NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of hysteroscopic metroplasty of a uterine septum for primary infertility or recurrent miscarriage

In some women the uterus (womb) is divided into 2 halves by a thin wall of tissue, called a septum. This may affect fertility and increase the risk of miscarriage. In hysteroscopic metroplasty a thin tube with a camera on the end (a hysteroscope) is inserted into the vagina, through the cervix and into the womb. Instruments are passed through the hysteroscope into the womb and the septum is removed.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make 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 IP overview was prepared in April 2014 and updated in November 2014.

Procedure name

- Hysteroscopic metroplasty of uterine septum in women with primary infertility or recurrent miscarriage

Specialist societies

- Royal College of Obstetricians and Gynaecologists (RCOG)
- British Fertility Society.

Description

Indications and current treatment

A septate uterus is a type of congenital uterine anomaly, in which the inside of the uterus is divided by a muscular or fibrous wall, called the septum. The septum may be partial or complete, extending as far as the cervix. It is more common in women with infertility and in women with repeated miscarriage and may therefore be one cause of this problem.

Surgical removal of the septum (metroplasty) is usually considered for women who have a septate uterus and repeated adverse reproductive outcomes, including miscarriage and preterm delivery. Metroplasty has also been used to manage primary infertility but the causal relationship between this problem and the presence of a uterine septum is less clear.

Surgery was traditionally done by a transabdominal approach. A hysteroscopic approach aims to reduce morbidity and shorten the recovery period. Unlike transabdominal metroplasty, caesarean section is not mandatory for patients who conceive after hysteroscopic metroplasty.

What the procedure involves

Hysteroscopic metroplasty of uterine septum in women with infertility or recurrent miscarriage aims to create the normal anatomy and function of the uterine cavity by removing the uterine septum, consequently increasing fertility or reducing the risk of miscarriage.

Hysteroscopic metroplasty is usually done under general or spinal anaesthesia. After cervical dilation, a hysteroscope is inserted into the uterus through the cervix. The uterine cavity is distended with fluid, and fluid control must be carefully monitored to avoid overload. The septum is excised, most commonly using microscissors, electrosurgery or laser. The procedure may be done under ultrasound or laparoscopic control. At the end of the procedure, a balloon filled with saline is sometimes placed in the uterine cavity to keep the uterine walls apart and to try to prevent intrauterine adhesions.

After a miscarriage, an interval of at least 6 weeks is left before doing a hysteroscopic metroplasty.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to hysteroscopic metroplasty of uterine septum in women with a history of recurrent miscarriage or primary infertility. Searches were conducted of the following databases, covering the period from their commencement to 31 March 2014: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial

registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with septate uterus and primary infertility or recurrent miscarriage.
Intervention/test	Hysteroscopic metroplasty.
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 IP overview

This IP overview is based on approximately 4548 patients from 1 review, 2 non-randomised comparative studies, 5 case series and 1 case report[1–9].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on hysteroscopic metroplasty of uterine septum in women with primary infertility or recurrent miscarriage

Study 1 Valle RF (2013)

Details

Study type	**Review and meta-analysis**
Country	USA
Recruitment period	1986–2011
Study population and number	n=**2528 (37 observational studies); 2074 (29 studies) included in meta-analysis** Women with septate uterus and recurrent miscarriage, infertility, spontaneous abortion or preterm delivery
Age and sex	Age not reported 100% female
Patient selection criteria	Studies that reported both pregnancy rate and live-birth rate after hysteroscopic metroplasty were included. Studies describing the same study population were included only once. Studies of hysteroscopic metroplasty in patients undergoing IVF were excluded.
Technique	Techniques for metroplasty included flexible, semi-rigid and rigid scissors, resectoscope, laser and electrosurgery. Some studies reported routine preoperative or postoperative therapy including danazol/gonadotropin-releasing hormone, oestrogen, progesterone, intrauterine device/foley catheter, antibiotics.
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: The authors of the review note that some studies contained inconsistent follow-up data, with findings published before reaching the outcome of live birth in some patients.

Study design issues: Studies were identified by searching Medline and by hand searching cross-references and review articles. The review identified 8 studies that were excluded from the initial meta-analysis but were listed in a table of reproductive outcome. The reason for excluding these 8 studies was not described. The 29 included studies were divided into 2 groups to eliminate studies with inconsistent definition of pregnancy (that is, all post-metroplasty pregnancies reported rather than just the index pregnancy) and studies with a substantial loss to follow-up or with ongoing pregnancies (n=10 studies). The initial meta-analysis was done on both groups and a second meta-analysis was done on the 19 ‘clean’ studies. A random-effects model was used to adjust for the heterogeneity within and between studies.

Study population issues: Indications varied between studies.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **2074 (29 studies)** **Overall pregnancy rate after hysteroscopic metroplasty** Group 1 only (n=1525, 19 studies, excluding 10 studies with inconsistent definition of pregnancy, substantial loss to follow-up or ongoing pregnancies)=63.5% (95% CI 56.6 to 69.9) All 29 studies (n=2074)=67.8% (95% CI 62.5 to 72.8) There was significant heterogeneity between studies (p<0.01). Significant within study variability was also noted. **Live birth rate after hysteroscopic metroplasty** Group 1 only (n=1525, 19 studies)=50.2% (95% CI 43.3 to 57.1) All 29 studies (n=2074)=53.5% (95% CI 47.8 to 59.1) The authors note that the reported event rates from group 1 are more reliable.	**Complications (n=2167, 35 studies)** • Uterine perforation=0.8% (17/2167) • Postoperative bleeding=0.4% (9/2167) • Cervical lacerations=0.09% (2/2167) • Postoperative uterine synechiae=0.05% (1/2167) • Pulmonary oedema=0.05% (1/2167) • Admission because of possible pulmonary aspiration=0.05% (1/2167) The review also describes 18 confirmed reports of uterine rupture during pregnancy or delivery identified in the literature. All reports described some complication during the metroplasty procedure such as excessive or overzealous excision, with substantial penetration of the myometrium; in 10 of the 18 cases, uterine perforation was recognised. The time from metroplasty to pregnancy ranged from 1 month to 2 years. The gestational age at rupture ranged from 19 to 41 weeks.
Abbreviations used: Cl, confidence interval; IVF, in vitro fertilisation.	

Study 2 Pang L-H (2011)

Details

Study type	**Non-randomised comparative study**
Country	China
Recruitment period	2006–11
Study population and number	n=**138 women with partial septate uterus** (78 women with recurrent miscarriage [46 hysteroscopic metroplasty versus 32 control] and 60 women with no history of poor reproductive outcomes [30 hysteroscopic metroplasty versus 30 control])
Age and sex	Mean ages in 4 study groups (years): 31, 32, 29, 29 100% female
Patient selection criteria	Women who had undergone only 1 spontaneous abortion were excluded from the study. All women underwent chromosome analysis together with their male partners. The women were also evaluated for haematological, endocrinological and immunological risk factors, presence of submucosal myomas, and maternal diabetes.
Technique	No details provided.
Follow-up	**Mean 11 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: The reproductive outcome of each woman was followed up for 15 months; all of the women were trying to become pregnant. Follow-up phone calls were made with particular emphasis on the desire to become pregnant, the achievement of pregnancy and its outcome.

Study design issues: Women with a history of recurrent miscarriage (defined as 2 or more first-trimester miscarriages) were given the choice of surgery or expectant management. Women with no history of adverse pregnancy outcome were randomly allocated to surgery or expectant management.

Study population issues: There were no significant differences between the study groups with regard to age or length of follow-up.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 138 (46 versus 30 [history of recurrent miscarriage] and 30 versus 30 [no history of poor reproductive outcomes])

Reproductive outcomes
Group A (women with a history of recurrent miscarriage)
<table>
<tr><th></th><th>Hysteroscopic metroplasty (n=46)</th><th>Expectant management (n=32)</th></tr>
<tr><td>Number of pregnancies (proportion of patients)</td><td>37 (80.4%)</td><td>18 (56.3%)</td></tr>
<tr><td>Miscarriage (proportion of pregnancies)</td><td>8 (21.6%)</td><td>9 (50.0%)</td></tr>
<tr><td>Preterm delivery (proportion of pregnancies)</td><td>2 (5.4%)</td><td>5 (27.8%)</td></tr>
<tr><td>Term delivery (proportion of pregnancies)</td><td>27 (73.0%)</td><td>4 (22.2%)</td></tr>
</table>
All values were significantly different between the groups ($p<0.05$)

Group B (women with no history of recurrent miscarriage)
<table>
<tr><th></th><th>Hysteroscopic metroplasty (n=30)</th><th>Expectant management (n=30)</th></tr>
<tr><td>Number of pregnancies (proportion of patients)</td><td>24 (80.0%)</td><td>25 (83.3%)</td></tr>
<tr><td>Miscarriage (proportion of pregnancies)</td><td>5 (20.8%)</td><td>8 (32.0%)</td></tr>
<tr><td>Preterm delivery (proportion of pregnancies)</td><td>1 (4.2%)</td><td>2 (8.0%)</td></tr>
<tr><td>Term delivery (proportion of pregnancies)</td><td>18 (75.0%)</td><td>15 (60.0%)</td></tr>
</table>
There were no significant differences in pregnancy rate or the reproductive outcomes between the groups.
</td><td>No safety outcomes were reported.</td></tr>
</table>

Study 3 Valli E (2004)

Details

Study type	**Non-randomised comparative study (prospective)**
Country	Italy
Recruitment period	1990–2001
Study population and number	n=**48 (33 hysteroscopic metroplasty versus 15 expectant management)** Women with septate uterus and recurrent miscarriage (2 or more unexplained first trimester miscarriages)
Age and sex	Mean age (years): 32 versus 31 100% female
Patient selection criteria	All patients had a complete evaluation to exclude other causal factors of pregnancy loss. Women with only septate uterus were enrolled.
Technique	The procedure included diagnostic laparoscopy to confirm the presence of a normal uterine fundal configuration. Metroplasty was done under general anaesthesia with a resectoscope. The uterus was distended with sorbitol/mannitol. Laparoscopic visualisation was used during the procedure to assess myometrial thickness to obtain optimal resection and to prevent or promptly identify a uterine perforation. Second-look hysteroscopy was used to evaluate the incidence of postoperative adhesions and the final results of septum removal.
Follow-up	**Mean 36 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: During the follow-up period, patients were seen in the outpatient clinic and/or contacted by phone. Two patients in the metroplasty group were lost to follow-up.

