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Interventions for non-tubal ectopic pregnancy (Review)

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[Intervention Review]

Interventions for non-tubal ectopic pregnancy

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ABSTRACT

Background

Non-tubal ectopic pregnancy is the implantation of an embryo at a site lying outside the uterine cavity or fallopian tubes. Sites include a caesarean scar, the cornua uteri, the ovary, the cervix, and the abdomen. There has been an increasing trend in the occurrence of these rare conditions, especially caesarean scar pregnancy (CSP).

Objectives

To evaluate the clinical effectiveness and safety of surgery, medical treatment, and expectant management of non-tubal ectopic pregnancy in terms of fertility outcomes and complications.

Search methods

We searched the Cochrane Gynaecology and Fertility (CGF) Group Specialised Register of Controlled Trials, CENTRAL, MEDLINE, Embase, ClinicalTrials.gov, the World Health Organization (WHO) search portal and nine other databases to 12 December 2019. We handsearched reference lists of articles retrieved and contacted experts in the field to obtain additional data.

Selection criteria

We included randomized controlled trials (RCTs) published in all languages that examined the effects and safety of surgery, medical treatment, and expectant management of non-tubal ectopic pregnancy.

Data collection and analysis

We used Cochrane standard methodological procedures. Primary outcomes were treatment success and complications.

Main results

We included five RCTs with 303 women, all reporting Caesarean scar pregnancy. Two compared uterine arterial embolization (UAE) or uterine arterial chemoembolization (UACE) plus methotrexate (MTX) versus systemic MTX and subsequent dilation and suction curettage; one compared UACE plus MTX versus ultrasonography-guided local MTX injection; and two compared suction curettage under hysteroscopy versus suction curettage under ultrasonography after UAE/UACE.

The quality of evidence ranged from moderate to very low. The main limitations were imprecision (small sample sizes and very wide confidence intervals (CI) for most analyses), multiple comparisons with a small number of trials, and insufficient data available to assess heterogeneity.

UAE/UACE versus systemic MTX prior to suction curettage

Two studies reported this comparison. One compared UAE with systemic MTX and one compared UACE plus MTX versus systemic MTX, in both cases followed by a suction curettage.

We are uncertain whether UAE/UACE improved success rates after initial treatment (UAE: risk ratio (RR) 1.00, 95% CI 0.90 to 1.12; 1 RCT, 72 women; low-quality evidence; UACE: RR 0.87, 95% CI 0.54 to 1.38; 1 RCT, 28 women; low-quality evidence).

We are uncertain whether UAE/UACE reduced rates of complications (UAE: RR 0.47, 95% CI 0.13 to 1.75; 1 RCT, 72 women; low-quality evidence; UACE: RR 0.62, 95% CI 0.26 to 1.48; 1 RCT, 28 women; low-quality evidence).

We are uncertain whether UAE/UACE reduced adverse effects (UAE: RR 1.58, 95% CI 0.41 to 6.11; 1 RCT, 72 women; low-quality evidence; UACE: RR 1.16, 95% CI 0.32 to 4.24; 1 RCT, 28 women; low-quality evidence), and it was not obvious that the types of events had similar values to participants (e.g. fever versus vomiting).

Blood loss was lower in UAE/UACE groups than systemic MTX groups (UAE: mean difference (MD) −378.70 mL, 95% CI −401.43 to −355.97; 1 RCT, 72 women; moderate-quality evidence; UACE: MD −879.00 mL, 95% CI −1135.23 to -622.77; 1 RCT, 28 women; moderate-quality evidence).

Data were not available on time to normalize β-human chorionic gonadotropin (β-hCG).

UACE plus MTX versus ultrasonography-guided local MTX injection

We are uncertain whether UACE improved success rates after initial treatment (RR 0.95, 95% CI 0.56 to 1.60; 1 RCT, 45 women; very low-quality evidence).

Adverse effects: the study reported the same number of failed treatments in each arm (RR 0.88, 95% CI 0.40 to 1.92; 1 RCT, 45 women).

We are uncertain whether UACE shortened the time to normalize β-hCG (MD 1.50 days, 95% CI −3.16 to 6.16; 1 RCT, 45 women; very low-quality evidence).

Data were not available for complications.

Suction curettage under hysteroscopy versus under ultrasonography after UAE/UACE.

Two studies reported this comparison. One compared suction curettage under hysteroscopy versus under ultrasonography after UAE, and one compared these interventions after UACE.

We are uncertain whether suction curettage under hysteroscopy improved success rates after initial treatment (UAE: RR 0.91, 95% CI 0.81 to 1.03; 1 RCT, 66 women; very low-quality evidence; UACE: RR 1.02, 95% CI 0.96 to 1.09; 1 RCT, 92 women; low-quality evidence).

We are uncertain whether suction curettage under hysteroscopy reduced rates of complications (UAE: RR 4.00, 95% CI 0.47 to 33.91; 1 RCT, 66 women; very low-quality evidence; UACE: RR 0.18, 95% CI 0.01 to 3.72; 1 RCT, 92 women; low-quality evidence).

We are uncertain whether suction curettage under hysteroscopy reduced adverse effects (UAE: RR 3.09, 95% CI 0.12 to 78.70; 1 RCT, 66 women; very low-quality evidence; UACE: not estimable; 1 RCT, 92 women; very low-quality evidence).

We are uncertain whether suction curettage under hysteroscopy shortened the time to normalize β-hCG (UAE: MD 4.03 days, 95% CI −1.79 to 9.85; 1 RCT, 66 women; very low-quality evidence; UACE: MD 0.84 days, 95% CI −1.90 to 3.58; 1 RCT, 92 women; low-quality evidence).

Non-tubal ectopic pregnancy other than CSP

No studies reported on non-tubal ectopic pregnancies in locations other than on a caesarean scar.

Authors' conclusions

For Caesarean scar pregnancies (CSP) it is uncertain whether there is a difference in success rates, complications, or adverse events between UAE/UACE and administration of systemic MTX before suction curettage (low-quality evidence). Blood loss was lower if suction curettage is conducted after UAE/UACE than after administration of systemic MTX (moderate-quality evidence). It is uncertain whether there is a difference in treatment success rates, complications, adverse effects or time to normalize β-hCG between suction curettage under hysteroscopy and under ultrasonography (very low-quality evidence). There are no studies of non-tubal ectopic pregnancy other than CSP and RCTs for these types of pregnancy are unlikely.

PLAIN LANGUAGE SUMMARY

Interventions for non-tubal ectopic pregnancy

Review question

How effective and safe are surgery, medical treatment, and expectant management for non-tubal ectopic pregnancy?

Background

Non-tubal ectopic pregnancy is the implantation of an embryo outside the womb (uterus) or fallopian tubes (which connect the uterus to the ovaries). Sites include a caesarean scar formed as the healing of an incision in the uterus after caesarean section, the cornua uteri (where the uterus and fallopian tubes meet), the ovary, the cervix, and the abdomen. There has been an increase in the occurrence of these rare conditions, especially caesarean scar pregnancy (CSP). Ectopic pregnancy makes up 80% of maternal deaths that occur in the first trimester, of which non-tubal ectopic pregnancy deaths account for a higher rate than tubal pregnancy deaths. Early diagnosis and effective treatment are essential to reduce the immediate and delayed side effects, and to avoid significant maternal illness and death. Treatments include surgery (e.g. uterine arterial embolization (UAE; a tube delivers small particles that block the blood supply to the uterus), uterine arterial chemoembolization (UACE; a tube delivers small particles that block the blood supply to the uterus and chemotherapy), dilation and suction curettage (to remove the products of the pregnancy)); medical treatment (e.g. a medicine called methotrexate); or expectant management (wait to see if a miscarriage occurs naturally).

Study characteristics

Cochrane researchers found five clinical trials including 303 women. The evidence is current to December 2019.

Key results

Caesarean scar pregnancy

Two studies compared UAE/UACE with methotrexate (surgery) versus systemic (into a vein or muscle) methotrexate injection (medical treatment) following suction curettage. Evidence was insufficient for treatment success, complications, and side effects. Moderate-quality evidence showed that blood loss from the treatment in the surgery group was lower than in the medical treatment group.There were no data for time for β-hCG levels to return to normal.

One study compared UAE with local (into uterine artery) methotrexate injection (surgery) versus ultrasound-guided local methotrexate injection (medical treatment). Evidence was insufficient for treatment success and time for β-hCG levels to return to normal. The study reported the same number of failed treatments in each arm There were no data for complications or other side effects.

Two studies compared suction curettage under hysteroscopy (insertion of a narrow telescope with a light and camera at the end into the uterus) versus suction curettage under ultrasound after UAE/UACE with methotrexate. Evidence was insufficient for treatment success, complications, side effects, and time for β-hCG levels to return to normal.

Non-tubal ectopic pregnancies other than caesarean scar pregnancy

No studies reported on non-tubal ectopic pregnancies in locations other than on a caesarean scar.

Quality of the evidence

The quality of evidence ranged from moderate to very low. The main limitations were small numbers of participants and trials, very wide range of results for most comparisons, and insufficient data to assess differences.

