⁴⁶ and Peters <i>et al.</i> (2010) ⁶⁸	L5 v → S3 v Intradural, unilateral Children with spina bifida	Yes (6–24 months)	Increased bladder capacity and decreased residual urine ⁴⁶ Increased bladder pressure with stimulation of related dermatome; increased bowel function ⁶⁸	No patient completely continent of urine; partial loss of motor function in lower limb in 1 patient ⁶⁸	Spina bifida

Abbreviations: →, transfer to; d, dorsal; EUS, external urethral sphincter; FES, functional electrical stimulation; L, lumbar; S, sacral; SCI, spinal cord injury; v, ventral.

voiding.⁷³ Based on these findings, an implantable device with tripolar electrodes, wires and a receiver generator controlled and powered by an external portable unit was developed.⁷⁴ The device could be programmed to generate a strong contraction of both detrusor muscle and striated muscle of the urethra, followed by a sphincter fatigue while the detrusor muscle was still contracting, resulting in effective voiding immediately after cessation of stimulation.⁷⁴

Multiple studies of selective FES of sacral roots have been performed in dogs.^{73,75–77} The results of these studies indicate that unwanted spinal reflexes that facilitate pain and sphincter contraction during stimulation are greatly diminished after dorsal root rhizotomy.⁷⁶ In addition, because voiding is controlled by both parasympathetic preganglionic neurons controlling the bladder and somatic motor neurons controlling the sphincter, pudendal neurotomy, in combination with dorsal rhizotomy, can eliminate neural influences on the sphincter, producing more efficient micturition in response to FES of ventral roots.⁷⁷

The Finetech-Brindley device is the most widely used FES system and has proven to be one of the most effective devices for triggering bladder contraction in patients with NBD by upper motor neuron lesion. It improves the degree of continence, bladder capacity and compliance, which results in abrogation of or a decrease in upper urinary tract dilatation and recovery of renal function. In addition, its use decreases residual urine volume, abolishes autonomic dysreflexia and eradicates high pressure ureteric reflux. Usually the electrodes are implanted extradurally and bilaterally on S2, S3 and S4 nerve roots after laminectomy, followed by anterior sacral root rhizotomy. The electrodes are then connected to a stimulator that is implanted in the abdominal wall. Postoperative follow-up of patients with this type of FES

system shows that the most common adverse event is stress incontinence owing to device failure. However, this malfunction occurs very rarely even after up to 20 years of implantation.⁶⁹

Future Research

The normal functions of the lower urinary tract structures are storage and elimination of urine. These functions are performed by coordinated actions of the detrusor and urethra under the control of the brain and lumbosacral spinal cord. After SCI, the voluntary control of the lower urinary tract can be lost owing to disconnection of the higher centres of the CNS from the detrusor muscle and the EUS, leading to NBD.^{1–4,48,78–80} During the past century, research into recovery of storage and emptying functions of a decentralized bladder after root injury or SCI has led to new concepts and methods for recreating the normal neural pathways of the lower urinary tract, or creation of new pathways for recovery of bladder function. However, to fully meet these goals, more research is still needed.

Key priorities for future investigation include the development of a means of restoring increased bladder volume without also inducing a large increase in pressure (that is, improving bladder compliance), as both functions are needed for efficient storage and continence. In addition, whether the surgical bladder reinnervation techniques discussed in this Review also reinnervate the EUS is unclear. If they do, future investigations should aim to develop a way to promote coordinated detrusor–EUS function, avoiding dyssynergia. Some surgical procedures reinnervate the detrusor muscle (and potentially the EUS). Is FES of the newly established efferent pathways needed, and what type of stimulation would be needed to promote efficient voiding at low pressures?

After injury, obstruction, or denervation, the collagen content of the bladder can increase and either compliance or efferent neural input of the bladder decrease, resulting in afferent firing followed by increased bladder sensation and a decreased volume threshold for micturition.^{81,82} However, some of the studies described in this Review suggest that the afferents of newly established pathways might be functional and contribute to bladder sensations.^{38,64,69,70} Is the increase in afferent firing caused by the increase in collagen and the associated decrease in muscle compliance, or are these afferents part of newly formed circuitry? A better understanding of the reorganization of central pathways after these reinnervation surgeries is needed to be able to answer this question.

More studies are needed to determine the end organ targets of the newly established efferents after reinnervation. We have previously found that transfer of the genitofemoral nerve (a mixed somatic sensory and motor nerve) to the pelvic nerve leads to innervation of neurons of intramural ganglia, as well as direct innervation of smooth muscle fibres.¹⁹ However, the end organ targets after transfer of other nerve types have yet to be examined. Lastly, the types of receptors activated by the transferred nerves for storage and voiding reflexes need to be determined in physiological studies. An understanding of the physiological events mediating micturition and continence after the varied reinnervation strategies is required for full management of lower urinary tract dysfunction.

Conclusions

Although UTIs and renal failure due to NBD are no longer the principal cause of death after SCI in humans, better management of the disorder and restoration of bladder functionality is very important to improve the quality of life of paraplegic and quadriplegic patients, and children with spina bifida. During the past century, diverse studies have focused on the development of surgical techniques to re-establish and/or create new pathways between the bladder and the spinal cord. These approaches have had some success but also identified limitations. Overall, the studies discussed in this Review indicate that rewiring of peripheral connections after upper or lower motor neuron lesions might improve and even restore lower urinary tract function.

Even though the findings of early studies were limited by small sample sizes or complications such as scar tissue formation, pioneers like Kilvington, Frazier, Mills, and Trumble were able to demonstrate that the bladder could be functionally reinnervated by nerve branches other than those that normally supply this organ.^{15–17,27} Their findings suggest that recovery of bladder emptying could be promoted by end-to-end transfer surgeries, using a variety of spinal roots or nerves, including transfer of thoracic or lumbar ventral roots to sacral ventral roots.

The field of neurourology has advanced considerably since these first attempts. Strategies, such as end-to-end root repair,^{23,25,26,36,53,54} intradural root-to-root cross-over repair,^{15,27,35} spinal-nerve-to-root cross-over repair,^{22,24,30,42}

or the reverse root-to-spinal-nerve repair,^{37,38,40,41} direct detrusor reinnervation,³² transfer of peripheral somatic or autonomic nerves to vesical branches of the pelvic nerve,^{17–21,29,33–36} and even creation of artificial skin–CNS–bladder pathways,^{43–47,66–68} have been developed to improve the management of NBD based on the concept that axons have the capacity to regenerate in the peripheral and central nervous systems.

In the clinical application of nerve rerouting surgeries for bladder reinnervation, the surgeon, the patient and the patient's family all desperately want the surgery to result in permanent improvement of bladder emptying and storage function. Because of this desire, the possibility is considerable that these patients and their families might report exaggerated improvements, even when there was no or only marginal actual change in bladder storage and emptying function. Similarly, the clinician might overestimate the success. Ideally, the effectiveness of the reinnervation surgeries should be evaluated using double-blind protocols, in which neither the patient and their families nor the clinician performing the functional evaluation are aware whether a reinnervation or sham procedure was performed. It is clearly not ethical to perform sham surgery in humans. However, it is also unethical to promote a surgical procedure that is not proven effective. One ethical possibility might be to perform a randomized surgical bladder reinnervation trial in a group of patients that are undergoing current standard of care spinal surgery, such as patients with spina bifida that require a spinal cord untethering procedure. During the untethering procedure, patients could be randomized to undergo either a reinnervation nerve transfer, such as the Xiao procedure, or a sham reinnervation. The patients, the patients' family members and the clinicians performing the follow-up urodynamic evaluations must be kept unaware whether the patient received the reinnervation or the sham surgery. Long-term follow-up evaluations of at least 2–3 years are required, so that initial positive results, which have been reported after up to 18 months following surgery,^{45,46,66,67} are not overinterpreted as indicators of permanent improvement. Ideally, these surgeries should be based on positive results in at least two different animal species with similar long-term follow-up results.

Review criteria

The resources for this Review consisted of a comprehensive survey of different surgical techniques used in animal models and patients between the years 1907 and 2013. Search criteria of publications were identified using a range of keywords, including “bladder”, “reinnervation”, “spinal cord injury”, “surgical techniques”, “functional electrical stimulation” and “FES” during online searches of Wiley-Blackwell journals, PubMed and Ovid. We also searched the reference lists of published papers (original research and review articles) from over 52 different authors in the field. Only data published as full papers in peer-reviewed journals in English were considered.

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Does It Work in the Long Term?—A Systematic Review on Pelvic Floor Muscle Training for Female Stress Urinary Incontinence

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Aims: There is level 1, grade A evidence that pelvic floor muscle training (PFMT) is effective in treatment of stress urinary incontinence (SUI), but long-term outcome has been questioned. The aim of this systematic review was to evaluate the long-term outcome of PFMT for female SUI. **Methods:** Computerized search on PubMed up to year 2012 was undertaken with the search strategy: pelvic floor AND (urinary incontinence OR stress urinary incontinence) AND (training OR exercise OR physical activity) AND (follow-up OR long-term). Limitations were: humans, female, clinical trial, English, and adults. Inclusion criteria were: studies on SUI using PFMT with or without biofeedback as the intervention, follow-up period of ≥ 1 year. Exclusion criteria were studies using electrical stimulation alone and studies in the peripartum period. **Results:** Nineteen studies were included (1,141 women followed between 1 and 15 years). Statistical meta-analysis was not performed due to high heterogeneity. Only two studies provided follow-up interventions. Losses to follow-up during the long-term period ranged between 0% and 39%. Long-term adherence to PFMT varied between 10% and 70%. Five studies reported that the initial success rate on SUI and MUI was maintained at long-term. Long-term success based on responders to the original trial varied between 41% and 85%. Surgery rates at long term varied between 4.9% and 58%. **Conclusions:** Short-term outcome of PFMT can be maintained at long-term follow-up without incentives for continued training, but there is a high heterogeneity in both interventional and methodological quality in short- and long-term pelvic floor muscle training studies. *Neurourol. Urodynam.* 32:215–223, 2013. © 2012 Wiley Periodicals, Inc.

Key words: exercise; follow-up; pelvic floor; urinary incontinence

INTRODUCTION

In 1948, Kegel¹ was the first to report pelvic floor muscle training (PFMT) to be effective in treatment of female urinary incontinence (UI). In spite of reports of cure rates of $>84\%$ in his series of patients, surgery soon became the first choice of treatment. Not until 1980s, there was renewed interest for conservative treatment. Today, there are >60 randomized controlled trials reporting statistically and clinically significant effects of PFMT on stress urinary incontinence (SUI) and mixed urinary incontinence (MUI) with predominately SUI symptoms, and several consensus statements based on systematic reviews have recommended conservative treatment and especially PFMT as the first choice of treatment for SUI/MUI.^{2–7}

Subjective cure/improvement rates of PFMT reported in RCTs in studies including groups with SUI and MUI vary between 56% and 70%.^{3–7} Short-term (immediately after cessation of training) cure rates of 44–80%, defined as ≤ 2 g of leakage on different pad tests, have been found after PFMT.^{8–16} The highest cure rates at short-term were shown in single blind RCTs of high methodological and interventional quality.^{14–16} The participants had thorough individual instruction by a trained physiotherapist, combined training with biofeedback or electrical stimulation, and had close follow-up once or every second week during the intervention period. Adherence was high, and dropout was low.^{14–16} Since biofeedback and electrical stimulation have not been conclusively shown to give additional effect to PFMT in RCTs and systematic reviews,^{3–5,7} one could hypothesize that the key factors for success include close follow-up and high adherence to the training protocol.

While there is Level 1, grade A evidence of short-term effect of PFMT for female SUI or MUI with predominately SUI symptoms, there are still questions on the long-term outcome. In a Cochrane review evaluating PFMT versus no treatment, or inactive control treatments for UI in women, it was concluded that few data are available from long-term follow-up after cessation of supervised training.⁶ The aim of the present systematic review was to present long-term results of PFMT with or without biofeedback on SUI and MUI with predominately SUI symptoms, including both RCTs and pre- post-evaluation studies.

MATERIALS AND METHODS

Results from intervention studies with a pre- and post-test design, non-randomized controlled trials and RCTs using PFMT with or without biofeedback to treat SUI and MUI with predominately SUI symptoms are reported. Computerized search on the PubMed with the following search strategy was undertaken: Pelvic floor AND (training OR exercise OR physical

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Christopher Chapple led the peer-review process as the Associate Editor responsible for the paper.

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activity) AND (urinary incontinence OR stress urinary incontinence) AND (follow-up OR long-term) with the following limits activated: humans, female, clinical trial, English, and all adults. In addition, computerized search on the PEDro database, abstracts from the International Continence Society (ICS) and International Association of Urogynecology (IUGA) from 1990 onwards, and hand-searching of reference list of studies eligible for inclusion and former systematic reviews and guidelines were carried out.^{2-7,17}

Long-term was defined as ≥ 1 year follow-up time after cessation of the original PFMT intervention. Excluded were studies in the peripartum period and studies using electrical stimulation only. Two researchers extracted data from the studies and classified them independently. Each study was classified according to pre-set criteria; original design, original intervention, short-term effect, length of the long-term follow-up period, whether there was follow-up intervention (yes or no), description of outcome measure at long-term follow-up, loss to follow-up and adherence to PFMT in the follow-up period and long-term outcome. Surgery rate during the follow-up period was the pre-set primary outcome and report of cure/maintenance of improvement was the secondary outcome. The PRISMA statement for reporting systematic reviews was followed¹⁸. For controlled studies, scores of internal validity given by independent raters of the PEDro database were used if available, if not, they were scored independently by the two reviewers using the PEDro score.¹⁹ PEDro is a 10 point scale giving 1 point for each of the following criteria: random allocation, concealed allocation, baseline comparability, blinding of subjects, blinding of therapist, blinding of assessor, adequate follow-up ($\geq 85\%$), intention to treat (ITT) analysis, report of statistical comparison between groups and provision of point estimates and measures of variability.

RESULTS

Search on PubMed identified 44 studies, with 17 long-term studies of PFMT fulfilling the inclusion criteria. Two additional studies were found by hand search of reference lists. The 19 studies included 1,141 women and are presented in Table I.^{11,20-37} Three research groups reported long-term results for the same original study at two time points (21 and 30, 27 and 35, 28 and 36). Follow-up results from both time-points are reported in the table. Five studies were excluded because of shorter follow-up period than 1 year.³⁸⁻⁴²

Nine of the long-term studies were based on an original pre- and post-(non-controlled) study design^{21,22,24,26,28,30,31,33,36} whereas nine studies were follow-up studies of original RCTs.^{11,20,23,27,29,32,34,35,37} One follow-up study was based on a non-randomized design with a control group.²⁵ Mean PEDro score for the nine RCTs was 5.1 (range 4-6). Eight of the original RCTs providing long-term follow-up studies compared different methods or intensities of PFMT while one RCT²⁹ and one non-randomized study²⁵ compared PFMT with untreated control groups and one RCT compared PFMT with surgery.²³ In the two trials with an untreated control group, the control group crossed over to PFMT after the short-term study period, and analyses of long-term results between the original treatment groups could not be carried out.

The follow-up period varied between 1 and 15 years. In all but two studies,^{31,37} there were no incentives for training in the follow-up period. Kiss et al.³¹ reported that the participants were told to continue training, and that reminders were used to incentive PFMT during the follow-up period. Kim et al.³⁷ provided monthly group training classes, and asked the women to do individual home training. In most studies,

loss to follow-up was reported, and varied between 0%^{21,27} and 39%³¹. Adherence reported as number of women doing PFMT varied between 10%²⁶ and 70%²⁷. Six of 17 studies did not report adherence to PFMT at follow-up or during the follow-up period.^{11,22,28,31,34,36}

Most of the studies used self-report questionnaires for outcome assessment. Eight long-term studies^{22,23,27,28,31,33,34,36} interviewed the patients and/or used different pad tests, tested PFM function or applied urodynamic assessments. Eight of the studies used instruments that have been tested for reliability and validity, for example, ICIQ, Leakage index, Severity index, 7 day bladder diary.^{27,29,31-35,37} Twelve long-term follow-up studies reported surgery rates occurring in the follow-up period.^{20-23,26-30,34,35}

Long-term results are shown in Table I. Because of high heterogeneity in study design, outcome measures, cross-over of interventions, length of follow-up and losses to follow-up, no meta-analysis was performed. The results at long-term vary between studies. Surgery rates at follow-up vary between 4.9% at 28 months²⁸ and 58% after 4-8 years.²³ In the two studies with the longest follow-up, surgery rates were 8% at 10 years³⁰ and 50% at 15 year.³⁵ Only one RCT originally compared PFMT with surgery.²³ After the initial intervention, which showed that surgery was superior to PFMT, the women were offered the other intervention. At follow-up, the initial satisfaction and cure rates were maintained in both the PFMT and surgery group. Bø et al.³⁵ found that operated women were more likely to report severe incontinence ($P = 0.03$) and leakage that interfered with daily life ($P = 0.04$) than non-operated women at 15 year follow-up.

Altogether five studies stated that the initial success rate was maintained at follow-up.^{23,24,29,32,33} Seven studies reported long-term outcome based on short-term success.^{22,23,28,30,34-36} All of these studies reported that the effect was better maintained in the responders than non-responders to the original program, and long-term success after short-term success varied between 41% and 85%. Kondo et al.²⁸ reported that 19% of non-responders to short-term training were successors at 28 months follow-up, not counting the 4.9% who had surgery. In a later 8 years, follow-up by the same research group, the increase in muscle strength during the original program was the only reported parameter predicting positive long-term effect.³⁶ No side effects from long-term PFMT have been reported.

DISCUSSION

This systematic review found 19 long-term studies on PFMT for women with SUI or MUI with predominately SUI symptoms. However, it is difficult to make meaningful comparisons between studies and to give pooled long-term cure rates, as the original short-term studies are heterogeneous when it comes to inclusion criteria, research design, outcome measures, exercise protocols with a huge variety of training dosages, use of adjuncts to PFMT such as biofeedback or vaginal cones, different adherence rates and finally different short-term success rates. For the long-term studies, further heterogeneity is added on in terms of length of the follow-up period, use of different outcome measures, co-interventions during the follow-up, competing events and losses to follow-up. This introduces what we would name "a double heterogeneity problem" in critical appraisal of long-term follow-up studies.

As for now, there are several recommendations on how to assess methodological quality of single RCTs^{19,43} and systematic reviews and meta-analysis,¹⁸ but we have not been able to find any specific guidelines on quality assessment of long-

TABLE I. Short and Long-Term Effect of Pelvic Floor Muscle Training for Female Stress Urinary Incontinence (SUI)

Author/year	Original design/Numbers (n)/type of UI/PEDro score	Original intervention	Short-term effect	Long-term follow-up period	Follow-up intervention?	Long-term outcome measure	Loss to follow-up/adherence of PFMT in follow-up period	Long-term effect
Ferguson et al. (1990) ²⁰	RCT/n = 20 SUI based on history and urodynamic assessment PEDro:5/10	Group 1 (n = 10): 6 weeks of PFMT at home with an audiotape with vaginal balloon as biofeedback; Group 2 (n = 10): As group 1 without biofeedback. Vaginal palp	No difference between groups. Sign reduction of UI episodes and leakage within groups	1 year	No	Questionnaire by letter or phone: Improvement of SUI and surgery rate	1 loss to follow-up. 50% reported to exercise	3 had surgery (15%); None out of 19 were worse; Those still exercising reported to be improved
Cammu et al. (1991) ²¹	Cohort/n = 52 SUI based on history and urodynamic assessment	10 weeks of PFMT 30 min with PT twice/week + training as frequent as possible at home and use pre-contraction with cough. Diary. Vaginal palp	Cured: 23% (12 of 52); Much improved: 29% (15 of 52); Some: 40% (21 of 52); Unchanged/worse: 8% (4 of 52); 7 had surgery (13%)	14 months	No	Postal questionnaire with multiple choice and open questions: Improvement of SUI	7 losses to follow-up. Adherence not reported	Cured: 20% (9 of 45); Much improved: 38% (17 of 45); Some: 31% (14 of 45); Unchanged/worse: 11% (5 of 45); 3 had surgery (5.8%)
Mouritsen et al. (1991) ²²	Cohort/N = 76; Women referred to surgery for SUI based on history and urodynamic assessment	3 months with PT. Individual instruction, self palpation. 45 min weekly group sessions. Anal pressure measurement	67% cure rate	1 year	No	Clinical assessment (?) with self report. Improvement of SUI + Pad test (unclear if this is included in follow-up cure rate)	Not reported	Cured: 30%; Much improved: 17%; 47% avoided surgery. 11 of 13 (85%) originally cured still cured. Of 37 patients improved 1/3 moved to cured
Klarskov et al. (1991) ²³	RCT with cross over to surgery or PFMT after short-term period/ N = 52; SUI based on urodynamic assessment; PEDro:6/10	Group 1 (n = 24): PFMT for 4 months with weekly group session with PT + home exercise in 4 positions with 5 contractions 4 times/day; Group 2 (n = 28): Surgery, Procedure chosen on basis of colpocystourethrography	42% satisfied with PFMT, 71% satisfied with surgery	Median 6 years (4–8)	14 out of 24 (58.3%) in the original PFMT group had surgery: 8 out of 28 (28.6%) in the originally operated had PFMT	Clinical assessment, interview or questionnaire on use of pads, improvement of SUI, number of incontinent patients, pad tests in 41, urinary diary in 37	4 loss to follow-up. 59% PFMT ≥ once a week, 28% occasionally, 14% never	10 had PFMT only, 2 of them worse, the rest were similar as short term. No change in number of pads and incontinence episodes; 20 had surgery only 22 had both treatments; Same satisfaction rates as after original intervention period
Dougherty al. (1993) ²⁴	Cohort/n = 80 PFMT started after control period. Mild to moderate SUI based on history and urodynamic assessment	Four week control period (no treatment); 16 weeks of PFMT 3 times/week with nurse. Palp. Measurement of PFM strength	Significant reduction in pad test and leakage episodes after PFMT compared to control period; Loss to short-term follow-up: 15/80 (18.7%)	14–26 months	No	Postal questionnaire asking about degree of urine loss	10 (15%) loss to follow-up at long term; 54% continued PFMT, 17% exercised 3 ≥/week	87% reported same urine loss as after cessation of training in original study or that it had diminished
Hahn et al. (1993) ²⁵	Cohort with control group/n = 197 women referred to surgery for SUI based on history/ urodynamic assessment Comparison group on waiting list for surgery PEDro:3/10	Individual training program with PT once a week for 5 weeks, vaginal palp, then exercise at home 6- times/day for mean 4.7 months (range 1–18); Control group on waiting list for surgery	23% cured; 48% improved; 29% unchanged; 64% cured/ improved on provocative test (coughing, jumping, running)	2–7 years	No	Postal questionnaire asking about improvement of SUI	11% loss to follow-up: 15% daily training	Long-term results only reported in PFMT group. 25% had surgery. Of the remaining 11% reported to be cured, 44% improved, 31% unchanged, 14% deteriorated

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TABLE 1. (Continued)

