NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of intramural urethral bulking procedures for stress urinary incontinence in women

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2004, updated March 2005.

Procedure names

- Intramural urethral bulking.
- Periurethral injection therapy.
- Transurethral injection therapy.
- Paraurethral injection therapy.

Specialty societies

- Royal College of Obstetricians and Gynaecologists (RCOG).
- British Association of Urological Surgeons (BAUS).

Description

Indications

Stress urinary incontinence in women.

Stress urinary incontinence is the involuntary leakage of urine during exercise or movements such as coughing, sneezing and laughing. It is usually caused by weak or damaged muscles and connective tissues in the pelvic floor, compromising urethral support, or by weakness of the urethral sphincter itself. Estimates of the overall prevalence of any incontinence have varied between 10 and 52% of adult women.[1]

Current treatment and alternatives

Typically, first-line treatment is conservative and includes pelvic floor muscle training, electrical stimulation, and biofeedback. If the condition does not improve, surgical alternatives in women may include colposuspension, tension-free vaginal tape (TVT), transobturator tape, and traditional suburethral slings. Of these four operation types, colposuspension and TVT are currently the most common.

Another treatment option is the injection of bulking agents into the wall of the urethra, with the aim of augmenting the urethral wall and increasing the resistance to urinary flow.

What the procedure involves

Intramural urethral bulking aims to augment the urethral wall and increase the urethral closure force. Several millilitres of bulking agent are injected into the submucosal tissue at the level of the proximal urethra just distal to the bladder neck. The injections are administered under local anaesthetic, either transurethrally or paraurethrally. Injections are undertaken either visually, using a cystoscope or blindly, using a non-endoscopic implantation device, with the aim of localising the material at the proximal urethral level.

There are a number of bulking agents currently available, including collagen, silicone particles, carbon beads, calcium hydroxylapatite and ethylene vinyl alcohol copolymer. Polytetrafluoroethylene and autologous fat have been used in the past but they are no longer used as urethral bulking agents. The agent should be non-immunogenic and biocompatible to reduce inflammatory response. The particles should be large enough to prevent migration away from the site of injection and durable enough to maintain the effect over time.

This procedure can be performed under local anaesthesia, so it has the potential benefit of avoiding the morbidity commonly associated with surgery for stress urinary incontinence.

Efficacy

The main outcomes were cure or improvement of incontinence, measured either subjectively or using objective assessments.

One small randomised controlled trial reported that a significantly lower proportion of patients treated by urethral bulking were cured at 12 months compared with patients treated by conventional open surgery (53% [34/64] versus 72% [39/54], relative risk = 1.69, 95% confidence interval 1.02 to 2.79). Four other randomised controlled trials reported no difference in efficacy between different bulking agents.

One case series of 90 patients treated with collagen reported that 42% (38/90) of patients achieved either a cure or improvement in symptoms, measured objectively, after 12 months. One case series of 102 patients treated with silicone particles reported that 68% (69/102) of patients were either cured or markedly improved after a mean follow-up of 3 months. This proportion decreased to 48% (40/84) after a mean follow-up of 18 months.

The Specialist Advisors considered that the efficacy may depend on case selection, the particular bulking agent being used and the injection technique.

Safety

Five case series reported safety data on a total of 389 patients. The most commonly reported adverse effects were urinary retention in 0% (0/40) to 11% (10/90) of patients and urinary tract infection in 1% (1/102) to 12% (11/90) of patients. Other reported complications included abscess at the injection site, de novo urgency, incomplete bladder emptying, and prolonged pain.

The Specialist Advisors stated that migration of the bulking agent, voiding difficulty, urinary tract infection and allergic reaction are potential adverse events. Haemorrhage was listed as a rare potential adverse event. One Specialist Advisor noted that potential adverse events may depend on the bulking agent being used.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to intramural urethral bulking procedures. Searches were conducted via the following databases, covering the period from their commencement to August 2004: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Women with stress urinary incontinence.
Intervention/test	Intramural injection of bulking agents.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on six studies, including one systematic review (Cochrane) and five case series.[2-7]

Seven randomised controlled trials met the inclusion criteria of the systematic review, which included literature up to February 2003.[8-14]

Other studies that were considered to be potentially relevant to this overview are listed in Appendix A.

