Hysteroscopic uterine septum resection. Does it improve live birth rate in primary unexplained infertility? A systematic review and meta-analysis

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ABSTRACT

Objective: To evaluate the effects of hysteroscopic uterine septum resection surgery in patients with primary unexplained infertility.

Design: Systematic review and meta-analysis

Objective: The aim of the study was to determine whether live birth rate improves in a cohort of patients with primary unexplained infertility undergoing hysteroscopic resection. Primary outcome was live birth rate. The patients with a uterine septum who underwent intervention were compared to women with primary unexplained infertility and uterine septum who refused the procedure and with women with primary unexplained infertility and no septum. Secondary outcomes include pregnancy rate and miscarriage rate.

Data sources: Electronic systematic search of the PubMed, EMBASE, Cochrane and Google Scholar databases was conducted from January 1994 to August 2019.

Methods of study selection: Two independent reviewers screened the studies and according to the inclusion and exclusion criteria, data was extracted and reviewed.

Integration and results: 18 studies were analysed involving 1,083 patients, including controls. Women with a history of primary and otherwise unexplained infertility had a live birth rate ranging between 11.1% and 92.85% after surgical intervention. The American Society for Reproductive Medicine (ASRM) classification, was the preferred classification system at present, however, will be possibly replaced by the recent European Society of Gynaecological Endoscopy/ European Society of Human Reproduction and Embryology (ESHRE/ESGE) classification system. Hysterosalpingogram (HSG) was the commonest diagnostic tool used to identify uterine anomalies, but is now being replaced by 3-dimensional (3D) ultrasound.

Conclusion: Women with primary unexplained infertility and a uterine septum have a statistically significantly higher live birth rate and pregnancy rate after hysteroscopic uterine septum resection.

KEYWORDS

Uterine septum, hysteroscopic resection, live birth rate, unexplained primary infertility.

Introduction

Congenital uterine anomalies are the result of abnormal müllerian (paramesonephric) duct development. Around 5.5% to 6.8% of women in the general population have some form of müllerian anomaly [1]. In the subfertile population, the prevalence is around 8%, and up to 24.5% when recurrent pregnancy loss is associated with infertility [1].

Different studies report different figures and this reflects the lack of standardization in the diagnosis and classification of uterine anomalies. In infertility patients, different studies are consistent in their results and agree that septate uterine defects are the commonest [1,2]. The ESHRE/ESGE classification system classifies a uterine septum as one in which fusion has occurred normally, however, the midline septum has been abnormally absorbed to different extents [3]. The ESHRE-ESGE classification defines septate uterus (class II or U2) as a "uterus with a normal outline and an internal indentation at the fundal midline exceeding 50% of the uterine wall thickness". The indentation caused by the septum can divide the uterus completely or partially [3]. The ASRM classification defines septate uterus (class V) as the depth from the interstitial line to the apex of the indentation to be more than 1.5 cm and the indentation angle of less than 900 [4].

The close association between the embryological development of the urological and genital system explains why patients

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who present with a congenital müllerian anomaly should be screened for concomitant kidney and ureteric anomalies and vice versa [5].

Published studies tend to group recurrent pregnancy loss patients and infertility patients with a uterine septum as one combined cohort of patients. However, the underlying pathophysiology differs in either population of women, and potentially even subsequent management.

This study aims to focus on how reproductive outcome in unexplained primary infertility patients with a uterine septum is altered with such a procedure. Unfortunately, no randomised controlled trials were included as such trials are non-existent in view of the ethical consequences that such experiments may hold. In addition, surgery adds extra health risks and costs and may delay fertility.

Materials and methods

Search strategy

A systematic search of published literature was conducted from the following databases: PubMed, EMBASE, Cochrane database and Google Scholar. A 25-year literature search was performed ranging from January 1994 till August 2019. An advanced search strategy was performed using terms "uterine septum" OR "metroplasty" AND "infertility". Results were limited to published, peer reviewed articles in full text and limited to humans. Other relevant articles were selected from the reference list of retrieved articles. Articles which were not English language based were included and translated to English. Retrieved articles were scanned by title and abstract and relevant articles were obtained in full text to assess eligibility for inclusion (Table 1).

Study selection

We included all cohort studies reporting the outcome of hysteroscopic resection of uterine septum in women with unexplained primary infertility with or without controls in women between 18 and 35 years of age. Supplementary Table 1 summaries the main demographic data collected, characteristics of the studies included and inclusion and exclusion criteria. Controls included patients with unexplained infertility with uterine septum who refused intervention or unexplained infertility patients without septum. Studies including patients with secondary infertility, recurrent miscarriages and infertility related to other pathology rather than uterine septum were excluded. Case reports and unpublished abstracts were also excluded. Studies were appraised and data collected in an unblinded fashion. When full text articles could not be retrieved the corresponding author was contacted. A reminder was sent after two and after four weeks if author failed to reply back. Two reviewers reviewed the literature and assessed the data and eligibility of the studies. Data collected included patients' demographics, study characteristics, details of surgical procedure, outcomes, diagnosis and follow up. In total, 18 articles [6-23] were selected including 1083 patients.

Primary and secondary outcomes

The primary outcome was the incidence of live birth rate in patients who underwent uterine septum resection. Secondary outcomes were pregnancy rate and incidence of miscarriage.

Risk of bias

The Scottish International Guideline Network (SIGN) methodology [24] checklist for studies was used as an objective tool to assess for bias within the individual studies as illustrated in supplementary Table 2. This process was done by an external reviewer.

Table 1 Inclusion and exclusion criteria for study selection.