Study design issues: All patients were offered hysteroscopic metroplasty; 15 patients refused surgery and were considered as the control group.

Study population issues: There were no differences between the groups with regard to age, mean number of miscarriages and mean parity. Five patients in the metroplasty group were diagnosed with bicornuate uterus and did not undergo operative hysteroscopy.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **43 (28 versus 15)**

Postoperative hysteroscopy confirmed the successful removal of septa in all patients and the absence of adhesions.

Reproductive outcomes

First pregnancy after enrolment

	Hysteroscopic metroplasty (n=28)	Expectant management (n=15)
Number of pregnancies (proportion of patients)	22 (78.5%)	14 (93.0%)
Abortions (proportion of pregnancies)	4 (18.2%)*	9 (64.3%)
Preterm delivery (proportion of pregnancies)	1 (4.5%)	1 (6.7%)
Term delivery (proportion of pregnancies)	17 (77.3%)* 95% CI 56% to 90%	4 (28.5%) 95% CI 14% to 49%

*p<0.001

All pregnancies

	Hysteroscopic metroplasty (n=28)	Expectant management (n=15)
Number of pregnancies	25	20
Abortions (proportion of pregnancies)	5 (20.0%)*	15 (75.0%)
Preterm delivery (proportion of pregnancies)	1 (4.0%)	1 (5.0%)
Term delivery (proportion of pregnancies)	19 (76%)* 95% CI 57% to 89%	4 (20.0%) 95% CI 8% to 42%

*p<0.001

Safety

Complications

- Small fundal perforation=3.6% (1/28) (treated by laparoscopic suture; postoperative hysteroscopy showed a normal uterine cavity. The patient became pregnant but aborted again at 8 weeks).

Abbreviations used: CI, confidence interval.

Study 4 Colacurci N (1998)

Details

Study type	**Retrospective case series**
Country	Italy (12 centres)
Recruitment period	1988–1997
Study population and number	n=**973** Women with septate uterus (57% recurrent miscarriage, 35% primary infertility)
Age and sex	Age not reported 100% female
Patient selection criteria	Hysteroscopically diagnosed septate uterus
Technique	A diathermal loop was used for 89% of procedures; laser resection was used in 3%; and scissors resection in 8%. The uterine cavity was generally distended with sorbitol/mannitol solution. Metroplasty was done without pretreatment in 40% of women; 28% of women were pretreated with gonadotropin-releasing hormone analogues and 20% with danazol. In 335 women, the procedures were done without intraoperative monitoring; 302 procedures were monitored laparoscopically and 265 procedures were monitored by ultrasound imaging. No postoperative treatment was given to 87% of women; an intrauterine device was used in 11% and gonadotropin-releasing hormone analogues in 2%.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: Of the 12 centres, 8 provided data on pregnancies. Data on pregnancy outcomes were available for only 344 women. Data from only 11 centres (n=923) were analysed.

Study design issues: Multicentre retrospective study. The recurrent miscarriage indication differed between centres with regard to the minimum number of miscarriages (2 or 3), type (retained or other) and trimester.

Study population issues: Study population included women with mixed indications (recurrent miscarriage, primary infertility and those who underwent metroplasty with a view to future pregnancies, rather than for current reproductive purposes).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: 923 Postoperative checks showed a normal-shaped uterine cavity in 89% (720/808) of women. Data from 8 of the centres recorded 446 pregnancies after 794 metroplasty procedures. **Pregnancy outcome (available for 344 women):** • Term delivery=78% (268/344) • Aborted at <12 weeks=14% (48/344) • Aborted after 12 weeks=4% (14/344) 14 patients were still pregnant at the close of the study. Of the 268 term pregnancies, birth was vaginal in 54% (144) and by elective caesarean section in 46% (124) of women.	Complications • Pulmonary oedema=0.1% (1/923) (procedure was done under laparoscopic control) • Intraoperative bleeding with interruption of the surgical procedure=0.1% (1/923) • Uterine perforation=0.9% (8/923) (3 under laparoscopic control, 3 under ultrasound guidance, 2 with no monitoring)

Study 5 Roy KK (2011)

Details

Study type	**Retrospective case series**
Country	India
Recruitment period	2000–8
Study population and number	n=**170** Women with partial or complete septate uterus and recurrent first or second trimester miscarriage (68%), repeated preterm deliveries (14%) or infertility (18%)
Age and sex	Mean age=25.6 years 100% female
Patient selection criteria	Inclusion criteria: hysteroscopically diagnosed septate uterus. Exclusion criteria: endocrine disease, uterine myoma, adnexal disease, abnormal semen parameters in the husband. In all patients with infertility, other causes of infertility were ruled out.
Technique	A hysteroscopic monopolar knife was used to incise the septum and glycine was used as the distending medium. Laparoscopy was not routinely used but it was done in all cases of infertility and in suspected cases of bicornuate uterus. Postoperative antibiotics were given for 5 days and hormonal treatment for 30 days. A second-look hysteroscopy was done within 2 months and repeat metroplasty was done if necessary.
Follow-up	**Mean 28.5 months (range 12–38)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Of the 170 women recruited to the study, 11 (6.5%) were lost to follow-up and 7 had other associated infertility factors and so were excluded from the analysis.

Study design issues: Retrospective single-centre study.

Key efficacy and safety findings

Efficacy

Number of patients analysed: 152

Three women had persistent septum, measuring more than 1 cm, and needed repeat septal resection. Five women had a residual fundal notch <1 cm.

Mean time of first pregnancy after metroplasty=8.6 months (range 3–19)

Reproductive outcome before and after hysteroscopic metroplasty (n=152)

	Number of pregnancies	Number of mis-carriages	Number of preterm deliveries	Number of term deliveries	Number of infertile patients
Before metroplasty	363	332 (91.5%)	22 (6.1%)	9 (2.5%)	23 (15.1%)
After metroplasty	186	24 (12.9%)	14 (7.5%)	148 (79.5%)	10 (6.6%)
p value		0.02	0.12	0.01	0.04

The take home baby rate was increased from 8.5 to 87.1%

Safety

Complications

- Cervical injury after a difficult dilatation=0.6% (1/170)
- Perforation=1.2% (2/170) (managed by laparoscopic bipolar coagulation; both patients were discharged on the same day. One of these patients had a pregnancy carried to term and was delivered by caesarean section.)
- Excessive bleeding=1.2% (2/170) (managed by an intrauterine balloon catheter kept in situ for 4 hours.)

Postoperative hysteroscopic examination showed mild adhesions in 11 women, all of whom were treated by hysteroscopic adhesiolysis: 7 of these women had pregnancy and subsequent term deliveries.

Study 6 Paradisi R (2011)

Details

Study type	**Case series**
Country	Italy
Recruitment period	1998–2007
Study population and number	n=**246** Women with septate uterus and recurrent miscarriage (56%) or unexplained infertility (44%)
Age and sex	Mean age (years)=35 (recurrent miscarriage) and 33 (infertility) 100% female
Patient selection criteria	Inclusion criteria: septate uterus diagnosed by hysteroscopy and 3-dimensional ultrasound; no endocrine disorders; patency of the fallopian tubes; partners with normal endocrine parameters and semen analysis results. Recurrent miscarriage was defined as 2 or more miscarriages in the previous 3 years. Patients were included if they wanted to conceive and had had more than 12 months of unprotected intercourse or assisted reproduction treatment cycles.
Technique	Hysteroscopic metroplasty was done under general anaesthesia, with a monopolar resectoscope and an equatorial semicircular loop. The uterine cavity was distended with a solution of sorbitol and mannitol. No hormonal treatment was given after the procedure. After 3–4 months, 3-dimensional ultrasound was used to evaluate the surgical outcome and patients were advised to have safe intercourse for 3 months.
Follow-up	**Mean 37±18 months**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Follow-up after surgery was done by phone with particular emphasis on the desire to become pregnant, the achievement of pregnancy, and its outcome.

Study design issues: Retrospective single-centre study.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: 246 **Reproductive outcomes in women with recurrent miscarriage (n=138):** • Pregnant=65.3% (90/138) • Number of pregnancies=129 • Abortions=34.1% (44/129) • Intrauterine fetal death=2.3% (3/129) • Preterm delivery=10.8% (14/129) • Term delivery=48.3% (57/129) • Live birth rate=60.1% (71/129) • Ongoing pregnancy=8.5% (11/129) **Reproductive outcomes in women with unexplained infertility (n=108):** • Pregnant=56.5% (61/108) • Number of pregnancies=71 • Abortions=19.7% (14/71) • Intrauterine fetal death=1.4% (1/71) • Preterm delivery=9.8% (7/71) • Term delivery=62.7% (37/71) • Live birth rate=74.5% (44/71) • Ongoing pregnancy=16.9% (12/71)	**Complications** There were no complications of bleeding, infection, risk of perforation, visceral injury or uterine dehiscence during pregnancy.