Existing reviews on this procedure

1. A systematic review on periurethral injection therapy for urinary incontinence in women was published in 2004.[2] This review is summarised in Table 1. Seven randomised controlled trials were identified; one study compared injection therapy with open surgery, one compared collagen injection with a placebo saline injection, four compared different types of bulking agents, and the final study compared the periurethral route of injection with the transurethral route.

   The review's author concluded that periurethral injection of established manufactured bulking agents results in subjective and objective short-term improvement of symptomatic stress urinary incontinence in women.

   The review states that injection therapy appears less efficacious than open surgery at 12 months but it has a better safety profile. The reviewer highlights the treatment-related death of a patient treated with autologous fat injection and recommends that this should not be used as a bulking agent. The report concludes that there is a lack of long-term follow-up and the durability of the available agents beyond 1 year remains unknown.

2. A review of the available urethral bulking agents was published in 2002.[3] The review presents limited data from 22 selected papers, including 8 different bulking agents. The proportion of patients who were cured or improved ranged from 27 to 100%. The author concludes that the procedure is associated with acceptably low rates of acute local complications, including transient haematuria, urinary retention, urinary tract infection, and de-novo urge incontinence.

Table 1 Summary of key efficacy and safety findings on intramural urethral bulking for stress urinary incontinence in women

Study details	Key efficacy findings	Key safety findings	Comments
Pickard R (2004)[2] Systematic review (Cochrane) Literature search date: February 2003 Seven randomised controlled trials met inclusion criteria: • Anders (1999)[8]; n = 60 (26 GAX-collagen, 34 Macroplastique), follow-up: 12 months • Corcos (2001)[9]; n = 133 (66 collagen, 67 open surgery), follow-up: 12 months • Dmochowski (2002)[10]; n = 40 (22 Coaptite, 18 bovine collagen), follow-up: 6 months • Dmochowski (2002)[11]; n = 58 (38 Uryx, 20 Contigen), follow-up: 6 months • Lee (2001)[12]; n = 68 (35 autologous fat, 33 saline), follow-up: 24 months • Lightner (2001)[13]; n = 355 (Durasphere versus Contigen), mean follow-up: 14 months • Nager (1998)[14]; n = 40 (20 periurethral route of injection, 20 transurethral route of injection), follow-up: 1 month.	Periurethral injection therapy versus no treatment Cure or improvement in symptoms at 3 months: • Autologous fat injection = 22% (6/27) • Saline injection (placebo) = 21% (6/29) RR 0.98, 95% CI 0.75 to 1.29 Periurethral injection therapy (collagen) versus open surgery: Patients completely satisfied at 12 months: • Injection therapy = 52% • Open surgery = 67% RR 1.45, 95% CI 0.92 to 2.29 Cure at 12 months, based on 24 hour pad test: • Injection therapy = 53% (34/64) • Open surgery = 72% (39/54) RR 1.69, 95% CI 1.02 to 2.79 Injection of carbon particles versus collagen Subjective cure or improvement at 12 months: • Carbon particles = 66% (76/115) • Collagen = 66% (79/120) RR 0.99, 95% CI 0.70 to 1.42 No significant difference in objective urine loss. Injection of silicon particles versus collagen Subjective cure or improvement at 12 months: • Silicone particles = 59% (20/34) • Collagen = 58% (15/26) RR 0.97, 95% CI 0.53 to 1.78 No significant difference in objective urine loss. There were no statistical differences in cure rate between calcium hydroxylapatite, ethylene vinyl alcohol copolymer and collagen. Paraurethral injection versus transurethral injection Subjective cure or improvement at 1month: • Paraurethral injection = 20% (4/20) • Transurethral injection = 45% (9/20) RR 1.45, 95% CI 0.92 to 2.29 No significant difference in objective urine loss.	Periurethral injection therapy versus no treatment Complication rate (% of injections): • Fat injection = 32% (29/91) • Placebo injection = 11% (11/98) Mortality: • Fat injection = 7% (2/27) (1 treatment related) • Placebo injection = 0% (0/29) Urinary retention: • Fat injection = 22% (6/27) • Placebo injection = 0% (0/29) Urinary tract infection: • Fat injection = 22% (6/27) • Placebo injection = 10% (3/29) Infection at liposuction site: • Fat injection = 0% (0/27) • Placebo injection = 7% (2/29%) Periurethral collagen injection versus open surgery Complication rate: • Collagen injection = 36 complications in 64 patients • Open surgery = 84 complications in 54 patients Complications were “significantly more frequent and severe in the open surgery group” Carbon particles versus collagen Transient urinary retention: • Carbon particles = 17% (30/177) • Collagen = 3% (6/178) Paraurethral versus transurethral Urinary retention: • Paraurethral injection = 30% (6/20) • Transurethral = 5% (1/20) $p \leq 0.05$	Two non-randomised studies were identified but not included. Limited data available prevented meta-analysis. One trial used an adequately concealed group allocation. In the other six studies, no description of concealment was given. Five of the seven studies were only published in abstract form. Of the remaining two studies, one was analysed before full maturation of data and the other was closed before full recruitment. No studies were identified that compared injection therapy with conservative management.