Author/year	Original design/Numbers (n)/type of UI/PEDro score	Original intervention	Short-term effect	Long-term follow-up period	Follow-up intervention?	Long-term outcome measure	Loss to follow-up/adherence of PFMT in follow-up period	Long-term effect
Holley et al. (1995) ²⁶	Cohort/n = 14 after Tchou et al. (1988); SUI, based on urodynamic assessment	4 weeks with individual PFMT sessions 30 min/2 times a week with PT	All subjects had subjective improvement. 9 (64.3%) had no leakage on cough or strain test	5 years	No	Postal questionnaire	4 (14.5%) loss to follow-up. 1 continued (10%) to exercise (she reported SUI, but reduction in frequency of leakage by training)	4/10 had surgery and were continent. 6/10 without surgery were leaking
Bo and Talseth (1996) ²⁷	RCT/n = 52 SUI after urodynamic assessment; PEDro: 6/10	Group 1 (n = 30): Home exercise: vaginal palp, measurement of PFM strength, 7 visits with PT for motivation and measurement of PFM strength, 8–12 contractions 3 times/day. Diary; Group 2 (n = 23): Intensive exercise: Same as home exercise + group training once a week. Emphasis on maximum contraction	Home exercise: 17% satisfied; Intensive exercise: 60 % satisfied and positive closure pressure during cough. Significantly more reduction of leakage on pad test, social activity index and leakage index than home exercise.	5 years	No	Clinical assessment, urodynamics, pad testing, interview, leakage index, social activity index, measurement of PFM strength	Only intensive training group reported. No loss to follow-up. 70% trained \geq once/week	Follow-up of Intensive group only (n = 23). 70% satisfied, did not want further treatment, same muscle strength, 15 (75%) no visible leakage during cough, 11 had positive UCP during cough, 30% no leakage on pad test. Significant increase in leakage on pad testing and leakage index, but no change in social activity index. 3 (13.6%) had surgery; two successful, one had 17 g leakage on pad test after surgery
Glavind et al. (1996) ¹¹	RCT/n = 40; SUI based on history and urodynamic assessment; PEDro: 6/10	Vaginal palp Group 1: 2–3 times with individual instruction. Home training at least 3 times/day; Group 2: same as group one + 4 times with biofeedback (EMG)	Sign better results subjectively and on pad test for group two. 58% cured in group two, 20 % in group one	2–3 years	No	Postal questionnaire, improvement of SUI	3% loss to follow-up. Adherence: Group 2: 89% did regular PFMT; Group 1: 50% did regular PFMT	Group two: 26% reported to be cured, 42% improved. 75% accept current situation. Group one: 0 reported to be cured, 29% improved. 50% accept current situation
Kondo and Yamada (1996) ²⁸	Cohort/N = 103 SUI and MUI based on history. Study group divided on age over 65 years (n = 15) and under 65 years (n = 108)	Vaginal palpation. Fast and long contractions. 90 min group training once a week with 10 participants for 8 weeks. Use of different postures in training group. Home exercise: 3 sets of 10 slow and 5 fast contractions + vaginal cones 15 min twice daily at home. Diary.	Success rate (cured or reduction of UI > 50%) 40% in group under 65 years and 20% in group over 65. Urine loss and bothersome scores improved in the youngest group only (pad test: from 13.00 g (SD 14.9) to 5.9 g (SD 10.1). 95% stated that training was valuable and would recommend it	Mean 28 months (range 12–52)	No	Clinical assessment: Pad test, bother, self-reported success rate, muscle strength by manometer	No loss to follow-up. Adherence not reported	Same success rate. 6 (4.9%) had surgery
Lagro-Janssen and van Weel (1998) ²⁹	Cohort with control group/n = 110, age 20–65 years; SUI, UUI, MUI based on history/	SUI: PFMT by GP, vaginal palp, written instruction, 5–10 daily sessions of 10 exercises;	60% dry/mildly incontinent in PFMT, one in control; 74% improved or cured; Leakage episodes: PFMT: 20–7;	5 years	No	Postal questionnaire with self-report + 7 days bladder chart	5 loss to follow-up + 7 who had surgery; SUI: adherence: 39% exercised \geq 1/day. 15%	7 had surgery (6.9%), 14 had received additional treatment. Number of continent women

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TABLE I. (Continued)

Author/year	Original design/Numbers (n)/type of UI/PEDro score	Original intervention	Short-term effect	Long-term follow-up period	Follow-up intervention?	Long-term outcome measure	Loss to follow-up/adherence of PFMT in follow-up period	Long-term effect
Cammu et al. (2000) ³⁰	urodynamic assessment PEDro: 3/10	UII: bladder training; MUI: bladder training + PFMT	Control: no change; Perceived improved: PFMT: 85%; Control: 0	10 years	No	Postal questionnaire, review of medical files for surgery rates, self-reported improvement of SUI	once a week, 43% no exercise	remained the same. Number who worsened increased. 40% remained in the same category. Wet episodes significantly increased. Long-term results dependent on type of incontinence. SUI stayed the same. 67% satisfied, did not want further treatment
Kiss et al. (2002) ³¹ (abstract)	Cohort/n = 52; SUI based on history and urodynamic assessment	See Cammu et al. (1991)	See Cammu et al. (1991)	6 years	Controls by PT and physician every 3 months	Clinical assessment. Pad test, UPP, PFM strength (vaginal manometry), QoL (results not reported)	13% loss to follow-up. 76% of those successful at short time had exercised, 55% of those not successful	16/24 (66.7%) successful patients remained satisfied. 2 (8%) had surgery.
Alewijnse et al. (2003) ³²	Cohort/n = 36; SUI based on history and urodynamic assessment	6 weeks PFMT by PT, assisted by biofeedback and electrical stimulation. Home training with PT controls every 3 months	Pad test: 10 dry; 17 improved; 7 unchanged; 2 worse; PFMT strength \times time: 171.5 cm H ₂ O sec	1 year	No	Postal questionnaire including 7 day diary, improvement of SUI, wet episodes	20% loss to follow-up. 67% followed behavioral advice	Pad test: 6 dry; 12 improved; 4 unchanged; Strength \times time: 120.6 cm H ₂ O sec
Parkkinen et al. (2004) ³³	RCT/n = 121; SUI/urge/mixed based on history; PEDro: 4/10	Four groups Group 1 (n = 29): Individual PFMT; Group 2–4 (n = 22, 25, 27). Individual PFMT + 1 out of 3 different adherence strategies; Diary	No difference between groups. Wet episodes reduced from mean 23 to 8 per week, 74.8% (ITT 64.4%) cured or improved by 50%. Same results for SUI; urge and mixed	5 years	No	Clinical examination; pad test and questionnaire including urinary incontinence severity score (UISS), self-reported cure/improvement of SUI. Assessment of PFM function with EMG	4 had surgery + one loss to follow-up. 25% exercised regularly after 12 months. 41% had physiotherapy in group 2 after 12 months	Group 1: 37.5% reported cure, 31.3% improvement; Group 2: 11.8% cure, 47.1% improved; Pad test: reduction from mean 23 g/14 g to 1 g in both groups; Significant improvements in strength in both groups. In general effect maintained

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TABLE 1. (Continued)

Author/year	Original design/Numbers (n)/type of UI/PEDro score	Original intervention	Short-term effect	Long-term follow-up period	Follow-up intervention?	Long-term outcome measure	Loss to follow-up/adherence of PFMT in follow-up period	Long-term effect
Aukee et al. (2004) ³⁴	RCT/n = 35; SUI based on history and urodynamic assessment; PEDro: 5/10	All participants had 5 visits with PT during 12 weeks. All registered adherence. In addition: Group 1 (n = 19): home exercise 20 min 5 times/week; Group 2 (n = 16): individual EMG- assisted biofeedback device for home training	No difference between groups in Leakage index or pad test. Group 2 had better improvement in EMG activity	1 year	Advised to continue training on their own initiative	Clinical assessment; Leakage index; surgery during follow-up; EMG	4 (11.4%), but two were interviewed by phone. No report of adherence during follow-up period	14 (45.2%) women had undergone surgery or waited for operation (9/19 (47.4%) in PFMT and 5/16 (31.3%) in the biofeedback group. Decrease in Leakage index during the intervention decreased the risk for an operation. 67% considered PFMT to be effective or very effective
Bo et al. (2005) ³⁵	RCT/n = 52; SUI based on history and urodynamic assessment; PEDro: 7/10	Comparison of two different training regimens. See Bø and Talseth (1996)	See Bø and Talseth (1996)	15 years	No	Postal questionnaire: number of pads used, ICIQ-UI SF, Severity index, leakage index	"Intensive exercise": 2 loss to follow-up; "Home exercise": 4 loss to follow-up; No difference between groups in exercise adherence: 28% exercised at least once/week, 36% periodically, 36% never	No difference between original groups in satisfaction or severity. 50% of each group had had surgery. Operated women more likely to report severe leakage and leakage interfering with daily life. Of those satisfied 15 years ago 39.4 had had surgery, of those not satisfied 78.6% had surgery
Kondo et al. (2007) ³⁶	Cohort/n = 123; SUI and MUI based on history	8 weeks PFMT: vaginal palp by nurses and physicians (60–90 min group training) + "perineal lock", 30 repetitions/day at home, diary, weekly checks	37% success rate at 6 weeks and 40% at 2 years	Mean 8 years (6–10)	No	Clinical assessment: cough stress test, 60 min pad test, manometry, Postal questionnaire on self-reported cure/improvement	Loss to follow-up: 36.8%	39% success rate. 19 of 46 successors were at 8 years (41%). 12 of 77 failures were successors at long-term (11.8%). The higher the improvement in muscle strength during initial training the better the results
Kim et al. (2007) ³⁷	RCT with cross-over, hence no follow-up of control/n = 70 SUI based on ICIQ; PEDro: 6/10	60 min twice a week for 3 months, no vaginal palpation. PFMT + general fitness class	Cured (leakage episodes): *54.5% of exercise group; *9.4% control; P < 0.001	1 year	VFS: 1.group training class once a month. 2. Individual home training twice week 30 min PFM + other exercises	Interview based on ICIQ (leakage episodes):	Loss to follow-up: 37.1%; Adherence: Every day: 30.3%; 2–3 times/week: 45.5%; Once/less week: 24.2%	30.8% cure rate

Studies are listed in chronological order.

MUI, mixed urinary incontinence; Palp, vaginal palpation; PFM, pelvic floor muscles; PFMT, pelvic floor muscle training; PT, physical therapist; SUI, stress urinary incontinence; UPP, urethral pressure profile; UIU, urgency urinary incontinence.

PEDro methodological quality score: random allocation, concealed allocation, baseline comparability, blinded assessors, blinded subjects, adequate follow-up ($\geq 85\%$), results analyzed on intention to treat, between group comparisons, results reported as point estimates and variability.

term follow-up studies. Independent raters from the PEDro database had provided scores of methodological quality of the nine original short-term RCTs presented in this systematic review. As it is impossible to blind subjects and therapists during PFMT, eight should be considered the top-score for exercise studies. Scores between 4 and 6 can be considered moderate, and thus make a meaningful meta-analysis. However, this systematic review found that only one of the original RCTs compared PFMT with an untreated control,²⁹ and that only five RCTs^{11,23,32,34,35} reported long-term effect according to the original treatment arms. These five trials were too heterogeneous to make a meaningful meta-analysis. In general, one may say that in spite of the fact that only two studies gave specific advice to continue PFMT or provided exercise classes during follow-up,^{31,37} some of the studies of PFMT showed surprisingly good long-term results assessed by self-report or surgery rates.

Eight of the studies^{22,23,27,28,31,33,34,36} had interviewed the patients and/or also conducted different clinical tests such as measurement of PFM function, pad testing or urodynamic assessments. Most of the studies used simple questionnaires and questions on satisfaction or improvement, but there were also use of instruments that had been tested for clinometric properties. Again, few studies had used the same outcome measures and if two studies had used the same, they were heterogeneous in other aspects, for example, design and interventions thus preventing meaningful comparison. As for surgery⁴⁴ and drug studies,⁴⁵ a combination of cure and improvement is often reported instead of absolute cure. Moreover, to date there is no consensus on what outcome measure to choose as the gold standard for cure (negative urethral closure pressure, number of leakage episodes, ≤ 2 g of leakage on pad test [tests with standardized bladder volume, 1, 24, and 48 hr], women's report etc).^{46,47} In general, we would recommend that the same outcome measures should be used at both short- and long-term, and that only outcome measures that have been tested and found to be responsive, reliable and valid should be used in future follow-up studies.

As PFMT for SUI is considered a treatment to delay or avoid surgery, surgery rate in the follow-up period was chosen as our primary outcome measure of non-success. Surgery rates varied between 4.9% after 28 months²⁸ and 58.3% after 4–8 years.²³ Only one original RCT was found comparing the effect of surgery with PFMT, and short-term effect was clearly in favor of surgery.²³ However, the short-term effect of both PFMT and surgery was maintained after 4–8 years. In the longest follow-up study,³⁵ 50% in both originally randomized groups had had interval surgery. At 15 year follow-up, the short-term significant effect of the more intensive training protocol was no longer present. However, more women in the less intensive training group had surgery within the first 5 years after ending the training program. Interestingly, there were no differences in reported frequency or amount of leakage between non-operated or operated women, and women who had surgery reported significantly more severe leakage and to be more bothered by UI during daily activities than those not operated. There is, however, a selection bias to surgery, and the politics of when to offer surgery and to which women, vary widely between hospitals and countries. In addition, many women would not opt for surgery although they are incontinent. Hence, opting for surgery is a very difficult outcome measure to analyze and compare between studies. Hilton and Robinson⁴⁷ have shown how cure rates of surgery vary widely with definitions and methods of measuring cure. For one surgical procedure cure rates varied between 9% and 85%

depending on the definition of cure. We suggest that future long-term studies should involve both assessment of the actual leakage (pad tests and 3 day report of leakage episodes) and assessment of perceived impact and quality of life.^{46,47}

Obviously, long-term effect will depend on the initial success rate of an intervention as one would not expect short-term non-responders to be long-term responders. Hence, responders to the original trial might be the ones that should be in focus for long-term studies. This review found that only seven studies reported long-term outcome based on short-term success or non-success.^{22,23,28,30,34–36} All of these studies reported that the effect was better maintained among the responders than non-responders to the original program.

A common problem with follow-up studies after RCTs on PFMT is that usually women in the non-treatment or less effective intervention groups have received other interventions after cessation of the study period (cross-over or follow-up treatments). This may be supervised PFMT if they have been in the control group or medication or surgery if the patients wanted further treatment. If long-term results are reported following the original randomization and cross-over to other treatments is not taken into account, many women in the control group may have trained the PFM and comparison is no longer between training versus no training. Since many women may have cross-over or follow-up treatments, an intention to treat analysis at long term would bear little meaning. Further, there might be a power problem if analyzing only those who neither crossed-over nor had any follow-up treatments.²⁸

However, the main question is: can long-term outcome be expected after cessation of the active PFMT intervention? The effect of any training program will diminish with time if not continued or the pre- or co-contraction of the PFM has not reached an automatic level. In general, strength gain declines in a slower rate than the rate in which strength increases, but a 5–10% loss of muscle strength per week has been shown after training cessation.⁴⁸ Greater losses have been shown in elderly (65–75 year olds) compared to younger (20–30 years old), and for both groups the majority of strength loss was from weeks 12 to 31 after cessation of training. The rate of strength loss may depend on length of the training period prior to detraining, type of strength test used and the specific muscle groups examined. Research has not yet indicated the exact resistance, volume, and frequency of strength training or the type of program needed to maintain training gains. However, studies indicate that to maintain strength gains or slow strength loss, the intensity should be maintained, but the volume and frequency of training can be reduced.⁴⁸ One or 2 days a week seem to be an effective maintenance frequency for those individuals already engaged in a resistance training program.⁴⁸

So far, no studies have evaluated how many contractions subjects need to perform to maintain PFM strength after cessation of organized training. Lagro-Janssen and van Weel²⁹ found that satisfaction was closely related to type of incontinence and adherence to training. Mixed incontinent women were more likely to lose the effect, and SUI women had the best long-term effect, but only 39% of them were exercising daily or “when needed.” In some studies, the long-term effect seemed to be attributed to use of conscious pre-contraction before coughing and increase in intra-abdominal pressure.^{27,30}

To date, little is known about the long-term motivation for PFMT. Some women may find the exercises hard to conduct at a regular basis. However, Alewijnse⁴⁹ found that most women followed advice of training 4–6 times a week 1 year after cessation of the training program. The following factors predicted adherence with 50%: positive intention to adhere, high

short-term adherence levels, positive self-efficacy expectations, and frequent weekly episodes of leakage before and after initial therapy. In general, patients with different diseases do not comply with treatment for a wide variety of reasons: long lasting and time-consuming treatments, requirement of life-style changes, poor client/patient interaction, cultural and health beliefs, poor social support, inconvenience, lack of time, motivational problems, and travel time to clinics have been listed as factors for non-adherence.⁵⁰

Strengths of the present systematic review are the comprehensive review of the literature based on both updated computerized search and use of published systematic reviews on short-term effect of PFMT.²⁻⁷ Due to published high quality systematic reviews of short-term effect studies in this area, we consider the risk of publication bias to be low. Limitations were the quality of individual studies, only one RCT comparing PFMT with no treatment, few reports of long-term effect following the original comparison groups, heterogeneity of interventions and outcome measures used, loss to follow-up, lack of reporting of co-interventions and cross-over and lack of reports of adherence, and incentives to follow-up training. These limitations will, however, also be present in long-term follow-up studies of surgery and medication interventions.^{44,45} There is a need for further high quality RCTs to evaluate the effect of different long-term incentives to continue PFMT after successful interventions. A possible way to maintain PFM strength after a treatment period is to include PFMT in general fitness classes for women. However, this will only involve those highly motivated for general fitness activities, and to date there is no knowledge about the effect of PFM maintenance training in fitness centers.

CONCLUSION

Nineteen long-term studies after PFMT were found. Meta-analysis of results was not possible due to high heterogeneity of both original and long-term studies. Long-term success based on responders to the original trial varied between 41% and 85%. Surgery rates at long term varied between 4.9% and 58%. Future high quality RCTs comparing different training dosages and follow-up strategies after cessation of short-term studies are warranted.

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Internet-based treatment of stress urinary incontinence: a randomised controlled study with focus on pelvic floor muscle training

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Trial registration number: <http://www.clinicaltrials.gov> (ID: NCT01032265)

What's known on the subject? and What does the study add?

- Stress urinary incontinence (SUI) affects 10–35% of women, and it is sometimes very distressful. Pelvic floor exercises are the first line of treatment, but access barriers or embarrassment may prevent women from seeking help. There is a need for new, simple, and effective ways to deliver treatment.
- Management of SUI without face-to-face contact is possible, and Internet-based treatment is a new, promising treatment alternative.

Objective

- To compare two treatment programmes for stress urinary incontinence (SUI) without face-to-face contact: one Internet-based and one sent by post.

Patients and Methods

- Randomised, controlled trial conducted in Sweden 2009–2011. Computer-generated block-randomisation, allocation by independent administrator. No 'blinding'.
- The study included 250 community-dwelling women aged 18–70 years, with SUI ≥ 1 time/week. Consecutive online recruitment.
- The women had 3 months of either; (i) An Internet-based treatment programme (124 women), including e-mail support and cognitive behavioural therapy assignments or (ii) A treatment programme sent by post (126). Both programmes focused mainly on pelvic floor muscle training.
- Primary outcomes: symptom-score (International Consultation on Incontinence Questionnaire Short Form, ICIQ-UI SF) and condition-specific quality of life (ICIQ-Lower Urinary Tract Symptoms Quality of Life, ICIQ-LUTSQoL). Secondary outcomes: (i) Patient Impression of Improvement, (ii) Incontinence aids, (iii) Patient satisfaction, (iv) Health-specific QoL (EQ5D-Visual Analogue Scale), and (v) Incontinence episode frequency. Follow-up after 4 months via self-assessed postal questionnaires.

Results

- In all, 12% (30 women) were lost to follow-up. Intention-to-treat analysis showed highly significant improvements ($P < 0.001$) with large effect sizes (>0.8) with both interventions, but there were no significant differences between groups in primary outcomes. The mean (SD) changes in symptom-score were: Internet 3.4 (3.4), Postal 2.9 (3.1) ($P = 0.27$). The mean (SD) changes in condition-specific QoL were: Internet 4.8 (6.1), Postal 4.6 (6.7) ($P = 0.52$).
- Compared with the postal-group, more participants in the Internet-group perceived they were much or very much improved (40.9% (43/105) vs 26.5% (30/113), $P = 0.01$), reported reduced usage of incontinence aids (59.5% (47/79) vs 41.4% (34/82), $P = 0.02$) and were satisfied with the treatment programme (84.8% (89/105) vs 62.9% (71/113), $P < 0.001$).
- Health-specific QoL improved in the Internet-group (mean change 3.7 (10.9), $P = 0.001$), but not in the postal-group (1.9 (13.0), $P = 0.13$).
- Overall, 69.8% (120/172) of participants reported complete lack of leakage or reduced number of leakage episodes by $>50\%$.

Conclusions

- Concerning primary outcomes, treatment effects were similar between groups whereas for secondary

outcomes the Internet-based treatment was more effective.

- Internet-based treatment for SUI is a new, promising treatment alternative.

Introduction

Stress urinary incontinence (SUI) is the involuntary leakage of urine when sneezing, coughing, or on exertion [1]. Prevalence of SUI is 10–35% among women [2,3], and quality of life (QoL) may be impaired [4]. Primary care professionals are usually the first to diagnose and treat the condition. Diagnosis can be based on structured history taking and bladder diaries [5]. The recommended first-line treatment is pelvic floor muscle training [3,5–8], which leads to improvement or cure in two-thirds of patients and has no serious adverse effects [5,7,8]. In addition, lifestyle changes (weight loss if body mass index $>30 \text{ kg/m}^2$, smoking cessation, reduction of fluid intake if high) may help [5–7], and a few small studies suggest that cognitive behavioural therapy may be useful in patients with incontinence [9,10]. Despite the existence of effective treatments, only $\approx 20\%$ of affected women seek medical care [11]. There are several explanations for this: the leakage may not be a problem to the individual, it may be considered a part of normal ageing, expectations of successful treatments are low, patients may think they can manage on their own, or they may be too embarrassed to seek help [3]. Also, access to care may be limited, depending on patients' location and health care organisation, and SUI is often given a low priority in times of financial constraint. Moreover, once the woman seeks care, management is variable, and some women perceive that they do not get any help when consulting their physician [12]. Such under-treatment may be due to a lack of confidence among healthcare providers in the management of UI [13], but could also be due to a lack of resources, as supervised pelvic floor muscle training is demanding of staff.

There is no consensus on how pelvic floor muscle training should best be performed [14]. As a guideline, the National Institute for Health and Clinical Excellence recommends at least eight contractions three times daily during a 3-month period [7]. Before training initiation, the strength of the pelvic floor muscle contraction should be digitally assessed [6], but it is unclear whether this enhances the effect [7]. Supervised training sessions might give the largest improvements [14], but self-help booklets with instructions for training at home are often used in everyday practice, and have been shown to reduce the number of leakage episodes by 50% [15].

Keywords

stress urinary incontinence, randomised controlled study, Internet, pelvic floor muscle training, self-management, cognitive behavioural therapy

E-health is a growing field that offers new, flexible, and easily accessible treatment possibilities [16]. Internet-delivered treatments have previously been developed and tested for several medical conditions, e.g. chronic pain, headache, irritable bowel syndrome, and obesity [17]. Women are known to often use the Internet for health issues [18], to seek second opinions, due to discontent with healthcare providers, and for embarrassing conditions [19]. Different methods for the delivery of SUI treatments, e.g. Internet-based or self-management, have been identified as an important research field [5]. If they are found effective, such treatments could potentially increase access to care for many women. The aim of the present study was to compare the effect of two different treatment programmes for SUI without face-to-face contact: an Internet-based programme and a programme sent by post.

Patients and Methods

We performed a randomised, controlled study with two open parallel treatment arms. In all, 250 community-dwelling women, aged 18–70 years, with SUI at least once weekly were recruited via our open access website, <http://www.econtinence.se>. Invitations to the study were published on national websites for medical advice, and as advertisements in daily newspapers. Table 1 reports inclusion and exclusion criteria.

Women answered an online, 17-item survey with automated immediate response for initial screening of

Table 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Female	Pregnancy
Age 18–70 years	Previous UI surgery
SUI ≥ 1 time/week	Known malignancy in lower abdomen
Ability to read and write Swedish	Difficulties with passing urine
Access to computer with Internet connection	Macroscopic haematuria
	Intermenstrual bleedings
	Severe psychiatric disorders, or HADS score >15 for depression or anxiety
	Neurological disease with affection on sensibility in legs or lower abdomen

HADS, Hospital Anxiety and Depression Scale.

Table 2 Description and comparison of the three months treatment programmes.