Study 7 Tehraninejad ES (2013)

Details

Study type	**Retrospective case series**
Country	Iran
Recruitment period	2005–9
Study population and number	n=**263** Women with septate uterus and infertility (196 primary infertility, 52 secondary infertility) or recurrent miscarriage (n=15); 93% partial septum, 7% complete septum.
Age and sex	Mean age=30 years 100% female
Patient selection criteria	All patients were diagnosed with septate uterus during the routine infertility work-up by hysterosalpingography and hysteroscopy. Septate uterus was considered to be the sole causative factor for infertility in 58 (23%) patients and the remaining patients presented with other causes for infertility.
Technique	General anaesthesia was used. In patients with a complete septum, laparoscopy was done to rule out a bicornuate uterus. The uterine cavity was distended with 1.5% glycin and a monopolar knife electrode was used. There were 18 patients with vaginal septum, which was removed with scissors. All patients received postoperative oral conjugated oestrogens for 2 months in addition to medroxyprogesterone acetate for the last 10 days per month of oestrogen therapy. A follow-up hysterosalpingogram was done after 2 months.
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: After the surgery, patients with more than 12 months of unprotected intercourse were followed up by phone and asked about their desire to become pregnant, pregnancy status and outcome; 23% (60/263) of patients were lost to follow-up.

Study design issues: Retrospective, single centre study.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **263**

The septum was completely removed in 92% (242/263) of patients; 8% (21/263) of patients had a residual septum that needed additional intervention.

Reproductive outcomes

	Primary infertility n=196	Secondary infertility n=52	Recurrent miscarriage n=15	Total n=263
Intent to get pregnant	149 (76%)	41 (79%)	13 (87%)	203 (77%)
Lost to follow-up	47 (24%)	11 (21%)	2 (13%)	60 (23%)
Assisted reproductive technology	61 (41%)	16 (39%)	3 (23%)	80 (39%)
Intrauterine insemination	19 (13%)	6 (15%)	2 (15%)	27 (13%)
Pregnant	57 (38%)	15 (37%)	8 (62%)	80 (39%)
Spontaneous pregnancy	27 (47%)	13 (87%)	5 (63%)	45 (56%)
Miscarriage	7 (12%)	3 (20%)	0	10 (13%)
Ectopic pregnancy	0	1 (7%)	0	1 (1%)
Preterm labour	0	1 (7%)	0	1 (1%)
Term delivery	50 (88%)	10 (67%)	8 (100%)	68 (85%)

Comparison of reproductive outcomes before and after metroplasty

	Miscarriage rate	Ectopic pregnancy rate	Preterm delivery rate	Term delivery rate
Before metroplasty	20.2% (41/203)	3.4% (7/203)	4.4% (9/203)	2.5% (5/203)
After metroplasty	4.9% (10/203)	0.5% (1/203)	0.5% (1/203)	33.5% (68/203)
p value	<0.0001	0.07	0.02	<0.0001

Safety

Complications

- Small perforation=1.1% (3/263) (no treatment needed)
- Postoperative bleeding=0.4% (1/263) (treated by a Foley catheter)

There were no cases of postoperative Asherman's syndrome.

Study 8 Ayas S (2011)

Details

Study type	**Retrospective case series**
Country	Turkey
Recruitment period	2005–9
Study population and number	n=**181** Women with septate uterus and unexplained infertility (n=98), or more than 1 miscarriage (n=83)
Age and sex	Mean age=30 years (range 18–38) 100% female
Patient selection criteria	The initial diagnosis of septate uterus was confirmed by hysterosalpingography for the patients with unexplained infertility; diagnostic hysteroscopy was done in the remaining 83 women, all of whom had experienced 1 or more miscarriage during the first or second trimester, preterm labour with the indication of habitual miscarriage, suspicious transvaginal ultrasound or referral to clinic for further investigation. Patients who underwent diagnostic laparoscopy and those with other possible causes of infertility were excluded. Patients who did not have information about the postoperative follow-ups (diagnostic hysteroscopy or hysterosalpingography) or did not agree to follow-up care were excluded from the study.
Technique	The metroplasty procedure was done using a resectoscope with a cutting monopolar knife electrode. The uterine cavity was distended with 1.5% glycine. In addition, the Versapoint system (Gynecare VersaPoint, Ethicon, USA) was used for 10 patients with saline solution as the distension medium.
Follow-up	**Mean 25 months (range 6–56)**
Conflict of interest/source of funding	Not reported

Analysis

Study design issues: Retrospective, single-centre study. Only spontaneous pregnancies were included in the statistical analysis.

Other issues: Patients who were not able to conceive within 12 months were advised to apply to the assisted reproductive technology department. The authors note that the control group was divided into women with 1 previous miscarriage and those with 2 or more previous miscarriages because the management of these groups is controversial. The authors also note that hysteroscopic metroplasty for septate uterus in women with unexplained fertility is controversial because the role of septate uteri in infertility has not been clearly established.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **181**

Repeated hysteroscopic metroplasty was necessary in 9 (5%) patients with a residual uterine septum (≥1 cm) seen on the follow-up diagnostic hysteroscopy.

Mean time to pregnancy after hysteroscopic metroplasty=9.8 months (range 2–42)

Reproductive outcomes before metroplasty

	Unexplained infertility (n=98)	**1 previous miscarriage (n=37)**	**2 or more previous miscarriages (n=46)**	**p value**
Pregnancies	0	42	174	
Miscarriage	0	88.1% (37/42)	96.6% (168/174)	0.001
Preterm delivery	0	9.5% (4/42)	2.3% (4/174)	0.004
Term delivery	0	2.4% (1/42)	1.1% (2/174)	0.384
Live births	0	4.8% (2/42)	2.9% (5/174)	0.149

Reproductive outcomes after metroplasty

	Unexplained infertility (n=98)	**1 previous miscarriage (n=37)**	**2 or more previous miscarriages (n=46)**	**p value**
Patients that conceived	43.9% (43/98)	70.3% (26/37)	82.6% (38/46)	0.001
Pregnancies	51	28	44	
Spontaneous pregnancies	36	22	41	
After assisted reproductive technology	15	6	3	
Live births	80.4 % (41/51)	78.6% (22/28)	79.5% (35/44)	0.981
Spontaneous pregnancies				
Miscarriage	16.7% (6/36)	13.6% (3/22)	17.1% (7/41)	0.935
Preterm delivery	22.2% (8/36)	22.7% (5/22)	12.2% (5/41)	0.430
Term delivery	61.1% (22/36)	63.6% (14/22)	70.7% (29/41)	0.658

Safety

Complications

- Uterine synechiae=2.2% (4/181) (treated surgically)
- Uterine perforations=1.7% (patients were hospitalised for 24–72 hours but no further intervention was needed.)

Study 9 Robson S (2001)

Details

Study type	**Case report**
Country	Australia
Recruitment period	Not reported
Study population and number	n=**1** Woman with septate uterus and history of ectopic pregnancy followed by intrauterine pregnancy that ended in severe abruption and consequent stillbirth, followed by 18 months of secondary infertility
Age and sex	Age 32 years
Patient selection criteria	Case report – interstitial ectopic pregnancy after hysteroscopic metroplasty
Technique	Hysteroscopic metroplasty was done under laparoscopic control at the same time as a laparoscopic left salpingectomy.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Key efficacy and safety findings

Interstitial ectopic pregnancy A cycle of in vitro fertilisation was started 3 months after the hysteroscopic metroplasty and the patient became pregnant. At 6 weeks' gestation, the patient had painless vaginal bleeding. Transvaginal ultrasound showed the presence of a fundal interstitial pregnancy and a laparotomy was done. A wedge of myometrium completely enclosing the gestational sac was resected. A hysteroscopy was done 4 months later and showed only a fine linear scar at the fundus, and the uterine cavity was otherwise normal.

Efficacy

Miscarriage

A non-randomised comparative study of 78 women with a partial septate uterus and a history of recurrent miscarriage reported miscarriage rates of 22% (8/37) after hysteroscopic metroplasty and 50% (9/18) with expectant management ($p<0.05$)[2]. A non-randomised comparative study of 48 women with a history of recurrent miscarriage reported miscarriage rates of 18% (4/22) after hysteroscopic metroplasty and 64% (9/14) with expectant management ($p<0.001$) for the first pregnancy after enrolment[3]. A case series of 973 women with a history of recurrent miscarriage or infertility reported the pregnancy outcomes of 344 women after hysteroscopic metroplasty: 14% (48/344) of women miscarried before 12 weeks' gestation and 4% (14/344) of women miscarried after 12 weeks' gestation (follow-up period not reported)[4]. A case series of 170 women with a history of recurrent miscarriage, preterm delivery or infertility reported that 92% (332/363) of pregnancies ended in miscarriage before hysteroscopic metroplasty compared with 13% (24/186) of pregnancies after hysteroscopic metroplasty ($p=0.02$)[5]. A case series of 246 women with a history of recurrent miscarriage or infertility reported that 65% (90/138) of women with a history of recurrent miscarriage became pregnant after hysteroscopic metroplasty; 34% (44/129) of the pregnancies were aborted and 2% (3/129) ended in intrauterine fetal death[6].

Preterm delivery

The non-randomised comparative study of 78 women with a partial septate uterus and a history of recurrent miscarriage reported preterm delivery after 5% (2/37) of pregnancies after hysteroscopic metroplasty and 28% (5/18) with expectant management ($p<0.05$)[2]. The non-randomised comparative study of 48 women with a history of recurrent miscarriage reported preterm delivery after 5% (1/22) of pregnancies after hysteroscopic metroplasty and 7% (1/14) with expectant management for the first pregnancy after enrolment[3]. The case series of 170 women with a partial or complete septate uterus and a history of recurrent miscarriage, preterm delivery, or infertility reported preterm delivery after 6% (22/363) of pregnancies before hysteroscopic metroplasty compared with 8% (14/186) of pregnancies after hysteroscopic metroplasty ($p=0.12$)[5]. The case series of 246 women with a septate uterus and a history of recurrent miscarriage or infertility reported that 11% (14/129) of the pregnancies in women with a history of recurrent miscarriage ended in preterm delivery[6].