Study details	Key efficacy findings	Key safety findings	Comments
Bent A (2001)[3] Prospective case series 1996–1998 USA 90 women Inclusion criteria: stress urinary incontinence with urethral hypermobility. Incontinence was 12 months in duration and resistant to a 3-month trial of conservative therapy Exclusion criteria: Type 3 incontinence (Blaivas and Olsson classification) defined as an open bladder neck at rest with associated urine leakage during absent detrusor activity, predominant urge incontinence, bladder capacity less than 250 ml, post-void residual urine greater than 50 ml, grade 3 or 4 uterine prolapse or cystocele, neurogenic bladder, fistula, bladder tumour, α-adrenergic drug therapy, positive skin test result to collagen, previous application of a periurethral bulking agent Mean age: 60.9 years (range 35 to 86) Follow-up: 12 months	Primary outcome measure: the number of patients dry at 12 months (incontinence grade = 0) Secondary outcome measures: improvement at 12 months, duration of improvement, and quality of life assessments Objective success at 6 months: • Incontinence grade 0 = 44% (30/68) • Improved by at least 1 grade = 35% (24/68) • Not improved = 21% (14/68) Objective success at 6 months (intent-to-treat analysis): • Incontinence grade 0 = 33% (30/90) • Improved by at least 1 grade = 27% (24/90) • Not improved = 40% (36/90) Objective success at 12 months: • Incontinence grade 0 = 33% (19/58) • Improved by at least 1 grade = 33% (19/58) • Not improved = 34% (20/58) Objective success at 12 months (intent-to-treat analysis): • Incontinence grade 0 = 21% (19/90) • Improved by at least 1 grade = 21% (19/90) • Not improved = 58% (52/90) Improvement was achieved after an average of 1.9 injections. Subjective success at 12 months (Quality of Life questionnaire): • Dry = 34% (20/58) • Wet, but socially acceptable = 62% (36/58) • Wet, not socially acceptable = 3% (2/58) • Improved = 83% (48/58) • No change = 14% (8/58) • Worse = 3% (2/58)	Complications • Urinary retention = 11% (10/90) • Urinary tract infection = 12% (11/90) • Abscess at injection site = 1% (1/90)	No randomisation. 6 study centres. Collagen injection (Contigen). 36% (32/90) patients withdrew before study completion (14 due to patient choice, 14 due to lack of improvement, 4 lost to follow-up). Intent-to-treat analysis included. Patients were given a total of three collagen injections in 6 months, with injections at least 1 month apart. Injections were periurethral or transurethral, according to investigator preference. All patients received 3 days of antibiotic prophylaxis. Incontinence status was measured on the Stamey scale (grade 0 = continence, grade 1 = urine loss with sudden increases in abdominal pressure due to coughing, sneezing or laughing, grade 2 = leakage with lesser degrees of physical stress, such as walking, or sitting up in bed, grade 3 = complete incontinence). Objective measures included cystometry and abdominal leak point pressure.