	Internet-based treatment programme	Postal treatment programme
Total extent, number of pages	20	8
Information, number of pages	9	4
Illustrations, <i>n</i>	33	7
Pelvic floor muscle training, design	Increasing intensity, login codes successively	Access to all exercises from start
Exercises (duration in s × repetitions × daily frequency):	Yes	Yes
– maximum contractions (for strength) (8 × 8–10 × 3)	Yes	Yes
– submaximal contractions (for endurance) (15–90 × 1 × 3)	Yes	Yes
– quick contractions (3 × 8–10 × 2–3)	Yes	Yes
– the ‘knack manoeuvre’*	Yes	Yes
Self-reported tests of progression	Yes	No
Training report	Once a week	At follow-up
Cognitive behavioural therapy assignments	Yes	No
E-mail support by urotherapist	Yes	No

*A conscious pelvic floor muscle contraction before and during physical stress.

eligibility criteria. Items included questions on type of UI and the Incontinence Severity Index [20]. Those found eligible were asked to register contact details and were sent a postal questionnaire for further evaluation. This included a detailed medical history, socio-economic data, lifestyle, Internet usage, motivation, symptoms of anxiety or depression (the Hospital Anxiety and Depression Scale [HADS]) [21], validated instruments for baseline investigation of outcome measures (see below), and a 2-day bladder diary (time and measured volume of micturition, time and estimated volume of leakage episodes). We (M.S. or E.S.) assessed all questionnaires, instruments, and bladder diaries. Finally, to confirm the clinical diagnosis of SUI, all participants were interviewed by an urotherapist via telephone. Any medical uncertainty was discussed, and if excluded, patients were contacted for medical advice and/or referral by one of the GPs in the project. Throughout the study, there was no face-to-face contact.

Randomisation

Randomisation was through a pre-specified computer-generated list, in blocks of eight [22]. An independent administrator kept the list and consecutively allocated eligible participants to one of the two intervention groups. There was no ‘blinding’ of group allocation to study participants, healthcare providers, or researchers.

Intervention

Both groups had 3 months of treatment, via either an Internet-based programme or a programme sent by post. Both programmes included:

- 1 Information on SUI and associated lifestyle factors.
- 2 Pelvic floor muscle training.
- 3 Training reports (frequency, time spent).

Table 2 describes and contrasts the two interventions. More specifics for each intervention are given below.

Internet-Based Treatment Programme

The programme contained eight escalating levels, and was modelled in line with other Internet-based interventions [23]. Progress was self-monitored, with individually tailored support by a urotherapist. The intensity of the pelvic floor muscle training gradually increased. The urotherapist gave the participant login codes for two levels at a time, with instructions to maintain training at each level for at least 1 week. Every week, participants completed a self-evaluated test and reported a training diary to the urotherapist. New login codes were given with the passing of every other test, but not at a faster rate than every 2 weeks. In addition, the programme included cognitive behavioural therapy assignments for lifestyle change (if applicable), and for the identification and change in behaviours of avoidance and redundant security measures (if applicable).

Urotherapists actively contacted participants who failed to send in their reports according to schedule. Participants could contact their urotherapist at any time for support or questions. All contact was asynchronous, with encrypted e-mail, requiring a separate login from both participants and urotherapists. Response from the urotherapist was promised within 3 working days. Separate technical support was offered through encrypted e-mail contact with the website manager. The programme was built on a secure platform, using a two-factor authentication and Secure Sockets Layer (SSL), to provide communication security over the Internet. All parts of the programme could be downloaded for printing.

Treatment Programme Sent by Post

In the print version, the first pages contained information, followed by instructions for pelvic floor muscle training. Participants were encouraged to increase the intensity of training successively, but had access to all exercises from the start. A training report was sent to the participants, for continuous registration throughout the treatment period, and it was returned together with the first follow-up. Participants in this group had no contact with the urotherapists.

Outcome Measures

Primary outcomes

The mean symptom score was measured by the International Consultation on Incontinence Questionnaire Short Form (ICIQ-UI SF) [24]. This instrument contains three items on frequency, amount of leakage, and overall impact on quality of life (QoL). Scoring is additive (0–21), with higher values indicating increased severity. The form also contains a fourth, non-scored item, used for the assessment of type of incontinence.

Condition-specific QoL was measured by the ICIQ-LUTSQoL [25,26]. The instrument includes 19 items on the impact of leakage on role, physical, and social life, personal relationships, emotions, and sleep. All items are scored 1–4 (not at all/never, slightly/sometimes, moderately/often, a lot/all the time). Three items concerning personal relationships have an additional scoring alternative of 'not applicable'. The overall score is 19–76, with higher values indicating increased impact on QoL.

Secondary outcomes

Patient global impression of improvement (PGI-I) [27] is a validated question asking the participants to rate their current condition compared to pre-treatment status. There are seven response options, ranging from 'very much better' to 'very much worse'.

Health-specific QoL was evaluated with the EuroQol 5D-Visual Analogue Scale (EQ5D-VAS) [28], a vertical VAS with the endpoints 0 (worst imaginable health state) and 100 (best imaginable health state).

Incontinence episode frequency (IEF) was calculated from self-reported leakage episodes in the 2-day bladder diaries. A reduction in leakage episodes of >50% was considered clinically relevant [5].

Usage of UI aids was determined by asking participants to rate their usage of absorbent UI aids after treatment, compared with before treatment. Only those using UI aids before treatment were included in this analysis.

Satisfaction with the treatment programme was evaluated by asking participants to rate their experience of the programme. There were five response options, ranging from 'very good' to 'very bad'.

Sample Size

We based our power calculation on the primary outcome ICIQ-UI SF [29] and the secondary outcomes PGI-I [30] and IEF [15]. The calculation for each outcome aimed to show a 20% difference between groups, with a power of 80% and a two-sided significance level of 0.05, allowing a dropout level of 20%. The resulting total sample sizes were 281 (ICIQ-UI SF), 203 (PGI-I), and 210 (IEF). For the ICIQ-UI SF, we anticipated a better effect in our study compared with the study protocol used for the calculations, because our participants would be younger and with pure SUI. Based on this, we decided to recruit a total of 250 participants (125 in each arm).

Data Collection

Data was collected with postal self-assessed questionnaires and 2-day bladder diaries at baseline, and at follow-up performed 4 months after treatment initiation. We reminded non-respondents after 2 weeks by e-mail, after 4 weeks with a new questionnaire, and after 6 weeks by telephone. If no response was received after 8 weeks, participants were considered lost to follow-up.

Statistical Analysis

To save overall scores in the ICIQ-UI SF and the ICIQ-LUTSQoL, we replaced missing answers at follow-up with the corresponding answer at baseline and vice versa in some questionnaires (ICIQ-UI SF, $n = 6$; ICIQ-LUTSQoL, $n = 13$). More than three missing answers in a row were considered deliberate, and left without action. When calculating the overall scores in the ICIQ-LUTSQoL, the answer 'not applicable' in questions concerning personal relationships was set to one, i.e. no impact. To obtain a weekly IEF measure, the values reported in the 2-day bladder diaries were multiplied by 3.5.

For baseline comparison of the two interventions groups, we used the Student's *t*-test for continuous variables and the chi-square test for categorical variables. Treatment effects within groups were analysed using paired *t*-tests. For comparison of treatment effects between groups, we used a mixed model analysis for the primary outcomes and for health-specific QoL. However, this model could not be used for the IEF, where data was skewed with a high proportion of zeros. Instead, we analysed the IEF using a negative binomial regression. The remaining secondary outcomes, all single questions with ranked answers, were analysed using the Wilcoxon/Mann-Whitney rank sum test for

differences between treatment groups. In addition, we calculated the effect sizes (mean standardised difference) with 95% CIs for each continuous measure. Effect sizes of >0.8 were considered large.

For additional analysis, the material was grouped by baseline UI severity, according to the overall score on the ICIQ-UI SF at inclusion (overall score 1–5, slight; 6–12, moderate; 13–18, severe; 19–21, very severe) [31].

A $P < 0.05$ was considered to indicate statistical significance. An intention-to-treat analysis was performed on all available data [32] using IBM-SPSS for Mac version 19.0 (IBM, Armonk, NY, USA).

Ethics

The Regional Ethical Review Board, Umeå University approved the study (number 08-124M). Information about the study was given on our website. An informed consent form was included in the postal package sent for baseline investigation and was provided by all participants. No reimbursements were given. The study is registered at <http://www.clinicaltrials.gov> (ID: NCT01032265).

Results

The study was conducted in Sweden from December 2009 to April 2011. As expected, a large number of women completed the online screening survey, but several did not meet the inclusion criteria. Throughout the enrolment procedure, the most common reason for exclusion was UI other than SUI (40.1%, 174/434). Figure 1 shows the flow of study participants.

There were no significant differences between the treatment groups in baseline demographics, e.g. age, body mass index, education, nulliparity, menopausal status, or mean score on the ICIQ-UI SF and ICIQ-LUTSQoL at inclusion (Table 3).

Overall, 12.0% (30/250) of participants were lost to follow-up, 13.7% (17/124) from the Internet arm and 10.3% (13/126) from the postal arm. Compared with completers, participants lost to follow-up were significantly younger, had more severe leakage, and reported a larger impact on their condition-specific QoL at baseline (Table 4).

Primary Outcomes

Within both groups, there were highly significant improvements in the primary outcomes as assessed by ICIQ-UI SF and ICIQ-LUTSQoL. Table 5 reports overall scores, mean differences, and the effect size for each measure. The differences between groups were not significant.

Participants with severe leakage at baseline achieved a significantly lower mean score on the ICIQ-UI SF (mean

score at follow-up 8.1 (95% CI 6.7–9.5) vs 11.0 (95% CI 9.4–12.5), $P = 0.006$) when treated with the Internet-based programme compared with the postal programme (Fig. 2).

Secondary Outcomes

Analysis of the PGI-I showed that significantly more participants in the Internet group rated their leakage as much better or very much better after treatment (40.9%, 43/105, 95% CI 31.9–50.5), compared with participants in the postal group (26.5%, 30/113, 95% CI 19.0–35.3), $P = 0.01$ (Fig. 3).

Health-specific QoL (EQ5D) improved significantly in the Internet group (mean change 3.7 (95% CI 1.55–5.83), $P = 0.001$), but not in the postal group (mean change 1.9 (95% CI –0.55 to 4.35), $P = 0.13$). However, the difference between groups was not significant (Table 5).

In both groups, the number of UI episodes per week (IEF) was significantly reduced. The mean reduction was significantly larger in the Internet group compared with the postal group (mean reduction 7.6 (95% CI 5.7–9.5) vs 4.5 (95% CI 2.9–6.0), $P < 0.01$), but when baseline values were taken into account, there was no significant difference between groups (Table 5). After treatment, 69.8% (120/172, 95% CI 62.6–76.3) of participants in both groups reported either complete absence of leakage or a reduction in leakage by $>50\%$ compared with baseline.

After treatment, more participants in the Internet group (59.5%, 47/79, 95% CI 48.4–69.9) than in the postal group (41.4%, 34/82, 95% CI 31.2–52.3), had either stopped using or reduced their usage of UI aids ($P = 0.02$).

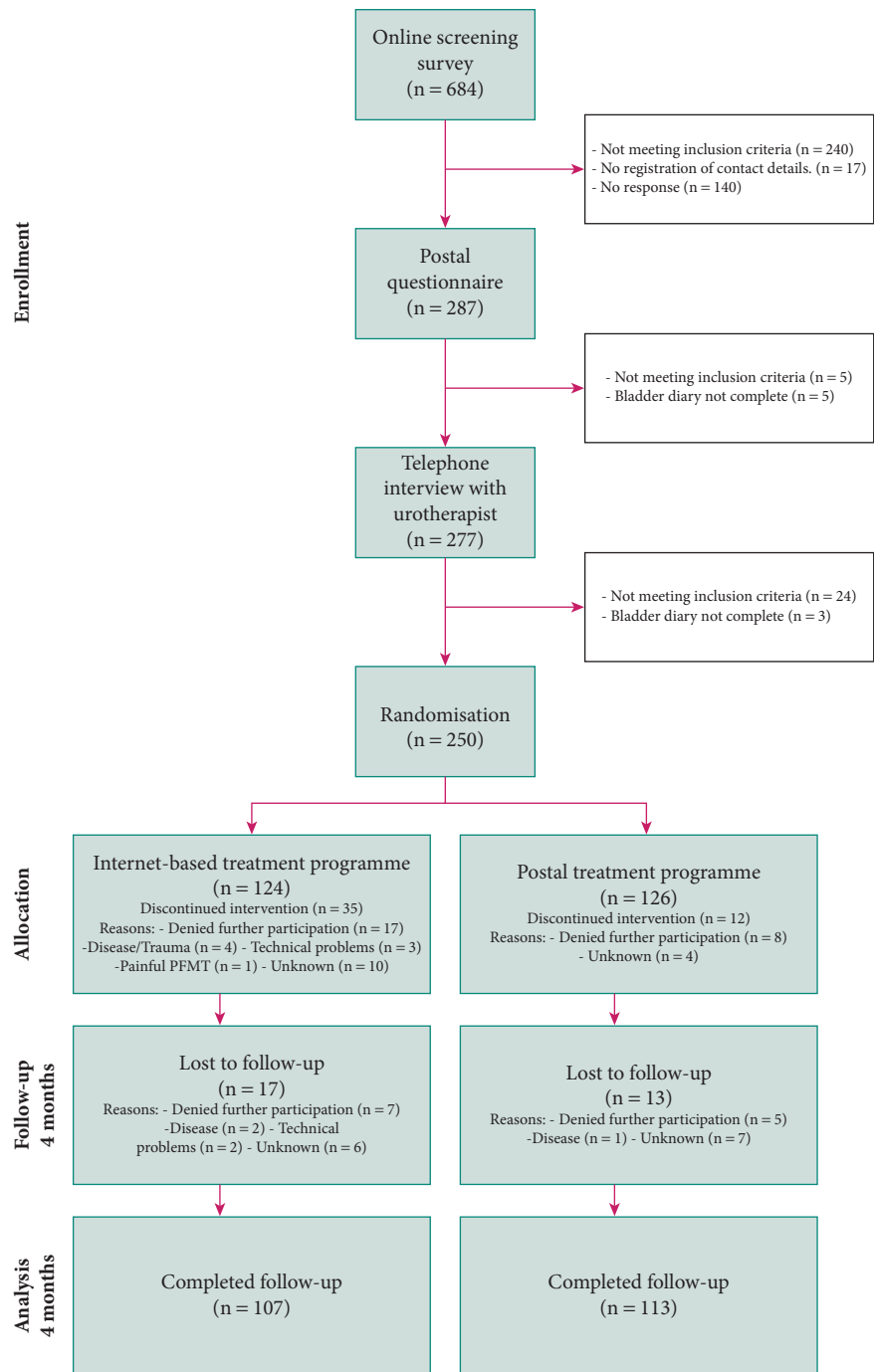
In the Internet group, 84.8% (89/105, 95% CI 76.9–90.7) of participants experienced the treatment programme as 'good' or 'very good', compared with 62.9% (71/113, 95% CI 53.7–71.4) in the postal group ($P < 0.001$).

Side-Effects

One woman in the Internet-group reported lower abdominal pain when conducting pelvic floor muscle training and discontinued her treatment. No other side-effects were reported.

Discussion

In both the Internet-based and the postal treatment group, there were highly significant improvements with large effects sizes for symptom-score and condition-specific QoL. However, no significant differences were found between groups. Women with more severe leakage at baseline improved significantly more when treated with the Internet-based programme compared with the postal programme. The Internet-based treatment was also more

Fig. 1 Flow of study participants.

effective for most secondary outcomes. Compared with the postal group, more women in the Internet group perceived their leakage as much or very much improved after treatment, more reported reduced usage of UI aids, and more indicated satisfaction with the treatment programme. Health-specific QoL improved in the Internet group but not in the postal group, and both groups had a clinically relevant reduction of leakage episodes.

Strengths and Weaknesses of the Study

To our knowledge, this is the first randomised, controlled trial of Internet-based treatment for SUI. The clinical diagnosis is well substantiated and we compared two active treatments. Information provided to the participants was balanced and did not favour either of the treatments. During the study period there were no major technical

Table 3 Baseline demographics and UI severity characteristics by treatment group.

Variable	Internet-based treatment programme, <i>n</i> = 124	Postal treatment programme, <i>n</i> = 126	<i>P</i> *
Baseline demographics			
Mean (SD):			
Age, years	47.9 (10.6)	49.4 (9.8)	NS
BMI, kg/m ²	24.7 (4.2)	24.5 (3.6)	NS
EQ5D-VAS score	79.1 (13.6)	79.2 (14.0)	NS
HADS score:			
Depression	2.2 (2.2)	2.3 (2.3)	NS
Anxiety	3.4 (2.6)	3.8 (3.2)	NS
<i>N</i> (%):			
Education:			
University level <3.0 years	25 (20.2)	28 (22.2)	NS
University level ≥3.0 years	63 (50.8)	72 (57.1)	NS
Daily smoker	4 (3.2)	5 (4.0)	NS
Nulliparous	9 (7.3)	7 (5.6)	NS
Postmenopausal	43 (35.8)	48 (39.7)	NS
Incontinence severity characteristics			
Mean (SD):			
ICIQ-UI SF score	10.4 (3.1)	10.3 (3.5)	NS
ICIQ-LUTSqOL score	33.6 (6.8)	33.6 (8.2)	NS

BMI, body mass index; *Based on Student's *t*-test (means) or chi-square test (numbers).

Table 4 Age and UI severity measures of participants lost to follow-up compared with completers.

Variable	Lost to follow-up, <i>n</i> = 30	Completed follow-up, <i>n</i> = 220	<i>P</i> *
Baseline characteristics			
Mean (SD):			
Age, years	44.2 (9.2)	49.2 (10.2)	0.01
ICIQ-UI SF score	11.9 (3.9)	10.2 (3.2)	0.01
ICIQ-LUTSqOL score	37.2 (8.5)	33.1 (7.3)	0.01

*Student's *t*-test.

Table 5 Summary of continuous outcome measures by treatment group. Values are the mean (SD) unless stated otherwise.

Outcome variable	Treatment group	Baseline (<i>n</i> = 250)	4-month follow-up (<i>n</i> = 220)	Difference *	Within group <i>P</i> [†]	Between groups <i>P</i> [‡]	Effect size [§] (95% CI)
Primary outcomes:							
ICIQ-UI SF	Internet	10.4 (3.1)	6.9 (3.1)	3.4 (3.4)	<0.001	0.27	0.99 (0.76–1.22)
	Postal	10.3 (3.5)	7.3 (3.9)	2.9 (3.1)	<0.001		0.95 (0.72–1.17)
ICIQ-LUTSqOL	Internet	33.6 (6.8)	27.8 (6.0)	4.8 (6.1)	<0.001	0.52	0.79 (0.57–1.01)
	Postal	33.6 (8.2)	28.8 (7.3)	4.6 (6.7)	<0.001		0.68 (0.47–0.89)
Secondary outcomes							
IEF	Internet	12.7 (12.0)	4.8 (7.7)	7.6 (9.1)	<0.001	0.23	0.84 (0.60–1.08)
	Postal	9.4 (8.6)	4.4 (6.7)	4.5 (7.1)	<0.001		0.63 (0.39–0.87)
EQ5D-VAS	Internet	79.1 (13.6)	83.3 (10.3)	3.7 (10.9)	0.001	0.30	0.34 (0.14–0.54)
	Postal	79.2 (14.0)	81.8 (13.9)	1.9 (13.0)	0.13		0.15 (–0.04 to 0.34)

*Based on participants with complete data on both occasions; [†]Based on paired *t*-tests; [‡]Based on a mixed model analysis (ICIQ-UI SF, ICIQ-LUTSqOL, and EQ5D-VAS), or a negative binomial regression (IEF); [§]Mean standardised difference.

problems or disruptions, and loss-to-follow up was low and similar between groups. Most outcome measures are established and recommended, and the research group included experienced GPs, urotherapists, and psychologists

with broad knowledge on the topic. Limitations of the present study include that both treatment programmes were newly developed. The use of an established comparator would have been ideal, but there is currently

Fig. 2 The mean ICIQ-UI SF scores at follow-up by baseline severity and treatment group.

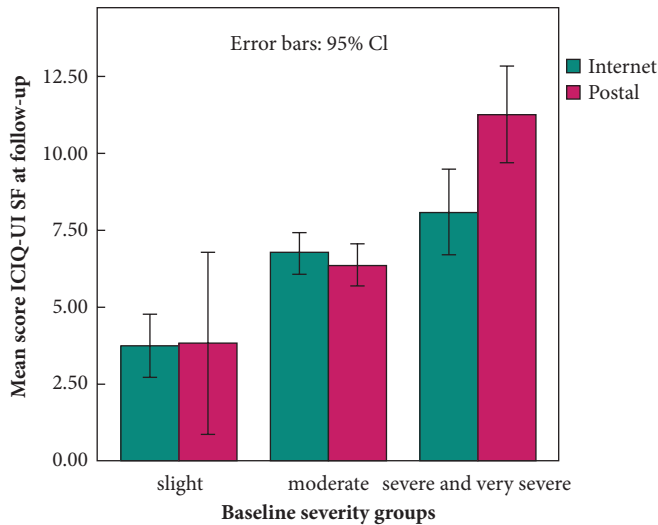
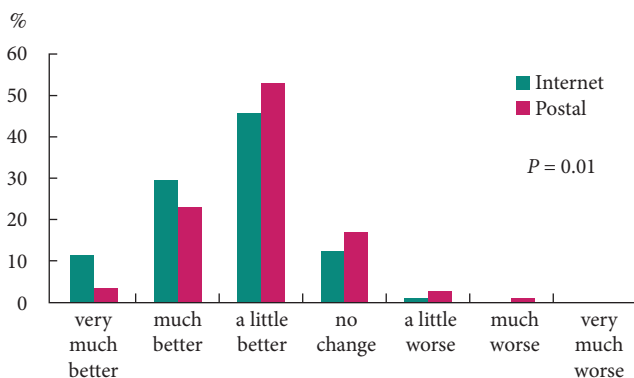


Fig. 3 Distribution of responses on the PGH rating scale by treatment group. *P* value based on the Mann-Whitney rank sum test.



no 'gold standard' for pelvic floor muscle training. A standardised face-to-face treatment or care-as-usual would have been an option, but we wanted the treatment programmes to be accessible for women from all over the country, even from remote areas or from areas with inadequate staffing. We also wanted to compare two simple and anonymous treatment alternatives, available to women that do not seek care because of lack of time, or because of embarrassment of their condition. In addition, the Internet-based treatment programme is a complex intervention and we cannot assess if any specific part of the programme is particularly important. Also, the programme required double log-ins from the participants, which was perceived as complicated by some women. A more simple technical solution might have lowered the discontinuation rate in the Internet group. Furthermore, it is possible that the study is underpowered. This is implied by all of the

results favouring Internet treatment, although significant differences are not observed in some measures. We chose the outcome measures because we found them clinically relevant and well balanced for the evaluation of symptoms reported by women with SUI. However, at the time we made the power calculations there were few published studies using these measures, and the anticipated differences between the groups may have been overestimated. In addition, differences between the groups may have decreased as participants lost to follow-up had significantly more severe leakage, and those with severe leakage were unexpectedly seen to benefit more from the Internet-based treatment.

Strengths and Weaknesses Compared with the Literature

Participants in the present study represent a clinically relevant group for a primary care setting, as they had moderate to severe leakage and all actively desired treatment. The wish for treatment is associated with the severity of the leakage and its impact on QoL [3,33], and is a prerequisite to succeed with a treatment completed on one's own. Other influencing factors for improvement in the present study may be the capability to absorb written instructions, put them into practice, and for the Internet group to adequately use a computer. Although the treatment programmes were written in lay language and richly illustrated, the fact that our population was more highly educated than Swedish women in general may indeed have affected this capability. For comparison, 28% of the Swedish women aged 25–64 years had a university education of ≥ 3 years or in 2011 [34]. In the same year, a full 93% of the Swedish population had access to a computer with Internet connection, but frequent usage of the Internet is still higher among younger individuals and in higher socioeconomic class cohorts [18]. Hence, the online recruitment might have limited our sample, and the results may not necessarily apply to a general population.

In both interventions, the minimum intensity of the training was the recommended eight contractions three times daily [7], but the pelvic floor muscle regimens were not exactly the same. The main difference was that the Internet group was supervised by urotherapists, whereas the postal group completed the training on their own. The interaction with the urotherapist may have influenced participants' compliance and motivation to training, and improved the results in the Internet group. On the other hand, in the Internet programme the login codes for an escalating regimen were disclosed successively every second week, whereas in the postal programme participants had access to all types of exercises from the start. Consequently, participants in the postal group may have had a longer

intense period of pelvic floor muscle training than participants in the Internet group.