	Inclusions	Exclusions
Participants	Women of reproductive age 18	Secondary infertility
	Unexplained primary infertility	Recurrent miscarriages
	Trial of COS/IUI/IVF/ICSI in a background of unexplained infertility	Infertility related to other pathology rather than uterine septum
	Cases – Patients with a uterine septum	Other forms of uterine anomalies other than uterine septum eg: arcuate uterus
Intervention	Comparison between hysteroscopic resection of uterine septum in women with unexplained infertility and controls. Controls included patients with unexplained infertility with uterine septum who refused intervention or unexplained infertility patients without septum.	Hysteroscopic resection of other uterine pathology then uterine septum
	Hysteroscopic resection	Abdominal resection of uterine septum
Types of Studies	Randomised controlled studies Prospective studies Retrospective studies	Case reports Unpublished abstracts Full text not available
Outcomes to be measured		
Primary outcome	Live birth rate	
Secondary outcomes	Pregnancy rate Miscarriage rate	

Supplementary Table 1 Describing the main characteristics and demographic data of the studies included.

Author and year	Study period	Country	Duration of Infertility (mean ± SD)	Inclusion Criteria	Exclusion Criteria	Type of Study	Number of Cases (N)	Age in Years mean ± SD (range)
Marabini *et al* 1994 [1]	Feb 1990 June 1993	Italy	N/S	Unexplained infertility	N/S	Retrospective Study	N = 9	33.2
Colacurci *et al* 1996 [2]	March 1990 Oct 1994	Italy	N/S	Primary unexplained infertility	N/S	Retrospective Study	N = 21	(24-32)
Saygili-Yilmaz *et al* 2002 [3]	1990-2000	Turkey	>2 yrs	Primary unexplained infertility	Endometriosis, PCO, unilateral or/ and bilateral tubal occlusion, hydrosalpinx and adhesion related to infertility, male factor infertility	Retrospective Study	N = 193	24
Venturoli *et al* 2002 [4]	Jan 1993 Dec 1997	Italy	>2 yrs. 4.1±2.9	Unexplained fertility x2 yrs, no endocrine disorders, at least 6 months of regular biphasic basal body temperature records, progesterone levels above 2mg/ml, patent fallopian tubes, partners with normal semen analysis	N/S	Retrospective Study	N = 69	30±4
Pabuccu *et al* 2004 [5]	1992-2001	Turkey	1-8 years	Septate uterus of variable length, <35 yrs, unexplained primary infertility	Age>35 yrs, endometriosis, abnormal endocrine analysis, abnormal semen analysis, STD detection, patent tubes	Prospective observational study	N = 61	(21-35)
Vahdat *et al* 2007 [6]	2003-2004	Iran	N/S	<35 yrs, primary unexplained infertility, idiopathic recurrent spontaneous abortion, BMI between 19-30	Abnormal TSH, FSH, prolactin, abnormal semen analysis, severe dysmenorrrhoea, dyspareunia, chronic pelvic pain, Ca125>35.	Descriptive Study	N = 13	(21-35) Total cohort
Mollo *et al* 2009 [7]	Nov 1997 Oct 2003	Italy	2.4±0.8 yrs	BMI between 18 - 28 Kg/ m^2, normogonadotrophic normoovulatory women, bilateral patent tubes, unexplained infertility, septate uterus	Diabetes, thyroid dysfunction, hypopituitarism, hyperprolactinaemia, luteal insufficiency, hyperandrogenism, positive auto-antibody screen, Chlamydia, Mycoplasma or Ureaplasma detection on cervical swabs, PCOS, Endometriosis, chromosomal abnormalities on karyotype	Prospective Controlled Study	N = 44 Cases N= 132 Controls unexplained infertility & no septum	29.7±3.2 (18-35)
Lin *et al* 2009 [8]	June 1998 April 2007	China	N/S	Unexplained primary infertility, complete uterocervical uterine septum	Uterine myoma, abnormal cervical smear test, previous delivery, abnormal semen analysis, other anomalies than complete uterocervical septum	Retrospective comparative single centre study	N = 9 Cases N = 7 Controls with uterine septum and not treated	27.7±4.6 cases, 28.1±5.9 controls
Pai *et al* 2009 [9]	N/S	India	N/S	Age between 18 and 35 yrs, septate uterus of variable length, primary unexplained infertility	>35 yrs, abnormal hormonal analysis, abnormal male semen analysis and STD detection, pelvic lesions on laparoscopy	Prospective observational study	N = 72 (8 lost to follow up)	(18 and 35)
Selvaraj *et al* 2010 [10]	Jan 2006 Dec 2008	India	N/S	<35 yrs of age, unexplained primary infertility	Myomas, endometriosis, PID, adhesions, > 35 years of age	Retrospective Study	N = 19	31.5±3.02