Study details	Key efficacy findings	Key safety findings	Comments
Zullo M A (2005) Prospective case series 1993-1999 Italy 61 women Inclusion criteria: Intrinsic sphincter deficiency without urethral hypermobidity Exclusion criteria: detrusor overactivity, residual bladder volume >100ml, neurogenic bladder, untreated urinary tract infection, genito0urinary prolapse, previous bulking agent injection, malignancy, psychiatric disease, pregnancy Mean age: 70years (range 55-82), mean parity =3 ±1.6, mean BMI =25.5 ±3.2 1993-1998 injection under local anaesthesia with direct cystoscopic guidance by endoscopic needle. Since 1998 macroplastique implantation system used. Median follow up =83 months (range 60 to 108)	Median operative time was 22 minutes (range 16 to 35 minutes) Mean spontaneous voiding occurs at 0.8 ±0.25 days. Median hospital stay was 1 day Mean maximum flow rate (ml/s): • Before treatment = 18.7 • After treatment = 18.8, p = not significant Mean maximum urethral closure pressure (cmH_2O): • Before treatment = 13.5 • After treatment = 27.5, p <0.001 Mean Valsava leak point pressure (cmH_2O): • Before treatment = 39.5 • After treatment = 60.9, p <0.001 For n=50 cases with postoperative urinary leakage Mean severity of urinary los perception (VAS): • Before treatment = 7.6 • After treatment = 2.8, p <0.05 Frequency of incontinence (episodes per 3 days) • Before treatment = 16.1 • After treatment = 7.7. p<0.05 At 60 months follow up the SUI cure rate was 18% (11/61), the improvement rate was 39% (24/61), and the failure rate was 43% (26/61)	No intraoperative or major early postoperative complications were observed late complications • Urgency = 7% (4/61) • Urinary tract infection = 3% (2/61) • Dysuria = 1% (1/61)	6% (4/65) cases lost to follow up, clinical outcome provided for 3 of these to last observation. No details of patients selection method. Do details of independent outcome assessment. Different delivery procedure within series Many outcomes reported separately for continent and incontinent cases postoperatively Patients given a total of 5 ml bulking agent at 3 sites.

Study details	Key efficacy findings	Key safety findings	Comments
Swami S (1997)[4] Prospective case series 1990–1995 UK 111 women Inclusion criteria: urodynamically confirmed genuine stress incontinence in patients unfit or unwilling to undergo surgical intervention Exclusion criteria: current urinary infection, uncontrolled detrusor instability, history of anaphylaxis, positive skin test result to collagen Age range: 33 to 90 years Mean follow-up: 38 months (range 24 to 70)	Subjective outcome and objective assessments (urodynamic variables and 1 hour pad test) Subjective cure or improvement at 6 months = 85% Subjective cure or improvement at end of study period = 65% Mean weight gain in one hour pad test (g): • Before treatment = 52 • After treatment = 20, $p < 0.001$ Mean maximum flow rate (ml/s): • Before treatment = 21.7 • After treatment = 16.3, $p < 0.05$ Mean functional urethral length (cm): • Before treatment = 2.5 • After treatment = 2.8, p = not significant Mean maximum urethral closure pressure (cmH_2O): • Before treatment = 34.2 • After treatment = 36.2, p = not significant Mean pressure transmission ratio (%): • Before treatment = 79 • After treatment = 78, p = not significant	Complications • Transient urinary retention = 10% (11/111) • Urinary tract infection = 2% (2/111) • Abscess at injection site = 1% (1/111)	No randomisation. Collagen injection (GAX Collagen, Bard, UK). Non-responders and partial responders were offered further injections up to a maximum of 3. 3% (3/111) of patients lost to follow-up. One patient died from an unrelated cause. Some patients with hypermobility were included.

