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.

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**

The injection of bulking agents into the wall of the urethra is usually performed under local anaesthesia. A cystoscope is inserted into the urethra to locate the areas where the bulking agent should be introduced. After injection of local anaesthetic, 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 may be administered transurethrally through the cystoscope or paraurethrally via small perineal incisions. A high pressure injection device is usually required because of the viscous nature of the bulking materials.

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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Criteria</th>
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</thead>
<tbody>
<tr>
<td>Publication type</td>
<td>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.</td>
</tr>
<tr>
<td>Patient</td>
<td>Women with stress urinary incontinence.</td>
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<tr>
<td>Intervention/test</td>
<td>Intramural injection of bulking agents.</td>
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<tr>
<td>Outcome</td>
<td>Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.</td>
</tr>
<tr>
<td>Language</td>
<td>Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.</td>
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</table>

**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. 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. 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

<table>
<thead>
<tr>
<th>Study details</th>
<th>Key efficacy findings</th>
<th>Key safety findings</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Pickard R (2004)²</td>
<td>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</td>
<td>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)</td>
<td>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.</td>
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<tr>
<td>Systematic review (Cochrane) Literature search date: February 2003</td>
<td>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</td>
<td>Injection of carbon particles versus collagen Subjective cure or improvement at 12 months: - Carbon particles = 66% (78/115) - 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 hydroxyapatite, ethylene vinyl alcohol copolymer and collagen. Paraurethral injection versus transurethral injection Subjective cure or improvement at 1 month: - 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.</td>
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<td>Seven randomised controlled trials met inclusion criteria:</td>
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<tr>
<td>- Anders (1999)⁸; n = 60 (26 GAX-collagen, 34 Macroplastique), follow-up: 12 months</td>
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<tr>
<td>- Corcos (2001)⁹; n = 133 (66 collagen, 67 open surgery), follow-up: 12 months</td>
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<tr>
<td>- Dmochowski (2002)¹⁰; n = 40 (22 Coaptite, 18 bovine collagen), follow-up: 6 months</td>
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<tr>
<td>- Dmochowski (2002)¹¹; n = 58 (20 Uryx, 20 Contigen), follow-up: 6 months</td>
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<tr>
<td>- Lee (2001)¹²; n = 68 (35 autologous fat, 33 saline), follow-up: 24 months</td>
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<tr>
<td>- Lightner (2001)¹³; n = 355 (Durasphere versus Contigen), mean follow-up: 14 months</td>
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<td>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.</td>
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IP overview: Intramural urethral bulking for stress urinary incontinence Page 5 of 15
<table>
<thead>
<tr>
<th>Study details</th>
<th>Key efficacy findings</th>
<th>Key safety findings</th>
<th>Comments</th>
</tr>
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</table>
| Bent A (2001)\(^7\) 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 = 27% (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. |
<table>
<thead>
<tr>
<th>Study details</th>
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<th>Key safety findings</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Swami S (1997)</td>
<td>Subjective outcome and objective assessments (urodynamic variables and 1 hour pad test)</td>
<td>Complications</td>
<td>No randomisation.</td>
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<tr>
<td>Prospective case series</td>
<td>Subjective cure or improvement at 6 months = 85%</td>
<td>• Transient urinary retention = 10% (11/111)</td>
<td>Collagen injection (GAX Collagen, Bard, UK).</td>
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<tr>
<td>1990–1995</td>
<td>Subjective cure or improvement at end of study period = 65%</td>
<td>• Urinary tract infection = 2% (2/111)</td>
<td>Non-responders and partial responders were offered further injections up to a maximum of 3.</td>
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<tr>
<td>UK</td>
<td>Mean weight gain in one hour pad test (g):</td>
<td>• Abscess at injection site = 1% (1/111)</td>
<td>3% (3/111) of patients lost to follow-up. One patient died from an unrelated cause.</td>
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<td>111 women</td>
<td>• Before treatment = 52</td>
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<td>Some patients with hypermobility were included.</td>
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<td>Inclusion criteria: urodynamically confirmed genuine stress incontinence in patients unfit or unwilling to undergo surgical intervention</td>
<td>• After treatment = 20, p &lt; 0.001</td>
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<td>Exclusion criteria: current urinary infection, uncontrolled detrusor instability, history of anaphylaxis, positive skin test result to collagen</td>
<td>Mean maximum flow rate (ml/s):</td>
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<tr>
<td>Age range: 33 to 90 years</td>
<td>• Before treatment = 21.7</td>
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<td>Mean follow-up: 38 months (range 24 to 70)</td>
<td>• After treatment = 16.3, p &lt; 0.05</td>
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<td>Mean functional urethral length (cm):</td>
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<td>• Before treatment = 2.5</td>
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<td></td>
<td>• After treatment = 2.8, p = not significant</td>
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<td>Mean maximum urethral closure pressure (cmH₂O):</td>
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<td></td>
<td>• Before treatment = 34.2</td>
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<td></td>
<td>• After treatment = 36.2, p = not significant</td>
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<td></td>
<td>Mean pressure transmission ratio (%):</td>
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<td></td>
<td>• Before treatment = 79</td>
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<td></td>
<td>• After treatment = 78, p = not significant</td>
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<td></td>
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<tr>
<td>Study details</td>
<td>Key efficacy findings</td>
<td>Key safety findings</td>
<td>Comments</td>
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</table>
| Corcos J (1999)
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

### 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)

### 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).

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## Key efficacy findings

### Herschorn S (2000)⁶

- 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

### Usman F (1998)⁷

- 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)**

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## Key safety findings

### Herschorn S (2000)⁶

**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)

### Usman F (1998)⁷

- **Complications**
  - Transient urinary retention = 6.8% (7/102)
  - Urinary tract infection = 1.0% (1/102)

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## Comments

### Herschorn S (2000)⁶

- Method of patient selection not described.
- Polytetrafluoroethylene injection (small volumes).
- Some patients with hypermobility were included.

### Usman F (1998)⁷

- 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


# 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.

<table>
<thead>
<tr>
<th>Article title</th>
<th>Number of patients/follow-up</th>
<th>Comments</th>
<th>Direction of conclusions</th>
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<tr>
<td>Article title</td>
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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