Term delivery

The non-randomised comparative study of 78 women with a partial septate uterus and a history of recurrent miscarriage reported term delivery after 73% (27/37) of pregnancies after hysteroscopic metroplasty and 22% (4/18) with expectant management ($p<0.05$)[2]. The non-randomised comparative study of 48 women with a septate uterus and a history of recurrent miscarriage reported term delivery after 77% (17/22) of pregnancies after hysteroscopic metroplasty and 29% (4/14) with expectant management ($p<0.001$) for the first pregnancy after enrolment[3]. The case series of 973 women with a septate uterus and a history of recurrent miscarriage or infertility reported term delivery after 78% (268/344) of pregnancies; 14 patients were

still pregnant at the close of the study[4]. The case series of 170 women with a partial or complete septate uterus and a history of recurrent miscarriage, preterm delivery, or infertility reported term delivery after 3% (9/363) of pregnancies before hysteroscopic metroplasty compared with 80% (148/186) of pregnancies after hysteroscopic metroplasty (p=0.01)[5]. The case series of 246 women with a septate uterus and a history of recurrent miscarriage or infertility reported that 48% (57/129) of the pregnancies in women with a history of recurrent miscarriage ended in term delivery[6].

Live birth rate

A review of 2528 women (37 studies) with a septate uterus and a history of recurrent miscarriage, infertility, spontaneous abortion or preterm delivery that included a meta-analysis of 2074 women (29 studies) reported a live birth rate of 50% after hysteroscopic metroplasty (95% confidence interval [CI] 43 to 57; 19 studies, n=1525) (follow-up period not reported)[1]. The case series of 170 women with a history of recurrent miscarriage, preterm delivery or infertility reported that the 'take home baby rate' increased from 9% before hysteroscopic metroplasty to 87% after the procedure[5]. The case series of 246 women with a septate uterus and a history of recurrent miscarriage or infertility reported a live birth rate of 60% (71/129) in women with a history of recurrent miscarriage after hysteroscopic metroplasty; there were 11 ongoing pregnancies at the close of the study[6].

Pregnancy rate in women with infertility

The case series of 246 women with a septate uterus and a history of recurrent miscarriage or infertility reported that 57% (61/108) of women with unexplained fertility became pregnant after hysteroscopic metroplasty, with a live birth rate of 75% (44/71) of pregnancies; there were 12 ongoing pregnancies at the close of the study; the preterm delivery rate was 10% (7/71)[6]. A case series of 263 women with a septate uterus and primary or secondary infertility or a history of recurrent miscarriage reported that 38% (57/149) of women with primary infertility became pregnant after hysteroscopic metroplasty, with a term delivery rate of 88% (50/57)[7]. A case series of 181 women with a septate uterus and unexplained infertility reported that 44% (43/98) of women with unexplained infertility became pregnant after hysteroscopic metroplasty; there were 51 pregnancies, 36 of which were spontaneous and the live birth rate was 80% (41/51). Of the 36 spontaneous pregnancies, 22% (8/36) had a preterm delivery[8].

Safety

Uterine perforation

Perforation was reported in 1% (17/2167) of women in a review of 2528 women (37 studies)[1]. Uterine perforation was reported in 1% (8/923) of women after hysteroscopic metroplasty in a case series of 973 women; 3 procedures were done under laparoscopic control, 3 were done under ultrasound guidance and 2 were done with neither[4]. Perforation was reported in 1% (2/170) of women in a case series of 170 women; these were managed by laparoscopic bipolar coagulation and both women were discharged the same day. One of these women subsequently had a term pregnancy, with delivery by caesarean section[5].

Uterine rupture during subsequent pregnancy or delivery

The review of 2528 women (37 studies) identified 18 confirmed reports of uterine rupture during pregnancy or delivery; in 10 of the 18 cases uterine perforation had occurred at the time of the hysteroscopic metroplasty[1].

Bleeding

Intraoperative bleeding with 'interruption of the procedure' was reported in 1 woman in the case series of 973 women[4]. Excessive bleeding was reported in 1% (2/170) of women in the case series of 170 women; this was managed by an intrauterine balloon catheter kept in situ for 4 hours[5].

Cervical laceration

Cervical laceration (not further described) was reported in 2 out of 2167 women in the review of 2528 women (37 studies)[1]. Difficult dilatation leading to cervical injury (not further described) was reported in 1 woman in the case series of 170 women[5].

Pulmonary oedema

Pulmonary oedema was reported in 1 woman in the review of 2528 women (37 studies) and in 1 woman in the case series of 973 women (no further details reported)[1,4].

Postoperative uterine synechiae/adhesions

Postoperative uterine synechiae was reported in 1 woman in the review of 2528 women (37 studies)[1]. Mild adhesions were reported in 7% (11/170) of women in the case series of 170 women (diagnosed by hysteroscopy), which were all treated by hysteroscopic adhesiolysis; 7 of the women became pregnant and had subsequent term deliveries[5]. Postoperative uterine synechiae was reported in 2% (4/181) of women in the case series of 181 women, and was treated surgically in each case[8].

Interstitial ectopic pregnancy

Interstitial ectopic pregnancy was reported in 1 woman after hysteroscopic metroplasty in a case report. The woman became pregnant after a cycle of in vitro fertilisation that was started 3 months after the hysteroscopic metroplasty. At 6 weeks' gestation, the woman had painless vaginal bleeding. Transvaginal ultrasound showed the presence of a fundal interstitial pregnancy and a laparotomy was done to resect a wedge of myometrium completely enclosing the gestational sac. A hysteroscopy was done 4 months later and showed only a fine linear scar at the fundus, and the uterine cavity was otherwise normal[9].

Other

Admission because of possible pulmonary aspiration was reported in 1 woman in the review of 2528 women (37 studies)[1].

Validity and generalisability of the studies

- There are no randomised controlled trials comparing hysteroscopic metroplasty with expectant management.
- Some studies compare the pregnancy outcomes of the same cohort of women before and after hysteroscopic metroplasty; this study design has been criticised

and it is possible that a woman will carry a pregnancy to term after recurrent miscarriage without any intervention.
- Age has an effect on reproductive factors and the ability to conceive – few studies report the mean age of the study population.
- The indications for treatment are mixed and include recurrent miscarriage, preterm delivery and primary infertility. The efficacy outcomes are likely to be different in women with a history of recurrent miscarriage compared with those presenting with primary infertility. The results have been presented separately by indication where possible.
- The extent of the septum may have an effect on the efficacy outcomes for this procedure. One study included only women with a partial septum[3], 1 specified that women with either a partial or complete septum were included[5] and the rest of the studies did not specify either.
- The technique of metroplasty varies within and between studies. The procedure can be done under laparoscopic or ultrasound control, and various methods are used to remove the uterine septum.

Existing assessments of this procedure

A Cochrane review on metroplasty compared with expectant management for women with a history of recurrent miscarriage and a septate uterus was published in 2011[10]. The review did not identify any randomised controlled trials for inclusion. The authors' concluded:

> 'This treatment has been assessed in non-controlled studies, which suggested a positive effect on pregnancy outcomes. However, these studies are biased due to the fact that the participants with recurrent miscarriage treated by hysteroscopic metroplasty served as their own controls. Until now, the effectiveness and possible complications of hysteroscopic metroplasty have never been considered in a randomised controlled trial. Taking this into account there is insufficient evidence to support this treatment in these women.'

The Royal College of Obstetricians and Gynaecologists published a green-top guideline in 2011, 'The investigation and treatment of couples with recurrent first-trimester and second-trimester miscarriage'[11]. This states:

> 'There is insufficient evidence to assess the effect of uterine septum resection in women with recurrent miscarriage and uterine septum to prevent further miscarriage. There are no published randomised trials assessing the benefits of surgical correction of uterine abnormalities on pregnancy outcome. Open uterine surgery has never been assessed in prospective trials but is associated with postoperative infertility and carries a significant risk of uterine scar rupture during pregnancy. These complications are less likely to occur after transcervical hysteroscopic resection of uterine septae; experience from case series appears promising. However, before a clear judgement can be made, this procedure must be evaluated in a prospective controlled trial.'

Related NICE guidance

Below is a list of NICE guidelines related to this procedure. Appendix B gives details of the recommendations made in each guideline listed.

- Fertility: assessment and treatment for people with fertility problems. NICE guideline CG156 (2013). Available from www.nice.org.uk/guidance/CG156
- Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. NICE guideline CG154 (2012). Available from www.nice.org.uk/guidance/CG154

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their specialist society or royal college. The advice received is their individual opinion and does not represent the view of the society.

Hysteroscopic metroplasty of uterine septum in women with a history of recurrent miscarriage

Mr A Rutherford (British Fertility Society); Professor A Coomarasamy, Professor J Thornton (Royal College of Obstetricians and Gynaecologists).

- Two advisers perform the procedure regularly and 1 has never performed the procedure.
- Two advisers consider the procedure to be established practice and no longer new and 1 adviser considers it to be definitely novel and of uncertain safety and efficacy.
- One adviser noted that the procedure is used fairly widely by enthusiasts but there is no decent evidence of efficacy or safety. Another adviser noted that the procedure seems to have become established in practice with no proven evidence of benefit, although circumstantial evidence suggests that hysteroscopic metroplasty is of value in women with a history of recurrent miscarriage. Another adviser stated that 'whilst there is an agreement that surgery is probably reasonable in women with a very high number of miscarriages or large septum, the evidence is still observational or anecdotal in nature. However many clinicians seem to feel confident that the treatment works and I am not certain if many clinicians in the UK will actually randomise their patients to a trial in which the patients may not receive the treatment.'
- The comparator would be expectant management.
- Theoretical adverse events are bleeding, uterine perforation, incomplete resection of the septum, intrauterine adhesions, uterine rupture in future pregnancies, placental accreta and percreta.
- Adverse events reported in the literature: uterine perforation, incomplete resection of the septum, intrauterine adhesions. One adviser noted that there is very good evidence that excessive distension media use can result in serious pulmonary, cerebral and renal complications.
- One adviser made the following statements:
  - The use of modern small operative hysteroscopes, placed in the cavity under direct vision, reduces the risk of uterine perforation.