The administration of a pamphlet for self-completion of pelvic floor muscle training is sometimes used as a sham treatment in clinical trials, and it could be argued that the improvements in the present study are merely placebo effects. However, the postal programme we used was extensive and the participants were informed that they received an active treatment. In addition, the improvements in the present study (mean change ICIQ-UI SF: Internet 3.4, postal 2.9) are of the same order of magnitude as in other studies on conservative management of SUI. For example, in a primary care setting in the Netherlands, where 384 participants with a baseline ICIQ-UI SF score of 11.2 were randomised to 3 months of either intense pelvic floor muscle training supervised by a nurse specialist or to care-as-usual, an improvement of the mean score by 2.0 was seen in the intervention arm [35]. In an Australian study, 83 women with a mean age of 71.8 years and a baseline ICIQ-UI SF score of 10.4 improved their score by 3.0 after 3 months of pelvic floor muscle training, or by 1.3 after bladder training [36]. In a study on duloxetine treatment, the active treatment arm obtained a 2.8 point improvement in the ICIQ-UI SF and the placebo arm improved by 1.7 points [37].

During a follow-up period of 4 months, some participants may have improved due to spontaneous remission. The annual remission rate of SUI has previously been calculated to be $\approx 7\%$ [38]. Based on this, about six women in our sample might have improved due to spontaneous remission, most likely with equal distribution in both groups.

Meaning of the Study and Future Research

Despite the lack of significant differences between the groups in primary outcomes, there are many indications that the Internet treatment may be more effective than the postal programme. We also showed that it is possible to treat SUI without face-to-face contact. For the future, it is important to establish patient subgroups that benefit the most from each treatment, and how the programmes can best be integrated in everyday practice. Internet-based treatment may not be suitable for all women, but could facilitate access to care for some. It might also help unload primary healthcare, as costs are likely to be lower than for face-to-face treatments because the healthcare professionals can handle more patients in parallel. Even if efficacy is equal to or even lower than that of face-to-face treatments, the low delivery cost may make Internet-delivered treatment a more cost-effective alternative [39]. The cost-effectiveness and the long-term effects of the treatments in the present study remain to be analysed, and will be reported in future articles.

Conclusion

Management of SUI without face-to-face contact is possible, and may increase access to care. Internet-based treatment is a new, promising, and effective treatment alternative.

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Conflict of Interest

None declared. Source of funding: this study was supported by The Swedish Council for Working Life and Social Research, The Swedish Society of Medicine, the Jämtland County Council, the Västerbotten County Council (ALF), and Visare Norr, Northern County Councils, Sweden.

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Abbreviations: EQ5D-VAS, EuroQol 5D-Visual Analogue Scale; HADS, Hospital Anxiety and Depression Scale; ICIQ-UI SF, International Consultation on Incontinence Questionnaire Short Form; IEF, incontinence episode frequency; PGI-I, Patient global impression of improvement; QoL, quality of life; (S)UI, (stress) urinary incontinence.



The management of overactive bladder: percutaneous tibial nerve stimulation, sacral nerve stimulation, or botulinum toxin?

Andrea Tubaro, Federica Puccini, and Cosimo De Nunzio

Purpose of review

We have reviewed the evidence published on botulinum toxin A (BoNT/A), percutaneous tibial nerve stimulation (PTNS), and sacral nerve stimulation (SNS) in the management of overactive bladder (OAB).

Recent findings

BoNT/A is effective irrespectively of the number of previous anticholinergic treatments and of the reason for failure. Doses up to 360U 3-monthly are well tolerated. BoNT/A is well tolerated and effective also in the pediatric population. Bladder instillation of liposome encapsulated BoNT/A is a new approach, deserving further research. When using PTNS, motor response from the electrical stimulus is not required, a sensory response suffices. PTNS has a lasting effect compared to oxybutynin alone. SNS is superior to standard medical treatment but the combination of SNS and anticholinergics is more effective than anticholinergic alone.

Summary

The evidence published in the last 18 months has increased the level of evidence on safety and effectiveness of BoNT/A, PTNS, and SNS in the management of OAB. BoNT/A is now recommended as standard third-line treatment for OAB (in the USA) and urgency incontinence (in the USA and in Europe) in selected patients refractory to pharmacological therapy. All available third-line treatment options for OAB/urgency urinary incontinence should be offered before surgery is contemplated.

Video abstract

<http://links.lww.com/COU/A7>.

Keywords

botulinum toxin A, overactive bladder, percutaneous tibial nerve stimulation, sacral nerve stimulation, urgency urinary incontinence

INTRODUCTION

Overactive bladder (OAB) syndrome is defined by the presence of urgency, with or without urgency urinary incontinence (UUI), usually with frequency and nocturia [1]. Symptoms may or may not be associated with detrusor overactivity (DO) [2–4]. First-line treatments include conservative strategies such as adjustment of fluid and food habits, review of drug treatment, timed voiding, bladder retraining, and pelvic floor muscle training. Second-line treatments include pharmacological therapy for a minimum of 3 months with either anticholinergic/antimuscarinic agents or β_3 agonists, as recommended by the International Consultation on Incontinence [5]. Notwithstanding the proven effectiveness of the pharmacological treatment of OAB and UUI, response to it is difficult to forecast in

the individual patient and adherence to the prescribed regimen is known to be low with only 31–36% of patients remaining on treatment at 52 weeks [6*,7].

Different third-line treatments of OAB/detrusor overactivity are available and may be offered to patients who do not respond or do not tolerate pharmacological treatment. The aim of this article

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KEY POINTS

- Third-line treatment of OAB/DO includes intravesical injection of botulinum toxin A, PTNS, and SNS.
- The available evidence confirms that all three treatment approaches are well tolerated and effective, although only BoNT/A and SNS can achieve cure of UII.
- In case of OAB/DO refractory to pharmacological treatment, the choice among the different second-line treatment relies on patient preference, availability, and local expertise.
- Further research is needed to identify ideal candidates for the different third-line treatments of OAB/DO.

was to review the evidence published over the last calendar year on intravesical injection of botulinum toxin A (BoNT/A), neuromodulation techniques [i.e., percutaneous tibial nerve stimulation (PTNS), and sacral nerve stimulation (SNS)].

TEXT OF REVIEW

MEDLINE database was searched for papers published over the last 18 months (September 2013–February 2015), using the following PICO: overactive bladder, BoNT/A, PTNS, SNS, no treatment, placebo, comparator, antimuscarinics, anticholinergics, improvement, cure. Two hundred and nine references were retrieved, 112 were obtained full-text, four additional references were obtained from full-text papers, and a total of 39 were found to be relevant to the current review.

Botulinum toxin A

The mechanism of action of BoNT/A in the urinary bladder has already been extensively described [8[¶]]. BoNT/A has been studied as a local therapy for the treatment of detrusor overactivity since the year 2000 [9]. Two different preparations of BoNT/A exist (Botox, onabotulinum toxin A and Dysport, abobotulinum toxin A) and they differ because of the isolation, manufacturing, and stabilization processes, their units are not interchangeable and results from studies with one product cannot be transferred to the other product [10^{¶¶},11].

Following the two pivotal trials that led to the registration of onabotulinum toxin A, phase IV studies addressing different issues of OAB/DO treatment with botulinum toxin have been published and reviews of randomized trials have been produced. Recently, two systematic reviews and meta-analyses have been published by Mangera *et al.* [10^{¶¶}] and Cui

et al. [12^{¶¶}], raising the level of evidence on this subject. A number of narrative reviews have also been published recently, providing a useful summary of the available evidence for the use of BoNT/A in the management of OAB and UII [13,11]. High-level evidence on the effectiveness of BoNT/A continues to accumulate. A randomized trial on BoNT/A versus placebo in male patients with refractory OAB persisting after benign prostatic hyperplasia (BPH) surgery showed improvement of daily frequency, which did not reach statistical significance [14^{¶¶}].

Interesting evidence was also published from nonrandomized studies. Nuanthaisong *et al.* [15[¶]] investigated the safety of onabotulinum toxin A for multiple indications, suggesting that a dose more than 360 units every 3 months was well tolerated in a small cohort of 13 patients with no life-threatening adverse events.

An interesting study from Sievert *et al.* [16] investigated the effect of 100 U of BoNT/A in patients with idiopathic UII and found the clinical response to be independent from the number of anticholinergic agents that patients received and from the reason of pharmacological treatment failure.

Sager *et al.* [17[¶]] reported on the use of BoNT/A in the management of children with neurogenic bladder, although a continence rate of 50–77% was achieved, urodynamic improvement was considered to be insufficient and five patients underwent augmentation cystoplasty. In a different study, 14 of 17 children avoided surgical reconstruction of the bladder following BoNT/A treatment, suggesting a significant role for such treatment approach in the pediatric population [18]. Amundsen *et al.* [19[¶]] published the design of the ROSETTA (The Refractory Overactive Bladder: Sacral Neuromodulation vs. Botulinum Toxin Assessment) trial aiming at randomizing patients with refractory UII between BoNT/A and SNS, the study will provide further evidence on the subject.

A totally new approach to reduce the invasiveness on BoNT/A was proposed by Chuang using liposome encapsulated BoNT/A. The intravesical instillation clearly represents an interesting step to reduce the invasiveness associated with the endoscopic injection. The preliminary data suggest a significant improvement of daytime frequency and urgency severity score, although no significant change in urgency and UII was observed. More research into this interesting concept is required [20[¶]].

Schurch and Carda reviewed the evidence on BoNT/A injection in the management of UII in patients with multiple sclerosis. According to the Swiss authors, the clinical response in patients with

multiple sclerosis is no different from the one observed in the spinal cord injury, one with a 75–90% efficacy; training for clean intermittent self catheterization is mandatory prior to initiate treatment [3].

Although the mechanisms of action of botulinum toxin are rather well known, new information becomes available every year. Hegele *et al.* [21[■]] published an interesting paper showing that BoNT/A is also effective in decreasing prostaglandin E2 blood levels in patients with OAB/IDO (overactive bladder (idiopathic detrusor overactivity) responding to treatment, suggesting prostaglandin E2 may be used as a biomarker during follow-up. A pharmaco-economic analysis by Hamid *et al.* [22[■]] confirms the cost-effectiveness of Botox + best supportive care versus best supportive care alone with a 100% probability of being cost-effective [22[■]]. Effectiveness of BoNT/A administration has also been investigated using patient reported outcome. Malde and coworkers reported OAB/IDO patients experienced and found high satisfaction rate with the service offered, especially in those who repeated treatments [4].

Based on the available evidence on BoNT/A, the AUA (American Urological Association) guidelines recently stated: clinicians may offer intradetrusor onabotulinum toxin A (100 U) as third-line treatment in the carefully selected and thoroughly counseled patient who has been refractory to first and second-line OAB treatments [23[■]]. The patient must be able and willing to return for frequent postvoid residual evaluation and to perform self-catheterization if necessary.

Percutaneous posterior tibial nerve stimulation

PTNS is a peripheral neuromodulation technique first described by Stroller in the 1990s for the treatment of OAB [24]. Mechanism of action is not yet fully understood, but it is likely to exert both motor and sensory neuromodulatory effects, such as increasing inhibitory tone, decreasing awareness of abnormal stimuli, and reorganization of the neuronal system, resulting in restoration of normal reflexes [25,26[■]].

The evidence published in 2014 on PTNS in the treatment of OAB is rather scarce. The last systematic review on PTNS in the management of lower urinary tract dysfunctions was published in 2013 by Graziev *et al.* PTNS was found to be effective in reducing urinary frequency, urinary incontinence episodes, and involuntary detrusor contractions in 37–100% of patients with OAB [27]. A less-invasive approach to PTNS by transcutaneous stimulation

seems to be effective in short term and long term, as after daily session for 30 days, 53% of patients showed symptoms of improvement and after a mean follow-up of 11 months, 49% of patients still used it [28].

The combined use of PTNS and anticholinergic has been explored. A randomized study by Souto *et al.* showed a comparable efficacy among oxybutynin ER (extended release) 10 mg/day and PTNS ± oxybutynin ER 10 mg/day at 12 weeks. However, 12 weeks after treatment cessation, the oxybutynin group had lower QoL (quality of life) measures compared to 12 weeks, but this was not true for both PTNS groups [29[■]].

A recent update of the AUA/SUFU (American Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction) guidelines for the management of OAB (non-neurogenic) in adults states that clinicians may offer PTNS as third-line treatment in a carefully selected patients [23[■]].

Sacral nerve stimulation

SNS works by delivering mild electrical impulses to the sacral nerve roots, thanks to an electrode implanted adjacent to the third sacral nerve root and connected to a neurostimulator placed in a subcutaneous pocket over the buttocks, thus controlling either bladder, detrusor sphincter, or bowel [30]. Effectiveness of SNS has been investigated but results should always be stratified for the different indications. Long-term follow-up of SNS treatment, in a single center cohort of 216 patients (86% of which were female), has been recently published by Peeters *et al.* [31[■]]. Success and cure rates of ≈70 and 20% for urgency incontinence and of 68 and 33% for urgency frequency syndrome were reported after a mean follow-up of 46.9 months (actually on 27.2 for UI and 31.6 for those usually with frequency patients). Forty-one percent of patients needed surgical reintervention and an average of 1.7 reinterventions were needed [31[■]].

Analysis of a large sample of the Medicare population (1474 patients) by Chungtai *et al.* [32] showed how 17.3% of devices were removed and 11.3 replaced over 5 years whereas 73.9% of patients maintained the original device. Bowel (constipation and diarrhea) and neurological (numbness and extreme pain) complaints were consistent with those observed in the year prior to implantation.

The effectiveness of the combined treatment with tolterodine and SNS versus tolterodine alone was explored by Tang *et al.* in a randomized trial. The results of the study show a significant advantage of the combination treatment in terms of urinary

frequency, mean voided volume, bladder volume at first desire to void, and maximum cystometric capacity. The observed clinical improvement was associated with a significant improvement in anxiety and depression [33^{***}].

Investigating mechanisms of action of SNS, Shalom *et al.* reported a significant decrease of uNGF (urinary Nerve Growth Factor) in patients receiving PNE (percutaneous nerve evaluation) test for SNS. Patients with detrusor overactivity have a higher baseline level of uNGF (19.82 vs. 7.88 pg/mg, $P < 0.002$) compared to controls. Patients with detrusor overactivity had a significant improvement in quality-of-life, using the urinary distress inventory and the incontinence quality-of-life scale; uNGF levels significantly decreased from 17.23 to 9.24 pg/mg ($P < 0.02$) [34]. Using a Markov model and a 10-year horizon, Walleser Autiero *et al.* were able to show that SNS with percutaneous needle evaluation is the most effective strategy, from a cost-utility analysis, for managing patients with idiopathic wet OAB [35^{***}].

Referral for SNS treatment of IDO is still considered to be limited. Kessler *et al.* investigated the urologist referral's attitude in the UK and identified three major factors preventing referral including absolute contraindications (low bladder compliance, progressive neurological disease, urinary tumors, etc.) and relative ones such as cardiac pacemaker and diabetes mellitus. Analysis of a neuro-urologists subgroup revealed that noncritical contraindications did not prevent referral, suggesting that proper information on SNS is of importance in improving management of OAB. The use of decision tools such as TIPS (Tool for InterStim Patient Selection) (www.tips-snm.org) is proposed to improve referral [36^{*}].

SNS is currently used in the management of voiding dysfunction including urinary frequency and urgency urinary incontinence, but a recent report suggests that beyond improving disease-specific quality of life, SNS ameliorates female sexual function. Benakhar *et al.* observed a significant improvement in female sexual function index total score ($P = 0.011$) and in the domains regarding desire ($P = 0.014$) and orgasm ($P = 0.035$) following implantation, even if no correlation was found between QoL domains and improvement of the female sexual function index score [37^{*}].

The recent update of the AUA/SUFU guidelines on the diagnosis and treatment of OAB suggests that clinicians may offer SNS, a third-line treatment, in a carefully selected patient population characterized by refractory OAB symptoms or patients who are not candidates for second-line therapy and are willing to undergo surgical procedure [23^{***}].

Open question: which third-line strategy is better?

As third-line treatments BoNT/A, PTNS, and SNS have proven to be well tolerated and effective and it is time to compare their cost and cost-effectiveness, as follow-up of up to 5–10 years are now available.

Using a Markov model, Walleser Autiero *et al.* evaluated cost-effectiveness of PTNS, SNS [both percutaneous nerve evaluation (PNE) and tined lead evaluation (TLE)], BoNT/A, and optimal medical therapy (OMT) for OAB wet/IDO in a 5 and 10-year time frame in the UK. QALYs (Quality Adjusted Life Years) were calculated and they included device and drug acquisition costs, preprocedure and postprocedure costs, and adverse events management costs. They found that at 5 years, SNS and BoNT/A were more effective and less costly than PTNS; at 10 years, SNS compared to OMT was more costly and more effective; at 10 years, SNS/PNE was less costly and more effective than BoNT/A; and at 10 years, SNS/TLE was more costly and more effective than BoNT/A. Authors concluded that SNS (PNE and TLE) is either cost saving and more effective compared to OMT, PTNS, and BoNT/A for idiopathic refractory wet OAB [35^{***}].

Cost-effectiveness is often related to the local health system. Bertapelle *et al.* performed a cost-effectiveness analysis of SNS versus BoNT/A for OAB/IDO in the Italian Healthcare system, similar to those already performed in Spanish, Dutch, and UK healthcare contexts. The same Markov model over a 10-year time horizon has been applied and QALYs gained, showing that SNS is cost-effective from year 3 onward and becomes cost saving at year 10 [38^{*}].

The decision to go for a third-line treatment of OAB and the choice of the treatment modality is certainly influenced by the consulting urologist, but it is ultimately taken by the patient. The decision relies on several factors. A cohort of 50 women with refractory OAB were counseled, regarding SNS and BoNT/A and the reasons associated with the individual choice were analyzed. Thirty-seven of 50 patients (74%) were elected to receive BoNT/A because of quicker improvement, easy access to treatment, easier treatment modality, being uneasy with the thought of a foreign body implanted, and management of battery and device in case of SNS. On the contrary, 14 of 50 patients (26%) chose SNS because it is more a permanent therapy, with long intervals between battery replacements (6 years) instead of more frequent reinjections, does not affect postvoid residual, and may also treat coexisting bowel symptoms [39^{*}].

CONCLUSION

The evidence on third-line treatment of OAB with PTNS, BoNT/A, and SNS continue to evolve allowing guidelines to provide more solid recommendations. All treatments proved to be well tolerated and patients' expectations can be properly set based on the available evidence. Health technology assessment of the different treatment suggests that what appears to be the more expensive treatment can be the more cost-effective in the long term. Evaluation of the peer-reviewed literature confirms the need for multiple treatment options being available for our patients and that PTNS, BoNT/A, and SNS must remain in our armamentarium. Clinical research on the management of OAB has often tried to understand which is the more effective treatment for the condition, but maybe it should better look into what is the best treatment option for the individual patient. Ultimately, patients do not necessarily choose the more effective treatment, but the one that best fits their needs, and this remains one of their fundamental rights.

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Have mini-slings come of age?

Valentine Frydman and Jean-Nicolas Cornu

Purpose of review

To highlight the recent data published about mini-slings for management of female stress urinary incontinence, focusing on the past 12 months.

Recent findings

Mini-slings, implanted by single vaginal incision, have been increasingly used in recent years.

Summary

A significant number of new clinical trials have investigated the efficacy of single incision mini-slings (SIMS) in the past years. Meta-analyses have shown growing evidence supporting their use, but a number of limitations go against a wide, immediate, and unconditional diffusion of these techniques. First, the majority of the trials published investigated the TVT-Secur device, which is considered to be inferior to traditional slings and is no more used in clinical practice. All other SIMS have been tested in clinical trials but there is insufficient evidence to routinely recommend their use, mainly because long-term data are lacking. SIMS have to be considered as a heterogeneous group, and results obtained with one device cannot be translated to another. The safety profile of recently introduced SIMS seems good, with potential reduction of postoperative pain and faster recovery. However, further research is necessary to clearly establish their noninferiority regarding efficacy after 1 year compared to traditional transobturator tapes and TVT, and ascertain their benefits in daily clinical practice.

Keywords

female, single incision slings, slings, stress urinary incontinence, urinary incontinence

INTRODUCTION

Implantation of a suburethral sling is a standard procedure for surgical management of stress urinary incontinence in women [1,2]. Since the mid-1990s, following the introduction of the tension-free vaginal tape concept, three generations of slings have emerged [3,4]. The oldest one is the retropubic Tension-free Vaginal Tape (TVT), although some minor modifications have been made and new devices have been recently introduced [5]. The second one is the transobturator tape that has been widely used, under many different shapes (in-out, out-in, with various ancillaries) [3]. The third generation of slings, so-called mini-slings, have been introduced in the late 2000s [6]. The latter are designed as single incision slings, allowing only one vaginal incision to place the sling, which is anchored or fixed to the transobturator membrane itself.

The rationale for the introduction of single incision mini-slings (SIMS) has been clearly stated. These slings aim at (i) avoiding frequent and bothersome side-effects and complications (such as groin pain) consecutive to traditional midurethral sling (MUS) implantation; (ii) being really minimally invasive with the ambition of purely local

anesthesia; and (iii) resulting in the same cure rate as traditional MUS do. Thus, the SIMS concept has been facing a double challenge: being noninferior to traditional MUS in terms of efficacy and superior to MUS in terms of complications. The present work summarizes the recent data about efficacy and complication of the various SIMS available on the market, before discussing the status of SIMS in current clinical practice.

MINI-SLING TYPES

Since their introduction in the mid-2000s, a number of SIMS have been introduced on the market: TVT-Secur (Gynecare), Ophira (Promedon, Cordoba, Argentina), MiniArc (American Medical Systems,

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KEY POINTS

- Single incision mini-slings (SIMS) have not yet proven their noninferiority compared to traditional mid-urethral sling, but the level of evidence supporting their use is growing.
- The major potential advantages of SIMS seem to be their low invasiveness (pure local anesthesia for implantation, fast recovery, and low pain after implantation).
- All mini-slings are not equivalent.
- There is no long-term data available for mini-slings; urologists are urged to include patients in clinical trials to improve our knowledge.

Minnetonka, MN, USA), Ajust (C.R. Bard, Inc., Covington, GA, USA), Needleless (Mayumana Healthcare, Lisse, The Netherlands), CureMesh (D.Med. Co., Inc., Seoul, Korea), MiniTape (Gynel-deas, Glasgow, UK), TissueFixationSystem TFS (TFS PTY Ltd, Sydney, Australia), Altis (Coloplast, Denmark), etc. All have their own design, length, fixation mechanism, ancillary, and potential advantages. For all these SIMS, the level of evidence available in the current literature is heterogeneous, as some of them have been evaluated through multiple randomized controlled trials (RCTs), whereas others have no data published over 1-year follow-up. Moreover, the results obtained with the different SIMS are not identical. Indeed, TVT-Secur has been readily removed from the market after that data have shown lower cure rates compared to traditional mid-urethral slings (both TVT and transobturator) and high rates of recurrence after mid-term follow-up [7^{***},8,9]. On the contrary, other devices have proven to be noninferior compared to traditional mid-urethral slings in well-designed RCTs [6^{***}]. It is thus of utmost importance to consider SIMS as a heterogeneous group, and to analyze the devices one by one.

EFFICACY

Efficacy of stress urinary incontinence surgery can be estimated by objective cure rate (usually by stress test or cough test at clinical examination) or subjective cure rate (namely, by assessing incontinence symptoms through dedicated questionnaires). Obviously, long-term follow-up data are critically important in the field, given that the gold standard traditional MUS have shown to stand the test of time, with an important sustainability of the results [10–12].