Study details	Key efficacy findings	Key safety findings	Comments
Corcos J (1999)[5] Prospective case series 1992–1993 Quebec, Canada 40 women Inclusion criteria: genuine stress urinary incontinence classified as type 1, 2 or 3, according to Blaivas classification Mean age: 62.3 years (range 38 to 82) Mean follow-up: 50 months (range 47 to 55)	Cure defined clinically as complete symptomatic dryness, negative pad test and no leak on the Valsalva leak point pressure (VLPP) test Clinical improvement defined as patient satisfaction with no desire for further injections or other treatments and amelioration of VLPP test and pad test results to more than 50% of pre-treatment values Results at 49 months: • Cure = 30% (12/40) • Improved = 40% (16/40) • Treatment failed = 30% (12/40) Reinjection rate = 33% (13/40) There was no statistically significant difference in the cure or improved rate in patients with or without hypermobility	Complications • Urinary retention = 0% (0/40) • Urinary tract infection = 7.5% (3/40) • De novo urgency = 10% (4/40) • Urge incontinence = 2.5% (1/40)	No randomisation. One operator. Collagen injection (Contigen). All injections were administered periurethrally. The last 32 patients received 3 days of antibiotic prophylaxis. Each follow-up visit included subjective symptom improvement, a uroflow test, postvoid residual volume evaluation, Valsalva leak point pressure, and pad test.

Study details	Key efficacy findings	Key safety findings	Comments
Herschorn S (2000)[6] Prospective case series 1996–1998 Ontario, Canada 46 women Inclusion criteria: stress urinary incontinence classified as type 1, 2 or 3, according to Blaivas classification Mean age: 68.9 years (range 26 to 88) Mean follow-up: 28.4 months (range 11 to 38)	Primary outcome measure was achievement of continence as determined by direct patient questioning about symptom grade and pad requirement by a physician interviewer not known to the patient. Cure was defined as no incontinence, improvement was defined as a decrease in pad requirement as well as a subjective improvement Results at last follow-up: • Cure = 30.4% (14/46) • Improved = 41.3% (19/46) • Treatment failed = 28.3% (13/46) No statistically significant differences in outcomes among women with type 1, 2 or 3 incontinence No statistically significant differences in outcomes among women with or without hypermobility	Complications • Transient urinary retention = 10.9% (5/46) • Urinary tract infection = 4.3% (2/46) • Slow stream and incomplete bladder emptying after 1 year = 2.2% (1/46) • Prolonged pain = 2.2% (1/46)	Method of patient selection not described. Polytetrafluoroethylene injection (small volumes). Some patients with hypermobility were included. No objective outcome data were obtained in this trial.
Usman F (1998)[7] Retrospective case series 1992–1996 UK 102 women Inclusion criteria: genuine stress urinary incontinence Mean age: 58.8 years (range 33 to 83) Mean follow-up: 3.2 months (range 3 to 5). Further data was available for 84 of the 102 women, with a mean follow-up of 17.6 months (range 11 to 44).	Subjective outcomes reported by patients: cure (no further treatment required), marked improvement (no further treatment required), slight improvement (further treatment required), no improvement (further treatment required) Outcome at mean follow-up of 3.2 months (n = 102): • Cure = 33% (34/102) • Marked improvement = 34% (35/102) • Slight improvement = 8% (8/102) • No improvement = 25% (25/102) Outcome at mean follow-up of 17.6 months (n = 84): • Cure = 20% (17/84) • Marked improvement = 27% (23/84) • Slight improvement = 20% (17/84) • No improvement = 32% (27/84)	Complications • Transient urinary retention = 6.8% (7/102) • Urinary tract infection = 1.0% (1/102)	Method of patient selection not described. Silicone macroparticles (Macroplastique). Transurethral injection. All patients were requested to complete a 5-day course of antibiotics after treatment. Results are presented following a single treatment only. Some patients improved after a second or third injection. No objective data were reported.

Validity and generalisability of the studies

- Of the seven randomised controlled trials included in the systematic review, five were reported as conference abstracts only. Results from these studies must be considered as preliminary and may be less reliable than those published as full articles in peer-reviewed journals.

- No studies were identified that compared this procedure with conservative treatment.

- The number of injections and the volume of bulking agent administered per injection vary between studies.

- One study excluded women with type 3 stress urinary incontinence (Blaivas classification), defined as an open bladder neck at rest with associated urine leakage during absent detrusor activity.[11] This study was also restricted to women with urethral hypermobility who did not respond to a 3-month period of conservative therapy.