SUMMARY OF FINDINGS

Summary of findings 1. UAE/UACE compared with systemic MTX for CSP

UAE/UACE compared with systemic MTX for CSP[a]

Patient or population: women with CSP

Settings: department of gynaecology in China

Intervention: UAE/UACE (surgery)

Comparison: systemic MTX (medical treatment)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Systemic MTX	UAE/UACE				
Treatment success after initial treatment **UAE vs systemic MTX** Follow-up: 6 months	**943 per 1000**	**943 per 1000** (849 to 1056)	**RR 1.00** (0.90 to 1.12)	72 (1)	⊕⊕⊖⊖ **Low** [b,c]	Defined as an decline of serum β-hCG to undetectable levels by the initial treatment.
UACE plus MTX vs systemic MTX Follow-up: 6 months	**769 per 1000**	**669 per 1000** (415 to 1062)	**RR 0.87** (0.54 to 1.38)	28 (1)	⊕⊕⊖⊖ **Low** [b,c]	
Complications **UAE vs systemic MTX** Follow-up: 6 months	**171 per 1000**	**80 per 1000** (22 to 299)	**RR 0.47** (0.13 to 1.75)	72 (1)	⊕⊕⊖⊖ **Low** [b,c]	Complications including heavy bleeding, recurrence of active bleeding, and hysterectomy.
UACE plus MTX vs systemic MTX Follow-up: 6 months	**538 per 1000**	**334 per 1000** (140 to 796)	**RR 0.62** (0.26 to 1.48)	28 (1)	⊕⊕⊖⊖ **Low** [b,c]	
Adverse effects **UAE vs systemic MTX**	**86 per 1000**	**136 per 1000** (35 to 525)	**RR 1.58** (0.41 to 6.11)	72 (1)	⊕⊕⊖⊖ **Low** [b,c]	Adverse effects in the MTX group included abnormal liver function and severe vomiting; in the UAE group in-

Follow-up: 6 months **UACE plus MTX vs systemic MTX** Follow-up: 6 months	**231 per 1000**	**268 per 1000** (74 to 979)	**RR 1.16** (0.32 to 4.24)	28 (1)	⊕⊕⊖⊖ **Low** [a,b]	cluded fever and pain and 1 readmitted woman. Adverse effects included mild increase in liver enzymes, mild vomiting, and moderate abdominal or pelvic pain.
Blood loss **UAE vs systemic MTX** Follow-up: 6 months	The mean blood loss in the control group was 415.63 mL	The blood loss in the intervention groups was 378.70 mL lower (–401.43 to –355.97)	—	72 (1)	⊕⊕⊕⊖ **Moderate** [c]	Blood loss was measured using the total volume of fluid in the bottle of the vacuum aspiration equipment after suction curettage minus the volume of amniotic fluid as assessed by ultrasonography at diagnosis.
UACE plus MTX vs systemic MTX Follow-up: 6 months	The mean blood loss in the control group was 471 mL	The mean blood loss in the intervention groups was 879.00 mL lower (–1135.23 to -622.77)	—	28 (1)	⊕⊕⊕⊖ **Moderate** [c]	
Time to normalize β-hCG	Not reported					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

β-hCG: β-human chorionic gonadotropin;**CI:** confidence interval; **CSP:** caesarean scar pregnancy; **MTX:** methotrexate; **RR:** risk ratio; **UACE:** uterine arterial chemoembolization; **UAE:** uterine arterial embolization.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]All the treatments were followed by suction curettage.
[b]Downgraded one level for imprecision (very small sample sizes and no clinically meaningful difference between groups).
[c]Downgraded one level, no data available to assess heterogeneity.

Summary of findings 2. Suction curettage under hysteroscopy compared with under ultrasonography for CSP

Suction curettage **under hysteroscopy compared with under ultrasonography for CSP**
Patient or population: women with CSP

Settings: department of gynaecology in China

Intervention: Suction curettage under hysteroscopy

Comparison: Suction curettage under ultrasonography

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Under ultrasonography	Under hysteroscopy				
Treatment success after initial treatment after UAE Follow-up: > 12 months	**1000 per 1000**	**910 per 1000** (810 to 1030)	**RR 0.91** (0.81 to 1.03)	66 (1)	⊕⊖⊖⊖ **Very low** [a,b,c]	Defined as an decline of serum β-hCG to undetectable levels by the initial treatment.
after UACE Follow-up: 2 months	**977 per 1000**	**997 per 1000** (938 to 1065)	**RR 1.02** (0.96 to 1.09)	92 (1)	⊕⊕⊖⊖ **Low** [a,b]	
Complications after UAE Follow-up: > 12 months	**30 per 1000**	**120 per 1000** (14 to 1017)	**RR 4.00** (0.47 to 33.91)	66 (1)	⊕⊖⊖⊖ **Very low** [a,b,c]	Complications in this study including recurrence of active bleeding, pelvic infection and hysterectomy.
after UACE Follow-up: 2 months	**45 per 1000**	**81 per 1000** (0 to 167)	**RR** 0.18 (0.01 to 3.72)	92 (1)	⊕⊕⊖⊖ **Low** [a,b]	Complications in this study including heavy bleeding, uterine perforation, pelvic infection, incomplete abortion and uterine adhesion.
Adverse effects after UAE Follow-up: > 12 months	See comment	See comment	**RR 3.09** (0.12 to 78.70)	66 (1)	⊕⊖⊖⊖ **Very low** [a,b,c]	Adverse effects in this study including chest congestion, and on 1 experienced it in the control group.
after UACE Follow-up: 2 months	See comment	See comment	Not estimable	92 (1)	⊕⊖⊖⊖ **Very low** [a,b,d]	Adverse effects in this study including low fever (37.3–38.5 °C) and abdominal pain, and all the participants had these adverse effects.
Blood loss	Not reported					
Time to normalize β-hCG after UAE	The mean time to normalize β-hCG in	The time in the intervention groups was 4.03 longer	—	66 (1)	⊕⊖⊖⊖ **Very low** [a,b,c]	—

Follow-up: > 12 months **after UACE** Follow-up: 2 months	the control groups was 30.15 days	(–1.79 to 9.85)				
	The mean time to normalize β-hCG in the control groups was 17.64 days	The time in the intervention groups was 0.84 days longer (–1.90 to 3.58)	—	92 (1)	⊕⊕⊖⊖ **Low** [a,b]	—

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

β-hCG: β-human chorionic gonadotropin;**CI:** confidence interval; **CSP:** caesarean scar pregnancy; **MTX:** methotrexate; **RR:** risk ratio; **UACE:** uterine arterial chemoembolization; **UAE:** uterine arterial embolization.

GRADE Working Group grades of evidence
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded one level for imprecision (very small sample sizes and no clinically meaningful difference between groups).
[b]Downgraded one level, no data available to assess heterogeneity.
[c]Downgraded one level for limitations in the design and implementation of available studies.
[d]Downgraded one level for publication bias (did not cover all the effects).

BACKGROUND

Description of the condition

Non-tubal ectopic pregnancy is the implantation of an embryo at a site lying outside the uterine cavity or fallopian tubes. Sites include a caesarean scar, the cornua uteri, the ovary, the cervix, and the abdomen. There has been an increasing trend in the occurrence of these rare conditions, especially caesarean scar pregnancy (CSP), which poses a diagnostic and treatment challenge for clinicians (Ngu 2011; Petersen 2016). The incidence of non-tubal ectopic pregnancy is estimated at 5.0% to 8.3% of all ectopic pregnancies, while the incidence of ectopic pregnancy is estimated at about 1% to 2% of all pregnancies (Bouyer 2002; Stucki 2008; Jurkovic 2011; Ngu 2011; Shan 2014; Yao 2005). Although relatively uncommon, these conditions are responsible for serious immediate and delayed complications (Bouyer 2002; Stucki 2008), with significant haemorrhages and a high rate of maternal fatality (Lewis 2007; Stucki 2008; Barnhart 2009; Orazulike 2013). Ectopic pregnancy makes up 80% of maternal deaths that occur in the first trimester, of which non-tubal ectopic pregnancy deaths account for a higher rate than tubal pregnancy deaths (Stucki 2008; Jurkovic 2011). Thus, it is important to recognize that the implantation site of ectopic pregnancy affects the severity of the condition (Bouyer 2002; Kirk 2014), and early diagnosis and effective treatment are essential to reduce the immediate and delayed adverse effects, and to avoid significant maternal morbidity and mortality.

CSP has increased because of the increased rate of caesarean sections performed (Maymon 2004; Seow 2004; Shen 2012; Gibbons 2012), and may account for up to 6.1% of all ectopic pregnancies in women with a history of at least one caesarean section (Seow 2004). The criteria for ultrasonography diagnosis include: (i) no fetal parts observed in the uterine cavity or cervical canal; (ii) a gestational sac located in the anterior part of the isthmic portion separated from the endometrial cavity or fallopian tube; (iii) a gestational sac embedded within the myometrium and the fibrous tissue of the caesarean section scar with diminished healthy myometrium between the bladder and the sac; and (iv) high velocity with low impedance blood flow surrounding the gestation sac (Jurkovic 2003; Pascual 2007; Seow 2004). CSP typing according to direction of growth of the gestational sac and thickness of the myometrium between the bladder and gestational sac has been proposed, and three types (I, II, and III) were divided as different ultrasonic manifestations (Yuan 2010).