  - Leaving a small amount of septum behind (less than 1 cm) does not appear to significantly reduce the chance of a successful outcome; a combined surgical and radiological approach allows accurate assessment of the extent of the surgical incision while the patient is under anaesthetic.
  - The risk of intrauterine adhesions depends on the extent of the septum and the raw area left behind that needs to be recovered with endometrium. To reduce risk, the following measures have been used: a copper intrauterine contraceptive device (IUCD) is often placed in the uterus at the time of surgery to provide a physical barrier to keep the uterine walls apart; commercial adhesion barriers include Hyalobarrier (a thick gel) that is placed in the cavity at the end of the operation; postoperative exogenous hormone administration, high-dose hormone replacement therapy (HRT) used for 4 weeks followed by 2 weeks of oestrogen and progesterone to stimulate endometrium development.
- The key efficacy outcomes are a normal-sized uterine cavity, pregnancy rate, reduced miscarriage rate and increased live birth rate.
- There have been no randomised controlled trials. The issue is compounded by the fact that the spontaneous pregnancy rate in women with a history of recurrent miscarriage is high. Many women with uterine septum do not suffer a miscarriage and have a live birth, therefore the causality and any benefit from the intervention is unclear.
- The Royal College of Obstetricians and Gynaecologists (RCOG), through the British Society of Gynaecological Endoscopy and the British Fertility Society, provides training for this procedure. Surgery is part of the RCOG subspecialist curriculum for candidates subspecialising in reproductive medicine. There are established training programmes throughout the UK. The equipment used is available in most hospitals that offer a gynaecology service.
- Two advisers consider the potential impact of the procedure on the NHS to be minor, in terms of numbers of patients eligible for treatment and use of resources, and 1 considers the potential impact to be moderate.

Hysteroscopic metroplasty of uterine septum in women with primary infertility

Mr Y Khalaf, Mr A Rutherford (British Fertility Society); Professor A Coomarasamy, Mr N Raine-Fenning, Professor J Thornton (Royal College of Obstetricians and Gynaecologists).

- Four advisers perform the procedure regularly (1 stated that he rarely did it when the sole indication is infertility) and 1 has never performed it.
- Three advisers consider the procedure to be established practice and no longer new, 1 adviser considers the procedure to be definitely novel and of uncertain safety and efficacy, and 1 adviser considers it to be a minor variation on an existing procedure.
- The comparator would be expectant management.
- Theoretical adverse events are uterine perforation, incomplete resection of the septum, intrauterine adhesions, bleeding, infection, uterine rupture, negative effect on fertility through damage to the endometrium, detrimental effect on uterine and endometrial blood flow.
- Anecdotal adverse events: uterine perforation, fluid overload, cervical trauma.

- Adverse events reported in the literature: uterine perforation and possible injury to adjacent organs such as bowel, bladder or blood vessels, incomplete resection of the septum, intrauterine adhesions, fluid overload, cervical trauma, bleeding and infection. One adviser noted that there is a small likelihood of complications from the distension media used for hysteroscopy.
- The key efficacy outcomes are normalisation of uterine cavity, improvement in pregnancy outcome, improvement in fertility, malpresentation, and difficulty in labour and delivery.
- There have been no randomised controlled trials.
- One adviser stated 'The diagnostic tests applied are unclear and much of the literature refers to tests with limited or unproven performance. There is also no agreed classification. When you add the test accuracy and lack of classification based on the technique used to diagnose, you almost have to ignore the current evidence base. I strongly believe many septums are misdiagnosed and incorrectly defined as sub-septate, septate and bicornuate. I know this through my talks when I show images of anomalies'.
- RCOG, through the British Society of Gynaecological Endoscopy and the British Fertility Society, provides training for this procedure. Surgery is part of the RCOG subspecialist curriculum for candidates subspecialising in reproductive medicine. There are established training programmes throughout the UK. The equipment used is available in most hospitals that offer a gynaecology service.
- There are the following uncertainties about the way in which the procedure is currently being done: scissors compared with electrodiathermy; ultrasound guidance to confirm if surgery is successful; whether laparoscopic guidance is necessary; diagnostic test used to define and classify the anomaly; whether to leave an IUCD in the uterus and recheck the cavity a few months later or to offer some form of check regardless (hysteroscopy, saline scan, hysterosalpingograph).
- The role of hysteroscopic metroplasty in patients with otherwise unexplained infertility remains uncertain, yet it remains in use. Recent NICE guidelines (2013) indicated the uncertainty of the benefits of performing metroplasty.
- Four advisers consider the potential impact of the procedure on the NHS to be minor, in terms of numbers of patients eligible for treatment and use of resources, and 1 considers it to be moderate.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- Ongoing study: The randomised uterine septum transection trial is ongoing in the Netherlands. The trial started in October 2008 and the target number of participants is 68. The finish date is unknown.
- When this procedure was originally scoped, the indication was 'septate uterus in women with recurrent miscarriage'. The evidence also included a number of studies in which hysteroscopic metroplasty was used to treat women with primary infertility. Several studies note that the use of hysteroscopic metroplasty to treat

primary infertility is controversial because the role that septate uterus plays in infertility is not clear. The evidence summarised in table 2 includes both groups of women.

References

1. Valle RF, Ekpo GE (2013) Hysteroscopic metroplasty for the septate uterus: review and meta-analysis. The Journal of Minimally Invasive Gynecology 20: 22–42
2. Pang L-H, Li M-J, Li M et al. (2011) Not every subseptate uterus requires surgical correction to reduce poor reproductive outcome. International Journal of Gynecology and Obstetrics 115: 260–3
3. Valli E, Vaquero E, Lazzarin N et al. (2004) Hysteroscopic metroplasty improves gestational outcome in women with recurrent spontaneous abortion. Journal of the American Association of Gynecologic Laparoscopists 11: 240–4
4. Colacurci N, De Placido G, Perino A et al. (1998) Hysteroscopic metroplasty. Journal of the American Association of Gynecologic Laparoscopists 5: 171–4
5. Roy KK, Singla S, Baruah J et al. (2011) Reproductive outcome following hysteroscopic septal resection in patients with infertility and recurrent abortions. Archives of Gynecology & Obstetrics 283: 273–9
6. Paradisi R, Barzanti R, Natali F et al. (2011) Metroplasty in a large population of women with septate uterus. Journal of Minimally Invasive Gynecology 18: 449–54
7. Tehraninejad ES, Ghaffari F, Jahangiri N et al. (2013) Reproductive outcome following hysteroscopic monopolar metroplasty: an analysis of 203 cases. International Journal of Fertility and Sterility 7: 175–80
8. Ayas S, Gurbuz A, Tuna G et al. (2011) Hysteroscopic resection of uterine septum improves reproductive performance in women with unexplained infertility. Turkish Journal of Medical Sciences 41: 595–601
9. Robson S, Pozza C, Kerin JF (2001) Interstitial ectopic pregnancy following hysteroscopic resection of an intrauterine septum. Gynaecological Endoscopy 10: 193–5
10. Kowalik CR, Goddijn M, Emanuel M (2011) Metroplasty versus expectant management for women with recurrent miscarriage and a septate uterus. Cochrane Database of Systematic Reviews (6) CD008576-2011
11. Royal College of Obstetricians and Gynaecologists. The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage Green-top Guideline No. 17. London: RCOG; 2011

Appendix A: Additional papers on hysteroscopic metroplasty of uterine septum in women with primary infertility or a history of recurrent miscarriage