- One study reported the results of a single injection.[15] Other studies treated patients with more than one injection over the study period.

- Some studies used the transurethral route of injection and some used periurethral injection. One study used both routes of injection, depending on the preference of the operator.[11] A small randomised controlled trial comparing the two routes reported that there was no statistically significant difference in objective urine loss but women treated with paraurethral injections were significantly more likely to have urine retention after the procedure than women treated with transurethral injections.[10]

- Two studies reported subjective outcome data only.[14,15]

Specialist Advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

- This is established practice and no longer new.

- The safety and efficacy of the procedure may depend on the bulking agent being used.

- There are many new products and administration devices available for this procedure.

- The different bulking materials need to be compared.

- The procedure appears to be highly operator dependent.

Issues for consideration by IPAC

A NICE consultation scope for a guideline titled 'Urinary incontinence: the management of urinary incontinence in women', was issued at the end of August 2004. The development of the guideline recommendations will begin in October 2004. The expected date of issue of the guideline is October 2006.

The BAUS Section of Female and Reconstructive Urology established an incontinence surgery database in August 2004. The database will be accessible to all members of the BAUS Section of Female and Reconstructive Urology. Initially, it will not be collecting outcome data and only those people who wish to submit their data will do so. The British Society of Urogynaecology (BSUG) has also established an audit system for incontinence surgery and this will include outcome data. At present, the database may only be accessed by BSUG members via the Secretariat.

References

1 Cody J, Stearns S, Wyness L, et al. Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence. *Health Technology Assessment* 2003; 7: No. 21.

2 Pickard R, Reaper J, Wyness L, et al. Periurethral injection therapy for urinary incontinence in women (Cochrane Review). In: *The Cochrane Library*, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.

3 Bent AE, Foote J, Siegel, et al. Collagen implant for treating stress urinary incontinence in women with urethral hypermobility. *Journal of Urology* 2001; 166: 1354–7.

4 Swami S, Batista JE, Abrams P. Collagen for female genuine stress incontinence after a minimum 2-year follow-up. *British Journal of Urology* 1997; 80: 757–61.

5 Corcos J ,Fournier C. Periurethral collagen injection for the treatment of female stress urinary incontinence: 4-year follow-up results. *Urology* 1999; 54: 815–8.

6 Herschorn S, Glazer AA. Early experience with small volume periurethral polytetrafluoroethylene for female stress urinary incontinence. *Journal of Urology* 2000; 163: 1838–42.

7 Usman F, Henalla S. A single transurethral Macroplastique ® injection as primary treatment for stress incontinence in women. *Journal of Obstetrics and Gynaecology* 1998; 18: 56–60.

8 Anders K, Khullar V, Cardozo L, et al. Contigen or macroplastique? A five year follow-up (Abstract). Proceedings of the International Continence Society (ICS), 32nd Annual Meeting, Heidelberg, Germany, 28–30 Aug. 2002: 183–4.

9 Corcos J, Collet JP, Shapiro S, et al. Surgery vs collagen for the treatment of female stress urinary incontinence (SUI): results of a multicentric randomised trial (Abstract). *Journal of Urology* 2001; 165 (5 Suppl): 198.

10 Dmochowski R, Appell R, Klimberg I, et al. Initial clinical results from coaptite injection for stress urinary incontinence comparative clinical study (Abstract). Proceedings of the International Continence Society (ICS), 32nd Annual Meeting, Heidelberg, Germany, 28–30 Aug. 2002: 184–5.

11 Dmochowski R, Herschorn S, Corcos J, et al. Multicenter randomized controlled study to evaluate uryx urethral bulking agent in treating female stress urinary incontinence (Abstract). Proceedings of the International Continence Society (ICS), 32nd Annual Meeting, Heidelberg, Germany, 28–30 Aug. 2002: 187.

12 Lee PE, Kung RC, Drutz HP. Periurethral autologous fat injection as treatment for female stress urinary incontinence: a randomized double-blind controlled trial. *Journal of Urology* 2001; 165: 153–8.