Ovarian pregnancy accounts for 1% to 6% of all ectopic pregnancies (Bouyer 2002; Comstock 2005; Tinelli 2008; Goyal 2014; Melcer 2015). Ovarian pregnancy is often confused with corpus luteum cysts. Ultrasonography examination is routinely required and laparoscopy often plays a key role in diagnosis, with confirmation by pathological examination of removed tissue. The criteria are as follows: (i) empty uterine cavity; (ii) tubes entirely intact, separated from the ovary; (iii) a gestational sac located at the normal position of the ovary; (iv) ovary and a gestational sac connected to the uterus by the ovarian ligament; and (v) trophoblastic tissue attached to the ovarian cortex in the tissue specimen (Nadarajah 2002; Comstock 2005). However, the new 'Green top' guideline summarizes that there are no agreed ultrasonography criteria for the diagnosis of ovarian pregnancy (Elson 2016).

Cornual pregnancy has a prevalence of 1.7% to 2.1% of all ectopic pregnancies (Stucki 2008; Shan 2014; Nadi 2017). The term cornual pregnancy is often used interchangeably in the literature with interstitial pregnancy, but it actually refers to a pregnancy located in the interstitial portion of a unicornuate or bicornuate uterus (Tulandi 2004; Chetty 2009). The diagnosis can be made by the following ultrasonography criteria: (i) a single interstitial portion of a fallopian tube in the main uterine body; (ii) a mobile gestational sac surrounded by myometrium but separated from the uterus; and (iii) a vascular pedicle adjoining the gestational sac to the unicornuate uterus (Jurkovic 2007; Levine 2007).

Cervical pregnancy is a rare form of ectopic pregnancy with an estimated frequency of less than 1% of all ectopic pregnancies (Chetty 2009; Faschingbauer 2011; Anev 2013). Cervical pregnancy can be diagnosed by the following ultrasonography presentations: (i) empty uterine cavity; (ii) dilated or barrel-shaped cervix; (iii) a gestational sac within the mucosa located in the endocervical canal; and (iv) a sliding sac sign (Jurkovic 1996; Kirk 2014).

Abdominal pregnancy is one of the rarest forms of ectopic gestation and occurs in 0.3% to 1.4% of all ectopic pregnancies (Bouyer 2002; Molinaro 2007; Stucki 2008; Goyal 2014; Shan 2014). It refers to a gestational sac implanted in the omentum, abdominal vital organs, or large vessels, and is described as either primary or secondary. A primary abdominal pregnancy is due to a failure of the fimbria to pick up the ovulated follicle, while a secondary abdominal pregnancy is believed to follow early rupture or abortion of a tubal pregnancy or uterine perforation of a intrauterine pregnancy into the peritoneal cavity. The following criteria have been suggested to diagnose abdominal pregnancy: (i) empty uterine cavity; (ii) absence of a dilated fallopian tube and a complex adnexal mass; (iii) absence of myometrial tissue between the bladder and pregnancy; (iv) a gestational sac surrounded by intestinal tissue and separated by the peritoneum; and (v) a free mobility similar to fluctuation of the sac (Varma 2003; Gerli 2004; Onan 2005; Kirk 2014).

See Table 1.

Description of the intervention

The diagnosis of, and treatment for, non-tubal ectopic pregnancy are challenging and frequently constitute a medical emergency. Thus, prompt and effective treatment is important to avoid potentially catastrophic consequences such as massive haemorrhaging, hysterectomy, and death. The improved ultrasonography technology widely used in early pregnancy assessment and high awareness of the possibility of ectopic pregnancy have contributed to earlier diagnosis of these pregnancies. This has led to advances in their management, aiming to limit morbidity and to preserve the uterus and subsequent fertility (Molinaro 2007). Treatments include surgery, medical treatment, and expectant management. Although many treatment options have been recommended, the optimal treatment is yet to be clarified.

Surgery is the primary treatment for most ovarian, cornual, and abdominal pregnancies (Ngu 2011; Shan 2014). Management of ovarian pregnancy usually requires ovariectomy or ovarian wedge resection. Ovarian wedge resection may be considered by women with future fertility in mind, whereas ovariectomy is limited to cases of advanced gestation (Einenkel 2000; Goyal 2014). cornual pregnancy has traditionally been treated using cornual resection or hysterectomy in the cases with severely damaged uteri (Molinaro 2007). The surgery can be completed through laparoscopy or

laparotomy, but laparotomy may be required for women with uterine rupture and haemoperitoneum (Tulandi 2004). Surgical management with ligation of the placental blood supply and removal of some early abdominal pregnancies implanted on a less vascular surface can be managed by laparoscopy (Molinaro 2007); in advanced pregnancies, selective arterial embolization is necessary before surgery to avoid haemorrhage (Rahaman 2004). For cervical and caesarean scar pregnancies, laparotomy and hysterectomy may be required for more advanced pregnancies (Hsieh 1998; Jin 2004; Fuchs 2015; Alammari 2017). Surgery is often performed as a life-saving emergency measure for women with massive active bleeding or failed conservative treatment.

Improvements in the early detection of these conditions, before rupture, have led to the utilization of possible conservative treatment options. For women who desire fertility preservation, conservative measures have become the first-line approach. These options include administration (local or systemic) of various chemotherapeutic agents (including methotrexate (MTX), etoposide, actinomycin D, and cyclophosphamide) and endoscopic removal techniques (laparoscopy or hysteroscopy), alone or as adjuvant therapies, with or without haemostatic techniques (balloon tamponade, uterine artery ligation, cerclage, and cervical stay sutures). With cervical pregnancies before 12 weeks' gestation where the women have lower serum β-human chorionic gonadotropin (β-hCG) levels and no fetal cardiac activity, it may seem reasonable to administer conservative treatment (Molinaro 2007). Systemic MTX administration is a common approach to cervical pregnancy and has high efficacy, but it may be associated with increased risk of primary failure for pregnancies greater than nine weeks' gestation, with β-hCG levels above 10,000 mIU/mL, crown–rump length greater than 10 mm, and fetal cardiac activity (Hung 1998). Suction curettage with balloon tamponade or uterine arterial embolization (UAE) may be a choice for first trimester cervical pregnancy (Fylstra 2014; Hu 2016). Local or systemic injection of chemotherapy has met with various degrees of success for treatment of CSP (Marchiole 2004; Graesslin 2005; Jabeen 2018). Advances in UAE have enabled a minimally invasive approach in these women (Yu 2009; Lian 2012; Shen 2012; Zhang 2012; Zhu 2016). Dilation and suction curettage can be used after chemotherapy but should not be the first-line approach in cervical and CSP because of the risk of perforation and catastrophic haemorrhage (Lee 1999). Medical management with MTX has been reported for ovarian pregnancy but may not be practical (Molinaro 2007). Conservative measures may be attempted for selective cornual pregnancies but carry a high risk of initial failure (Bernstein 2001; Molinaro 2007). However, Horne and colleagues reported five successful cases with gefitinib plus MTX (Horne 2014). Systemic MTX chemotherapy and ultrasonography-guided injection of potassium chloride for management of early abdominal pregnancies has been reported (Mitra 2003).

Expectant management does not seem to be an appropriate choice for most cases and may be only suitable for women with declining β-hCG levels and absence of fetal cardiac activity (Chetty 2009; Timor-Tritsch 2015; Jabeen 2018). However, women should be closely monitored in case the lesion ruptures or the situation deteriorates.

How the intervention might work

Although surgery is not a routine method of diagnosis, due to improvements in the early ultrasonography diagnosis of these challenging pregnancies, it remains the main treatment option for ectopic pregnancy. Laparoscopy has been recommended in preference to laparotomy in clinically stable women because of shorter operating time, reduced recovery time, lower blood loss, and shorter duration of hospitalizations (Seinera 1997; Einenkel 2000; Shaw 2007). However, laparotomy is preferable to laparoscopy in women who have had heavy abdominal haemorrhaging and who have to undergo immediate haemostasis (Jurkovic 2011). Conservative surgery (preservation of uterus or ovary) to remove only the products of gestation or a part of the ovary is more desirable, especially for women who wish to preserve their fertility. Hysterectomy or ovariectomy is a radical modality used for urgent blood control or in women at an advanced gestational age and following misdiagnosis and failed conservative treatment or with severely damaged uteri (Ushakov 1997; Molinaro 2007; Chetty 2009).

Suction curettage can serve to extract the products of gestation and achieve haemostasis, used either as a single treatment or as an adjuvant therapy (Jurkovic 2003; Marchiole 2004).

Systemic and local administration of drugs is considered a safe and effective treatment. MTX is the most widely used chemotherapy drug, and, combined with folic acid, it is similar to treatment of gestational trophoblastic disease (Ory 1986; Sauer 1987; Liang 2010).

UAE involves blocking the arteries using gelatin beads or other materials (Shen 2012). It has been used as an adjuvant therapy to prevent excessive haemorrhage before uterine surgery or curettage procedures (Frates 1994; Honey 1999; Trambert 2005). Bilateral uterine arterial chemoembolization (UACE) is a combination of arterial embolization and local administration of chemotherapy. During the procedure, MTX is delivered directly into the gestational foci via the bilateral uterine arteries, which provide the blood supply. Then occlusive agents are injected into the delivery catheter to block the blood vessels. The procedure uses both chemotherapy and tissue ischaemia and thus uses a higher concentration of MTX leading to more effective embryocide, with fewer systemic toxic effects and reduced haemorrhage. As a minimally invasive treatment, it has been considered as a conservative method for treating CSP (Zhang 2009; Liang 2010; Li 2011a; Litwicka 2011; Lian 2012; Shen 2012).