Author and year	Study period	Country	Duration of Infertility (mean ± SD)	Inclusion Criteria	Exclusion Criteria	Type of Study	Number of Cases (N)	Age in Years mean ± SD (range)
Ayas *et al* 2011 [11]	Jan 2005 Oct 2009	Turkey	4±2.9 yrs	Unexplained primary infertility	Medical conditions such as Diabetes, thyroid dysfunction, hypopituitarism, hyperprolactinaemia, luteal insufficiency, hyperandrogenism, abnormal semen analysis	Retrospective Study	N = 98	29.47±5.84
Paradisi *et al* 2011 [12]	Jan 1998 Dec 2007	Italy	3.2±2	No endocrine disorders, at least 6 months of regular biphasic basal body temperature records, progesterone level >4ng/ml in the mid-luteal phase, patent fallopian tubes, normal semen analysis and male endocrine parameters	N/S	Retrospective Comparative single centre study	N = 108	33±5 cases, 35±4 controls
Tonguc *et al* 2011 [13]	Jan 2006 Jan 2009	Turkey	5.6±2.1	Bilateral patent tubes on HSG, between 20 and 35 years of age, normal basal hormone profiles, vaginal and abdominal ultrasound showing no pathology apart from septum	History of tuberculosis or endometriosis, diabetes, thyroid disease, hyperandrogenaemia, PCOS, history of abdominal surgery, semen analysis with: volume <2ml, count <20 million per ml, motility <50%, normal shape in 30% of sperm.	Retrospective Study Comparative Study	N = 102 Controls = 25 Patients with uterine septum and infertility who refused surgery	24.4±3.3 (19-35)
Shokeir *et al* 2011 [14]	Jan 2002 Oct 2009	Egypt	3.4±1.4	Age 18-45 years, unexplained primary infertility >48 months, presence of uterine septum	Endometriosis, past history of spontaneous/induced abortions, contraindications to anaesthesia, patients unwilling to complete follow-up	Prospective Comparative Study	88	36±2.1 (25-43)
Bakas *et al* 2012 [15]	Jan 2004 Nov 2010	Greece	2.7±0.9 yrs	Primary infertility, age up to 35 years, regular menses, BMI between 19 and 30, normal TFT's, FSH<10Iu/l, normal prolactin, negative thrombophilia screen,	> 35 yrs old, evidence of endometriosis, severe dysmenorrhoea, internal dyspareunia, recurrent pelvic pain, Ca125>35 IU/ml, PCOS, male factor infertility	Observational Study	N = 68	31.2 +/-4.5
Haxhihyseni *et al* 2014 [16]	N/S	Albania	N/S	Primary unexplained infertility	>35 yrs of age, pelvic lesions, pathology other than uterine septum	Prospective Study	N = 28 (5 lost to follow up)	(18-35)
Bhat *et al* 2014 [17]	2010-2014	India	N/S	Primary (or secondary) unexplained infertility	Endometriosis, adhesions, PID, fibroids	Retrospective Study	N = 62	27+/-3.02
Karadag *et al* 2015 [18]	Jan 2007 Dec 2008	Turkey	39.9±32	<35 yrs old, uterine septum, patent tubes, unexplained primary (or secondary) infertility	Diabetes, thyroid dysfunction, hypopituitarism, hyperprolactinaemia, luteal insufficiency, hyperandrogenism, FSH >12, abnormal semen analysis	Retrospective Study	N = 27	26.2+/-5 Total cohort

***PCO:** Polycystic Ovaries, **STD:** Sexually Transmitted Diseases, **BMI:** Body Mass Index, **PCOS:** Polycystic Ovarian Syndrome, **PID:** Pelvic Inflammatory Disease, **N/S:** Not Specified.*

Supplementary Table 2 Risk of bias in individual study using the SIGN questionnaire for case-control and cohort studies.

Author and Year	Internal validity													
	Selection of Subjects						Assessment						Confounding	Statistical Analysis
	1.1 [I]	1.2 [II]	1.3 [II]	1.4 [III]	1.5 [IV]	1.6 [IV]	1.7 [V]	1.8 [V]	1.9 [V]	1.10 [V]	1.11 [V]	1.12 [V]	1.13 [VI]	1.14
Marabini 1994	No	N/A	N/R	N/A	7.5%	No	Yes	N/A	N/A	Yes	Yes	N/A	No	No
Colacurci 1996	Yes	No	N/R	Yes	N/R	N/A	Yes	No	No	Yes	Yes	Yes*	No	No
Saygili-Yilmaz 2002	Yes	No	N/R	Yes	N/R	N/A	Yes	N/A	N/A	Yes	Yes	Yes	Yes	No
Venturoli 2002	Yes	Yes	N/R	Yes	0%	N/A	Yes	No	N/A	Yes	Yes	N/R	Yes	No
Pabuccu 2004	Yes	N/A	N/R	Yes	N/R	N/A	Yes	N/A	N/A	Yes	Yes	Yes	Yes	No
Vahdat 2007	No	N/A	N/R	Yes	15.79% 36.8%∞	N/A	No	N/A	N/A	Yes	Yes	No	Yes	No
Lin 2009	Yes	No	N/R	Yes	4.76% 0%	No	Yes	N/A	No	Yes	Yes	No	Yes	Yes
Pai 2009	Yes	N/A	Yes	Yes	11.11%	N/A	Yes	N/A	N/A	Yes	Yes	Yes**	Yes	No
Mollo 2009	Yes	Yes	N/R	Yes	2.27% 2.27%	No	Yes	N/A	No	Yes	Yes	No	Yes	Yes
Ayas 2010	Yes	No	N/R	Yes	N/R	N/A	Yes	N/A	N/A	Yes	Yes	Yes***	Yes	Yes
Selvaraj 2010	Yes	No	N/R	Yes	N/R	N/A	Yes	N/A	N/A	Yes	Yes	N/A	Yes	No
Shokeir 2011	Yes	N/A	Yes	Yes	12.4%	N/A	Yes	N/A	N/A	Yes	Yes	N/R	Yes	Yes
Paradisi 2011	Yes	Yes	N/R	Yes	N/R	N/A	Yes	No	N/R	Yes	Yes	No	Yes	Yes
Tonguc 2011	Yes	Yes	N/R	Yes	N/R	N/A	Yes	No	N/R	Yes	Yes	Yes	Yes	Yes
Bakas 2012	Yes	N/A	N/R	Yes	4.4%	No	Yes	No	N/R	Yes	Yes	Yes	Yes	No
Haxhihyseni 2014	Yes	N/A	N/R	Yes	N/R	N/A	No	N/A	N/A	Yes	Yes	No	Yes	No
Bhat 2014	Yes	N/A	N/R	Yes	N/R	N/A	Yes	N/A	N/A	Yes	Yes	N/R	Yes	No
Karadag 2015	Yes	No	N/R	Yes	N/R	N/A	Yes	No	N/R	Yes	Yes	Yes	Yes	Yes

*Key: **N/A** – Not Applicable, **N/R** – Not Reported*
** Colacurci 1.12 – 2 of 69 participants required second surgery; **Pai 1.12 – 24% of participants required second surgery; ***Ayas 1.12- 4.97% of participants required second surgery; ∞ Vahdat 1.14 – 36.8% were not included as follow-up period was too short*
i) Question 1.1 assesses whether a study has a well-defined aim; ii) Questions 1.2 and 1.3 regard selection bias; iii) Question 1.4 relate performance bias; iv) Question 1.5 and 1.6 are about attrition bias; v) Questions 1.7 to 1.12 are related to the risk of detection bias; vi) Question 1.13 queries the possibility of confounding factors affecting the study; vii) Questions 2.1-2.3 are there to rate the quality of the study.