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies. Case series with fewer than 50 patients have not been included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Bakas P, Gregoriou O, Hassiakos D et al. (2012) Hysteroscopic resection of uterine septum and reproductive outcome in women with unexplained infertility. Gynecologic & Obstetric Investigation 73: 321–5	n=68 (primary infertility)	At 12 months' follow-up, the clinical pregnancy rate, the live birth rate and the abortion rate were 44% (30/68), 37% (25/68) and 17% (5/30), respectively. At total follow-up time, the overall pregnancy rate, the live birth rate and the abortion rate were 54% (35/65), 42% and 14% (7/35), respectively, while the stillbirth rate was 3% (1/35).	Larger studies are included
Ban-Frangez H, Tomazevic T, Virant-Klun I et al. (2009) The outcome of singleton pregnancies after IVF/ICSI in women before and after hysteroscopic resection of a uterine septum compared to normal controls. European Journal of Obstetrics, Gynecology, & Reproductive Biology 146: 184–7	n=137	The abortion rate before hysteroscopic metroplasty was significantly higher, both in women with a small partial septum (79% before resection versus 24% in the normal controls, OR 12.08) and a large septum (83% before resection versus 17% in normal controls, OR 25.00) compared to women with a normal uterus. After the surgery, the abortion rate was comparable to the abortion rate in women with normal uterus: in both women with a small partial and women with a larger septum	Study focuses on the outcome of pregnancies after in vitro fertilisation.
Bendifallah S, Faivre E, Legendre G et al. (2013) Metroplasty for AFS Class V and VI septate uterus in patients with infertility or miscarriage: reproductive outcomes study. Journal of Minimally Invasive Gynecology 20: 178–84	n=128 (primary infertility or recurrent miscarriage)	After metroplasty, 78 women (61%) became pregnant, and 70 live neonates were delivered. The first live birth rate in infertile women was 53%. Of the 25 pregnancies, 13 (52%) resulted from assisted reproductive technology. In women who experienced recurrent miscarriage, the miscarriage rate was significantly improved. Outcomes differed significantly according to anatomical type of septum after surgery.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Berkkanoglu M, Isikoglu M, Arici F et al. (2008) What is the best time to perform intracytoplasmic sperm injection/embryo transfer cycle after hysteroscopic surgery for an incomplete uterine septum? Fertility & Sterility 90: 2112–5	n=282	Starting an ICSI/embryo transfer cycle just after the hysteroscopic procedure does not result in any impairment in implantation rate or PR compared with those started 10 or more weeks after the operation	Study focuses on timing of embryo transfer after hysteroscopic metroplasty.
Bosteels J, Weyers S, Puttemans P et al. (2010) The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review. Human Reproduction Update 16: 1–11	30 studies	Hysteroscopic metroplasty for septate uterus resulted in fewer pregnancies in patients with subfertility when compared with those with recurrent pregnancy loss (RR=0.7; 95% CI: 0.5-0.9).	Review of hysteroscopy in subfertile women – includes outcomes for other procedures and other indications.
Cararach M, Penella J, Ubeda A et al. (1994) Hysteroscopic incision of the septate uterus: scissors versus resectoscope. Human Reproduction 9: 87–9	n=70	**Scissors versus resectoscope** There were 51 pregnancies after a mean period of 9 months following hysteroscopic metroplasty, of which 29 (57%) were carried to term, 12 (24%) were spontaneous abortions, and 10 (20%) are in progress. The post-treatment pregnancy success rate was 73%. The number of spontaneous abortions, pregnancies to term and mean time between surgery and conception was similar in both groups. There were three cases of perforation in the group of excision with hysteroscopic scissors and a case of pulmonary oedema in the group of the resectoscope. Although different advantages are provided by each technique, and more pregnancies were established using scissors, it seems that operator experience is a major consideration in performing these therapeutic hysteroscopic operations.	Larger studies are included. Included in Valle et al, 2013 systematic review and meta-analysis.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Colacurci N, De Placido G, Mollo A et al. (1996) Reproductive outcome after hysteroscopic metroplasty. European Journal of Obstetrics, Gynecology, & Reproductive Biology 66:147–150	n=69	Of the 48 patients affected by repeated abortion, 40 became pregnant after the metroplasty whereas, to date, in the infertile group only six out 21 (29%) conceived. 31 pregnancies (67%) were carried to term, five (11%) ended in preterm delivery, six (13%) ended in spontaneous abortion and four (9%) are in progress.	Larger studies are included. Included in Valle et al, 2013 systematic review and meta-analysis.
Colacurci N, De Franciscis P, Mollo A et al. (2007) Small-diameter hysteroscopy with Versapoint versus resectoscopy with a unipolar knife for the treatment of septate uterus: a prospective randomized study. Journal of Minimally Invasive Gynecology 14: 622-627	n=160	**Resectoscopy with monopolar knife versus small-diameter hysteroscopy with a Versapoint device** Small-diameter hysteroscopy with bipolar electrode for the incision of uterine septum is as effective as resectoscopy with unipolar electrode regarding reproductive outcome and is associated with shorter operating time and lower complication rate	Included in Valle et al, 2013 systematic review and meta-analysis.
Dalal RJ, Pai HD, Palshetkar NP et al. (2012) Hysteroscopic metroplasty in women with primary infertility and septate uterus: reproductive performance after surgery. Journal of Reproductive Medicine 57: 13-16	n=72	Thirty-three women (46%) conceived within one year of surgery. 4 women (12%) had spontaneous abortions, and 5 (15%) had preterm delivery.	Larger studies are included.
Daly DC, Maier D, Soto-Albors C (1989) Hysteroscopic metroplasty: six years' experience. Obstetrics & Gynecology 73: 201-205	n=70	Hysteroscopic metroplasty was very effective in treating patients with septa and a history of first-trimester abortion; patients with first-trimester loss and either second-trimester abortion or preterm birth benefited from metroplasty but were still at risk for preterm labour; and hysteroscopic metroplasty does not "cure" unexplained infertility.	Larger studies are included. Included in Valle et al, 2013 systematic review and meta-analysis.
DeChereney AH, Russell JB, Graebe RA et al. (1986) Resectoscopic management of mullerian fusion defects. Fertility and Sterility 45: 726-728	n=72	At the time this article was written, there were 58 term deliveries and 5 ongoing pregnancies > 30 weeks (1 had a spontaneous abortion after surgery and subsequently conceived a term pregnancy), for a successful pregnancy rate of 86%.	Larger studies are included. Included in Valle et al, 2013 systematic review and meta-analysis.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Doridot V, Gervaise A, Taylor S et al. (2003) Obstetric outcome after endoscopic transection of the uterine septum. Journal of the American Association of Gynecologic Laparoscopists 10: 271-5	n=70	Endoscopic transection of uterine septum may improve obstetric outcomes in women with late abortion, decrease abortion rates in those with recurrent abortions, and avoid pregnancy loss for patients with primary infertility.	Larger studies are included.
Ergenoglu M, Yeniel AO, Yildirim N et al. (2013) Recurrent uterine rupture after hysteroscopic resection of the uterine septum. International Journal of Surgery Case Reports 4: 182-184	n=1	**Recurrent uterine rupture** Uterine rupture may occur in pregnancies after hysteroscopic resection of the uterine septum. The patient must be informed about both the risks of uterine rupture during pregnancy after hysteroscopic septum resection and that recurrent ruptures may occur at earlier gestational weeks than during previous pregnancies.	Uterine rupture is already described as a safety outcome.
Fedele L, Arcaini L, Parazzini F et al. (1993) Reproductive prognosis after hysteroscopic metroplasty in 102 women: life-table analysis. Fertility & Sterility 59: 768-772	n=102	At 36 months the cumulative pregnancy and birth rates were 89% and 75%, respectively, in the septate uterus group and 80% and 67% in the subseptate uterus group.	Included in Valle et al, 2013 systematic review and meta-analysis
Fedele L, Bianchi S, Marchini M et al. (1996) Residual uterine septum of less than 1 cm after hysteroscopic metroplasty does not impair reproductive outcome. Human Reproduction 11: 727-9	n=68	The cumulative 18 month probability of becoming pregnant was 45% in the patients with residual septum and 53% in those with no residual septum (not significantly different), and the cumulative 18 month probability of giving birth to a child was 28 and 36% respectively (also not significant).	Larger studies are included.
Ghahiry AA, Refaei Aliabadi E, Taherian AA et al. (2014) Effectiveness of hysteroscopic repair of uterine lesions in reproductive outcome. International Journal of Fertility & Sterility 8: 129-134	Case series n=65 FU=1 year	Among all patients with recurrent abortion, 6 patients (75%) completed their pregnancy successfully. Pregnancy rate after metroplasty was 58%.	Small case series with different kinds of surgical treatment, including metroplasty, myomectomy, adhesiolysis and polypectomy under laparoscopic guide.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Giacomucci E, Bellavia E, Sandri F et al. (2011) Term delivery rate after hysteroscopic metroplasty in patients with recurrent spontaneous abortion and T-shaped, arcuate and septate uterus. Gynecologic & Obstetric Investigation 71: 183-188	n=170	Before surgery, the overall term delivery rate was 6%. After surgery, the overall term delivery rate was 59% (absolute benefit increase, ABI, was 54.5) and correlated with the number of previous abortions. Data stratified according to uterine malformations yielded the following term delivery rate: 67% for T-shaped uterus, 63% for septum/partial septum and 56% for arcuate uterus (NS, log-rank test). The number of previous abortions and maternal age also affected the term delivery rate.	Includes other uterine malformations as well as septate uterus.
Grimbizis G, Camus M, Clasen K et al. (1998) Hysteroscopic septum resection in patients with recurrent abortions or infertility. Human Reproduction 13: 1188-1193	n=57	After hysteroscopic metroplasty, 42 patients were interested in pregnancy. All patients with recurrent abortions conceived spontaneously. 21 (64%) infertile patients achieved a pregnancy, 13 (62%) of them after treatment with various assisted reproduction techniques. The reproductive outcome after septum resection yielded 44 pregnancies: 11 (25%) abortions, 1 (2%) ectopic pregnancy, 2 (5%) preterm deliveries (both twins), 28 (64%) term deliveries and 2 (5%) as-yet ongoing pregnancies.	Larger studies are included. Included in Valle et al, 2013 systematic review and meta-analysis.
Gundabattula SR, Joseph E, Marakani LR et al. (2014) Reproductive outcomes after resection of intrauterine septum. Journal of Obstetrics & Gynaecology 34: 235-7	n=124 (41 primary infertility, 21 secondary infertility, 52 prior pregnancy losses)	40 (32%) women were lost to follow-up after resection; 63 of the remaining 84 (75%) conceived and there were a total of 98 pregnancies. A cerclage was done in 28 (33%) of these pregnancies. Miscarriage and live birth rates were 93% and 4% pre- and 32% and 61% post-resection, respectively.	Larger studies are included.
Haberal A, Batioglu S, Ugur M (1996) Hysteroscopic treatment of septate uterus. Journal of Gynecologic Surgery 12: 241-6	n=59 (recurrent abortion and primary infertility)	There were a total of 25 pregnancies after a mean period of 18 months following the procedure, of which 16 (64%) were carried to term, 4 (16%) ended with spontaneous abortion, and 5 (20%) are ongoing.	Larger studies are included.
Heinonen PK (1997) Reproductive performance of women with uterine anomalies after abdominal or hysteroscopic metroplasty or no surgical treatment. Journal of the American Association of Gynecologic Laparoscopists 4: 311-7	n=192 (32 hysteroscopic metroplasty, 20 abdominal metroplasty, 140 no operative treatment)	Fetal survival improved from 13% to 91% after hysteroscopic metroplasty and from 3% to 86% after the abdominal procedure. A living child was born in 67% of 264 pregnancies in 116 women with septate uterus with no surgical treatment. When 19 patients with hysteroscopic metroplasty were matched by age, gravidity, and type of uterine anomaly with 19 women not subjected to metroplasty, the rates were 86% and 68%, respectively (p=0.089)	Retrospective study with a small number of women treated by hysteroscopic metroplasty.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Homer HA, Li TC, Cooke ID (2000) The septate uterus: a review of management and reproductive outcome. Fertility & Sterility 73: 1–14	Review n=658	Metroplasty is indicated in women with a history of repeated adverse reproductive outcomes, including fetal loss in the first and second trimesters and preterm labour. Hysteroscopic metroplasty is a safe, simple, and expeditious method of treating the septate uterus.	Extensive overlap with Valle et al, 2013 systematic review.
Kamel MAM, El-Tawab SS, El-Ashkar OS et al. (2014) Mini-scissor versus bipolar twizzle in ambulatory hysteroscopic metroplasty: A prospective randomized study. Journal of Gynecologic Surgery 30: 147-151	RCT n=40 FU=3 months	Ambulatory-based hysteroscopic metroplasty, using either a mini-scissor or bipolar twizzle, is a safe and effective procedure. Electrosurgical electrodes induce significantly higher pain scores than mechanical cold instruments. If an electrosurgical electrode is the only available device, a preoperative analgesic is recommended, especially for such patients.	Study compares 2 different methods of incising the uterine septum.
Kerimis P, Zolti M, Sinwany G et al. (2002) Uterine rupture after hysteroscopic resection of uterine septum. Fertility & Sterility 77: 618-620	n=1	**Uterine rupture** The patient had an uneventful pregnancy and spontaneous labour at 41 weeks. Caesarean section was performed because of suspected fetal distress. During caesarean section, the uterus was ruptured transversely along the fundus at the line of the attachment of the septum.	Case report of safety outcome already included.
Kormanyos Z, Molnar BG, Pal A (2006) Removal of a residual portion of a uterine septum in women of advanced reproductive age: obstetric outcome. Human Reproduction 21: 1047-1051	n=94	Women with a remnant uterine septum have an increased chance of successful pregnancy with an improved obstetric outcome after normalization of the uterine cavity.	Larger studies are included.
Kupesic S, Kurjak A (1998) Diagnosis and treatment outcome of the septate uterus. Croatian Medical Journal 39: 185-190	n=116	The pregnancy rate in 116 patients following the operative hysteroscopy for an intrauterine septum in a prospective follow-up period of 24 months was 51%: 44 patients (75%) had term deliveries, 11 (19%) had first trimester abortion, and 4 (7%) had preterm delivery.	Included in Valle et al, 2013 systematic review and meta-analysis
Lin K, Zhu X, Xu H et al. (2009) Reproductive outcome following resectoscope metroplasty in women having a complete uterine septum with double cervix and vagina. International Journal of Gynaecology & Obstetrics 105: 25-28	n=36 (21 metroplasty versus 15 controls)	Resectoscope metroplasty was found to improve the pregnancy outcomes of women having primary infertility or a history of pregnancy loss associated with a complete uterine septum with double cervix and vagina.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Litta P, Spiller E, Saccardi C et al. (2008) Resectoscope or Versapoint for hysteroscopic metroplasty. International Journal of Gynaecology & Obstetrics 101: 39-42	n=63	**Versapoint versus resectoscope using the Collins loop** Operative hysteroscopy with Versapoint does not require cervical dilation, thus avoiding cervical incompetence, cervical lacerations, and uterine perforation. The Versapoint technique is a safe and effective alternative to the resectoscope. It could be used predominantly in nulligravida women, especially in those with cervical canal stenosis.	Study focuses on technique. Included in Valle et al, 2013 systematic review and meta-analysis.
Lobaugh ML, Bammel BM, Duke D et al. (1994) Uterine rupture during pregnancy in a patient with a history of hysteroscopic metroplasty. Obstetrics & Gynecology 83: t-40	n=1	**Uterine rupture** A patient with a history of hysteroscopic resection of a uterine septum presented in preterm labour. This was her second pregnancy following the procedure; the first resulted in a term vaginal delivery. This second pregnancy ended with a preterm caesarean delivery. A fundal rupture was discovered during the caesarean. The metroplasty had been performed with the KTP laser under direct laparoscopic visualisation. No surgical complications had occurred.	Case report of safety outcome already included.
Ludwin A, Ludwin I, Pitynski K et al. (2014) Role of morphologic characteristics of the uterine septum in the prediction and prevention of abnormal healing outcomes after hysteroscopic metroplasty. Human Reproduction 29: 1420-1431	Case series n=96	A wide septum and large surface area may be indications for adhesion barrier. The European Society of Human Reproduction and Embryology (ESHRE) and European Society for Gynaecological Endoscopy (ESGE) criteria may cause greater frequency of recognition of residual septum than the American Society of Reproductive Medicine >1 cm criterion, which could result in more frequent reoperations with use of the ESHRE-ESGE criteria, possibly without any significant effect on reproductive performance.	Small case series assessing the diagnosis of residual septum and the use of adhesion barriers.
March CM, Israel R (1987) Hysteroscopic management of recurrent abortion caused by septate uterus. American Journal of Obstetrics & Gynecology 156: 834-842	n=91	Among those patients who conceived after therapy, the gestational outcome markedly improved. 87% of the pregnancies have resulted in a living infant or have progressed beyond 20 weeks of gestation.	Larger studies are included. Included in Valle et al, 2013 systematic review and meta-analysis.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Mencaglia L, Tantini C (1996) Hysteroscopic treatment of septate and arcuate uterus. Gynaecological Endoscopy 5: 151-4	n=122 (septate and arcuate uterus)	Hysteroscopic results were excellent, with 84 pregnancies out of 122 cases of septate or arcuate uterus. Of the 94 patients who had previously miscarried, 72 (77%) conceived, while this occurred in only 12 (43%) of the 28 previously infertile patients. Out of 84 pregnancies 80 had normal full-term deliveries and four women miscarried. We performed 32 caesarean sections for obstetric indications; no placental anomalies were observed. One uterine rupture occurred during labour at 39 weeks.	Includes women with septate or arcuate uterus.
Mollo A, De Franciscis P, Colacurci N et al. (2009) Hysteroscopic resection of the septum improves the pregnancy rate of women with unexplained infertility: a prospective controlled trial. Fertility & Sterility 91: 2628-31	n=176 (infertility; 44 hysteroscopic metroplasty versus 132 expectant management)	Hysteroscopic resection of the septum improves fecundity of women with septate uterus and otherwise unexplained infertility. Patients with septate uterus and no other cause of sterility have a significantly higher probability of conceiving after removal of the septum than patients affected by idiopathic sterility.	Included in Valle et al, 2013 systematic review and meta-analysis.
Nawroth F, Schmidt T, Freise C et al. (2002) Is it possible to recommend an "optimal" postoperative management after hysteroscopic metroplasty? A retrospective study with 52 infertile patients showing a septate uterus. Acta Obstetricia et Gynecologica Scandinavica 81: 55-7	n=52	A postoperative 3-months HRT + IUD insertion or a HRT alone after hysteroscopic metroplasty are not necessary.	Larger studies are included.
Nouri K, Ott J, Huber JC et al. (2010) Reproductive outcome after hysteroscopic septoplasty in patients with septate uterus--a retrospective cohort study and systematic review of the literature. Reproductive Biology & Endocrinology 8: 52	n=64	In 2/64 (3%) women, intraoperative uterine perforation occurred. Complete follow-up was available for 49/64 (76%) patients. Mean follow-up time was 68.6+/-5.2 months. The overall pregnancy rate after hysteroscopic septoplasty was 69% (34/49). The overall life birth rate (LBR) was 49% (24/49). The mean time interval between surgery and the first life birth was 35.8+/-22.5 months.	Larger studies are included. Included in Valle et al, 2013 systematic review and meta-analysis