Why it is important to do this review

To date, there has been no systematic review presenting evidence from randomized controlled trials (RCTs) to show the optimal management of non-tubal ectopic pregnancy. The optimal treatment, treatment success rate, and complications are largely unknown. In this review, we evaluated the clinical effectiveness and safety of surgery, medical treatment, and expectant management of non-tubal ectopic pregnancy in terms of primary treatment success and preservation of the uterus and future fertility, and collated the best evidence on interventions for non-tubal ectopic pregnancy.

OBJECTIVES

To evaluate the clinical effectiveness and safety of surgery, medical treatment, and expectant management of non-tubal ectopic pregnancy in terms of fertility outcomes and complications.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs that compared one treatment with another in the management of non-tubal ectopic pregnancy, in all languages. The allocation to either treatment was by random allocation. We excluded quasi-RCTs from this review.

Types of participants

Women of childbearing age with a diagnosis of caesarean scar, abdominal, cornual, cervical, or ovarian pregnancy. All these types of pregnancy were analyzed both separately and together.

Types of interventions

We made comparisons of surgery or medical treatment versus expectant management, and surgery versus medical treatment, subgrouped by location of pregnancy and specific type of intervention.

Surgery

- Laparoscopic removal
- Hysteroscopic evacuation
- Dilation and curettage
- Sac aspiration by suction, also called suction curettage
- Selective uterine arterial embolization
- Open surgery

Medical treatment

- Systemic MTX
- Local MTX
- Local embryocides (potassium chloride, sodium chloride, hyperosmolar glucose, or crystalline trichosanthin under ultrasonography guidance)

Expectant management

- No therapeutic intervention, only serum β-hCG monitoring

Types of outcome measures

Primary outcomes

- Treatment success (success after initial treatment) - defined as an uneventful decline of serum hCG to undetectable levels by the initial treatment. Also defined as 'a steady decline in serum β-hCG to normal levels by the initial treatment, coupled with a lack of major complications (including massive acute bleeding, recurrence of active bleeding, incomplete abortion and hysterectomy)'.
- Complications (need for further treatment for reasons such as heavy bleeding, recurrence of active bleeding, pelvic infection, organ injury, hysterectomy, or death).

Secondary outcomes

- Quality of life. If studies reported more than one scale, preference was given to the 36-item Short Form (SF-36), then other validated generic scales, and finally condition-specific scales.
- Adverse effects (blood loss, fever, nausea and vomiting, stomatitis, alopecia, pneumonitis, abdominal or pelvic pain, leukopenia, and abnormal liver or renal function).
- Time to normalize β-hCG.
- Hospital stay.
- Financial costs.
- Future fertility (restoration of normal menstrual cycles, repeat ectopic pregnancy).

Search methods for identification of studies

We developed a comprehensive search strategy for all published and unpublished RCTs of interventions for non-tubal ectopic pregnancy in consultation with the Information Specialist of the Cochrane Gynaecology and Fertility (CGF) Group. Two review authors (YL and HZ) independently conducted the systematic searches regardless of language or publication status.

Electronic searches

We searched the following databases:

- Cochrane CGF Group Specialised Register of Controlled Trials, PROCITE platform (searched December 2019; Appendix 1);
- CENTRAL, via the Cochrane Register of Studies Online (CRSO), Web platform (searched December 2019; Appendix 2);
- MEDLINE, Ovid platform (searched from 1946 to December 2019; Appendix 3);
- Embase, Ovid platform (searched from 1980 to December 2019; Appendix 4);
- PsycINFO, Ovid platform (searched from 1806 to December 2019; Appendix 5);
- CINAHL, Ebsco platform (searched from 1961 to December 2019; Appendix 6);
- Chinese Biomedicine DISC (CBM), Web platform (searched from 1978 to December 2019; Appendix 7).

Other electronic sources of trials included:

- the Cochrane Library – Database of Abstracts of Reviews of Effects (reference lists from non-Cochrane reviews on similar topics; www.cochrane.org/index.htm);
- ClinicalTrials.gov (a service of the US National Institutes of Health; www.clinicaltrials.gov);
- World Health Organization International Trials Registry Platform search portal (apps.who.int/trialsearch/);
- Citation Indexes (scientific.thomson.com/products/sci/);
- Conference abstracts in the Web of Knowledge (wokinfo.com/);
- LILACS database for trials from the Portuguese and Spanish-speaking world (pesquisa.bvsalud.org/portal/);
- PubMed (www.ncbi.nlm.nih.gov/pubmed/) and Google for recent trials not yet indexed in the major databases;
- OpenGrey database (opengrey.eu/) and Google for grey literature.

Searching other resources

We handsearched reference lists of articles retrieved by the search and contacted experts in the field to obtain additional data. We also handsearched relevant journals and conference abstracts that are

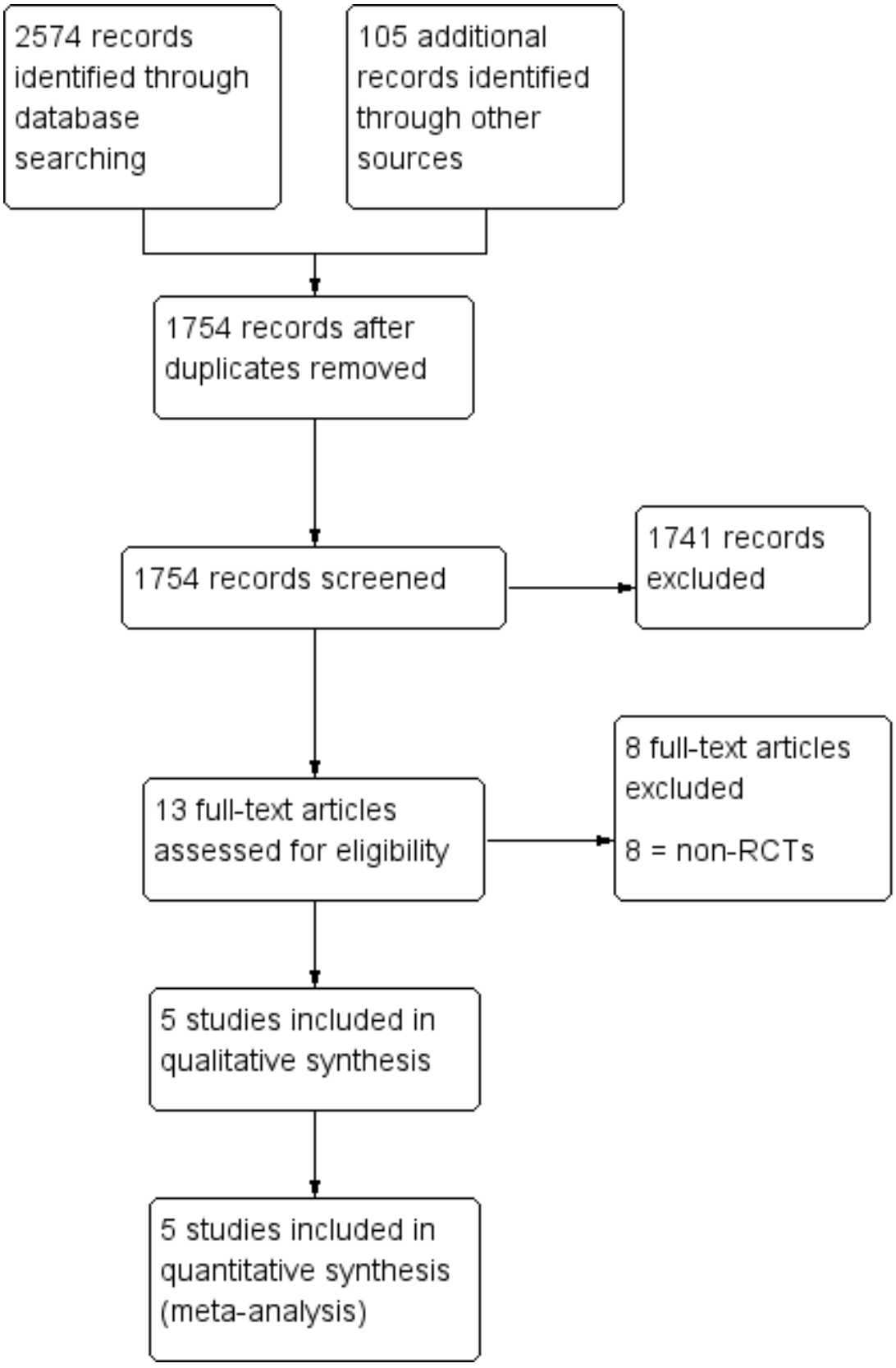
not covered in the CGF Group Specialised Register in liaison with the Information Specialist.

Data collection and analysis

Selection of studies

We downloaded the title, abstract, and keywords of every trial retrieved by electronic searching to a reference management database (EndNote) and removed duplicates. Two review authors (YL and HZ) independently screened these titles and abstracts, and retrieved the full texts of all potentially eligible studies. Two review authors (YL and HZ) independently examined the full-text articles and selected studies for inclusion in the review. We excluded studies that clearly did not comply with the inclusion criteria and documented the reasons for exclusion. We resolved disagreements by discussion with a third review author (JF). Figure 1 documents the PRISMA flow chart.

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (YH and LS) independently extracted data from eligible studies using a data extraction form designed and pilot-tested by the review authors.

Data extraction included:

- participants' characteristics;
- number of participants in each arm;
- number of participants excluded from the analysis;
- type of intervention;
- proportion of participants who received all, part, or none of the intended treatment;
- methods of randomization, blinding, and allocation concealment;
- length of follow-up;
- data on outcomes.