In a recent systematic review and meta-analysis about 21 randomized clinical trials, Mostafa *et al.* [6^{***}] have reported that the patient-reported cure rate was not significantly different after SIMS compared to MUS [odds ratio (OR) 0.94; 95% confidence interval (CI), 0.88–1.00], provided that TVT-Secur studies were excluded from the analysis. This was also true for objective cure rate (OR 0.98; 95% CI, 0.94–1.01). It is, however, interesting to see that the authors point out a trend for less favorable outcomes in the SIMS group. Added to the fact that all the SIMS were gathered in the main analysis (except TVT-Secur), the results have to be taken cautiously for several reasons. First, the mean follow-up was only of 18.6 months, showing that there is still no relevant data for medium and long-term results. Second, a meta-analysis of heterogeneous data does not replace valuable, adequately powered, noninferiority trials, which are very scarce [13,14]. Indeed, the meta-analysis conducted by Mostafa *et al.* did include a number of studies that had no clear a-priori hypothesis. Despite this, the evidence is growing because the same group of authors, 3 years before, had failed to demonstrate noninferiority of SIMS compared to MUS [15]. The most important message given in this work may not be the main results, but rather the fact that some devices clearly show to be inferior to MUS (Ophira and TVT-Secur), whereas other (Aust) generate a bit of hope.

Another meta-analysis has been released last year by the Cochrane collaboration group [7^{***}]. In this in-depth evaluation of the literature, Nambiar *et al.* have raised a lot of issues. They retrieved 31 trials involving 3290 patients and pointed out some caveats among the available data about random sequence generation, allocation concealment, incompleteness of data reported, issues with blinding of participants and personnel, and blinding of outcome assessment. The analysis led to the conclusion that TVT-Secur was indeed probably inferior to traditional MUS in terms of efficacy, but the authors stated that insufficient data were available to draw any conclusion about other SIMS versus traditional MUS. Moreover, the detailed evaluation has shown not enough power for specific comparison of each sling versus TVT or transobturator tapes separately. Hence, the authors advocated for the need to conduct long-term, well-designed randomized trials to reach a reliable conclusion.

Some new data have been released in the past months, and were not included in the systematic reviews. MiniArc has been compared to traditional transobturator tape through two additional RCTs. Schellart *et al.* [16^{*}] compared Monarc to MiniArc, focusing on subjective cure rate, Patient Global Impression of Improvement (PGI-I) after 1 year

being the main outcome criterion (in addition to postoperative pain). A total of 193 patients were randomized with 173 available for final analysis. They found that efficacy at 1 year based on subjective cure rate but also objective cure rate was not significantly different in the two groups [subjective cure: 83% vs. 86% ($P=0.46$) and objective cure: 89% vs. 91% ($P=0.33$) after MiniArc and Monarc, respectively]. In another trial, Lee *et al.* [17] have randomized 225 women between MiniArc and Monarc. Subjective cure was based on patient symptoms (absence of leakage during efforts on a validated questionnaire) and objective cure on cough test. They found no statistically significant difference about subjective results (92.2% vs. 94.2%; $P=0.78$), and objective results (94.4% vs. 96.7%; $P=0.50$) cure rates after MiniArc and Monarc at 12 months.

New devices have been recently introduced with a new fixation system, and were not included in the recent meta-analyses. The results of implantation of the new Altis sling have been investigated in two cohort studies to date [18,19]. In a preliminary report about 52 patients, Dias *et al.* [18] have reported an objective cure rate of 90.2% at 12 months in 52 patients, with 84% of patients being subjectively cured and 8% improved. Complication rate was low with one case of erosion requiring explantation, and three cases of exposure of the adjustment thread, managed conservatively. In a larger North American study, Kocjancic *et al.* have reported the outcomes at 1 year in 101 patients [19]. Cough test was negative in 92.2% of cases, and 90% of patients had a reduction of 50% or more according to pad-test. Although the vast majority of patients were satisfied with the treatment, no severe complication occurred (no erosion, no explantation). Further research about this new device is currently ongoing, and comparative trials are urgently awaited.

Beside comparisons to transobturator tapes and TVT, it has to be kept in mind that no study is currently available about SIMS versus conservative management, colposuspension, or autologous procedures. Despite that some groups have made attempts to compare different SIMS to each other [20], no clear level 1 data can lead to choose one SIMS over another (except TVT-Secur, which is anyway no more marketed in the USA and in many European countries).

COMPLICATIONS

Most of the available literature focused on short-term and perioperative complications. Although these evaluation criteria were rarely the primary outcomes of the trials, a number of assumptions

can be postulated according to the meta-analyses and recent published data.

After exclusion of TVT-Secur from the analyses, it seems that with SIMS, intervention was shorter, and postoperative pain was lower [6[■]]. Groin pain was significantly lower after SIMS when compared to transobturator tape placement [6[■]]. This has been confirmed recently by Schweitzer *et al.* [21]. The authors have conducted a remarkable study in which patients were randomized to receive either Ajust sling implantation or a traditional transobturator tape. The primary endpoint of the study postoperative pain, evaluated on a visual analog scale 1 and 2 h after the end of anesthesia, on a daily basis for 3 days and weekly during 6 weeks. The results have shown a significantly better profile for SIMS during the first week, with comparable results thereafter. In a recent randomized trial, Schellart *et al.* [16[■]] have pointed out that SIMS implantation led to a significantly lower visual analog scale score in the first postoperative days (coprimary outcome of their study).

For Mostafa *et al.* [6[■]], patients had an earlier return to their normal activities and went back to work more rapidly after SIMS implantation. This aspect has been specifically evaluated with the Ajust sling, leading to potential advantages of SIMS from an economic point of view [13]. The fact that SIMS implantation is possible under pure local anesthesia could lead to specific benefits in everyday practice and cost-effectiveness.

Well-known potential complications, such as bladder or urethral injury, obstruction, urgency, and erosion, seemed to be comparable after SIMS and traditional MUS. This analysis was, however, based on data of limited quality and short-term follow-up as exposed above.

CONSEQUENCES FOR CLINICAL PRACTICE

Although evidence about SIMS is growing slowly, a number of issues remain about their efficacy. The TVT-Secur experience has shown that long-term results and adequately powered, rigorously designed randomized trials are mandatory before recommending an unlimited diffusion of SIMS. Indeed, after some reports have led to deception about the long-term results, TVT-Secur has progressively been withdrawn and is no more considered for everyday practice.

A number of expert groups still do recommend preferring traditional MUS rather than SIMS for surgical management of stress urinary incontinence [22[■]], and the current guidelines clearly state the uncertainty of efficacy after 1 year [1]. SIMS for which no clear level 1 evidence has been released

have to be considered only in the setting of a clinical trial.

However, past experience with SIMS, even if not always successful, should not be the reason for burying single incision approach; it would rather be used to improve and stimulate further research. SIMS have indeed a lot of potential advantages in term of reduction of postoperative pain, with potential use of pure local anesthesia, and faster recovery. Given the very high prevalence of stress urinary incontinence in the Western world [23], but also in other parts of the world [24], the story has certainly to be continued.

CONCLUSION

SIMS have not yet been shown to be noninferior in terms of efficacy compared to traditional mid-urethral sling (especially in the long term), but evidence supporting their use is slowly growing. This minimally invasive option has still to be considered for further research, with adequately powered and designed randomized clinical trials against traditional transobturator slings and TVT, which remain the standards for daily practice.

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Female Urology – Incontinence

Midterm Prospective Evaluation of TVT-Secur Reveals High Failure Rate

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Abstract

Background: TVT-Secur has been described as a new minimally invasive sling for women's stress urinary incontinence (SUI) management, showing promising results in short-term studies.

Objective: Our goal was to evaluate the outcome of this procedure after a midterm follow-up.

Design, setting, and participants: A prospective evaluation involved 45 consecutive patients presenting SUI associated with urethral hypermobility. Fourteen patients preoperatively reported overactive bladder (OAB) symptoms, but none had objective detrusor overactivity. Eight patients had low maximal urethral closure pressure (MUCP). Four patients had pelvic organ prolapse (POP).

Intervention: Patients with POP were treated under general anesthesia by Prolift and TVT-Secur procedure. The 41 other patients received TVT-Secur under local anesthesia on an outpatient basis. All interventions were made by the same surgeon.

Measurements: Postoperative assessment included pad count, bladder diary, clinical examination with stress test, evaluation of satisfaction with the Patient Global Impression of Improvement (PGI-I) scale, and evaluation of side effects. Patients were classified as cured if they used no pads, had no leakage, and had a PGI-I score ≤ 2 ; as improved in case of reduction of SUI symptoms $>50\%$ and PGI-I score ≤ 3 ; and as failure otherwise.

Results and limitations: Mean postoperative follow-up was 30.2 ± 9.8 mo (range: 11–40 mo). Short-term evaluation showed a 93.5% success rate, but, at last follow-up, only 18 (40%) patients were cured, while 8 (18%) were improved, and 19 (42%) failed. Twelve patients underwent implantation of TVT or transobturator tape during follow-up. Age, MUCP, or OAB were not associated with failure. Side effects were limited to five cases of de novo OAB and three cases of urinary tract infection. This work is limited by the absence of a comparison group.

Conclusions: Our experience shows that despite its good short-term efficacy, TVT-Secur is associated with a high recurrence rate of SUI. Therefore, TVT-Secur does not seem appropriate for SUI first-line management in women.

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1. Introduction

The prevalence of urinary incontinence in women varies with age from 10–40% [1,2]. This condition, in certain social domains, affects quality of life [3]. Stress urinary incontinence (SUI), defined by the International Continence Society as an involuntary loss of urine with effort or exertion or on sneezing or coughing [4], is frequently reported by women. It can be pure or associated with overactive bladder (OAB) symptoms; the latter is called *mixed incontinence*. Mechanisms underlying SUI can be intrinsic sphincter deficiency, bladder neck hypermobility, or both [1].

SUI management is based on surgical options in case of failure of noninvasive therapies. Placement of a suburethral sling is the gold standard for the management of SUI associated with urethral hypermobility [5,6]. TVT and transobturator tape (TOT) are widely used in this indication with a high success rate and few complications [7–9].

In 2006, to minimize the risk of postoperative pain and organ perforation, a new generation of suburethral slings was described that avoided skin incision to pull out and tension the sling. The first available device, the so-called mini-sling, was the TVT-Secur [10]. Evaluation of this device through prospective short-term series has shown controversial results compared with other tension-free techniques. To our knowledge, all available published reports present <15 mo of follow-up data, concern 32–154 patients, and show an overall success rate between 62–100% at 1 yr [11–17]. Although preliminary series have shown promising results [12,17], other authors have reported an overall success rate of 70% on SUI and mild degradation of results after 1 yr [13].

Therefore, longer follow-up is needed and indications of this device still remain to be assessed. Our aim was to present our 3-yr experience with TVT-Secur in current clinical practice, focusing on the sustainability of the results.

2. Materials and methods

2.1. Patients

From September 2006 to March 2007, 45 consecutive patients underwent TVT-Secur implantation in our institution. A prospective evaluation was conducted. The following data were preoperatively collected: age; complete medical history; results of clinical examination with cough test; clinical evidence of urethral hypermobility; and preoperative urodynamics, which included maximal urethral closure pressure (MUCP), cystomanometry, and urine flow rate. Four patients had organ prolapse stage 3 in the Pelvic Organ Prolapse Quantification (POP-Q) system with associated SUI and underwent combined placement of a Prolift and a TVT-Secur. Fourteen patients had mixed incontinence with OAB symptoms; 11 of them were treated by anticholinergics at the time of surgery. No patient had objective detrusor overactivity (DO) on urodynamics, and all presented urethral hypermobility. Eight patients had a MUCP <40 cm H₂O. All patients did appropriate pelvic floor muscle exercises that failed to improve symptoms. Patients' characteristics are presented in Table 1.

2.2. Procedures

Forty-one patients were managed on an outpatient basis, received the sling under local anesthesia, and were discharged after surgery without

Table 1 – Preoperative data

Variable	Data
Age, yr, mean plus or minus SD (range)	60.3 ± 10.6 (35–87)
Preoperative symptoms	
Mixed incontinence (SUI and OAB), n (%)	14 (31)
Pure SUI, n (%)	31 (69)
Pads per day, mean plus or minus SD (range)	1.4 ± 0.7 (0–3)
Urodynamics	
Maximal urethral pressure closure, mean plus or minus SD (range)	54.6 ± 22 (20–100)
ISD (MUCP <40 cm H ₂ O), n (%)	8 (18)
Q _{max} , mean plus or minus SD (range)	24.8 ± 4.7 (16–33)
DO on urodynamics, n (%)	0
SUI = stress urinary incontinence; OAB = overactive bladder; ISD = intrinsic sphincter deficiency; MUCP = maximum urethral pressure closure; Q _{max} = urine flow rate; DO = detrusor overactivity.	

catheter. All these patients received the TVT-Secur sling according to the procedure described elsewhere [12]. Four patients were hospitalized for 24 h and operated on under general anesthesia with a 24-h catheterization because of combined placement of a Prolift anterior mesh and a TVT-Secur sling. Mean operating time was 15 min under local anesthesia and 1 h under general anesthesia.

2.3. Perioperative evaluation and follow-up

Follow-up for continence and satisfaction was done at 1, 3, 6, and 12 mo and yearly thereafter. Each visit included evaluation of pad usage, clinical examination with stress test, validated Patient Global Impression of Improvement (PGI-I) scale [18], and assessment of side effects possibly related to the procedure.

The main criterion for analysis was efficacy on SUI symptoms. Patients were considered cured in case of no pad usage, no stress-related leakage, and PGI-I score of 1 or 2. Improvement was defined as a reduction >50% of leakage episodes associated with a satisfaction level of 1, 2, or 3 according to PGI-I. Other cases were classified as failure. Further medical and/or surgical management of cases presenting failure was also assessed during follow-up.

2.4. Statistical evaluation

Statistical evaluation was conducted with XLStat2009 for Windows (Addinsoft, Paris, France). Quantitative values were compared with the Mann-Whitney test. We evaluated the durability of the results by assessing a Kaplan-Meier analysis with respect to the recurrence of pad use or SUI episodes on bladder diary during the follow-up period.

3. Results

Forty-five patients underwent the placement of a TVT-Secur sling for SUI. All patients operated on under local anesthesia were discharged the day of surgery, and the four patients who had combined Prolift placement and sling implantation were discharged at day 1. No perioperative complication was noted.

3.1. Follow-up

Mean postoperative follow-up was 30.2 ± 9.8 mo (range: 11–40 mo). Evaluation of efficacy showed that at last follow-up, 18 (40%) patients were cured, 8 (18%) patients were improved,

Table 2 – Evolution of results during follow-up (n = 45)

	First follow-up, n	6 mo follow-up, n	Last follow-up, n
Cured	28	24	18
Improved	11	8	8
Failure	6	13	19

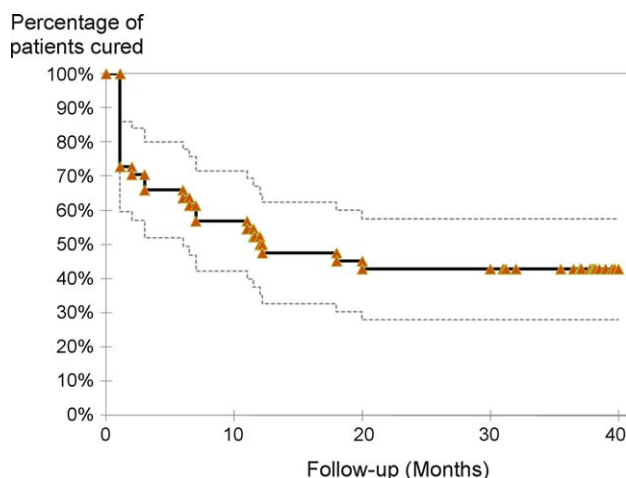
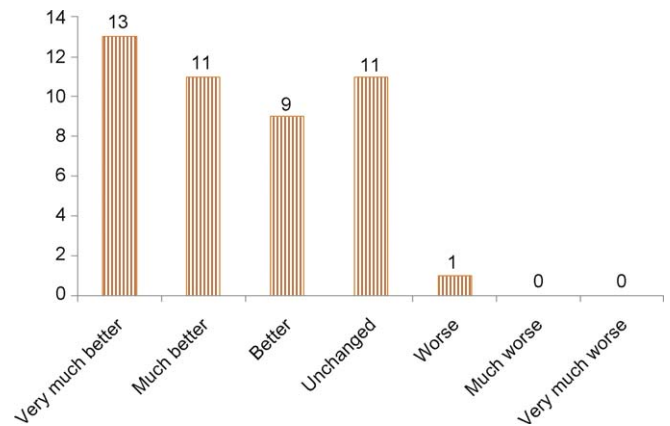
and 19 (42%) patients were classified as failure, either because of recurrent or persistent pad usage, leakage at clinical examination, or nonsatisfaction. Table 2 shows the evolution of the results at 1 and 6 mo and at last follow-up.

Fig. 1 represents the evolution of patients initially cured during follow-up. At first postoperative evaluation, 28 patients were cured with no leakage, and 17 patients had persistent SUI (improved in 11 and failed in 6). Recurrence of SUI occurred in 10 of the 28 cases initially cured. These types of failure can be late onset until 24 mo. Among the six patients having presented a late onset failure (after 6 mo), three had preoperative OAB, three had pure SUI, none had prolapse, and none had a MUCP <40 cm H₂O. Satisfaction results at last follow-up are presented in Fig. 2.

Twelve patients underwent supplementary surgery for SUI, with a TVT placement in 10 cases and TOT in 2 cases. Eleven of them were cured at last follow-up, and one failed. Other patients presenting failure underwent reeducation and/or adjuvant therapy with duloxetine and/or intravaginal pads. Thirteen of the 14 patients presenting OAB symptoms preoperatively were still suffering from OAB at last follow-up and were taking oral anticholinergic medication. Univariate analysis showed that failure was not significantly linked with age ($p = 0.17$), low MUCP <40 cm H₂O ($p = 0.71$), or OAB ($p = 0.51$). Patients who underwent combined surgery with Prolift and TVT-Secur were all cured at last follow-up, with no recurrence of organ prolapse.

3.2. Side effects

De novo urgency and OAB symptoms appeared in five patients and required medical management by trospium

**Fig. 1 – Survival without recurrence of pad usage, any stress urinary incontinence episode, and any degradation of satisfaction.****Fig. 2 – Patient's Global Impression of Improvement Scale-I results at last follow-up. Number of patients for each class is noted at the top of each column.**

chloride. No other side effect was noted during follow-up, except three cases of urinary tract infection treated with antibiotics.

4. Discussion

Management of SUI by suburethral slings expanded rapidly after the first description of the TVT technique in 1996 [19]. Indeed, this approach avoids a number of complications linked to such abdominal surgeries as colposuspension [19,20,22], is regarded as a successful technique to treat SUI, and has an estimated cure rate of around 80% in long-term follow-up studies [21]. TOT, introduced several years later, brought additional security by avoiding penetration of the retropubic space and thus also avoiding several complications, such as bladder perforation, hematoma, or pelvic organ injury [20]. However, the TOT approach is associated with postoperative thigh pain, and obstruction, infection or erosion can also happen [23–25]. Complications are therefore seen as an important outcome for further innovative slings [26]. New so-called minimally invasive devices have been developed to limit groin pain after sling placement while aiming at comparable success results. TVT-Secur minimizes operative dissection and risk of injury of periurethral elements and pelvic organs as well as the risk of nerve or adductor muscle damage.

In our experience, this innovative device failed to demonstrate high clinical efficacy on SUI symptoms. After 30 mo, numerous patients in our series presented recurrence of urinary leakage. Overall, only 40% of patients remained cured at last follow-up, whereas 42% failed and 18% were improved. Twelve patients of 45 required additional TOT or TVT surgery. All but one patient who underwent supplementary surgery were dry at last follow-up, in line with the data recently published by Liapis et al about TVT as a secondary procedure after initial failure of midurethral sling for SUI [27].

Data analysis shows two different patterns of failure. The first is a primary failure, diagnosed at the first

postoperative visit (13% of our cases). This kind of event is well known by all practitioners in the field of sling surgery and is usually related to technical failure (sling misplacement, failure of the device itself, bad patient selection, learning curve [27]). However, all procedures were led by an experienced surgeon, and no erosion or sling misplacement was demonstrated. Furthermore, a similar proportion of short-term failure has already been reported in the literature about TVT-Secur. Indeed, failure rate was 6.5% at 2 mo for Debodinance et al. [13], 15% at 14 mo for Oliveira et al. [15], 21% at 13 mo for Meschia et al. [17], and 8–20% at 1 mo according to Neuman [28]. Finally, a recent report on short-term results of TVT-Secur by Lee et al shows a cure rate of 84% based on stress test versus 76.4% based on satisfaction questionnaires [29]. Some other papers [11,12] report a cure rate >95% at 1 mo, but in selected cases (eg, excluding patients presenting low MUCP and/or OAB symptoms preoperatively).

The second pattern of failure emerging from our data analysis after a 3-yr follow-up is of greater significance and is linked to the long duration of our prospective evaluation. We observed recurrence of symptoms in 33% of patients initially cured, leading to pad use, decrease of satisfaction, and/or objective leakage at clinical examination. At last follow-up, only 40% of patients remained cured. Twelve patients underwent further surgical management with TVT or TOT slings. All but one of these reinterventions led to satisfactory results, indicating that traditional sling would have been preferred as a first-line treatment in these patients.

To our knowledge, this high rate of recurrence has not been described previously, and can be explained by several factors. The first one is the follow-up duration of our study, since no longer evaluation has yet been published in the available literature. The other is the heterogeneity of our cohort, including patients with OAB, low MUCP, or prolapse. No link could be shown between these variables and failure in univariate analysis, but statistical significance is very low given the small number of patients. However, this kind of series is more able to reflect daily practice than carefully selected populations usually presented for the evaluation of a new device. The last reason could be the failure of the device itself (self-fixing secure tip), since it had not been evaluated yet in long-term studies. The system may not resist periurethral tissue modifications with time, and slip and lose its efficacy.

Side effects were limited to postoperative pain in 10 patients, de novo OAB symptoms in 5 patients, and urinary tract infection in 3 patients, easily managed by antibiotics. These data compare favorably to previous studies.

This evaluation is limited by the small number of patients treated and patient-selection criteria, which were very large to reflect daily practice. Moreover, the design of this study is prospective but did not include a comparison group. However, these results, if confirmed on larger series, should lead us to reconsider indications of this device. Our results should encourage authors who have presented large series based on short-term evaluation to present their results with updated follow-up.

5. Conclusions

Our midterm experience evaluating TVT-Secur for SUI in women shows that this new technique is safe and quick and is associated with limited and mild side effects. However, under current clinical conditions, if results are satisfactory in the short term, they are not sustainable. Indeed, a significant degradation over time was assessed with an overall failure rate of 42% at 3-yr follow-up. These results demonstrate the importance of a long follow-up when a new device is evaluated in the field of urinary incontinence. Indications of TVT-Secur for SUI in women should be reconsidered.

Author contributions: Jean-Nicolas Cornu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Haab.

Acquisition of data: Peyrat, Sèbe.

Analysis and interpretation of data: Cornu, Sèbe.

Drafting of the manuscript: Cornu.

Critical revision of the manuscript for important intellectual content: Sèbe, Cussenot.

Statistical analysis: Ciofu, Peyrat.

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Other (specify): None.

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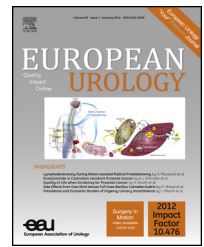
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Female Urology – Incontinence

A Randomized Comparison of a Single-incision Midurethral Sling and a Transobturator Midurethral Sling in Women with Stress Urinary Incontinence: Results of 12-mo Follow-up

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Abstract

Background: Midurethral sling procedures have become the prime surgical treatment for women with stress urinary incontinence (SUI). Single-incision mini-slings (SIMS) potentially offer similar efficacy with reduced morbidity. This international multicenter trial compared the efficacy and morbidity of a SIMS (MiniArc) and a transobturator standard midurethral sling (SMUS) (Monarc).

Objective: To compare subjective and objective cure, morbidity, and surgery-related discomfort following SIMS and transobturator SMUS.

Design, setting, and participants: Prospective randomized controlled trial with an initial follow-up period of 12 mo. Women with symptomatic SUI were eligible.