Statistical analysis

The statistical analysis was performed using the meta [25] and the metafor [26] packages of the R programming language [27]. Random-effects model was used. All the analyses were carried out using the RStudio integrated development environment [28]. Dichotomous variables were analysed by means of odds ratio (OR) for the case control studies and probabilities for the cohort studies All confidence intervals are 95% confidence intervals (CI). Significance level was set at a p-value of less than 0.05 and $I^{\circ 2}$ and chi-square was used to assess for heterogeneity.

Effects of intervention

Case-control studies

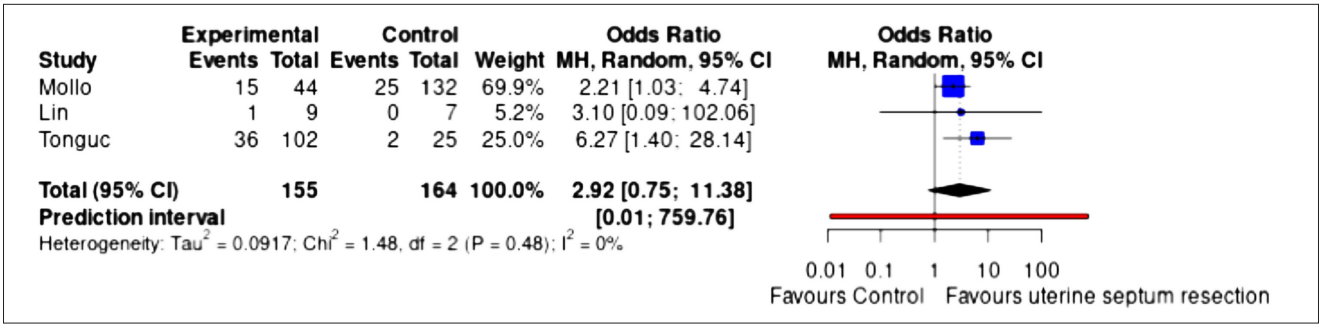
Cohort studies and case-control studies were analysed separately in view of their distinctive statistical nature. We had only three case-control studies and the results of their meta-analysis are summarised in the forest plots of Figure 1-3.

Figure 1 shows the analysis of the number of live births of the three studies. Two of the individual studies showed a significantly higher live birth rate in women with primary unexplained

infertility who underwent hysteroscopic uterine septum resection (Mollo, OR=2.21, 95% CI [1.03; 4.74], and Tonguc [17], OR=6.27, 95% CI [1.40; 28.14]) compared to controls (women with primary unexplained with or without a uterine septum who refused the intervention). The pooled effect was almost significant (OR=2.92, 95% CI [0.75; 11.38]). This was mainly due to the Lin *et al*.[13] study which had an OR of 3.10 but a very wide confidence interval. This study only had nine participants. The forest plot of Figure 2 summarises the case-control meta-analysis for pregnancy rates. Here, in spite of the Lin *et al*.[13] study, the pooled OR was significant (OR=2.7, 955 CI [1.60: 4.59]).

Forest plot 3 illustrates the analysis of the number of miscarriages in the case-control studies. The results show a controversial pattern. Two of the studies showed a higher incidence of miscarriage after uterine septum resection surgery in women with primary unexplained infertility who managed to get pregnant (Mollo, OR=3.1 CI [0.42-22.6]) and Lin, OR=3.10, CI [0.09-102.06]). These events were compared to controls who had a uterine septum and refused the intervention and controls with primary unexplained infertility and without a uterine septum. On the other hand, Tonguc *et al*.[23], revealed a lower rate of miscarriage after uterine septum resection surgery compared to controls (OR=0.38, CI [0.08-1.70]). However, Tonguc *et al*.[18], recruited 102 patients in the study in contrast to 53 patients in both Mollo

Figure 1 Meta-analysis of live birth rate in case-control studies (women who underwent uterine septum resection vs women with uterine septum and primary unexplained infertility who refused surgery or primary unexplained infertility and no uterine anomaly.



Supplementary Figure 1 Illustrating how studies were selected, following the PRISMA Flowchart.