We resolved disagreements by discussion or by an appeal to a third review author (WH). There was no blinding of review authors to article authors or journal titles. We corresponded with study authors for further information, as required.

Assessment of risk of bias in included studies

Two review authors (YL and YH) independently assessed the methodological risk of bias of each trial according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). According to the Cochrane 'Risk of bias' assessment tool, risk of bias assessment for included studies addressed seven criteria, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias; with a judgement of low risk, high risk, or unclear risk of bias. We resolved differences by discussion among the review authors or by consulting the Cochrane Menstrual Disorders and Subfertility Group. We took care to search for within-trial selective reporting, such as trials failing to report obvious outcomes, or reporting them in insufficient detail to allow inclusion. We sought published protocols and compared the outcomes between the protocol and the final published study.

Measures of treatment effect

We extracted both dichotomous and continuous data from the included studies. For dichotomous data (e.g. reintervention rates), we used the numbers of events in the control and intervention groups of each study to calculate risk ratios (RR). For continuous data (e.g. hospitalization duration and financial costs), we calculated mean differences (MD) between treatment groups if all studies reported using the same scales to measure outcomes. If similar outcomes are reported on different scales, we calculated the standardized mean difference (SMD). We treated ordinal data (e.g. quality of life scores) as continuous data. We calculated the 95% confidence intervals (CI) for all outcomes.

Unit of analysis issues

The primary unit of analysis was per woman randomized. We planned to report data that did not allow a valid analysis in an additional table and not include them in a meta-analysis.

Dealing with missing data

We analyzed data on an intention-to-treat basis, where possible, and attempted to obtain missing data from the original investigators. Where these were unobtainable, we undertook imputation of individual values for the primary outcomes only. If studies reported sufficient details to calculate MDs but provided no information on associated standard deviations (SD), we assumed the outcome to have an SD equal to the highest SD from other studies within the same analysis. For other outcomes, we analyzed only the available data.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots and by estimation of the I^2 statistic, which summarizes the percentage of heterogeneity between trials that cannot be ascribed to sampling variation. An I^2 value greater than 50% indicated substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, we aimed to minimize the potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data.

Data synthesis

We performed statistical analysis in accordance with the guidelines developed by the Cochrane Gynaecology and Fertility Group. Two review authors (YL and HZ) independently analyzed data in Review Manager 5 (Review Manager 2014).

- Surgery versus medical treatment, stratified by location of pregnancy:
  - caesarean scar;
  - abdominal;
  - cornual;
  - cervical;
  - ovarian pregnancy.
- Surgery versus medical treatment, stratified by specific type of surgery and mode of administration.
  - Surgery:
    - laparoscopic removal;
    - hysteroscopic evacuation;
    - dilation and curettage;
    - sac aspiration;
    - selective uterine arterial embolization;
    - open surgery.
  - Medical treatment:
    - systemic MTX;
    - local MTX;
    - local embryocides (potassium chloride, sodium chloride, hyperosmolar glucose, or crystalline trichosanthin under ultrasonography guidance).
- Surgery or medical treatment versus expectant management.
- One surgery versus another surgery

For an increase in the odds of a particular outcome, which may be beneficial (e.g. treatment success) or detrimental (e.g. complications), we displayed graphically in the forest plots to the

right of the centre line and a decrease in the odds of an outcome to the left of the centre line.

Subgroup analysis and investigation of heterogeneity

If we detect substantial heterogeneity, we explored possible explanations in sensitivity analyses. We took any statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect.

Sensitivity analysis

We conducted sensitivity analyses for the primary outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding the eligibility and analysis of studies and data. These analyses included consideration of whether the review conclusions would have differed if:

- eligibility was restricted to studies without high risk of bias;
- a random-effects model had been adopted;
- alternative imputation strategies had been implemented;
- the summary effect measure was odds ratio rather than RR.

Overall quality of the body of evidence: 'Summary of findings' table

We generated 'Summary of findings' tables using GRADEpro software (GRADEpro GDT). One table evaluated the overall quality of the body of evidence for the main review outcomes (treatment success and complications) using GRADE criteria (study limitations, that is risk of bias, consistency of effect, imprecision, indirectness, and publication bias), for the main review comparison UAE/UACE compared with systemic MTX. We prepared additional 'Summary of findings' tables for review comparisons UACE plus MTX versus ultrasonography-guided local MTX, and suction curettage under hysteroscopy versus suction curettage under ultrasonography. We justified, documented, and incorporated judgements about evidence quality (high, moderate, or low) into reporting of the results for each outcome.

RESULTS

Description of studies

Results of the search

The search retrieved 1754 articles after removing duplicates. Thirteen articles were potentially eligible and were retrieved in full text. Five studies (five articles) met our inclusion criteria. We excluded eight studies. See Characteristics of included studies table, Characteristics of excluded studies table, and the PRISMA flow chart (Figure 1).

Included studies

Study design and setting

We included five parallel-design RCTs (Zhuang 2009; Li 2011b; Qian 2015; Wang 2015; Li 2016). All were single-centre studies conducted in Chinese hospitals.

Participants

The studies included 371 women with CSP confirmed by ultrasonography. We found no studies reported other non-tubal ectopic pregnancies.

Interventions

For CSP, Li 2011b compared systemic MTX alone versus UACE with MTX; Zhuang 2009 compared systemic MTX alone versus UAE, both followed by suction curettage; Wang 2015 compared UACE with MTX versus ultrasonography-guided local MTX injection; Qian 2015 compared suction curettage under hysteroscopy versus under ultrasonography after UAE; and Li 2016 compared suction curettage under hysteroscopy versus under ultrasonography after UACE.

Outcomes

All five studies reported primary treatment success or complications, or both (our primary outcomes), four studies reported adverse effects (Zhuang 2009; Li 2011b;Li 2016;Qian 2015), three studies reported time to normalize β-hCG (Wang 2015; Li 2016; Qian 2015), and two studies reported hospital stay (Zhuang 2009;Li 2011b).

Excluded studies

We excluded eight studies as they were not RCTs (Wei 2007; Yan 2007; Zhuang 2008; Gu 2010; Li 2010; Wu 2014; Liu 2015; Peng 2015). Two described systematic approaches in the sequence generation process (Wei 2007; Peng 2015), and five involved subjective judgement or some method of non-random categorization of participants (Yan 2007; Zhuang 2008; Gu 2010; Li 2010; Liu 2015; Peng 2015). One was a cohort study (Wu 2014).

Risk of bias in included studies

Refer to the 'Risk of bias' tables and Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

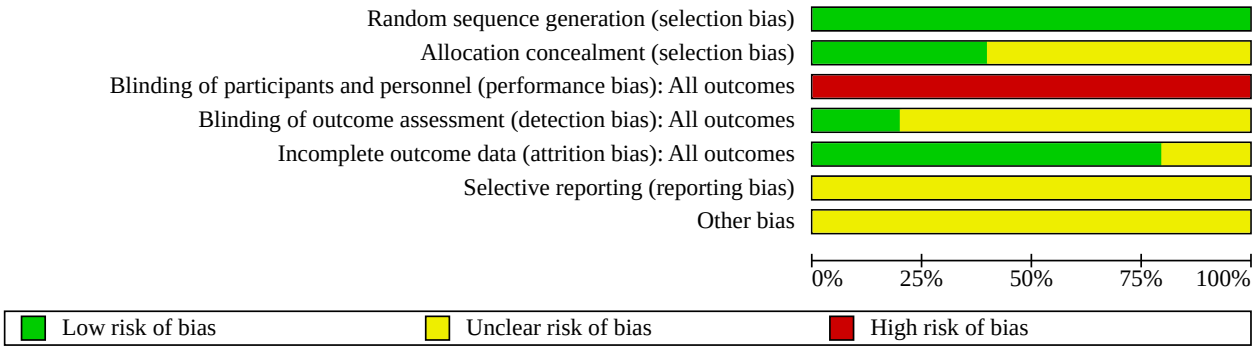
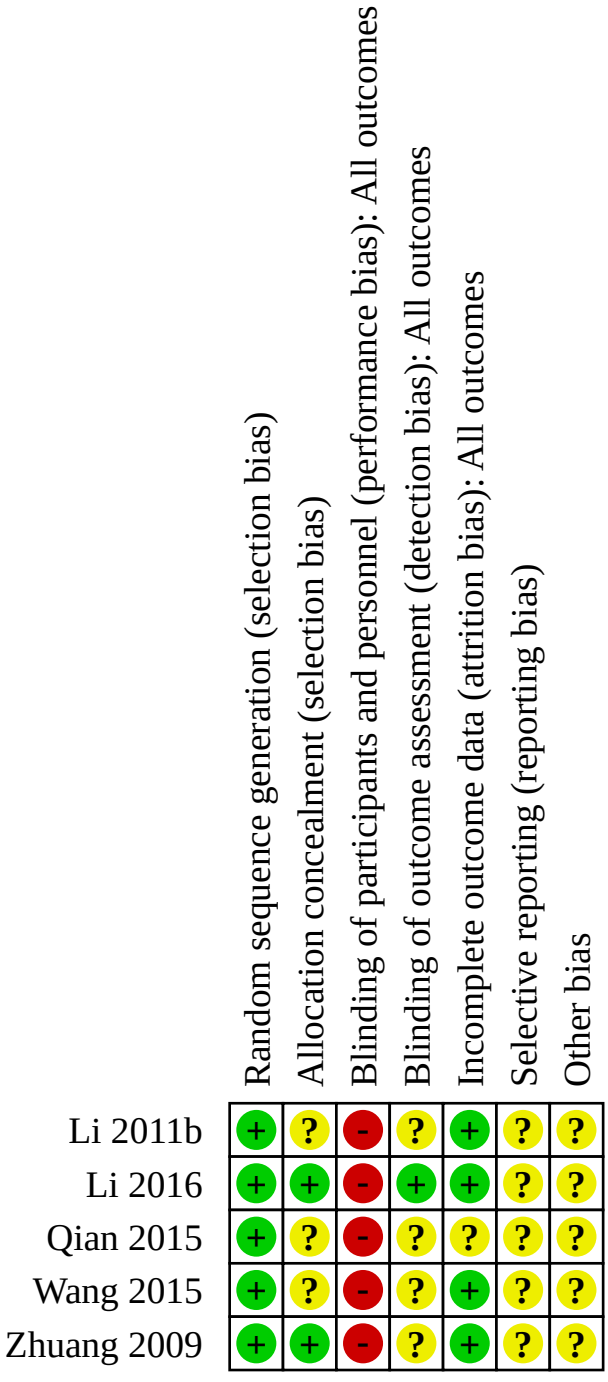


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

All five included studies were at low risk of selection bias related to sequence generation, as they used computer randomization or a random numbers table.