Outcome measurements and statistical analysis: Primary outcome was subjective cure, defined as an improvement on the Patient Global Impression of Improvement (PGI-I). Coprimary outcome was the mean visual analog scale (VAS) pain score (0–100) during 3 d after surgery. Secondary outcomes were objective cure based on the cough stress test (CST), disease-specific quality of life determined by the Urogenital Distress Inventory (UDI-6) score, surgical parameters, and physical performance during recovery. Analysis was by intent to treat. Differences between the MiniArc and Monarc groups on dichotomous variables were chi-square tested and presented as relative risks (RR) with corresponding 95% confidence intervals. We hypothesized that MiniArc was noninferior to Monarc concerning subjective cure and superior concerning postoperative pain.

Results and limitations: We randomized 97 women to MiniArc and 96 to Monarc. At 12-mo follow-up, subjective cure was 83% following MiniArc and 86% following Monarc ($p = 0.46$). Objective cure was 89% following MiniArc and 91% following Monarc ($p = 0.65$). The mean pain VAS score during the first three postoperative days was 9 following MiniArc and 22 following Monarc (Mann-Whitney U test, $p < 0.01$).

Conclusions: At 1-yr follow-up, MiniArc was noninferior to Monarc with respect to subjective and objective cure and superior with respect to postoperative pain.

Patient summary: This 1-yr randomized clinical trial showed that MiniArc, a single-incision midurethral sling, is noninferior to Monarc, a transobturator sling, with respect to cure and superior with respect to pain and recovery.

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1. Introduction

Stress urinary incontinence (SUI) affects 35% of adult women and severity and prevalence increase with age [1]. To date, midurethral slings are the preferred treatment option for SUI [2].

Retropubic tension-free vaginal tape (TVT) has high cure rates, but concerns exist about the risk of bladder perforation and major vessel injuries, occurring in 1–5% of all women [3]. For that reason, a transobturator approach was developed, which appears to have similar cure rates as the retropubic approach on short-term follow-up [4,5]. The transobturator route is safer, faster, and associated with a lower risk of postoperative urinary retention and overactive bladder symptoms. However, due to perforation of the adductor muscles and injury to the posterior branch of the obturator nerve, patients might experience pain in the groin and upper legs [6]. Single-incision mini-slings (SIMS) have been developed to reduce procedure-related discomfort without negatively affecting the benefit. Like transobturator slings, SIMS perforate the obturator internus muscle and the foramen obturatum, but do not perforate the adductor muscles, resulting in less postoperative pain [7].

During the last decade, varying success rates have been reported for SIMS [8,9]. The understanding that most types of SIMS are to be positioned with slight tension at the midurethral level has improved outcome.

Extensive evidence to support the use of SIMS has not yet been provided and for that reason we initiated a European, multicenter, randomized controlled trial (RCT) with a follow-up period of 36 mo to compare efficacy, safety, and procedure-related discomfort between MiniArc and Monarc. This article reports the 12-mo follow-up data of this RCT.

2. Methods

We performed a RCT comparing MiniArc versus Monarc in five teaching hospitals with special interest in pelvic floor surgery, located in three European countries. Investigators at these sites had extensive experience in the surgical treatment of female SUI. The research group standardized the surgical procedures during a joint theater session with involvement of all surgeons. Besides intensive monitoring, the centers were audited by two independent external institutions.

Patients indicated for surgical correction of symptomatic SUI were asked to participate. Exclusion criteria were pelvic organ prolapse stage ≥ 2 (International Continence Society classification), prior surgery for SUI, and body mass index > 35 kg/m² [10]. The trial was registered at the Netherlands Trial Register NTR3783 (<http://www.trialregister.nl/trialreg/index.asp>) and was approved by the medical ethical committees of all participating centers (MEC nr NL28973.018.09; B32220107859; F 201-A00147-32).

Patients were randomly allocated in a 1:1 ratio to either a MiniArc or Monarc procedure, stratified by center and in blocks of different size (ie, four or six).

Before surgery, a standardized medical history was taken and a pelvic examination including Pelvic Organ Prolapse Quantification (POP-Q) staging and a cough stress test (CST) were performed in the supine position. Performing routine, preoperative, urodynamic investigation was not mandatory, as findings of multicenter trials did not show added value [11,12].

Patients received a single dose of antibiotics 30 min prior to surgery. Both procedures were performed under spinal or general anesthesia. Operation time and blood loss were collected during surgery.

2.1. MiniArc procedure

MiniArc is introduced through a single 1.5-cm incision at the level of the midurethra, after bilateral periurethral dissection with Metzenbaum scissors to the posterior portion of the ischiopubic ramus (about 1–1.5 cm). The needle is tracked along the posterior surface of the ischiopubic ramus until the midline mark on the mesh is approximately at the midline position under the urethra. After fixation of the sling tip into the obturator internus fascia, the needle is removed. The same procedure is repeated on the contralateral side. The sling is *pillowing* with gently tension on the midurethra. The incision is closed using a delayed absorbable suture.

2.2. Outcomes

The primary outcome was subjective cure of SUI, both in the short-term (12 mo) and the long-term (36 mo) follow-up. This article reports the 12-mo follow-up data. Subjective cure was chosen, as all studies on patients' treatment objectives demonstrate that patients find it more important to experience improvement than to be completely dry. Subjective cure was measured with the Patient Global Impression of Improvement (PGI-I) [13]. The PGI-I assesses perceived improvement, using a seven-option single item ranging from very much better to very much worse. Cure was defined as *very much improved* or *much improved*.

Coprietary outcome was postoperative pain. Patients were asked to record in a diary during the first 4 wk after surgery the postoperative pain they experienced, using a visual analog scale (VAS) ranging from 0 to 100. Pain scores were documented daily during the first 7 d and at 2 and 4 wk after surgery. The use of pain medication was noted and the patients were counseled to use pain medication only if necessary.

A secondary outcome was objective cure, defined as a negative CST during physical examination. The CST was performed in the supine position with a bladder volume of ≥ 250 ml (checked by bladder scan) or $> 70\%$ of the maximum bladder capacity according to a voiding diary. The voiding diary recorded during a period of 3 d the time and volume of each void, the moment and volume of fluid intake, the number of urgency episodes, the number and severity of incontinence episodes, and the number of pads used.

Other secondary outcomes were adverse events during surgery, admission, and during the first 12 mo of follow-up, use of pain medication, and re-interventions during the first year after surgery. Short-term (within 4 wk of surgery) and midterm (until 12 mo postsurgery) adverse events were registered.

Questionnaires were completed during each visit. To assess the presence and severity of stress or urge incontinence symptoms, the short version of the Urogenital Distress Inventory (UDI-6) (range: 0–100), which comprises six questions, was used [14]. The Patient Global Impression of Severity (PGI-S) item was used to measure the severity of experienced micturition symptoms [13].

A validated item set from the Academic Medical Center Linear Disability Score (ALDS) item bank to assess patients' functional disability concerning activities of daily living was completed 1 d before surgery and at 1, 2, and 4 wk thereafter [15]. The original units of the ALDS scale are logistic regression coefficients, expressed in logits. These logit scores were used in the statistical analysis; for interpretation purposes, they were linearly transformed into values between 0 (dead) and 100, with 1 representing the lowest and 100 representing the highest level of functional status possible [16].

2.3. Sample size calculation

We hypothesized that the subjective cure rate of MiniArc was noninferior to Monarc and that MiniArc was superior with respect to postoperative pain. We expected to observe a subjective cure rate of 90% in each group and needed 85 patients per group to obtain 90% power

with a one-sided α equal to 0.025 to establish the noninferiority of MiniArc compared with Monarc within a 15% absolute margin of the cure rate. This number was also sufficient to obtain 90% power with a two-sided α of 0.05 to detect a 20% difference (minus 8 points, from 40 to 32) in the postoperative VAS pain score, averaged over the first 3 d after surgery, using a two-sample *t* test. Anticipating an attrition rate of 10% of patients who would not be evaluable at the primary midterm end point at 12 mo, we planned to include 192 patients in this trial.

2.4. Statistical analysis

Analysis was by intent to treat. Differences between the MiniArc and Monarc groups on dichotomous variables were presented as relative risks (RR) with corresponding 95% confidence intervals, followed by chi-square testing. Normally distributed, continuous variables were described with means and standard deviations, with differences assessed using the student's *t* test. Non-normally distributed continuous variables were described with medians and ranges, followed by Mann-Whitney *U* (M-WU) testing for significance. The Fisher exact test was used if the expected value was <5 . A linear mixed model was used to assess the difference in functional status during the first month after surgery. Statistical analysis was performed using SPSS v.20 (IBM Corp, Armonk, NY, USA). A *p* value <0.05 was considered statistically significant.

3. Results

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram is presented in Figure 1. Between December 2009 and December 2011, we informed 225 eligible patients

about this trial. There were 193 patients randomized in the study; 97 patients were allocated to MiniArc and 96 to Monarc. In the Monarc group, one patient underwent MiniArc and vice versa, as the surgeon had understood that was the allocated intervention.

Table 1 lists baseline characteristics of the study groups. In the MiniArc group, more patients were postmenopausal, although the difference was not significant.

Table 2 shows surgery-related outcomes. Duration of surgery and amount of blood loss were both lower in the MiniArc group. During surgery, two perforations of the lateral fornix occurred in the MiniArc group and five in the Monarc group. All perforations were recognized and repaired during surgery and none of these patients reported symptoms after surgery that could be related to this event.

The mean pain VAS score during the first three postoperative days was 9 following MiniArc and 22 following Monarc (M-WU, $p < 0.001$). In the MiniArc group, fewer patients used pain medication than in the Monarc group (43% vs 69%).

Table 3 lists the results at 12-mo follow-up. Subjective cure was 83% in the MiniArc group and 86% in the Monarc group ($p = 0.46$). Objective cure was 89% in the MiniArc group and 91% in the Monarc group ($p = 0.65$).

During the first month, both groups improved similarly in functional status (based on the ALDS) to reach baseline levels again ($p = 0.33$).

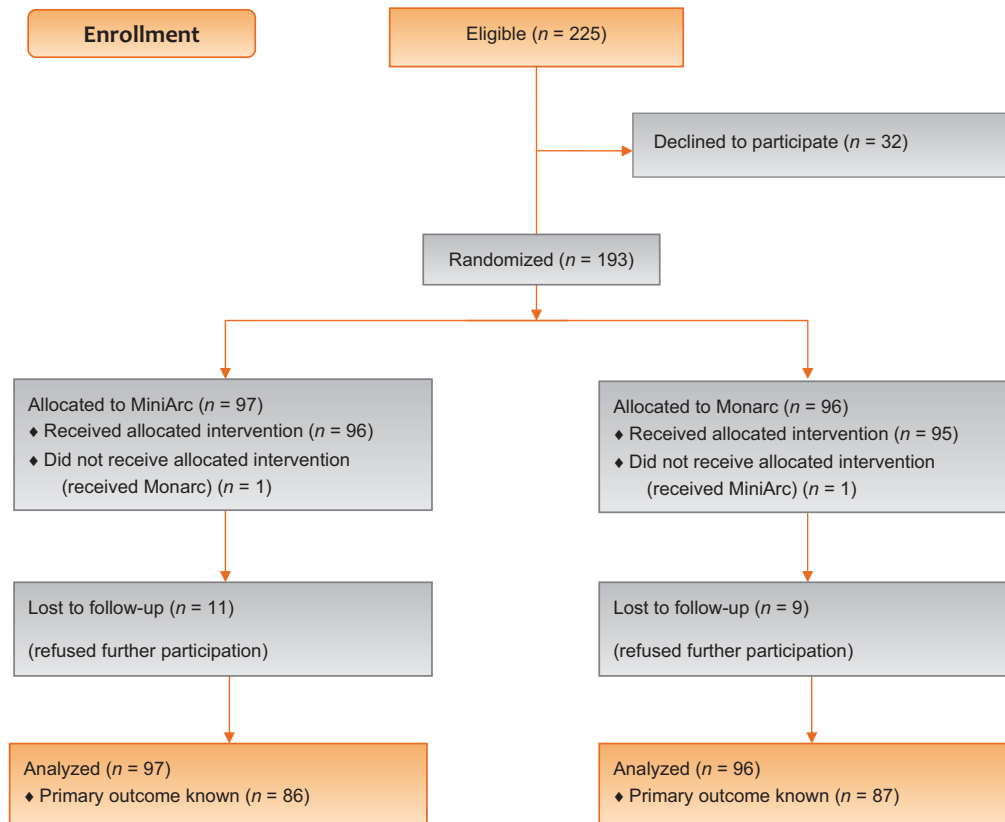


Fig. 1 – Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Table 1 – Baseline characteristics

	MiniArc (n = 97)	Monarc (n = 96)
Age, yr, mean (SD)	53 (11)	53 (11)
BMI, kg/m ² , mean (SD)	26.0 (4.3)	25.7 (3.7)
Parity, median (IQR)	2 (2)	2 (2–3)
Postmenopausal, no. (%)	26 (47)	20 (36)
Previous POP surgery, no. (%)	13 (13)	9 (9)
Any known chronic disease ^a , no. (%)	60 (62)	52 (54)
UDI domain scores, mean (SD)		
Irritative	47 (28)	45 (27)
Stress	66 (20)	66 (22)
Obstructive/discomfort	20 (22)	17 (24)
ALDS, mean (SD)	89 (2.4)	88 (5.8)
ALDS = Academic Medical Center Linear Disability Score; BMI = body mass index; IQR = interquartile range; POP = pelvic organ prolapse; SD = standard deviation; UDI = Urogenital Distress Inventory.		
^a Includes: hypertension, cardiac disease, pulmonary disease, gastroenterologic disease, renal disease, endocrine disease, neurologic disease, psychiatric disease, orthopedic disease, immunologic disease, metabolic disorder, infectious disease, malignant disease, diabetes mellitus, depression, chronic constipation, and recurrent urinary tract infection.		

During the first 12 mo after randomization, 34 adverse events occurred in the MiniArc group and 43 in the Monarc group. Of these adverse events, 14 versus 19 were procedure related and 1 versus 3 were device related, according to the

Table 3 – Subjective and objective outcomes at 12 mo after intervention

	MiniArc (n = 86)	Monarc (n = 87)	p value
Urinary incontinence, no. (%)			
Subjective cure	71 (83)	76 (86)	0.46
Objective cure	74 (89)	73 (91)	0.65
UDI domain scores, mean (SD)			
Irritative	24 (23)	23 (25)	0.71
Stress	16 (21)	13 (18)	0.39
Obstructive/discomfort	16 (22)	9 (14)	0.01
ALDS, mean (SD)			
During first month after surgery	87 (5.1)	87 (5.9)	0.33
At 1 wk after surgery	85 (8.0)	85 (7.5)	
At 2 wk after surgery	87 (4.3)	87 (5.0)	
At 1 mo after surgery	88 (3.0)	88 (5.2)	
ALDS = Academic Medical Center Linear Disability Score; SD = standard deviation; UDI = Urogenital Distress Inventory.			

clinical evaluation committee. In the MiniArc group, 9 patients had a urinary tract infection versus 13 patients in the Monarc group. All were successfully treated with antibiotics. Five patients in the MiniArc group and seven patients in the Monarc group initially had a postvoiding residual (PVR) bladder volume of >150 ml. In all patients, the PVR bladder volume normalized within the first week after

Table 2 – Surgical-related outcomes, recovery after surgery, and postoperative adverse events

	MiniArc (n = 97)	Monarc (n = 96)	p value	
Duration of surgery, min, median (IQR)	10 (7–15)	15 (11–20)	<0.01	
Blood loss, ml, median (IQR)	20 (5–50)	50 (10–78)	<0.01	
Residual after first voiding, ml, median (IQR)	40 (20–90)	27 (0–53)	0.03	
Complications perioperative, %				
Unintentional perforation of the lateral fornix	2	5	0.28 [#]	
Blood loss >500 ml	2	1	1.00 [#]	
Hemorrhage in right groin	0	2	0.25 [#]	
Complaints of postoperative vomiting	2	0	0.50 [#]	
VAS pain score, mean				
Any pain medication used, %				
Average VAS score during the first 3 d, mean (SD)	9 (11.3)	21.8 (19.3)	<0.01	
Day 1	11	25	<0.01	
	43	68	<0.01	
Day 2	9	22	<0.01	
	27	47	<0.01	
Day 3	7	18	<0.01	
	20	36	0.02	
Week 1	4	9	<0.01	
	15	17	0.79	
Week 4	2	3	0.90	
	8	5	0.37	
Adverse events during 12-mo follow-up, %	0–4 wk	>4 wk–12 mo	0–4 wk	>4 wk–12 mo
Urinary tract infection	7	2	9	4
Pyelonephritis	0	1	0	0
Reoperation	0	1	0	3
Bladder retention	5	0	6	1
IQR = interquartile range; SD = standard deviation; VAS = visual analog scale.				
[#] Fisher exact test.				

surgery, except for one patient in the Monarc group, who needed 4 wk to normalize.

Three patients were indicated for repeated surgery in the Monarc group: two retropubic slings were placed because of failure and one patient underwent a correction of a tape exposure 3 mo after initial placement. All three procedures were performed in day surgery and were successful.

In the MiniArc group, one retropubic sling was successfully placed because of failure. Another patient underwent correction of a tape exposure by removing the MiniArc and placing a retropubic tension-free vaginal tape in the same session. This patient left the hospital the same day and was cured afterward.

At 12-mo follow-up, the UDI domain score for *irritative* did not show a difference between the MiniArc and Monarc. The domain score for *stress* and *obstructive* showed a tendency in favor of the Monarc, although not significantly.

4. Discussion

This trial demonstrates the noninferiority of SUI treatment with MiniArc to Monarc regarding subjective and objective cure and superiority regarding postoperative pain and recovery. There were no differences in surgery-related adverse events and re-interventions during the first year postoperatively.

The subjective cure rate of the MiniArc (83%) was slightly lower when compared to the Monarc group (86%). Whereas the reported results of Monarc are quite consistent, there is a relative large variation in reported success rates of MiniArc [17–19]. Differences in technique probably account for this phenomenon. When the SIMS was first introduced, one was unaware that the required tension was slightly higher than for SMUS [20]. Also, the cure rates of SIMS have been debated. An early SIMS on the market was TVT-Secur (Ethicon Endo-Surgery Inc, Cincinnati, OH, USA). When compared to TVT-obturator, both subjective and objective cures were significantly lower, probably due to anatomic variability of a relatively short tape and an unusually wide dissection needed to insert TVT-Secur [21,22].

A review by Abdel-Fattah et al reflected the primary suboptimal results of SIMS with inferior patient-reported and objective cure rates on the short-term follow-up and higher reoperation rates for SUI when compared with standard midurethral tapes [9].

SIMS results have significantly improved, however [23]. The design of SIMS has been altered, which helped standardize the trajectory and improved surgeons' understanding of how to implant a SIMS.

MiniArc showed significantly lower pain scores and less use of pain medication during the first three postoperative days, as compared to Monarc, probably resulting from not perforating the adductor muscles and the tape not lying approximate to peripheral branches of the obturator nerve [6]. The lower pain scores related to faster return to normal daily activities may be economically preferable, if quicker return results in faster resumption of work, too.

The risk of adverse events was low for both interventions. This is in line with other studies [24,25]. As SIMS needs to be tensioned slightly tighter, higher de novo urgency rates have been reported [26]. This was not observed during the first year of follow-up, but it might take a longer follow-up to observe a difference in overactive bladder symptoms between both interventions [27].

The strength of this trial is its multicenter, randomized design allowing for generalizability of the trial findings. Other strengths include the standardization of the surgical technique, developed by consensus of the complete trial group, the low attrition rate, and the external monitoring.

There are also some limitations. One could argue that more objective outcome measures, such as a urodynamic investigation, postoperative voiding diaries, or pad test should have been used. However, like Tincello and coworkers, we have chosen a subjective outcome measure because of its greater clinical value to prove effectiveness of an intervention in continence surgery [28].

Another point of concern could be the selection of the comparative intervention. We decided to compare MiniArc to Monarc, as these procedures share most of their surgical route, and the mesh is similarly horizontally positioned below the midurethra. Consequently, it is unknown whether MiniArc is also noninferior to retropubic slings. In patients with low urethral closure pressure, retropubic tapes might be superior to transobturator tapes, but according to a Cochrane analysis [29] and to Richter and coworkers [5], retropubic and transobturator tapes generally have comparable outcome.

In this study, neither patients nor assessors were blinded to the treatment. Generally, a double-blinded study design would be the design of first choice to avoid expectation biases in clinical trials. However, both therapeutic procedures have specific complications patients should be and have been informed about prior to their consent to trial participation. Further, the complications would have revealed patients' treatment status during follow-up. Hence, it was decided not to blind patients and assessors. However, in addition to subjective cure as the primary outcome, we added objective cure as a secondary outcome measure to help interpret the main results.

Our data contribute to the changed perspective about SIMS [23]. The recently revised guidelines of the European Association of Urology now state that there is level 1b evidence that the SIMS is equally effective to other midurethral slings in improving SUI in women in the short term [30].

Prior to recommending SIMS to all patients, however, a few more steps are necessary. First, longer term follow-up is needed to confirm our observations, and for that reason we will continue follow-up until 3 yr after surgery. Second, we plan to perform a cost-effectiveness analysis, as it is important to determine the exact positioning of the SIMS in the treatment paradigm of surgery for SUI. Additionally, we have to learn more about the patient characteristics that are related to failure and success, to optimize counseling and facilitate shared decision making based on individual characteristics.

5. Conclusions

This 1-yr, international, multicenter, randomized trial demonstrates that MiniArc is noninferior to Monarc with respect to subjective and objective cure and superior with respect to postoperative pain and recovery. Both procedures had low complication rates. Although our trial results support the improved appreciation of the surgical outcome of SIMS, more data are mandatory prior to offering this technique to all patients indicated for SUI surgery.

Author contributions: René P. Schellart had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Schellart, Roovers.

Acquisition of data: Schellart, Roovers, de Ridder, Kimpe, Lucot.

Analysis and interpretation of data: Schellart, Roovers, Oude Rengerink, Dijkgraaf.

Drafting of the manuscript: Schellart, Roovers, Dijkgraaf, Oude Rengerink, Van der Aa.

Critical revision of the manuscript for important intellectual content: Schellart, Roovers, Oude Rengerink, Dijkgraaf, Van der Aa, de Ridder.

Statistical analysis: Schellart, Roovers, Oude Rengerink, Dijkgraaf.

Obtaining funding: Schellart, Roovers.

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Management of complications of mesh surgery

Dominic Lee and Philippe E. Zimmern

Purpose of review

Transvaginal placements of synthetic mid-urethral slings and vaginal meshes have largely superseded traditional tissue repairs in the current era because of presumed efficacy and ease of implant with device 'kits'. The use of synthetic material has generated novel complications including mesh extrusion, pelvic and vaginal pain and mesh contraction. In this review, our aim is to discuss the management, surgical techniques and outcomes associated with mesh removal.

Recent findings

Recent publications have seen an increase in presentation of these mesh-related complications, and reports from multiple tertiary centers have suggested that not all patients benefit from surgical intervention.

Summary

Although the true incidence of mesh complications is unknown, recent publications can serve to guide physicians and inform patients of the surgical outcomes from mesh-related complications. In addition, the literature highlights the growing need for a registry to account for a more accurate reporting of these events and to counsel patients on the risk and benefits before proceeding with mesh surgeries.

Keywords

Food and Drug Administration, mesh excision, mid-urethral sling, surgical outcomes, vaginal mesh complications

INTRODUCTION

Pelvic organ prolapse (POP) and stress urinary incontinence (SUI) have an estimated prevalence of 11% [1]. Traditional approaches such as abdominal mesh sacrocolpopexy for prolapse and autologous fascial slings for SUI were too invasive and synthetic mesh use for both SUI [mid-urethral sling (MUS)] and prolapse (transvaginal mesh placement) as minimally invasive alternatives were introduced with a plethora of device kits flooding the market [2]. Novel complications from mesh became apparent with reports of mesh erosions, pelvic pain, dyspareunia and contractions surfacing, prompting two Food and Drug Administration (FDA) safety warnings in both 2008 and 2011 [3,4]. Mesh-related complications not only impact negatively on quality of life but also cause considerable financial liability to the community with increasing loss of productivity from this cohort of women [5,6]. Currently, most of the tertiary referral centers are seeing an increase in vaginal mesh-related complications, but outcome data from surgical management are scarce.