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Ozgur K, Isikoglu M, Donmez L et al. (2007) Is hysteroscopic correction of an incomplete uterine septum justified prior to IVF? Reproductive Biomedicine Online 14: 335-40	n=236 (119 women with septate uterus versus 116 women with normal uterine cavity)	A similar pregnancy outcome was found after the incision of the incomplete septum compared with a group with normal uterine cavity. Larger prospective and randomised controlled studies are needed to prove the positive effect of correction of an incomplete uterine septum on IVF outcome.	Study focuses on IVF outcome.
Pabuccu R, Atay V, Urman B et al. (1995) Hysteroscopic treatment of septate uterus. Gynaecological Endoscopy 4: 213–5	n=59 (49 recurrent miscarriage, 10 infertility)	Of subjects with recurrent abortion, 86% achieved at least one term delivery following operative hysteroscopy. The viable delivery rate per achieved pregnancy increased from 7% preoperatively to 91% postoperatively. 5 of 8 women with otherwise unexplained infertility conceived.	Larger studies are included.
Pabuccu R, Gomel V (2004) Reproductive outcome after hysteroscopic metroplasty in women with septate uterus and otherwise unexplained infertility. Fertility and Sterility 81: 1675-8	n=61 (infertility)	Of 61 women, 25 (41%) conceived within 8-14 (mean 11) months after hysteroscopic metroplasty. Of these, 18 (30% of the total group) had live births (13 carried to term and 5 had preterm deliveries), and 7 (12% of the total group) had spontaneous abortions.	Larger studies are included.
Pace S, Cipriano L, Pace G et al. (2006) Septate uterus: reproductive outcome after hysteroscopic metroplasty. Clinical & Experimental Obstetrics & Gynecology 33: 110-112	n=75	Forty patients attempted pregnancy and a total of 30 spontaneous pregnancies resulted (75% pregnancy rate). The uterine cavity was normal at hysteroscopic follow-up in 68% of cases.	Larger studies are included. Included in Valle et al, 2013 systematic review and meta-analysis.
Pai H, Kundnani M, Palshetkar N et al. (2009) Reproductive performance after hysteroscopic metroplasty in women with primary infertility and septate uterus. Journal of Gynecological Endoscopy and Surgery 1: 17-20	n=72 (infertility)	33 women (46%) conceived within one year of surgery. Only 4 women (12%) had spontaneous abortions and only 5 (15%) had preterm delivery.	Included in Valle et al, 2013 systematic review and meta-analysis.
Paradisi R, Barzanti R, Natali F et al. (2014) Hysteroscopic metroplasty: reproductive outcome in relation to septum size. Archives of Gynecology & Obstetrics 289: 671-6	n=112 (recurrent miscarriage and infertility)	In the overall population the reproductive performance after surgery is greatly improved. No significant differences in reproductive performance were evident between patients with small and large partial uterine septa. The reproductive performance was also similar in infertile patients and in women with history of miscarriage.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Porcu G, Cravello L, D'Ercole C et al. (2000) Hysteroscopic metroplasty for septate uterus and repetitive abortions: reproductive outcome. European Journal of Obstetrics, Gynecology, & Reproductive Biology 88: 81-84	n=63	Obstetrical prognosis of patients presenting with repeated pregnancy loss and septate uterus is statistically improved by hysteroscopic metroplasty.	Larger studies are included. Included in Valle et al, 2013 systematic review and meta-analysis.
Satiroglu MH, Gozukucuk M, Cetinkaya SE et al. (2009) Uterine rupture at the 29th week of subsequent pregnancy after hysteroscopic resection of uterine septum. Fertility & Sterility 91: 934.e1-934.e3	n=1	**Uterine rupture** Patient was admitted with symptoms of hemodynamic shock at the 29th week of gestation. A laparotomy was done and a midfundal complete uterine rupture was observed at the site of the resected uterine septum, accompanied by an extrauterine exanimate fetus.	Case report of safety outcome already included.
Saygili-Yilmaz E, Yildiz S, Erman-Akar M et al. (2003) Reproductive outcome of septate uterus after hysteroscopic metroplasty. Archives of Gynecology & Obstetrics 268: 289–92	n=361	A total of 180 (50%) pregnancies were achieved after metroplasty during the follow-up period of 18 months. Of the 180 pregnancies 117 (57%) reached to term and 34 (19%) ended in preterm delivery and the remaining 29 (16%) resulted in abortion. Of the preterm babies 18 (53%) were able to live. We obtained 135 (75%) live babies totally.	Included in Valle et al, 2013 systematic review and meta-analysis.
Scoccia B, Demir H, Elter K et al. (2009) Successful medical management of post-hysteroscopic metroplasty bleeding with intravenous estrogen therapy: a report of two cases and review of the literature. Journal of Minimally Invasive Gynecology 16: 639–42	n=2	**Postoperative bleeding** After surgical resection of the septum, significant late post-hysteroscopic bleeding was seen in the fourth and eighteenth day of surgery, respectively. Both patients were successfully treated with intravenous conjugated equine oestrogen.	Case report of safety outcome already included.
Shokeir T, Abdelshaheed M, El-Shafie M et al. (2011) Determinants of fertility and reproductive success after hysteroscopic septoplasty for women with unexplained primary infertility: a prospective analysis of 88 cases. European Journal of Obstetrics, Gynecology, & Reproductive Biology 155: 54–7	n=103 (infertility)	Fertility and pregnancy after hysteroscopic septoplasty in women with unexplained primary infertility and uterine septum as a sole cause for reproductive failure seems to depend on patient age, duration of infertility before septoplasty, and septum size. Women with a septum size larger than one-half of their uterine length have a higher chance of successful pregnancy after hysteroscopic septoplasty.	Larger studies are included.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Sugiura-Ogasawara M, Lin BL, Aoki K et al. (2014) Does surgery improve live birth rates in patients with recurrent miscarriage caused by uterine anomalies? Journal Obstetrics Gynaecology 1-4 doi:10.3109/01443615.2014.936839	Case series n=170	In patients with a septate uterus, the live birth rate (81%) at the first pregnancy after ascertainment of anomalies with surgery tended to be higher than that (62%) in those without surgery. The infertility rates were similar in both groups, while the cumulative live birth rate (76%) tended to be higher than without surgery (60%).	Case series includes a variety of uterine anomalies.
Tofoski G, Dimitrov G, Georgievska J et al. (2011) Reproductive outcome after hysteroscopic metroplasty in patients with infertility and recurrent pregnancy loss. Makedonska Akademija na Naukite i Umetnostite Oddelenie Za Bioloshki i Meditsinski Nauki Prilozi 32: 141-154	n=202 (recurrent miscarriage and infertility)	Analysis of the reproductive outcome before and after hysteroscopic metroplasty showed a significant ($p<0.05$) decrease in the abortion rate from 90% to 12%, as well as an increase of term delivery rate from 1% to 74%. In the group of preterm deliveries there was a rise from 9% to 13%, which was not significant. The group of patients with primary infertility had a pregnancy rate of 36%.	Patients had a mixture of uterine malformations including bicornuate and arcuate uterus.
Tonguc EA, Var T, Batioglu S (2011) Hysteroscopic metroplasty in patients with a uterine septum and otherwise unexplained infertility. International Journal of Gynaecology & Obstetrics 113: 128–30	n=127 (infertility; 102 hysteroscopic metroplasty versus 25 controls)	Of the 102 patients who underwent hysteroscopic metroplasty, 44 (43%) were able to achieve pregnancy, as compared with 5 (20%) of the 25 patients who did not undergo the operation ($p=0.03$). The abortion rate was 11% (5/44) in group 1, compared with 60% (3/5) in group 2 ($p=0.02$). The live birth rate was 35% (36/102) in group 1, as compared with 8% (2/25) in group 2 ($p=0.008$)	Included in Valle et al, 2013 systematic review and meta-analysis.
Valle RF (1996) Hysteroscopic treatment of partial and complete uterine septum. International Journal of Fertility & Menopausal Studies 41: 310–5	n=124 (115 recurrent miscarriage, 9 infertility)	Following treatment, 101 patients achieved pregnancy (81%). There were 84 term pregnancies (83%) and 7 preterm viable pregnancies (7%). There were 12 spontaneous abortions, all in the first trimester (12%); 23 patients had not become pregnant as yet (19%). Of the seven patients with complete uterine septum, including the cervix, six had delivered an infant at term.	Included in Valle et al, 2013 systematic review and meta-analysis
Venturoli S, Colombo F M, Vianello F et al. (2002) A study of hysteroscopic metroplasty in 141 women with a septate uterus. Archives of Gynecology & Obstetrics 266: 157–9	n=141 (69 infertility, 72 recurrent miscarriage)	The mean+/-SD post-operative follow up period was 36+/-19.5 months. 36 Group I patients (52%) and 38 Group II patients (53%) achieved pregnancy, with respective abortion rates of 20% and 25%.	Included in Valle et al, 2013 systematic review and meta-analysis