Allocation concealment

Li 2016 applied a sealed opaque envelope with a serial number on the surface and a random number inside (low risk of bias). Zhuang 2009 also applied a system of sealed and numbered envelopes (low risk of bias). Li 2011b, Qian 2015, and Wang 2015 did not describe the method used and were at unclear risk of bias for this domain.

Blinding

Blinding of participants and personnel (performance bias)

All five included studies were at high risk of performance bias, because the blinding method could not be conducted, although most studies did not describe that.

Blinding of outcome assessors (detection bias)

Li 2016 was at low risk because data analysts were masked to group assignment. Four studies did not supply this information, so we rated them at unclear risk of bias (Zhuang 2009; Li 2011b; Qian 2015; Wang 2015).

Incomplete outcome data

Four studies analyzed all women randomized, and we judged them at low risk of attrition bias (Zhuang 2009; Li 2011b; Wang 2015; Li 2016). Qian 2015 did not clearly state attrition rates, and we rated them at unclear risk.

Selective reporting

All five included studies were at unclear risk owing to insufficient information to permit judgement.

Other potential sources of bias

We assessed all the five studies at unclear risk of other sources of bias.

Effects of interventions

See: **Summary of findings 1** UAE/UACE compared with systemic MTX for CSP; **Summary of findings 2** Suction curettage under hysteroscopy compared with under ultrasonography for CSP

See: Summary of findings 1 and Summary of findings 2.

1. Surgery alone or surgery plus medical treatment versus medical treatment alone (prior to suction curettage)

For CSP, Zhuang 2009 compared medical treatment (systemic MTX) versus surgery (UAE) following suction curettage at 24 hours, Li 2011b compared medical treatment (systemic MTX) versus surgery and medical treatment (UACE plus MTX) following suction curettage, and Wang 2015 compared medical treatment (local MTX) versus surgery and medical treatment (UAE plus MTX).

1.1. Caesarean scar pregnancy

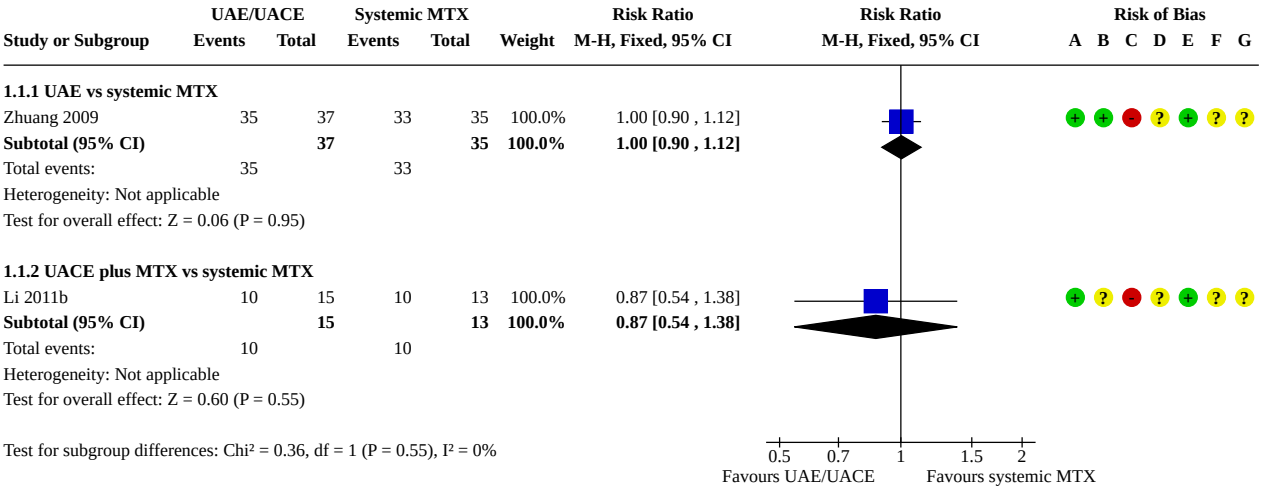
1.1.1 UAE/UACE versus systemic MTX (prior to suction curettage)

Primary outcomes

- Treatment success after initial treatment

Two studies reported treatment success after initial treatment (defined as an uneventful decline of serum β-hCG to undetectable levels by the initial treatment) between UAE (Zhuang 2009)/UACE (Li 2011b) and systemic MTX. We are uncertain whether UAE/UACE improved treatment success after initial treatment (UAE: RR 1.00, 95% CI 0.90 to 1.12; 1 RCT, 72 women; low-quality evidence; UACE: RR 0.87, 95% CI 0.54 to 1.38; 1 RCT, 28 women; low-quality evidence; Analysis 1.1; Figure 4).

Figure 4. Forest plot of comparison: 1 UAE/UACE versus systemic MTX, outcome: 1.1 Treatment success after initial treatment.

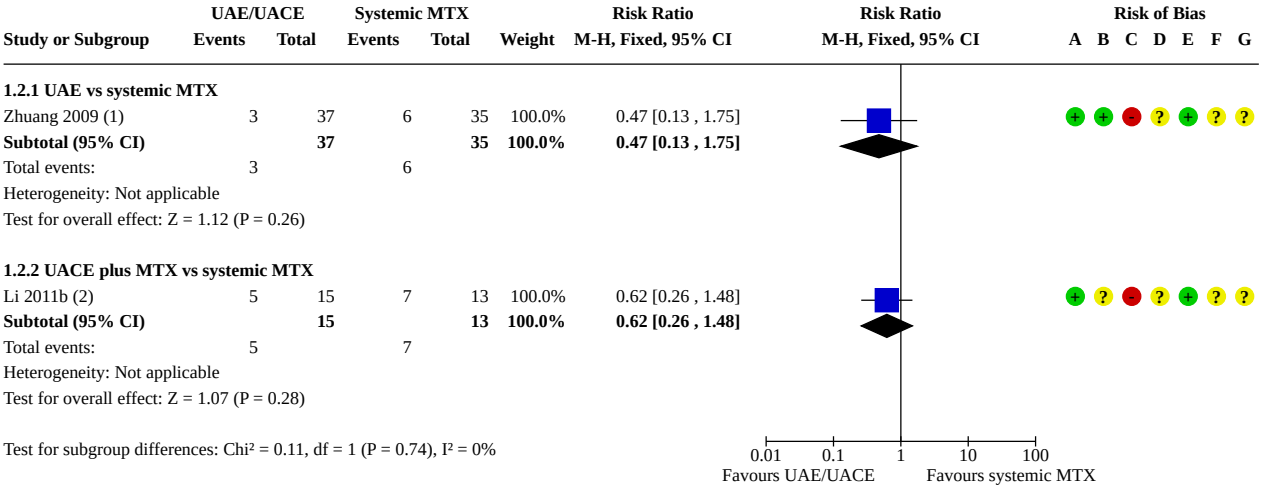


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

- Complications

Two studies reported rates of complications (heavy bleeding, recurrence of active bleeding, and hysterectomy) between UAE (Zhuang 2009)/UACE (Li 2011b) and systemic MTX. We are uncertain whether UAE/UACE reduced rates of complications (UAE: RR 0.47, 95% CI 0.13 to 1.75; 1 RCT, 72 women; low-quality evidence; UACE: RR 0.62, 95% CI 0.26 to 1.48; 1 RCT, 28 women; low-quality evidence; Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: 1 UAE/UACE versus systemic MTX, outcome: 1.2 Complications.