In this review, we aim to review the evaluation, surgical techniques and outcomes of mesh-related complications. For term simplification, in this review, the terms 'tape' for mid-urethral sling and 'mesh' for vaginal wall prolapse repair are used,

recognizing the many different products on the market, with variable availability, mesh composition, weaves and tensile properties.

PREVALENCE/SYMPTOM PROFILING

The rate of mesh/tape complications is hard to determine for various reasons. Firstly, the number of randomized controlled trials (RCTs) with adequate duration of follow-up that allows for adequate assessment is limited. In addition, contributing factors including a lack of systematic registration of mesh-related complications and the high attrition rate in follow-up further hamper the establishment of any true incidence as the true denominator is not fully known [7,8]. The revised Cochrane database for surgical management of POP reports data for morbidity 'as lacking' with estimates of mesh erosions in women receiving transvaginal

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KEY POINTS

- Management of mesh complications in POP and SUI is now a rapidly growing field for surgeons (meshology) and should be part of FMPRS specialty.
- Chronic pelvic pain and dyspareunia can remain despite maximal mesh/tape excision.
- An assessment tool to uniformly report on outcomes associated with revision surgeries is required.
- Full disclosure of risks and benefits to all patients undergoing mesh/tape surgery, as recommended by the FDA, is strongly advised.

mesh repairs for cystocele alone as 11.4% (64/563), with surgical reinterventions rate of 6.8% (32/470). The overall reoperation rate was higher for vaginal mesh repair 11% (2/194) than for native tissue repair 3.7% (7/189) [relative risk 3.1, 95% confidence interval (CI) 1.3–7.3] [9]. A recent multicenter RCT comparing native tissue with mesh placement for cystocele found superior anatomical results at 24 months but no difference in objective and subjective cure rates [10]. On a larger scale, the Austrian Urogynecology working group established a transvaginal mesh registry. A total of 726 transvaginal procedures with 10 different transvaginal kits were registered over a 5-year period with mesh erosion reported in 11% at 3 months and 12% at 12 months, respectively. Of the sexually active women, 7% (265) at 3 months and 10% (181) at 12 months reported dyspareunia postoperatively [11[■]].

In evaluating complications, a multicenter retrospective study by Abbott *et al.* [12[■]] highlighted the concerns in 347 women presenting with mesh complications. Index surgeries were either stand-alone or in combination. Of these, pelvic/vaginal pain and mesh/tape erosion were common presentations. In turn, 77% had a grade three or four (severe) complication according to the Accordion system with a median of two treatments for mesh complications (range 1–9). In identifying the referral pattern of these women, Peters *et al.* [13] evaluated a cohort of 51 women and reported that only 3.6% of the patients were referred by their original surgeons and furthermore, one in three patients had delayed presentations as a result of prereferral treatments.

EVALUATION OF PATIENTS WITH MESH/TAPE-RELATED COMPLICATIONS

The literature reporting mesh complications is mostly retrospective with highly variable and divergent outcomes. In an effort to standardize

terminology for more precise reporting and to facilitate the implementation of a reliable registry [11[■],14], a new classification system of complications directly related to prosthesis placement in female pelvic floor surgery has been endorsed by both the International Urogynecological Association and International Continence Society [15].

Mesh/tape-related complications can occur early or late. For this reason, patients with mesh/tape should have long-term (more than 10 years) follow-up to monitor for complications or delayed onset of symptoms [16,17]. As emphasized in the FDA notification of 2011, patients with mesh/tape who do not have complications should not undergo mesh/tape explantation [4]. A detailed clinical history should screen for vaginal discharge/bleeding, pelvic/groin pain, dyspareunia, hispareunia, urinary tract infections, voiding dysfunction, incontinence as well as prolapse recurrence and bowel complaints. Onset of the symptoms, type of mesh used, prior pelvic surgeries, investigations and treatments should be attained. The use of standardized questionnaires such as the urinary distress inventory short form-6, incontinence impact questionnaire-7, visual analogue scale (VAS) for pain, patient global impression of improvement scale (PGI-I), pelvic floor disorder inventory short form (PFDI SF-20), pelvic floor impact questionnaire short form (PFIQ SF-7) and female sexual function index (FSFI) should be encouraged to establish a baseline and to assess longitudinal outcomes following intervention. A pelvic examination and vaginoscopy are necessary to assess for mesh exposure in the relevant compartments, scar tissue/contraction ‘banding’, prolapse recurrence or SUI, vaginal discharge/bleeding, and areas of tenderness or discomfort. In severe cases, an examination under anesthesia is warranted in patients intolerant of pelvic examinations in clinic.

Cystourethroscopy is useful to identify mesh/tape exposed in the lower urinary tract and distortion of the urethral lumen (Fig. 1a and b). For voiding complaints, urodynamic studies (UDS) and voiding cystourethrogram (VCUG) or video-urodynamics when available have been useful (Fig. 2a and b) [18]. For bladder outlet obstruction (BOO) following tape placement, patients may demonstrate detrusor overactivity but more consistently will exhibit a prolonged or intermittent flow curve with an elevated detrusor pressure on UDS (Fig. 2b). Urethral narrowing and kinking at the level of the tape with proximal urethral dilatation on lateral voiding views of the VCUG is another sign suggesting BOO (Fig. 2a). Imaging with pelvic MRI is still a novelty as mesh/tape implants are difficult to visualize. Some findings, such as bladder wall indentation from a retropubic tape, distortion of

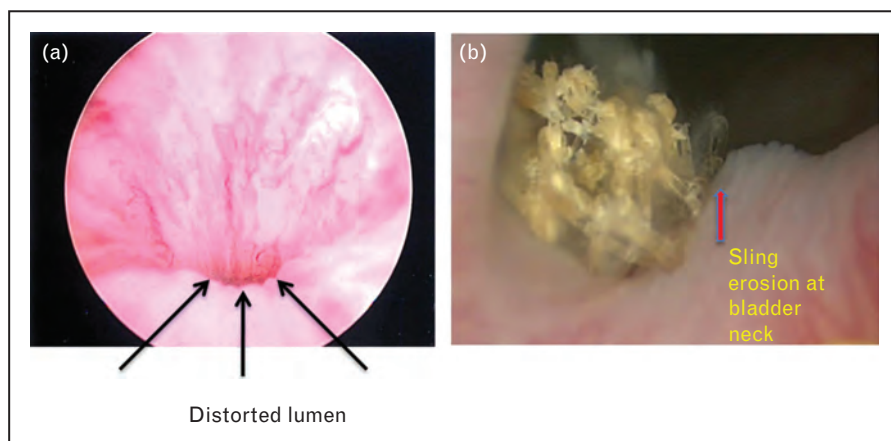


FIGURE 1. Cystoscopy (a) very narrow lumen with elevation and flattening of urethral floor depicted by the arrow. (b) Calcified mesh extended at the right side of the bladder neck.

the bladder base from an anterior mesh, localization of the lateral extensions of the mesh arms, and thickened areas consistent with possible mesh infection, can provide valuable insights for surgical planning. Translabial ultrasound has been utilized for presurgical planning to identify the course of suburethral tape. Staack *et al.* [19[•]] reviewed a series of 51 women with translabial ultrasound who had vaginal tape and/or mesh placement comparing clinical with definitive intraoperative findings. They were able to accurately locate the position of MUS and its type (retropubic vs. transobturator), and to detect all anterior or posterior compartment prolapse meshes. The technique was found inferior in evaluating vaginal mesh extrusion, which is not unexpected as the vaginal thickness is variable.

MANAGEMENT OPTIONS

Mid urethral slings

Erosion/extrusion

Management of tape involving the urinary tract has been reported with excision via either the vaginal or abdominal approaches, endoscopically with ablation with holmium laser or transurethral resection with electrocautery [20,21]. Combined laparoscopic and endoscopic procedures have also been described [22]. Recently, we have used the holmium laser in urethral erosion patients involving more than a quarter of the urethral lumen to ablate the exposed mesh segment endoscopically and allow for secondary re-epithelialization. This is minimally invasive and potentially avoids the need for major urethral reconstruction,

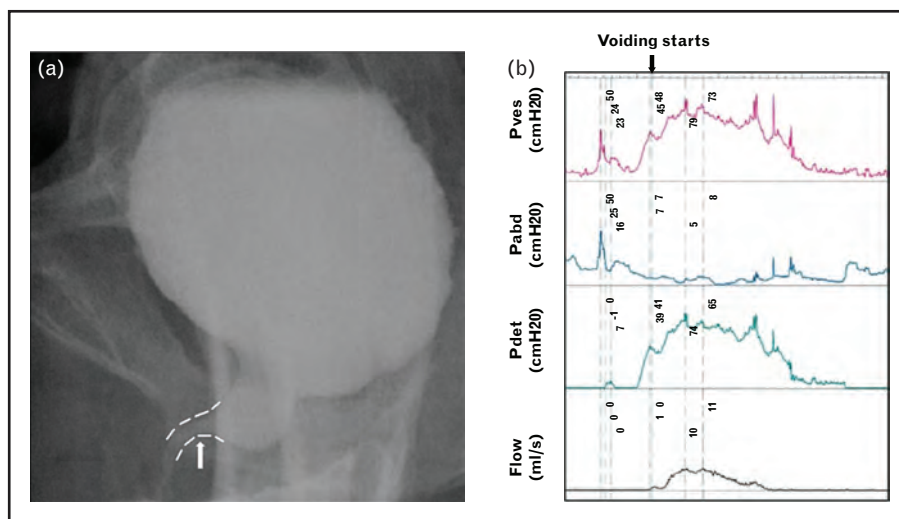


FIGURE 2. (a) Lateral voiding cystourethrogram confirmed obstruction and its site (arrow on 2a). (b) Uroynamics confirmed obstruction with high pressure low flow on voiding phase. Reproduced with permission from [18].

which could compromise urethral caliber [23]. Shah *et al.* [24] reported on their series of 21 women with mesh tape extrusion and erosion into the lower urinary tract. They advocated for total mesh tape excision, urethral reconstruction, and concomitant autologous PVS. Their surgical technique was to approach the tape transvaginally with either a midline or transverse incision following hydro-dissection. The identified tape and pseudocapsule are dissected with cautery on 'cut' to the extremes of the tape arms with retropubic arms retrieved abdominally and transobturator arms to obturator externus. The tract was lavaged with antibiotic solution, and the urinary tract was repaired in four layers. An autologous PVS was placed in all patients with urethral perforation, bladder neck involvement, and evidence of preoperative SUI. At mean 22 months follow-up, 71% with urethral perforation and all patients with bladder perforation were continent.

Bladder outlet obstruction

For urinary retention following tape placement that persists for more than 1 week, loosening the sling or sling incision is recommended. It is likely that the longer BOO goes untreated, prolonged compression and ischemia of the mid-urethra can result in permanent scarring of the urethral lumen and consequential voiding dysfunction and bladder remodeling [25]. Urgency symptoms frequently occur as a result of BOO, and this should be excluded for any de-novo symptoms after a tape procedure [26,27]; and tape excision to relieve the BOO would be necessary. Our tape excision technique is depicted in Figure 3 [28]. Specific complications following tape removal include recurrent SUI, urethral stricture, persistent pain, or dyspareunia if those pre-existed, bladder neck injury, urethral injury requiring immediate or delayed repair, urethro-vaginal fistula, and need for

repeat surgery. This needs to be disclosed as part of the counseling and consent process.

TRANSVAGINAL MESH

Mesh extrusion/erosion

For transvaginal prolapse meshes, varying approaches have been published depending on degree of exposure and institution experience. Vaginal extrusions and exposure may be managed conservatively if exposure is less than 1 cm and not associated with any complicating factors [29,30]. Local estrogen therapy is often employed, but the literature reflects mixed results [29,31] and mesh excision considered with failures [29–32]. Often, a limited excision of mesh is attempted under local anesthesia [31,32]. In our experience, exposed vaginal mesh is considered infected and will be hard to eradicate with antibiotics and local estrogen therapy alone. Mesh removal is challenging as visualization is often limited and extent of tissue damage from the mesh is often unknown. It can be approached vaginally or in a combination with abdominal and, either complete or partial mesh removal undertaken (Fig. 4 a–c). Success of mesh removal often depends on surgical experience in dealing with these complications, and many patients travel great distances to tertiary referral centers for management [33]. Complications following removal of transvaginal mesh are related to the affected compartment. Ureteral stents may be needed when the mesh is very close to the bladder wall or there is bladder base deformation noted on preoperative pelvic MRI. Following mesh removal, we routinely perform cystoscopy with indigo carmine to exclude ureteric injury. For the posterior compartment, bowel injury and need for colostomy have been reported [29]. We routinely place a betadine soaked rectal pack to help with identification

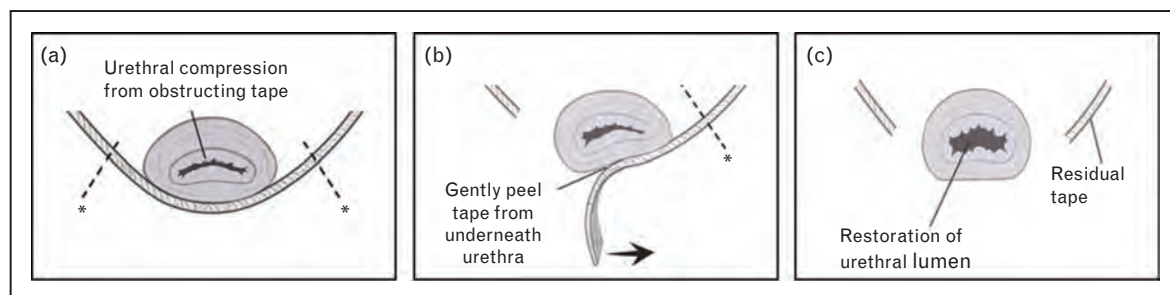


FIGURE 3. (a) MUS tensioned-free can result in urethral kinking and distortion. We recommend lateral sling incision (marked by asterisk) to reduce risk of urethral injury. (b) Tape is carefully peeled away from underneath the urethra. (c) Following MUS tape excision, urethroscopy helps confirm no urethral injury and documents restoration of a normal urethral lumen. Reproduced with permission from [28].

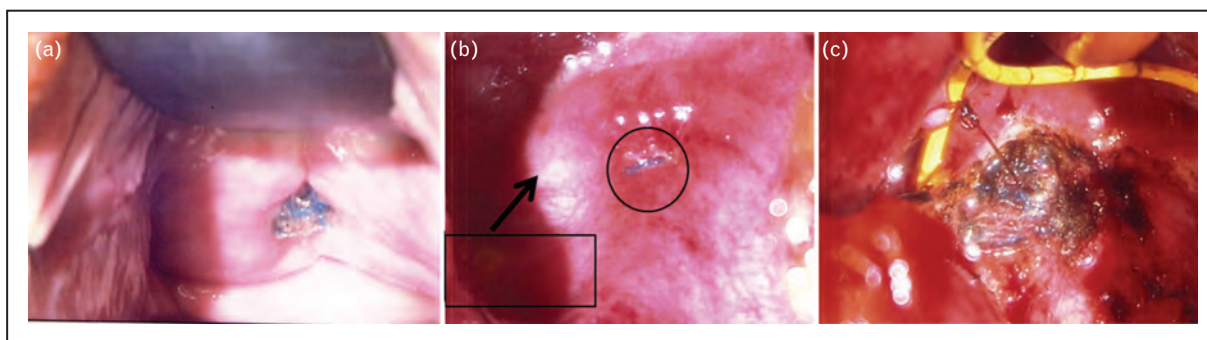


FIGURE 4. (a) Vaginal mesh extrusion and vesico-vaginal fistula in trigone. (b) Open approach was undertaken due to proximity of left ureteric orifice and concerns for reimplantation. (c) Ureteric orifice cannulated and mesh exposed and removed subsequently with perivesical fat pad interposition.

of the lateral mesh arm dissection/excision, and detect small rectal wall tears. Other complications associated with mesh excision include large vaginal defects, possibly requiring skin grafting, residual pain which can be unremitting and life altering, and/or need for repeat surgery for secondary prolapse. Fir-oozi *et al.* [34] published their surgical technique and outcomes in a series of 23 women who developed mesh complications following placement of commercial prolapse kits. All patients had transvaginal or transperineal mesh removal. Their described technique includes lithotomy positioning with cystoscopic examination and prophylactic stenting of ureters (if bladder involvement). Following hydro-dissection, a U-shaped vaginal incision is made (with the apex directed at the exposed mesh if visible). When the lateral dissection is completed, the identified mesh is divided in the midline when and dissected off the bladder wall. Mesh is excised at the lateral edge and any vesicovaginal fistula is repaired and the U flap resutured without overlap of suture lines. Of the 23 patients, 20 had resolution of symptoms at a mean of 3 months follow-up.

Mesh causing dyspareunia or pain

This is a difficult situation to deal with, as the exact source of pain is usually unknown. It can arise from a low-grade infection, to excessive tensioning of the mesh, excessive scarring and local nerve irritation, or unrelated to the mesh. Therefore, as outlined in the FDA mesh notifications of 2008/2011, mesh removal alone may not be curative and debilitating, and life-altering changes may persist [35]. In addition, extent of mesh removal is not predictable, but the aim is maximal mesh excision within safety margins. The vaginal incision can be inverted U-shaped to ease access to the pelvic sidewalls, or midline, or directed to one vaginal sulcus or another depending on the location of the pain and should allow for tissue interposition in case of intraoperative adjacent organ injury.

Another issue is concurrent prolapse repair at the time of mesh removal to prevent further prolapse recurrence. This is a concern to many patients, which should be discussed preoperatively. Our preference has been to remove the mesh only, and not to interpose any new biological or synthetic material. In our review of a series of women with a mean follow-up at 30 months after mesh removal only, we identified a recurrence rate of less than 10% and a persistent rate of 21% on follow-up examination, with a relative small proportion of women ultimately undergoing secondary repairs for POP [36].

MANAGEMENT AND OUTCOMES

As stated, there is a paucity of long-term outcomes for the treatment of mesh complications in the current literature. Majority of these are single center case study series with short-term follow-up. See Table 1 [23,33,34,36–44] for summary. Hammett *et al.* [37] recently reported on their series of 57 patients (26 tapes, 23 transvaginal prolapse and nine intraperitoneal prolapse) with mean follow-up of 6 weeks. Majority of the patients had transvaginal mesh excision (91%). At 6 weeks follow-up, 95% had either complete or partial resolution of chronic pain but overall only 57.3% achieved complete symptom resolution, whereas 14.6% were improved. In a similar multicenter retrospective study, Unger *et al.* [38] reported on their management outcomes on 101 out of 260 women with vaginal mesh-related complications (prolapse and slings) using standardized questionnaires (PGI-I, PDFI SF-20, PFIQ SF-7 and FSFI). Of the 101 survey responders, 51% had reintervention with less than 10% requiring repeat surgeries. Of the 30% (30/101) of respondents who reported pelvic pain prior to intervention, 63% (19/30) reported improvement, 30% (9/30) were worse, and 7% (2/30) reported no change. Of the 33% (33/101) who reported voiding

Table 1. Outcomes of transvaginal mesh removal 2012–2015

Study	N	Follow-up (months)	Route V = vaginal, A = abdominal, P = perineal	Symptoms	Cure	Outcome (%)	
						Improved	Overall
Shah <i>et al.</i> ^b [23]	21	22.0	V/A	E/P/I/BOO/UTI			71.5–100
Firoozi <i>et al.</i> +[33]	23	3.0	V/P	P/E/D/UTI/POP			87
Lee <i>et al.</i> ^a [34]	58	13.0	V/A	P/E/F/D/UTI/POP	24		86
Hammett <i>et al.</i> ^a [36]	67	1.5	V/A	P/D/E/DC	57.3	14.6	71.9
Unger <i>et al.</i> ^a [37]	101	N/S	N/S	P/E/D/VD/POP			39–63
Crosby <i>et al.</i> +[38]	84	4.0	V	P/E/F/D/UTI/POP	51		64
Hokenstad <i>et al.</i> +[39]	41/68	N/S	V/A	D/P/VD/DC			54
Hansen <i>et al.</i> ^a [40]	84/111	27.6	V/A	P/E/D/VD/C			71
Hou <i>et al.</i> ^a [41]	123	22–35	V	P/E/D/UTI			67–81
Danford <i>et al.</i> ^a [42 [■]]	233	12.0	V	E/P			73
Agnew <i>et al.</i> ^b [43]	47	N/S	V	E/P			100
Coskun <i>et al.</i> ^b [44]	17	17.0	V	E/P/D/UTI	35		57–80

^aMixed series, + mesh kit series.

^bSling series. N/S not stated; BOO, bladder outlet obstruction; C, contraction; DC, discharge; D, dyspareunia; E, erosion/extrusion; F, fistula; I, incontinence; P, vaginal/pelvic pain; POP, prolapse; VD, voiding dysfunction; UTI, urinary tract infection.

dysfunction prior to intervention, only 39% of patients with voiding dysfunction improved after intervention.

Similarly, in our transvaginal mesh excision series of 58 women (mesh and tape) with a median of 13 months follow-up, 17 (29%) required re-excision of residual mesh. Five women developed recurrent symptomatic POP (7%). The residual rate of dyspareunia and pelvic pain was 14 and 22%, respectively. Fourteen women (24%) were treated successfully, with complete resolution of all presenting symptoms [35].

For transvaginal prolapse mesh patients alone, Crosby *et al.* [39] reported follow-up data in 84 of 90 women undergoing mesh excision with a median follow-up of 4 months (range 2–11.5). Overall, 51% ($n=43$) had resolution of all presenting symptoms with mesh exposure treated successfully in 95% of patients, whereas pain was only successfully treated in 51% of patients. Interestingly, 56% had concomitant surgeries and how much they contributed to the overall symptom-burden is difficult to quantify. On a similar trend, Hokenstad *et al.* [40] reported on the outcomes of 68 women with mesh excision for prolapse mesh-related complications. With a 44 (65%) response rate from their administered surveys, 22 (54%) patients reported a successful outcome after mesh excision. Of 29 (71%) sexually active patients, 23 had dyspareunia before mesh excision and only three patients reported resolution of dyspareunia after excision. On logistic regression, higher successes were those identified as complete mesh excision, new

overactive bladder symptoms after mesh placement, and BMI higher than 30 kg/m²; with adjusted odds ratio (OR) (95% CIs) 5.46 (1.10–41.59), 7.76 (1.18–89.55), and 8.41 (1.35–92.41), respectively. In a longer term study, Hansen *et al.* [41] reported on 111 women with index surgeries that included prolapse mesh (47%), tape (37%), abdominally placed vaginal mesh (11%), and prolapse mesh with concomitant tape (5%). Of the 111 women, 98 women underwent treatment with 85 receiving surgical management and 84 (76%) provided follow-up data at mean follow-up duration of 2.3 years. Overall, a total of 71% reported being better, whereas 29% reported no change or being worse.

For pain outcomes, Hou *et al.* [42[■]] reported on a series of 123 patients with prolapse mesh (69) and suburethral tape (54) excision using an objective VAS for pain. Pain-free status, considered a score of 0, was achieved in 81% of tape and 67% of mesh cases, respectively. Similarly, Danford *et al.* [45] looked into a larger cohort of 233 women with a median follow-up of 12 months (range 1–120) who underwent vaginal mesh revision, excision, or urethrolisis for pelvic pain related to original mesh placement of which 121 (65%) were tape alone and 66 (35%) with concomitant prolapse procedure. Outcome was based on patient's perception of pain improvement following revision/removal surgery categorized as better, worse, or unchanged. Overall, 169 (73%) patients reported improvement in pain postsurgery, whereas 45 (19%) reported no change in pain, and 19 (8%) reported worsened pain.

Comparatively, those with mesh exposure (131 patients) were more likely to be improved than those without (102 patients), (77 vs. 67%) and less likely to be worse after excision (5 vs. 12%). On multivariate regression models, prior history of chronic pelvic pain was the only associated risk factor for poorer outcomes (OR 0.28, 95% CI 0.12–0.64, $P=0.003$).