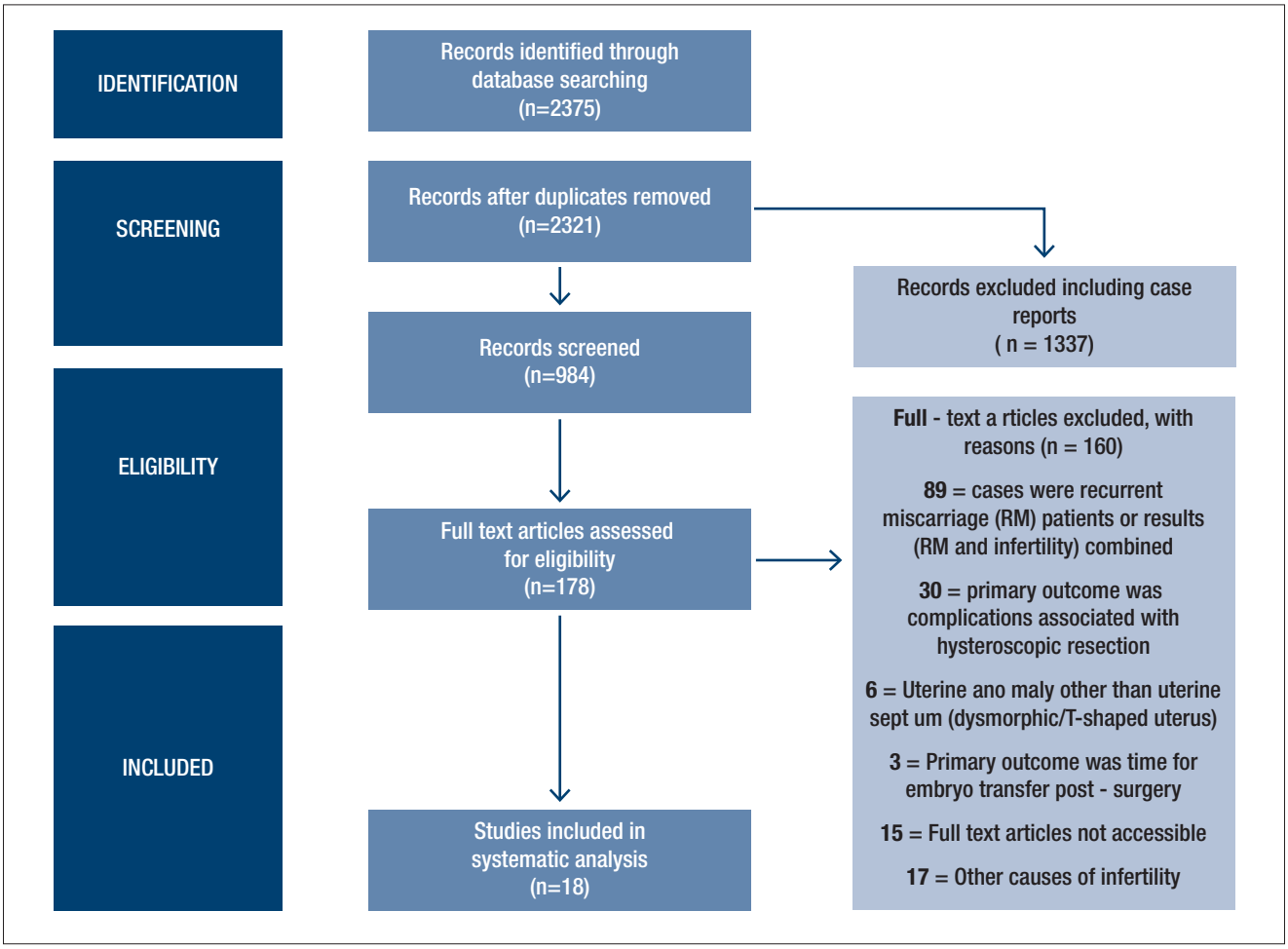


Figure 2 Meta-analysis of pregnancy rate in case-control studies (women who underwent uterine septum resection vs women with uterine septum and primary unexplained infertility who refused surgery or primary unexplained infertility and no uterine anomaly).

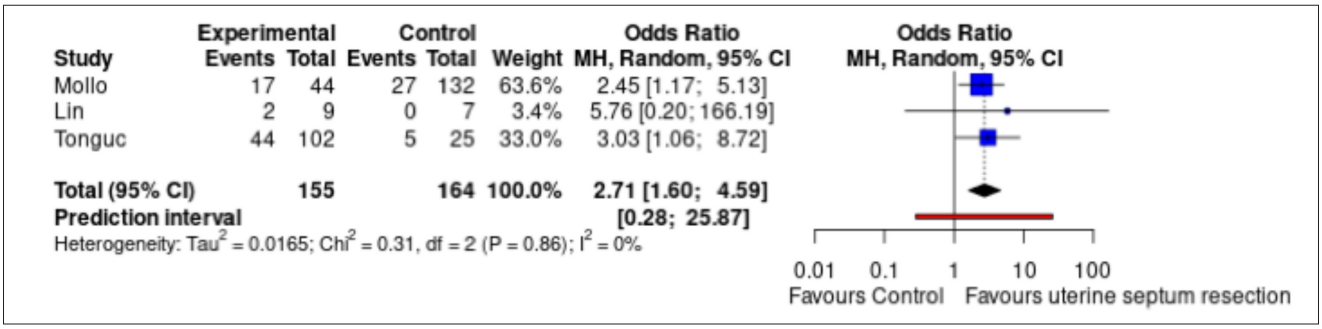


Figure 3 Meta-analysis of miscarriage rate in case-control studies (women who underwent uterine septum resection vs women with uterine septum and primary unexplained infertility who refused surgery or primary unexplained infertility and no uterine anomaly).