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Wang S, Shi X, Hua X et al. (2013) Hysteroscopic transcervical resection of uterine septum. Journal of the Society of Laparoendoscopic Surgeons 17: 517–20	n=190 (mixed indications)	Among the 115 patients that were followed up, 86 became pregnant and delivered infants, 81 of which were born at term and 5 that were born premature.	Larger studies are included.

Appendix B: Related NICE guidance for hysteroscopic metroplasty of uterine septum in women with primary infertility or a history of recurrent miscarriage

Guidance	Recommendations
Clinical guidelines	**Fertility: assessment and treatment for people with fertility problems. NICE guideline CG156 (2013).** There are no recommendations related to hysteroscopic metroplasty in the NICE guideline. The full guideline has the following statement: 'Uterine septum is a congenital anomaly of the female reproductive tract. The incidence is not increased among women with infertility compared with other women (2–3%). It is more common in women who have had recurrent pregnancy loss or preterm birth. Hysteroscopic metroplasty has not been shown to increase pregnancy rates in women with infertility who have a septate uterus. [Evidence level 2b–3]'
Clinical guidelines	**Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. NICE guideline CG154 (2012).** There are no recommendations related to hysteroscopic metroplasty.

Appendix C: Literature search for hysteroscopic metroplasty of uterine septum in women with primary infertility or a history of recurrent miscarriage

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	27/08/2014	Issue 8 of 12, August 2014
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	27/08/2014	Issue 3 of 4, July 2014
HTA database (Cochrane Library)	27/08/2014	Issue 3 of 4, July 2014
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	27/08/2014	Issue 7 of 12, July 2014
MEDLINE (Ovid)	27/08/2014	1946 to August Week 2 2014
MEDLINE In-Process (Ovid)	27/08/2014	August 26, 2014
EMBASE (Ovid)	27/08/2014	1974 to 2014 Week 34
PubMed	27/08/2014	n/a
JournalTOCS	27/08/2014	n/a

Trial sources searched on 31 March 2104

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 31 March 2104

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Uterine Diseases/
2 Uterus/ab [Abnormalities]
3 ((Uter* or womb* or endometrial*) adj4 (septum* or septate* or septa* or anomal* or abnormal* or diseas* or malformat*)).tw.
4 or/1-3
5 abortion, spontaneous/ or abortion, habitual/
6 miscarr*.tw.
7 ((Spontaneous* or habitual* or recurrent*) adj4 abort*).tw.
8 ((Loss* or lose or lost) adj4 (pregnan* or fetus* or foetus* or baby or babies or child*)).tw.
9 Infertility, Female/ or Infertility/
10 Infertil*.tw.
11 or/5-10
12 Gynecologic Surgical Procedures/
13 Hysteroscopy/
14 (Hysteroscop* or hysteroplast* or metroplast* or uteroplast* or uteroscop* or septoplast* or resectoscop*).tw.
15 (Endoscop* adj4 (uter* or urogenital* or womb*)).tw.
16 or/12-15
17 4 and 11 and 16
18 Animals/ not Humans/
19 17 not 18