Footnotes

(1) Complications: heavy bleeding, recurrence of active bleeding, and hysterectomy
(2) Complications: hysterectomy and heavy or active uterine bleeding

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Secondary outcomes

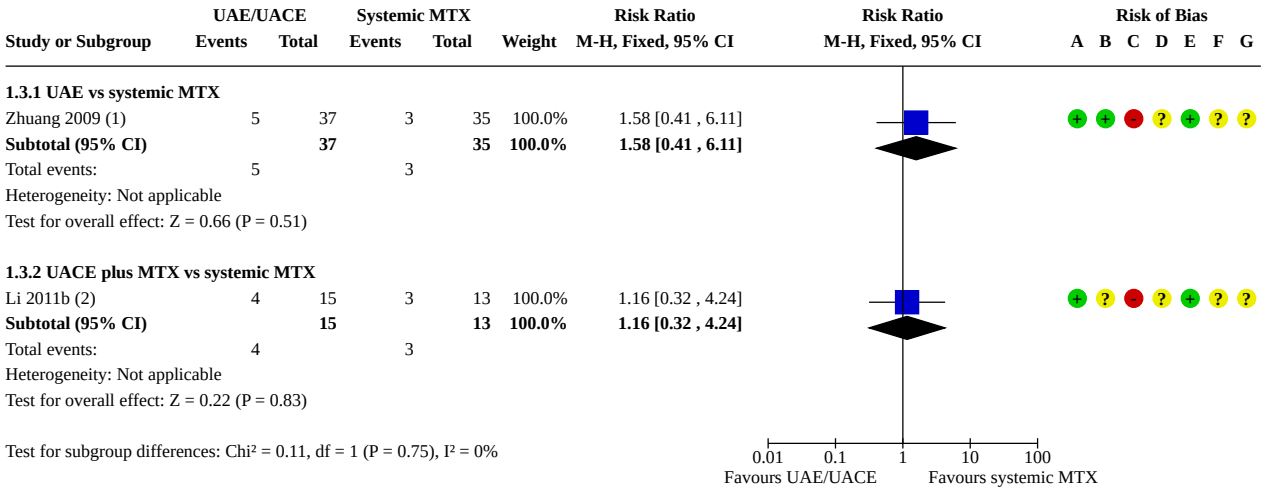
- Quality of life

No study reported this outcome.

- Adverse effects (overall)

One study comparing UAE with systemic MTX reported rates of adverse effects (UAE: including fever and pain and one readmitted woman; MTX group: including abnormal liver function and severe vomiting) (Zhuang 2009). The other study compared rates of adverse effects (mild increase in liver enzymes, mild vomiting, and moderate abdominal or pelvic pain) between UACE and systemic MTX (Li 2011b). We are uncertain whether UAE/UACE reduced adverse effects (UAE: RR 1.58, 95% CI 0.41 to 6.11; 1 RCT, 72 women; low-quality evidence; UACE: RR 1.16, 95% CI 0.32 to 4.24; 1 RCT, 28 women; low-quality evidence; Analysis 1.3; Figure 6). It was not obvious that the types of events had similar values to participants (e.g. fever versus vomiting).

Figure 6. Forest plot of comparison: 1 UAE/UACE versus systemic MTX, outcome: 1.3 Adverse effects (overall).



Footnotes

(1) Included: abnormal liver function, severe vomiting, fever, pain and readmission

(2) Included: mild increase in liver enzymes, mild vomiting, and moderate abdominal or pelvic pain.

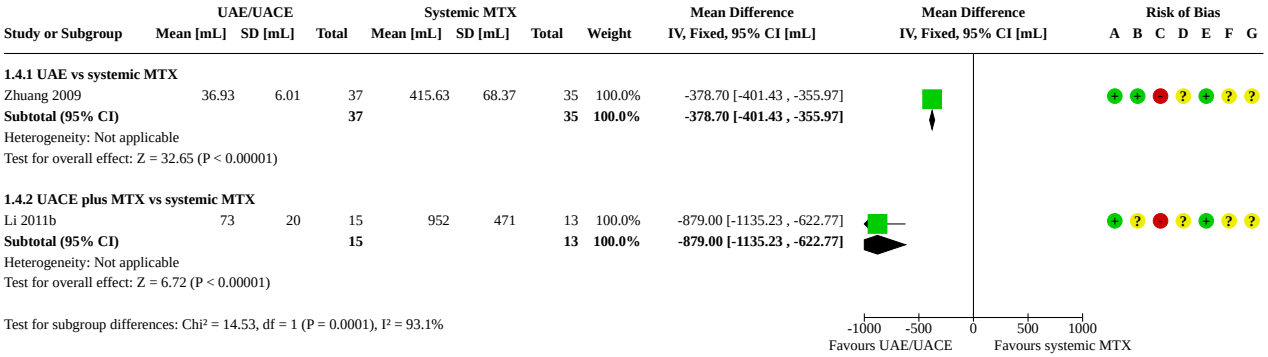
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

- Blood loss

Two studies comparing UAE (Zhuang 2009)/UACE (Li 2011b) with systemic MTX reported blood loss. It was lower in the UAE/UACE groups than in the systemic MTX groups (UAE: MD –378.70 mL, 95% CI –401.43 to –355.97; 1 RCT, 72 women; moderate-quality evidence; UACE: MD –879.00 mL, 95% CI –1135.23 to -622.77; 1 RCT, 28 women; moderate-quality evidence; Analysis 1.4; Figure 7).

Figure 7. Forest plot of comparison: 1 UAE/UACE versus systemic MTX, outcome: 1.4 Blood loss [mL].



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

- Time to normalize β-hCG

No study reported this outcome.

- Hospital stay

Two studies comparing UAE (Zhuang 2009)/UACE (Li 2011b) with systemic MTX reported hospital stay. It was shorter in the UAE/UACE

groups than in the systemic MTX group (UAE: MD –27.90 days, 95% CI –29.44 to –26.36; 1 RCT, 72 women; low-quality evidence; MD –23.00 days, 95% CI –27.80 to –18.20; 1 RCT, 28 women; low-quality evidence; Analysis 1.5).

- Financial costs

No study reported this outcome.

- Future fertility

No study reported this outcome.

1.2. Ovarian pregnancy

No study reported on ovarian pregnancy.

1.3. Cornual pregnancy

No study reported on cornual pregnancy.

1.4. Cervical pregnancy

No study reported on cervical pregnancy.

1.5. Abdominal pregnancy

No study reported on abdominal pregnancy.

2. Surgery plus medical treatment versus medical treatment alone

2.1. Caesarean scar pregnancy

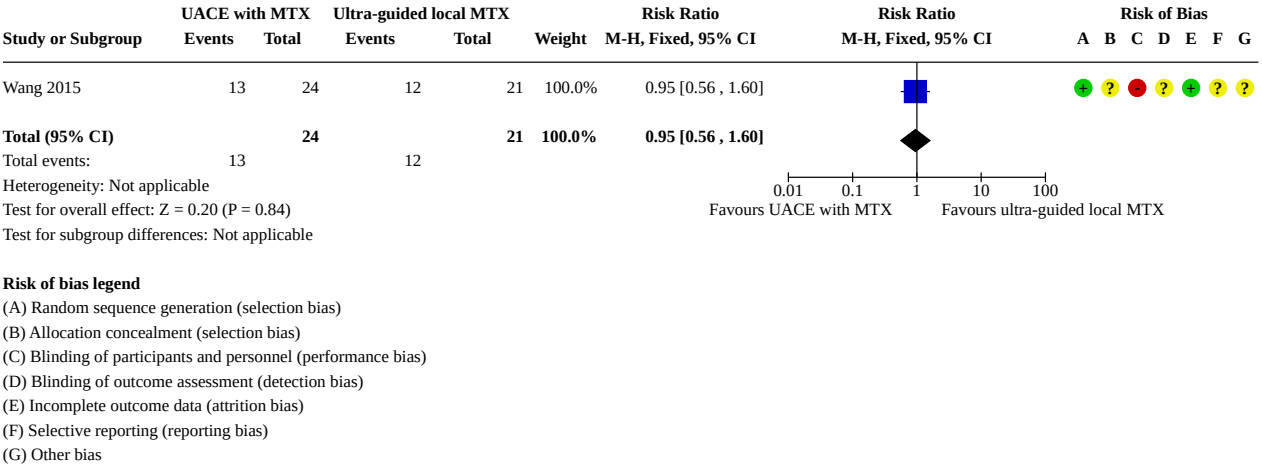
2.1.1 UACE plus MTX versus ultrasonography-guided local MTX injection

Primary outcomes

- Treatment success after initial treatment

One study reported treatment success after initial treatment (defined as an uneventful decline of serum β-hCG to undetectable levels by the initial treatment) (Wang 2015). We are uncertain whether UACE improved treatment success after initial treatment compared with local MTX injection (RR 0.95, 95% CI 0.56 to 1.60; 1 RCT, 45 women; very low-quality evidence; Analysis 2.1; Figure 8).

Figure 8. Forest plot of comparison: 2 UACE plus MTX versus ultrasonography-guided local MTX injection, outcome: 2.1 Treatment success after initial treatment.



- Complications

No study reported this outcome.

Secondary outcomes

- Quality of life

No study reported this outcome.

- Adverse effects (overall)

The study reported the same number of failed treatments in each arm ((RR 0.88, 95% CI 0.40 to 1.92; 1 RCT, 45 women).

No study reported this outcome.

- Time to normalize β-hCG

One study reported time to normalize β-hCG (Wang 2015). We are uncertain whether UACE shortened the time to normalize β-hCG (MD 1.50 days, 95% CI –3.16 to 6.16; 1 RCT, 45 women; very low-quality evidence; Analysis 2.2).

- Hospital stay

No study reported this outcome.

- Financial costs

No study reported this outcome.

- Future fertility

No study reported this outcome.

2.2. Ovarian pregnancy

No study reported on ovarian pregnancy.

2.3. Cornual pregnancy

No study reported on cornual pregnancy.

2.4. Cervical pregnancy

No study reported on cervical pregnancy.