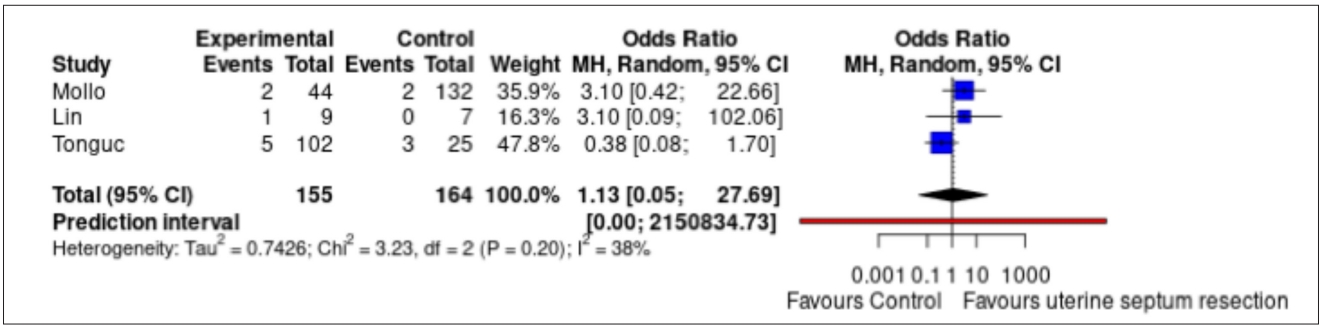
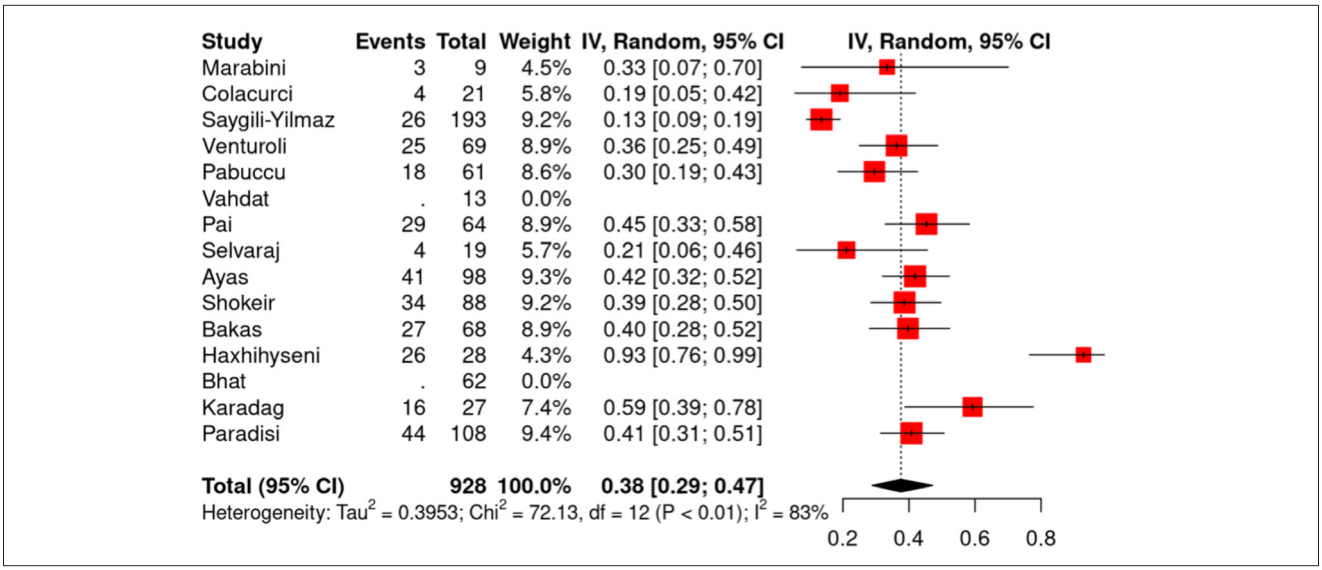


Figure 4 Meta-analysis of live birth rate in cohort studies (women who underwent uterine septum resection).



et al.[17] and Lin *et al*. studies[13]. This can be reflected in the wide confidence interval of the latter two studies. The pooled effect was hence, favouring a slightly increased risk of miscarriage. In all three studies the heterogeneity measured by $I^{\circ 2}$ and chi-square was low ($I^{\circ 2}$=0% for the first two and $I^{\circ 2}$=38% for the third one).

Cohort studies

We analysed fifteen cohort studies. The pooled live birth rate under the random effects model was 38% with a 95% CI equal to [0.29; 0.47], as shown in figure 4. These patients had no previous live births. The pooled live-birth rate for the three control groups in the case-control studies was 33%. The chi-square statistic and the value of $I^{\circ 2}$=83% indicate that the heterogeneity between the samples was high, confirming that a random effects model is very appropriate. In our analysis of the number of pregnancies of the cohort studies, the pooled pregnancy rate was 49% (95% CI [0.40; 0.59]), as shown in figure 5. The pooled pregnancy rate for the three control groups in the case-control studies was 39%. The studies were very heterogeneous with a value of 85% for $I^{\circ 2}$ and a very significant chi-square (p<0.59). In cohort studies the pooled miscarriage rate in women who underwent hysteroscopic uterine septum resection was 8% (95% CI [0.07; 0.10]), as shown in figure 6. The pooled miscarriage rate for the three case-control studies was 6%.

Figure 5 Meta-analysis of pregnancy rate in cohort studies (women who underwent uterine septum resection).