When evaluating tape complications alone, Agnew *et al.* [43] reported on 47 women who underwent revision. Of these, 39 women (83%) had an identifiable mesh extrusion with or without pain, whereas eight women (17%) presented with pain alone. Complete tape removal was performed in 23 (49%) cases and partial excision (for localized non-infected exposures/extrusions) in 24 (51%). Of the eight women presenting with pain alone with no identifiable tape exposure/extrusion; all reported pain resolution. For those who had failed prior attempts with tape complication, Blaivas *et al.* [46] reviewed their outcomes in a series of 47 women with heterogeneous presentation with a median follow-up of 2 years. Presenting conditions included BOO 24 (51%), recurrent SUI 23 (49%), mesh erosion 11 (23%), stone five (11%), vaginal mesh extrusion four (9%), and ureteral injury two (4%). Corrective surgeries included sling incision, sling excision, urethrolisis, urethral reconstruction, ureteroneocystotomy, cystectomy and urinary diversion, and enterocystoplasty. Overall, a successful outcome was achieved in 34 of 47 patients (72%) after the first salvage surgery and in 82% after multiple operations. For individual symptoms and conditions, the success/improvement rate ranged from 50% for pain to 100% for urethral obstruction. Of the 13 patients with initial treatment failure, nine subsequently underwent a total of 14 subsequent procedures, and success/improvement was achieved in five (56%).

In recent times, the single incision mini-slings were marketed to alleviate most of the trocar-related complications associated with retropubic or trans-obturator approach. Although incontinence outcomes are comparable with conventional mid urethral slings, reports of mesh complications are no exception. Coskun *et al.* [44] reported on their sling excision outcomes in a series of 17 women with 76% presenting with more than one complaint. At a mean follow-up of 17 ± 9 months (range 7–44), they achieved cure in six (35%) women; cure defined as continent, pain free and sexually active. Among the 11 women with pelvic pain, eight (73%) were cured or improved and three (27%) had persistent pain. Dyspareunia persisted in three women. Of 14 with incontinence, eight (57%) had cure or improvement, and obstructive symptoms resolved in four of five (80%).

Although these surgeries conducted in tertiary surgical centers are considered safe, the outcome trends are concerning as the effects of unresolved pelvic pain can be persistent. Furthermore, the effects can be far reaching beyond just personal discomfort for the patient. We have observed countless times the impact of these procedures on work assignments, interpersonal relationships, and marital discord eventually ending at times in divorce and loss of insurance coverage.

On a lesser presentation, for those who developed fistula, reconstructive repair was generally met with mixed results. Blaivas and Mekel [47] reported on a small series of 10 cases with mean follow-up of 26 months. Encountered fistula included: one each of ureterovaginal and enterovesical, six vesicovaginal, and seven urethrovaginal fistulas. Seven patients (78%) underwent successful fistula repair with one requiring continent urinary diversion. A high rate of tissue interposition was used. We recently presented our outcomes in management of urethrovaginal fistula. We treated 18 women with mean follow-up duration of 51 months (range 6–164). Of the 18 patients, nine were mesh-sling related. Repair success rate was 100% with eight out of nine requiring tissue interposition (five autologous PVS). Comparing with the nonsling cause, the sling group had poorer overall functional outcomes with statistical difference noted for Q4 on UDI-6: 1.9 vs. 0.8 ($P=0.03$) and Q5: 1.3 vs. 0 ($P=0.02$, and in VAS favoring the nonsling group; 1.5 (0.6) vs. 5 (4) ($P=0.05$) [48].

CONCLUSION

The management of mesh/tape complications remains challenging, and is often dealt with in tertiary care centers. Although the denominator remains largely unknown, the increase in mesh-related complications is concerning. Symptoms are not always reversible following surgical management/removal even in high-volume specialized centers. The need for future large prospective cohort studies and national registries in assessing outcomes of patients following mesh/tape removal has never been more desirable.

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Conflicts of interest

There are no conflicts of interest.

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The time course of development of late side effects after irradiation of the prostate with multiple fractions per day

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Abstract

Background and purpose. A group of patients with prostate cancer was irradiated in the early 1980s with a TID schedule, resulting in a very high frequency of side effects. The time course of development of severe late complications was evaluated. **Materials and methods.** We retrospectively reviewed the records of 91 patients with prostate cancer, irradiated on a linear accelerator or a cobalt unit between 1980 and 1983. They received a split-course irradiation with multiple fractions per day (MFD) up to a nominal dose of 60 Gy. The rate of development of severe late urological and gastrointestinal complications, grade 3 or more according to the RTOG scoring system, was analysed. **Results.** The 5-year actuarial incidence of urological complications was 51%. After a lag time of a few months, patients develop 'first events' at a nearly constant rate of 10% for 5 years after treatment. Subsequent events ('all events') seem to continue to appear even after 5 years. The actuarial incidence at 5 years of gastrointestinal complications was 14%, with no new events developing later than 3 years after treatment. **Conclusions.** The irradiation schedule used resulted in an unacceptable high incidence of late side effects, probably due to incomplete repair between fractions. MFD fractions to the pelvis should be avoided, unless sufficient time in between fractions can be allowed. Moreover, the fact that after this treatment schedule with very pronounced biological effects, new severe complications continued to develop up to 5 years after therapy, indicates that sufficiently long follow-up time has to be respected when investigating new radiation techniques for pelvic tumours.

Keywords: Prostate cancer; Late side effects; Time course; Radiotherapy

1. Introduction

In 1986 we reported on the unusually high incidence of late complications occurring after irradiation treatment for prostate cancer, using multiple fractions per day (MFD) [19]. In the present paper, we review the same cohort of patients with special attention for the time course and annual incidence rate of severe late complications. Knowledge of these factors could help in evaluating new, more intensive, radiation treatment schedules for pelvic tumours, as it could provide an indication of the time interval that should be allowed before the total incidence of late side effects can ac-

curately be predicted. This is important if one wants to step up the treatment intensity.

2. Materials and methods

2.1. Patients

Between February 1980 and December 1983, 109 patients with prostate carcinoma were treated with a multiple fractions per day irradiation schedule. For the present retrospective review 100 patient charts were available. Of these, 9 had clinical signs of local recurrence and were considered unsuitable to assess treatment related side effects, leaving 91 patients in the study. Their age at the time of treatment varied between 48 and 85 years with a median age of 73. The minimum, maxi-

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mum and median follow-up was 2 months, 156 months and 35 months, respectively.

2.2. Radiation treatment

Two different split-course MFD schedules were used: (1) (2 Gy TID \times 5 — split of 3–4 weeks — 2 Gy TID \times 5), i.e. a total dose of 60 Gy in 30 fractions over 5–6 weeks; and

(2) (2 Gy TID \times 3.3 — split of 2.5 weeks — 2 Gy TID \times 3.3 — split of 2.5 weeks — 2 Gy TID \times 3.3), i.e. a total dose of 60 Gy in 30 fractions over 6.5 weeks.

These schedules were based on the assumption, at that time widely accepted, that 4 hourly intervals were sufficient. Moreover these schemes were convenient for an older population, as they only required short periods of hospitalisation. Finally, the preliminary results as described by Ang et al. [1] showed a very good acute tolerance.

Three different radiation treatment techniques were used. They have been reported in detail previously [19]. In short:

(A): 'cobalt pelvis': 21 patients, cobalt, 4 field technique with AP-PA fields encompassing the pelvis (total dose 40 Gy, irradiated at 08:00 h and 16:00 h) and lateral fields, limited to the prostate (total dose 60 Gy, irradiated at noon). The dose was normalised to the 90% isodose resulting in a hot spot of 66 Gy in part of the prostate and the bladder. In the boost volume, the dose to the rectum varied in the AP direction between the 90% and the 80% isodose;

(B): 'linac pelvis': 57 patients, linac, 18 MV, 3 field technique (1 AP field and 2 lateral fields, irradiated every session), 40 Gy to the pelvis, 60 Gy to the prostate with a similar hot spot area of 66 Gy, due to the 90% reference isodose used, the AP rectum dose varied between the 90% and 30% isodose.

(C): 'linac prostate': 13 patients, linac, 18 MV, 3 field technique, limited to the prostate (all fields irradiated every session), tumordose 60 Gy at the 100% isodose, no hot spot. The AP rectum dose varied between the 100% and 30% isodose. As the number of patients in the (C) group is very small, these are only used in the global analysis and not discussed separately.

2.3. Side effects

Gastrointestinal and urological side effects were assessed according to the RTOG late side effects scoring table (Table 1). Only complications grade 3 or more, persisting more than 6 months after completion of treatment or developing after a 6 month symptom free period were scored. They were analysed actuarially.

For urological side effects we evaluated pollakisuria, nycturia, hematuria, incontinence and urethral stricture; for gastrointestinal complications diarrhea, rectal bleed-

Table 1
RTOG morbidity grading system

Grade 1:	Minor symptoms requiring no treatment.
Grade 2:	Symptoms responding to simple out-patient management, life style (performance status) not affected.
Grade 3:	Distressing symptoms altering patients life style (performance status). Hospitalization for diagnosis or minor surgical intervention (such as urethral dilatation) may be required.
Grade 4:	Major surgical intervention (such as laparotomy, colostomy, cystectomy) or prolonged hospitalization are required.
Grade 5:	Fatal complications.

ing, tenesmi, incontinence, rectal ulcer, rectal stenosis and obstruction were scored.

The 'first events' were defined as the first complications, either urological or gastrointestinal, occurring in a patient. For 'all events' we considered the actuarial sum of all complications, developing in a patient. The cumulative actuarial rate of development of late complications was calculated (referred to as 'absolute') as well as the rate of development of complications as a percentage of the total number of patients ultimately developing side effects (referred to as 'relative'). This enables the direct evaluation of rate of occurrence of complications independently of the absolute incidence of complications.

3. Results

3.1. Urological complications

For all patients the 5 year actuarial incidence of urological complications is 51%, for patients treated with 'cobalt pelvis' and 'linac pelvis' fields, the incidence is 79% and 40%, respectively.

The 5 year incidence of nocturnal incontinence for all patients, for patients treated with 'cobalt pelvis' and 'linac pelvis' fields is 26%, 41% and 24%, respectively. For complete incontinence corresponding numbers are 26%, 49% and 23%. Finally for urethral stricture the respective incidence is 25%, 46% and 16%. Due to the small total patient numbers, differences between the various treatment techniques are not statistically significant.

Table 2 summarizes the yearly incidence of 'first events', i.e. the development of complications in patients previously free of symptoms. For the first 5 years the incidence is at least 10% a year, with a peak of 16% in the second year. After 5 years the number of patients at risk becomes too small to evaluate. In relative terms, as a percentage of all patients developing complications, the appearance rate is ~20% a year (Fig. 1).

Table 2
Frequency of urological complications

Year after treatment	First events				All events			
	Cobalt pelvis	Linac pelvis	Linac prostate	Total/pts. at risk (%)	Cobalt pelvis	Linac pelvis	Linac prostate	Total/pts. in study (%)
0–1	3	6	1	10/91 (11.8)	4	6	1	11/91 (12)
1–2	5	7	0	12/73 (16.5)	4	11	1	16/80 (20)
2–3	2	2	1	5/47 (10.5)	3	4	0	7/60 (11.5)
3–4	1	2	0	3/29 (10.5)	4	3	0	7/45 (15.5)
4–5	1	0	1	2/15 (13)	1	1	1	3/28 (10.5)
5–6	0	0	0	0/10 (0)	1	0	0	1/22 (4.5)
6–7	0	0	0	0/5 (0)	0	1	0	1/21 (4.5)
Total/initial no. of patients	12/21	17/57	3/13	32/91	17/21	23/57	3/13	46/91

Looking at 'all urological events' (i.e. including additional complications in patients who already had first events), new complications continue to appear, as long as patients have been followed (Table 2).

3.2. Gastrointestinal complications

The actuarial 5 year incidence of gastrointestinal complications, i.e. rectal stenosis, bleeding and chronic diarrhea, for all patients is 14%.

For patients treated with cobalt and linac pelvis fields, the incidence is 15% and 13%, respectively. Nearly all complications occurred within the first 2 years with no new 'first events' after 3 years (Table 3).

3.3. Comparison of time course of urological and gastrointestinal complications

For 'first events' (Fig. 1) as well as for 'all events', the development of gastrointestinal side effects follows a steeper slope than the urological ones, with a plateau reached 3 years after treatment. At 2 years post-treatment, 85% of the gastrointestinal 'first events' and 95% of 'all events' have occurred, compared to only 39% and 54% for urological complications.

3.4. Comparison of time course of side effects in patients treated with cobalt or linac pelvis

Although the complication incidence was higher in

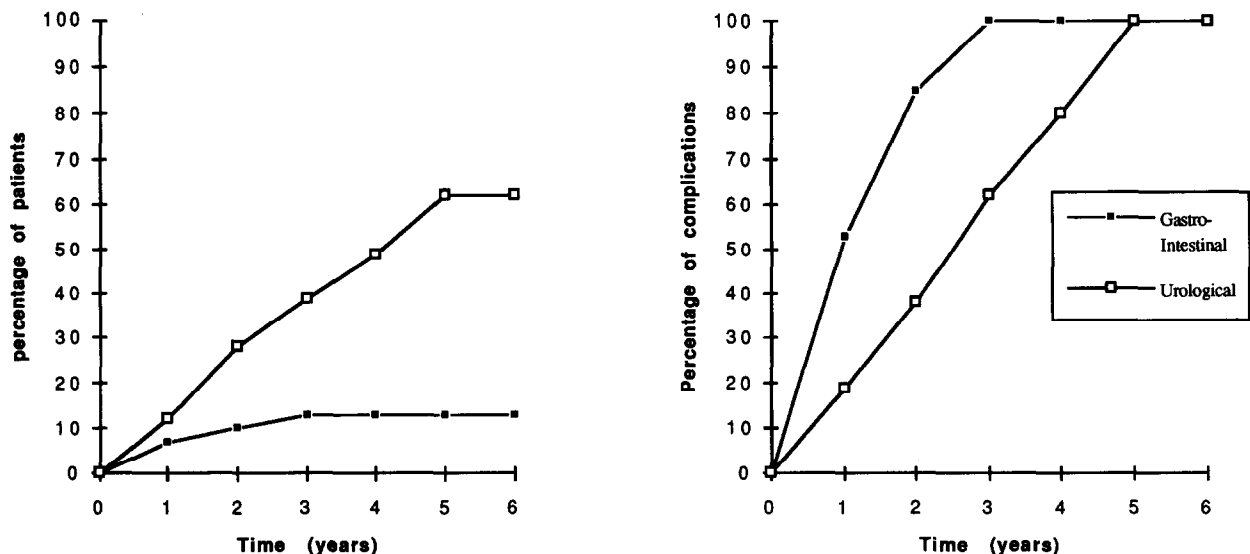


Fig. 1. Urological vs. gastrointestinal complications. Absolute incidence (left) and relative incidence (right), cf. text for details.

Table 3
Frequency of gastrointestinal complications

Year after treatment	First events				All events			
	Cobalt pelvis	Linac pelvis	Linac prostate	Total/pts. at risk (%)	Cobalt pelvis	Linac pelvis	Linac prostate	Total/pts. in study (%)
0-1	3	3	0	6/91 (6.5)	8	8	0	16/91 (17.5)
1-2	0	2	1	3/77 (4)	3	4	2	9/80 (11)
2-3	0	1	0	1/56 (1.8)	0	1	0	1/60 (1.5)
3-4	0	0	0	0/42 (0)	0	0	0	0/45 (0)
4-5	0	0	0	0/28 (0)	0	0	0	0/28 (0)
Total/initial no. of patients	3/21	6/57	1/13	10/91	11/21	13/57	2/13	26/91

the 'cobalt' than with the 'linac' group, probably the result of poorer ballistics, no difference in the rate of appearance of complications was demonstrated (Fig. 2).

4. Discussion

In the present paper we investigated the time course and actuarial incidence of serious late complications (RTOG grade 3 or more) occurring after MFD radiation treatment for prostate cancer. The urological side effects are thought to be due to progressive fibrosis in the region of the bladder neck, urethra and sphincter complex [19]. This region lies inevitably in the target volume to be treated to full dose.

Urological complications, as first events, started to develop a few months after the end of radiotherapy and continued to occur, at a nearly constant rate, for at least 5 years after treatment. As numbers get too small, it is

difficult to derive from the present data whether complications continue to develop even after the fifth year in patients previously free of problems. However, from the data on 'all events', it seems likely that fibrosis, once established, continues to progress.

This is in good agreement with earlier studies in other organ systems.

Turesson [16] found that skin telangiectasia in breast cancer patients continue to progress for at least 10 years. This was shown as well for progression in the individual patients (comparable to our 'all events'), as for the number of patients showing a certain stage of telangiectasia ('first events'). The broad variation of latency found in our study, i.e. 'first events' developing throughout the first 5 years, was also observed in her study and would be inversely related to the total dose; whereas the rate of progression would increase with dose.

Spanos et al. [12] evaluated late effects, i.e. severe fi-

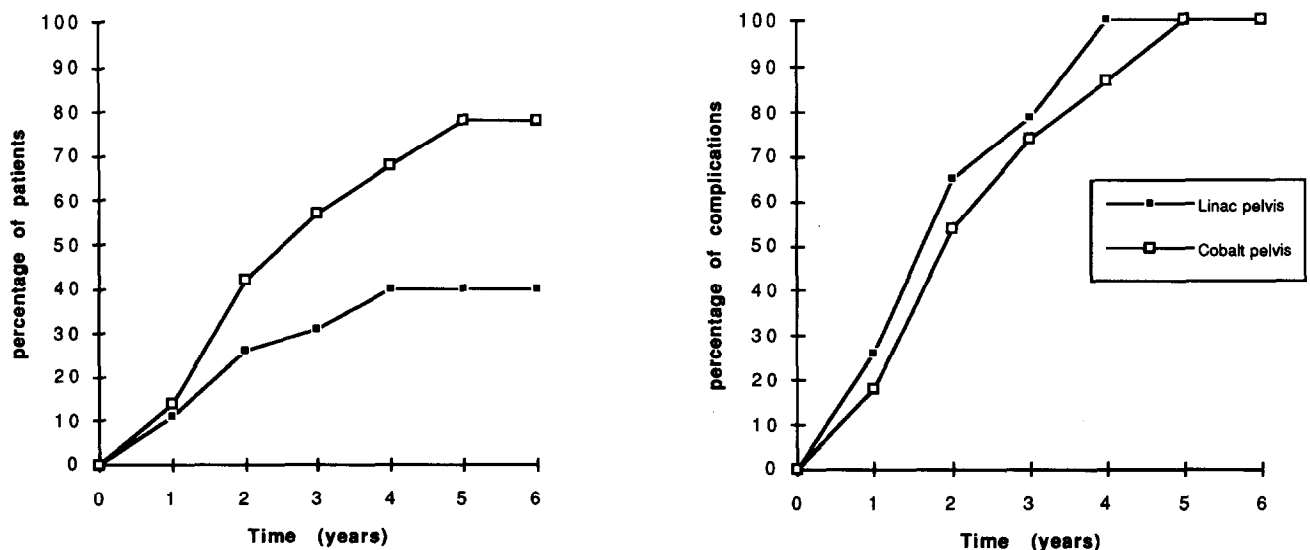


Fig. 2. Urological 'first events' in cobalt pelvis (schedule A) and linac pelvis (schedule B) treatment. Absolute incidence (left) and relative incidence (right), cf. text for details.

brosis and necrosis, in radiotherapy of the breast with an undiminished rate of occurrence up to 10 years.

In head and neck cancers, the same tendency has been observed. Kogelnik et al. [7] described late side effects occurring between 5 and 10 years after treatment, and recently also in patients treated with MFD radiation schedules for head and neck patients [17], a continuous progression of fibrosis was reported up to 5 years after treatment and probably even thereafter.

Looking at this steady complication rate for at least the first 5 years after treatment in our study, it seems possible to make early extrapolations about the number of patients who will suffer from late side effects after 5 years. This could indeed be very useful in treatment schedules where one wants to step up the treatment intensity. According to Turesson et al. [15,16] and to Bentzen et al. [2], the higher the total dose, the quicker late side effects will occur, so that there would be no big risk of underestimating complications. Still one has to keep in mind that even after 5 years there seems to be a continuous development of complications, albeit at a lower rate [7,12,16,17].

The gastrointestinal side effects, 'first events' as well as 'all events', seem to reach a plateau at 3 years. The reason for this earlier maximum as compared to urological complications, could be that the amount of side effects is too small to show any further progression in this study with a limited number of patients. Another explanation could be differences in end organ architecture and cellular kinetics. Also Eifel et al. [4] reported a difference in incidence and rate between gastrointestinal and urological complications in patients treated for carcinoma of the uterine cervix, with a sharp decline in actuarial risk for gastrointestinal complications after 2 years as compared to a much less pronounced and slower decline in risk for urological complications.

Compared to recently published long-term complications of conventional radiation schedules for prostate carcinoma [8,11], our overall actuarial incidence of grade 3 or higher side effects at 5 years is very high, both for urological (51%) and for gastrointestinal (14%) complications.

The volume treated was identified by Perez et al. as the most important factor for late morbidity in an analysis of treatment complications in a large series of patients treated for prostate cancer [10].

The difference in incidence of complications between the patients irradiated over the whole pelvis with cobalt and linac could probably be attributed to the poor dose distributions of the cobalt set-up, leading to large volumes being treated to high doses. However, the field sizes used in both linac treatment techniques in the present series are smaller than those used by Perez et al. [10]. The incidence of severe effects is nevertheless substan-

tially higher, and volume therefore cannot be the major contributing factor in this subset of patients.

Nearly all patients had a pre-irradiation TUR. It should however be noted that this was a common practice at the time and that only patients who were continent at the start of radiation were evaluated. Moreover an analysis by Pilepich et al. [8] of two large Radiation Therapy Oncology Group trials (7506 and 7706), including 1020 patients, did not show a significant difference in incidence of urethral stricture between patients who had a pre-irradiation TURP compared to those who did not.

An unexpected high radiobiological effect of this MFD treatment schedule is a more likely explanation for the differences observed. Applying the 'incomplete repair model', the equivalent effective dose of the present MFD schedules was estimated for schedules using 1 daily fraction of 2 Gy [13]. It is obvious that a range of equivalent doses can be obtained depending on the assumed values of the α/β ratio and $T_{1/2}$ of repair for connective tissue fibrosis. From animal and human studies the α/β value for skin fibrosis is estimated to be 2–4 Gy [18]. While the $T_{1/2}$ for late skin reactions is of the two compound type [14], for practical reasons a value of 1.5–2 h could be adopted in analogy with values for late effects in CNS, lung and kidney [18]. For a schedule using 2 Gy/fr, the iso-effect dose (with 2 Gy fractions given daily) would be between 67 Gy and 71 Gy. It is clear that the present incidence of severe late side effects is higher than reported in the literature after prostate treatment to 70 Gy [8,11]. Still, the pelvic field set-ups resulted in a hot spot in the prostate and part of the bladder. Because of the position on the steep part of the dose effect curve, this overdosage of 10% in a critical zone may be sufficient to explain the huge amount of urological side effects.

Another reason could be that (a component of) the $T_{1/2}$ for repair of connective tissue, is substantially longer than the estimated 1.5–2 h and that therefore the 4 h interval was insufficient. The fact that irradiation schedules with intervals shorter than 4.5 h give rise to more acute morbidity than those with larger intervals, was first suggested in clinical studies in the late 1980s [9]. Denekamp, based on biological data, confirmed that 3–4 h intervals are not sufficient to allow full repair of radiation injury in many systems [3]. According to Fowler [5], even worse late reactions could be foreseen in radiotherapy schemes with multiple fractions per day, since late reactions require longer intervals than early reactions, even if the half-lives of repair are not different. A recent publication of Fu et al. in head and neck cancer confirms these expectations [6].

Although immediate tolerance for the present MFD radiation schedules, used to treat prostate cancer, was excellent [1], late effects are pronounced. MFD

schedules, using 3 fractions per day, should therefore be avoided, at least for pelvic localisations, unless the intervals between fractions can be substantially longer than 4 h.

When evaluating new radiation treatment schedules, one should be aware of the possibility of the protracted time course of development of first event complications. Tolerance estimates based on acute and short term intermediate side effects should be interpreted with caution because they are very likely to underestimate the real incidence of complications.

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