13 Lightner D, Calvosa C, Andersen R, et al. A new injectable bulking agent for treatment of stress urinary incontinence: results of a multicenter, randomized, controlled, double-blind study of Durasphere. *Urology* 2001; 58: 12–5.

14 Nager CW, Schulz JA, Stanton SL. Bulking agents for GSI: short term results and complications in randomized comparison of periurethral and transurethral injections. *Neurourology & Urodynamics* 1998; 17: 314–5.

15 Lightner DJ. Review of the available urethral bulking agents. *Current Opinions in Urology* 2002; 12: 333–8.

Appendix A: Additional papers on intramural urethral bulking for stress urinary incontinence in women not included in the summary tables

The following table outlines studies that are considered potentially relevant to the overview but were not included in the main data extraction table and is not an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Ang LP, Tay KP, Lim PH, et al. Endoscopic injection of collagen for the treatment of female stress urinary incontinence. *International Journal of Urology* 1997; 4: 254–8.	105 women. 12 month follow-up.	Case series. Collagen.	Success at 1 year = 82%. 6% transient urinary retention, 2% urinary tract infection.
Barranger E, Fritel X, Kadoch O, et al. Results of transurethral injection of silicone micro-implants for females with intrinsic sphincter deficiency. *Journal of Urology* 2000; 164: 1619–22.	21 women. 2 year follow-up.	Case series. Sillicone.	19% cure, 29% improved, 52% failure.
Cross CA, English SF, Cespedes RD, et al. A follow-up on transurethral collagen injection therapy for urinary incontinence. *Journal of Urology* 1998; 159: 106–8.	139 women. Median follow-up = 18 months.	Case series. Telephone interview and chart review.	74% substantially improved, 20% improved, 5% no improvement.
Faerber GJ, Belville WD, Ohl DA, et al. Comparison of transurethral versus periurethral collagen injection in women with intrinsic sphincter deficiency. *Techniques in Urology* 1998; 4: 124–7.	45 women. Mean follow-up = 6 months.	Compares periurethral route with transurethral route.	Periurethral method needed more collagen. Both techniques had similar results.
Game X, Malavaud B, Mouzin M, et al. Periurethral collagen injections: results after 2 years in 25 patients with severe urinary incontinence. *Progres en Urologie* 2001; 11: 283–7.	25 women. Mean follow-up = 24 months.	Case series. Collagen. Article in French.	33% cured, 39% improved, 28% failures.
Gorton E, Stanton S, Monga A, et al. Periurethral collagen injection: a long-term follow-up study. *BJU International* 1999; 84: 966–71.	61 women.	Case series. Collagen.	Subjective improvement = 35% Objective cure = 18% Decline in success rate over time.
Groutz A, Blaivas JG, Kesler SS, et al. Outcome results of transurethral collagen injection for female stress incontinence: assessment by urinary incontinence score. *Journal of Urology* 2000; 164: 2006–9.	63 women. Mean follow-up = 12 months.	Case series. Collagen.	13% cure, 10% good, 17% fair, 42% poor, 18% failure.
Gurdal M, Tekin A, Erdogan K, et al. Endoscopic silicone injection for female stress urinary incontinence due to intrinsic sphincter deficiency: impact of coexisting urethral mobility on treatment outcome. *Urology* 2002; 60: 1016–9.	29 women. Median follow-up = 29 months.	Case series. Sillicone.	Cure = 67% in women with intrinsic sphincter deficiency, 21% in women with urethral hypermobility.
Haab F, Zimmern PE, Leach GE. Urinary stress incontinence due to intrinsic sphincteric deficiency: experience with fat and collagen periurethral injections. *Journal of Urology* 1997; 157: 1283–6.	67 women. Mean follow-up = 7 months.	Comparing fat with collagen.	Collagen significantly more effective than fat.