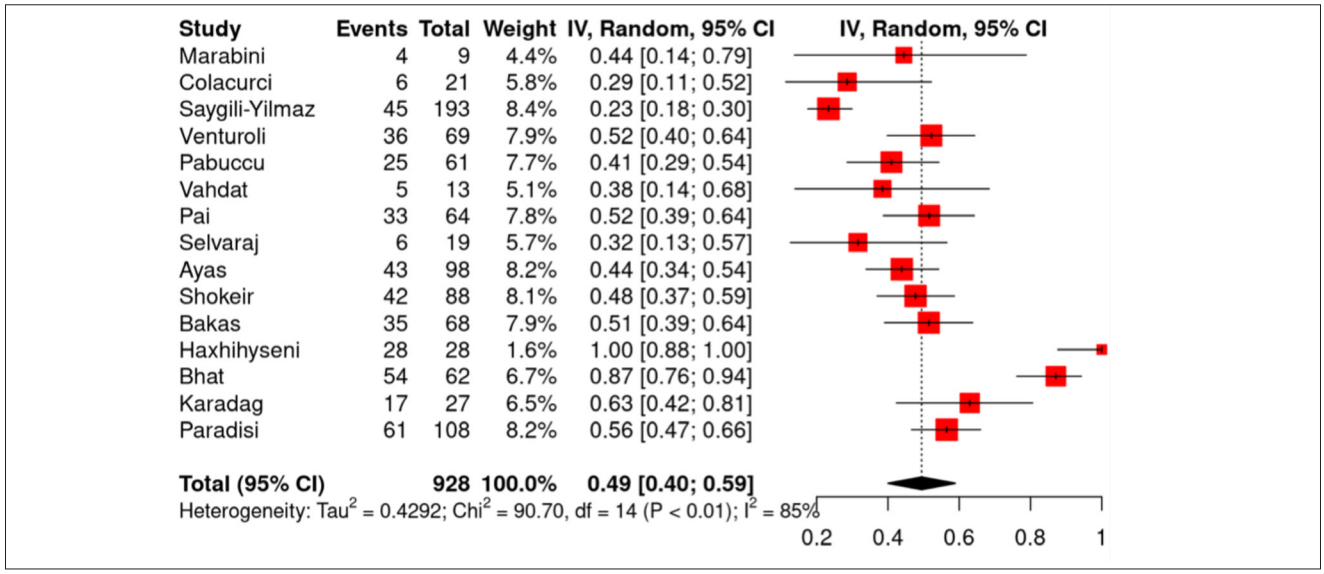
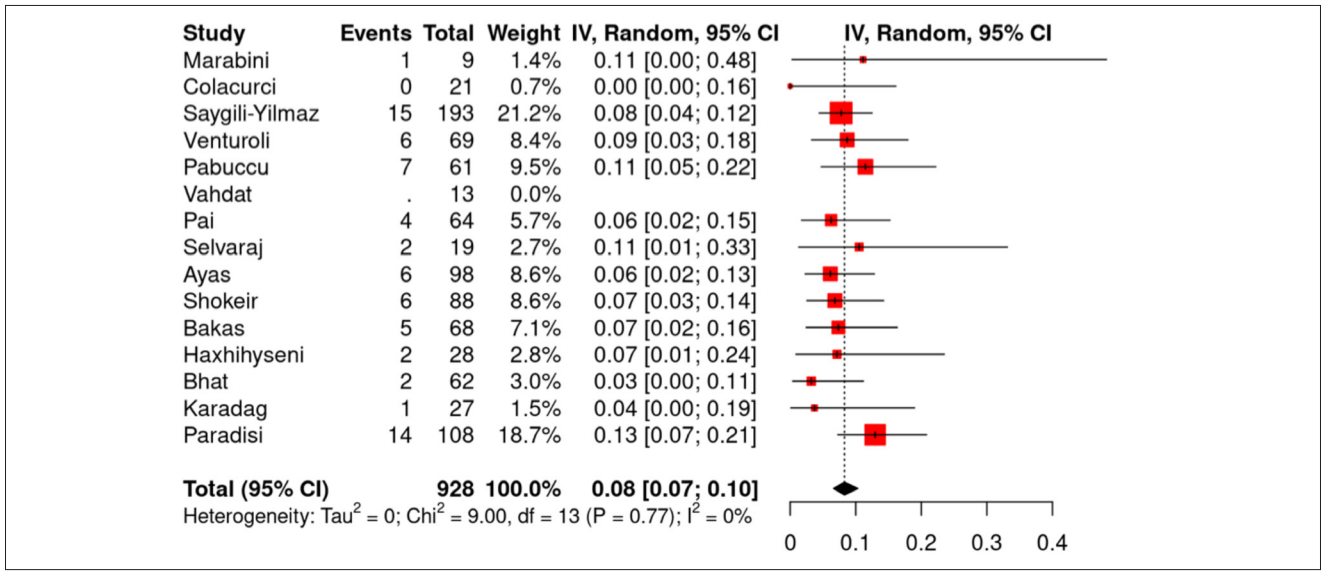


Figure 6 Meta-analysis of miscarriage rate in cohort studies (women who underwent uterine.



Discussion

Main findings – Live birth and pregnancy rate

This systematic review and meta-analysis of 18 studies concludes that hysteroscopic uterine septum resection in patients with primary unexplained infertility is beneficial in improving live birth rate and pregnancy rate. A trend of higher number of live births in the cohort of patient classified as cases compared to live birth in control groups, can be noted throughout the prospective comparative studies. These results indicate that live birth rate in patients with primary unexplained infertility is higher in those who underwent hysteroscopic uterine septum resection, not only when compared to patients who refused surgery, but also when compared to patients who underwent surgery but had a history of recurrent pregnancy loss [17]. Moreover, pregnancy rates achieved after hysteroscopic resection were statistically significant higher compared to controls who did not undergo surgery. Hence, underlining the negative consequences of a uterine septum on achieving a pregnancy and subsequently a live birth. Moreover, these results support the idea that resection of the septum results in an increase in fecundity rate, since live birth rate after septum resection was higher when compared to live birth rate in patients with unexplained primary infertility and normal uterine cavity [12].

Miscarriage rate was lower in a well powered study (n=102 cases) of Tonguc *et al.* [18], however, the results of the latter were diluted with two other studies consisting of a total of 51 cases and 141 controls. Moreover, the controls recruited by Mollo *et al.* [12], consisted of patients with primary unexplained infertility and no uterine septum. This may have added an additional confounding factor to the study. In contrast, Tonguc *et al.* [18], compared their cases to patients with a uterine septum and primary unexplained infertility who did not undergo surgery. Given the narrow confidence interval of the results of Tonguc [18] study, compared to the other Mollo [12] and Lin [13] study, it is closer to statistical significance than the other two [12,13] grouped together.

A uterine septum in a background of primary unexplained infertility might exert a different effect on fecundity compared to patients with adverse obstetric outcome such as recurrent miscarriages. It has been hypothesized that the endometrium lining the uterine septum is deficient of glandular ostia and has irregular non-ciliated cells with less microvilli, this is accompanied by defective ciliogenesis and reduced number of ciliated cells, rendering the endometrium less receptive to hormonal changes [29]. Moreover, the presence of a uterine septum may be associated with abnormal uterine contractions and this may hinder the passage of sperm within the female tract [29].

Conversely, the effect of hysteroscopic resection on pregnancy loss in patients with primary infertility is complex and controversial and current knowledge is based on retrospective studies. In the context of uterine septum and primary unexplained infertility, septum resection may result in a higher chance of pregnancy, however, the background risk of pregnancy loss may still remain high and this could be linked to the cause of their infertility affecting embryo quality and endometrial receptivity such as in endometriosis [30].

This hypothesis is challenged by results reported by Ozgur *et al*., (2007), [31] who claim that the miscarriage rate in patients who had a uterine septum resected followed by IVF, was 10.5% compared to 20.4 % in patients who had IVF for other reasons rather than a uterine septum. A similar study reported a 12.2% miscarriage rate in IVF patients who underwent hysteroscopic septoplasty and 12.9% in IVF patients with a normal endometrial cavity [32]. Theories explaining the relationship between the presence of uterine septum and pregnancy loss vary. One possible reason is that the septum is associated with reduced vascular supply hence hindering implantation of the blastocyst and if an embryo implants the process of decidualization may be affected [29]. Moreover, the uncoordinated uterine activity within the septum increases the risk of pregnancy loss [33].

Hence, our results show that pregnancy rate improves post uterine septum resection hence surgery improves implantation rate. However, uterine septum resection does not seem to alter the miscarriage rate. This effect dilutes the benefits of uterine septum resection, as the live birth rate achieved is diluted with a number of women who do get pregnant but end up experiencing a miscarriage.

Uterine septum classification

The majority of authors in the studies included in the review followed the ASRM classification [3] system, even though the studies were European, however, the ESHRE-ESGE classification [4] was only introduced in 2013. The ESHRE-ESGE criteria was developed to replace the morphometric criteria in the ASRM classification and achieve a more objective method of diagnosing a septate uterus based on clinical orientation and anatomy of the female genital tract with the main sub-classes reflecting this [4].

Diagnosis of a uterine septum

In the studies included in the review, HSG was the most common modality used to diagnose a uterine septum, followed by ultrasound and hysteroscopy. Possibly, HSG was one of the initial investigations performed in females who were trying to conceive, in order to assess for tubal patency and incidentally a uterine septum would be diagnosed.

The ASRM recommend the use of 3D ultrasound or magnetic resonance imaging (MRI) combined with hysteroscopy to diagnose uterine septa rather than combined hysteroscopy and laparoscopy [4].

Comparison with existing studies

A trend of positive outcome associated with uterine septum resection was reported in the majority of studies in the literature. In a meta-analysis of 29 studies, Valle and Ekpo (2013) [34], report a live birth rate of 50.2%, however, their cohort included also patients with recurrent pregnancy loss. In a retrospective study, analysing patients with primary infertility, a live birth rate of 40% was reported, however, this cohort included a number of endocrine disorders, tubal and male factor infertility [35].

Our review challenges earlier studies stating that patients with primary unexplained infertility with a uterine septum, have comparable reproductive outcomes to the general infertile population [2]. Moreover, Grimbizis *et al*. (1998), [2] argued that hysteroscopic metroplasty in unexplained primary infertility does not alter rate of conception but may increase the pregnancy outcome. Similarly, another study showed that hysteroscopic metroplasty in infertility patients does not increase the chances of pregnancy but once pregnancy occurs, the live birth rate improves when compared to controls [36]. To the contrary of our results, a prospective study by Pang *et al*. (2011), [37] demonstrated that amongst other measures of reproductive outcome, the difference in live birth rate after surgery, was not statistically significant when compared to controls who had conservative management [37].

In a study evaluating obstetric outcomes in patients with a history of primary and secondary infertility who underwent hysteroscopic septum resection, the miscarriage rate was 25% in patients with a history of early miscarriage and 16% in patients with a history of recurrent miscarriages [35]. Bendifallah *et al*., (2013) report no miscarriages in their group of primary infertility patients, and a significant drop in the miscarriage rate in women with a history of recurrent miscarriages or late abortions [38]. Grimbizis *et al*. (1998), report a miscarriage rate of 25% while Tehraninejad (2013), report a miscarriage rate of 12.3% in patients with primary infertility after hysteroscopic resection of uterine septum [2, 39]. However, in both studies, the patients included had other forms of infertility apart from a uterine septum. In contrast, a multicentre randomised control study published recently by Rikken *et al*., concluded that septum resection does not increase live birth rate or miscarriage rate [40]. Although infertility cohort of patients were stratified from recurrent pregnancy loss cohort of patients, the cohort of infertility patients included male factor and infertility secondary to pelvic pathology. The latter might have contributed to bias and introduced a number of confounding factors that may have altered the live birth rate. In view of our strict inclusion criteria, this randomised control study had to be excluded since infertility patients, had other factors rather than a uterine septum [40].

Till date, no randomised controlled trial has been published that can prove or refute the outcome of this procedure in unexplained primary infertility.

Strengths and limitations

Our review is unique as it solely focuses on women with a uterine septum and with a history of primary unexplained infertility, hence excluding confounding factors. This contrasts with previous reviews and studies, that combined women with recurrent pregnancy loss and infertility. Since the pathophysiology of a uterine septum differs in cases of infertility and recurrent pregnancy loss or preterm labour, we firmly believe that these cohort of patients cannot be combined together when studying the effect of such a septum on live birth rate. Selection bias was adjusted for by exclusion of studies that included identifiable causes for the infertility. Although the individual studies included a relatively small group of patients, the overall pooled sample size spanned over a 15-year period, yielding a large and representative cohort of patients.

Unfortunately, none of the included studies were randomised controlled studies and the majority were retrospective cohort studies. However, given it's a surgical intervention and a uterine septum is a relatively uncommon problem in unexplained infertility, prospective trials will take time for enough patients to be recruited as cases and controls. Lack of standardised definitions and diagnostic criteria of a uterine septum within the studies was a frequent encounter. In most studies included in the review, miscarriages were not clearly defined and moreover, not classified according to trimester. Information regarding septum size was universally lacking. Moreover, between 1994 and 2019, methods of diagnosis and interventions have changed as the field of hysteroscopic surgery continues to evolve. Hence, this could translate into better results secondary to advanced embryology techniques and equipment. Another limitation we encountered, was the combined cohort of controls including both patients with a uterine septum and unexplained infertility and patients with unexplained infertility and no uterine septum. The latter is a heterogenous group of patients and may have acted as a confounding factor.

Conclusion

In this review, hysteroscopic uterine septum resection, in this specific group of women improves the live birth rate and pregnancy rate compared to controls. The inferences of such results are specific to the primary unexplained infertility cohort of patients, which is unique to this review. A multi-centre prospective double-blind controlled trial, randomising patients to surgery or conservative management should be the gold standard. However, since we are dealing with a surgical treatment, trials can be difficult to arrange, both practically and ethically.

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