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Henalla SM, Hall V, Duckett JR, et al. A multicentre evaluation of a new surgical technique for urethral bulking in the treatment of genuine stress incontinence. *BJOG: an International Journal of Obstetrics & Gynaecology* 2000; 107: 1035–9.	40 women. 3 month follow-up.	Case series. Silicone.	Overall success = 74%
Hidar S, Attyaoui F, de Leval J. Periurethral injection of silicone microparticles in the treatment of sphincter deficiency urinary incontinence. *Progres en Urologie* 2000; 10: 219–23.	25 women. 3 year follow-up.	Case series.	Success rate at 6 weeks = 80%. Success rate at 3 years = 60%.
Inadome A, Yoshida M, Kitani K, et al. Transurethral collagen injection for the treatment of urinary stress incontinence. *Nishinihon Journal of Urology* 1998; 60: 116–9.	16 women.	Collagen.	Significant improvement = 62%. Significant residual urine = 25%, dysuria = 19%.
Koelbl H, Saz V, Doerfler D, et al. Transurethral injection of silicone microimplants for intrinsic urethral sphincter deficiency. *Obstetrics & Gynecology* 1998; 92: 332–6.	32 women. 12 month follow-up.	Case series. Silicone.	Time-dependent decrease in efficacy.
Madjar S, Covington-Nichols C and Secrest CL. New periurethral bulking agent for stress urinary incontinence: modified technique and early results. *Journal of Urology* 2003; 170: 2327–9.	46 women. Mean follow-up = 9.4 months.	Case series. Durasphere. 66% response rate.	65% cured or improved.
Mantovani F, Del Nero A, Confalonieri S, Pisani E. Collagen for U.I. minimal dose injections in scheduled steps to improve clinical results. *Urogynaecologia International Journal* 2002; 16: 29–33.	18 women. 12 month follow-up.	Case series. Collagen.	67% cure.
Steele AC, Kohli N and Karram MM. Periurethral collagen injection for stress incontinence with and without urethral hypermobility. *Obstetrics & Gynecology* 2000; 95: 327–31.	40 women. Mean follow-up = 8 months.	Case series. Compares patients with and without hyper-mobility.	There was no difference in outcomes with regards to hypermobility.
Stenberg AM, Larsson G, Johnson P. Urethral injection for stress urinary incontinence: long-term results with dextranomer/hyaluronic acid copolymer. *International Urogynecology Journal* 2003; 14: 335–8.	20 women. 6 year follow-up.	dextranomer / hyaluronic acid copolymer.	Sustained response = 57%. Incontinence reoccurred in 25%.
Stothers L, Goldenberg SL, Leone EF. Complications of periurethral collagen injection for stress urinary incontinence. Journal *of Urology* 1998; 159: 1507–9.	337 women.	Case series. Collagen.	Delayed reaction at skin test site = 1%, associated with arthralgia in 0.6% of patients.
Tamanini JT, D'Ancona CA, Tadini V, et al. Macroplastique implantation system for the treatment of female stress urinary incontinence. *Journal of Urology* 2003; 169: 2229–33.	21 women. 12 month follow-up.	Case series. Silicone.	According to patients, cure = 57%, improved = 19%, failure = 24%.
Tschopp PJ, Wesley-James T, Spekkens A, et al. Collagen injections for urinary stress incontinence in small urban urology practice: time to failure analysis of 99 cases. *Journal of Urology* 1999; 162: 779–83.	99 women. Mean follow-up = 9.5 months.	Case series. Collagen.	Mean incidence of success = 56%. Mean duration of success = 4.7 months.
Winters JC, Chiverton A, Scarpero HM, et al. Collagen injection therapy in elderly women: long-term results and patient satisfaction. *Urology* 2000; 55: 856–861.	58 women. Mean follow-up = 24 months.	Case series. Collagen.	Long-term success after repeated injections = 60%.

Appendix B: Literature search for intramural urethral bulking for stress urinary incontinence in women

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

1. URINARY INCONTINENCE, STRESS/ or URINARY INCONTINENCE/
2. (bulk$ adj agent$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
3. exp Biocompatible Materials/ad, ae, tu, to [Administration & Dosage, Adverse Effects, Therapeutic Use, Toxicity]
4. (urethra$ or periurethra$ or transurethra$ or paraurethra$).mp. [mp=title, original title, abstract, name of substance, mesh subject heading]
5. 2 or 3
6. 1 and 4 and 5
7. injection$.mp.
8. 1 and 4 and 7
9. limit 8 to human
10. 1 and 2 and 4
11. 9 or 10