2.5. Abdominal pregnancy

No study reported on abdominal pregnancy.

3. Surgery versus another surgery

3.1. Caesarean scar pregnancy

3.1.1. Suction curettage under hysteroscopy versus under ultrasonography after UAE/UACE

Primary outcomes

- Treatment success rates after initial treatment

Two studies reported treatment success after initial treatment (defined as an uneventful decline of serum β-hCG to undetectable levels by the initial treatment (Qian 2015; Li 2016). We are uncertain whether suction curettage under hysteroscopy improved treatment success after initial treatment compared with under ultrasonography (UAE: RR 0.91, 95% CI 0.81 to 1.03; 1 RCT, 66 women; very low-quality evidence; UACE: RR 1.08, 95% CI 0.96 to 1.09; 1 RCT, 92 women; low-quality evidence; Analysis 4.1; Figure 9).

- Complications

One study reported rates of complications including heavy bleeding, recurrence of actively bleeding, pelvic infection, and hysterectomy (Qian 2015). The other study reported rates of complications including heavy bleeding, uterine perforation, pelvic infection, incomplete abortion, and uterine adhesion (Li 2016). We are uncertain whether suction curettage under hysteroscopy reduced rates of complications after UAE(Qian 2015) or UACE(Li 2016) compared with under ultrasonography (UAE: RR 4.00, 95% CI 0.47 to 33.91; 1 RCT, 66 women; very low-quality evidence; UACE: RR 0.18, 95% CI 0.01 to 3.72; 1 RCT, 92 women; low-quality evidence; Analysis 4.2; Figure 10).

Secondary outcomes

- Quality of life

No study reported this outcome.

- Adverse effects (overall)

One study reported rates of adverse effects (chest congestion) (Qian 2015), and the other study reported all the participants had a low fever (37.3–38.5 °C) and abdominal pain (Li 2016). We are uncertain whether suction curettage under hysteroscopy reduced adverse effects after UAE (Qian 2015)/UACE (Li 2016) compared with under ultrasonography (UAE: RR 3.09, 95% CI 0.12 to 78.70; 1 RCT, 66 women; very low-quality evidence; UACE: not estimable; 1 RCT, 92 women; very low-quality evidence; Analysis 4.3; Figure 11).

- Time to normalize β-hCG

Two studies reported time to normalize β-hCG (Qian 2015; Li 2016). We are uncertain whether suction curettage under hysteroscopy shortened the time to normalize β-hCG after UAE (Qian 2015)/UACE (Li 2016) compared with under ultrasonography (UAE: MD 4.03 days, 95% CI −1.79 to 9.85; 1 RCT, 66 women; very low-quality evidence; UACE: MD 0.84 days, 95% CI −1.90 to 3.58; 1 RCT, 92 women; low-quality evidence; Analysis 4.4).

- Hospital stay

No study reported this outcome.

- Financial costs

No study reported this outcome.

- Future fertility

No study reported this outcome.

3.2. Ovarian pregnancy

No study reported on ovarian pregnancy.

3.3. Cornual pregnancy

No study reported on cornual pregnancy.

3.4. Cervical pregnancy

No study reported on cervical pregnancy.

3.5. Abdominal pregnancy

No study reported on abdominal pregnancy.

4. Surgery versus expectant management

No study compared surgery versus expectant management.

Other analyses

Data were too few for review authors to conduct planned subgroup and sensitivity analyses, or to construct a funnel plot to assess reporting bias.

DISCUSSION

Summary of main results

Caesarean scar pregnancy

Most of our included studies performed suction curettage for CSP, and there was no evidence showing a preference for using hysteroscopy or ultrasonography-guided surgery, after systemic MTX, or after UAE/UACE for success, complications, and effects; however, hospital stay of the surgery group was shorter than in the medical treatment group and blood loss was less. Results were based on very limited evidence and thus should be interpreted with caution.

Non-tubal ectopic pregnancy other than caesarean scar pregnancy

RCTs are probably not feasible owing to low incidence and because it is usually an emergency surgery.

Overall completeness and applicability of evidence

The included studies partially answered the review question. We found few studies meeting our criteria, and among them, results showed a lack of consistency in methods of interventions and outcome measures, which leads to difficulties in combining data in a suitable meta-analysis, thus making it difficult for review authors

to draw clinically relevant conclusions. Before suction curettage, UAE/UACE showed less blood loss than systemic MTX, but more evidence is needed. As all the included studies were conducted in China, we consider there could be a specific concern about generalization of the results.

Quality of the evidence

All five studies were RCTs with adequately described randomization, and four studies reported allocation concealment. The interventions could not be blinded, but there was a limited impact on our primary outcomes. However, most outcomes in the comparisons had very low/low-quality evidence, except blood loss which was of moderate quality. The main limitations were serious imprecision (associated with small sample sizes and very wide CIs for most comparisons), the issue of multiple comparisons with a small number of trials, and no data available for heterogeneity. In addition, some outcomes were downgraded for indirectness or publication bias.

Potential biases in the review process

We made every effort to minimize biases in the review process. We aimed to identify all relevant studies by performing comprehensive database searches. We followed Cochrane methods in the review process. In addition, we emailed the authors of included and excluded articles.

Agreements and disagreements with other studies or reviews

One non-Cochrane review concluded that an interventional rather than a medical approach is better for CSP based on efficacy and safety, but their recommendations were primarily based on case series (Petersen 2016). Our review did not draw a similar conclusion although UAE/UACE showed less blood loss than systemic MTX. We consider more robust evidence is needed.

AUTHORS' CONCLUSIONS

Implications for practice

It is uncertain whether there is a difference in success, complications, and adverse effects between UAE/UACE and administration of systemic MTX before suction curettage (low-quality evidence).

Blood loss may be lower if suction curettage is conducted after uterine arterial embolization (UAE)/uterine arterial chemoembolization (UACE) than after administration of systemic methotrexate (MTX) (moderate-quality evidence).

It is uncertain whether there is a difference in success, time to normalize β-hCG (low-quality evidence), complications, or adverse effects (very low-quality evidence) between suction curettage under hysteroscopy and under ultrasonography.

Implications for research

Population: subgroup according to caesarean scar pregnancy type (size and direction of growth of the gestational sac and thickness of the myometrium between bladder and gestational sac) could be considered (Jin 2016). More studies could be conducted in countries other than China.

Intervention: researchers could focus on UAE/UACE and suction curettage under monitoring.

Comparison: researchers could focus on surgery versus medical and between different surgeries.

Outcome: important complications such as heavy bleeding, recurrence of actively bleeding, serious pelvic infection, and hysterectomy could be more specific. Researchers could continue to follow-up future pregnancy outcomes and quality of life after treatment.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Li 2016

Study characteristics	
Methods	Randomization using sealed, opaque and numbered envelopes, with a randomization table
Participants	92 women with CSP
Interventions	All participants underwent UACE (MTX 50 mg infused bilaterally into the gelatin sponge particles). Within 24–48 hours, suction curettage under hysteroscopy monitoring (31A,17B. 48 cases, age: > 35y, n = 29; < 35y, n = 19), or suction curettage under ultrasonography monitoring (28A,16B. 44 cases, age: > 35y, n = 31; < 35y, n = 13) (A: diameter of the gestational sac ≤ 3.0 cm; B: diameter of the gestational sac > 3.0cm)
Outcomes	Primary outcomes: • success after initial treatment • complications (including heavy bleeding, uterine perforation, pelvic infection, incomplete abortion, and uterine adhesion) Secondary outcomes: • adverse effects (including low fever (37.3–38.5 °C) and abdominal pain, and all the participants had these adverse effects) • time to normalize β-hCG
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a sealed opaque envelope with a serial number on the surface and a random number inside."
Allocation concealment (selection bias)	Low risk	Quote: "The random number had been packed in the serially numbered envelopes by hospital staff members who had no contact with patients, clinicians, and investigators."

Li 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Clinicians were not masked to group assignment, but participants and data analysts were."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Clinicians were not masked to group assignment, but participants and data analysts were."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias existed.

Li 2011b

Study characteristics	
Methods	Randomization using a randomization table
Participants	28 women with CSP
Interventions	Systemic MTX intravenously 50 mg/m^2 of body surface area (size of sac/mass: 129.6 ± 96.7 cm^3; 13 cases, age:33.2 ± 4.5y) treatment vs UACE plus MTX 40 mg and gelatin sponge particles (size of sac/mass: 161.1 ± 102.1 cm^3; 15 cases, age:34.2 ± 5.5y) suction curettage performed when β-hCG decreased to < 50 mIU/mL in systemic MTX group suction curettage performed after 24 hours in UACE group
Outcomes	Primary outcomes: • success after initial treatment • complications: emergency hysterectomy, tamponade with iodoform gauze, a second UAE Secondary outcomes: • adverse effects (including mild increase in liver enzymes, mild vomiting, moderate abdominal or pelvic pain) • blood loss • hospital stay
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "By using a randomization table."

Li 2011b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No data available for this specific type of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No data available for this specific type of bias, and blinding was not possible with this methodology.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No data available for this specific type of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias existed.

Qian 2015

Study characteristics	
Methods	Used computerized randomization
Participants	66 women with CSP who had no internal bleeding and were haemodynamically stable, unruptured, and were at < 10 weeks of gestation.
Interventions	All women underwent UAE After 24 hours, hysteroscopy surgery (gestational sac diameter: 2.97 ± 1.53 cm. 33 cases, age: 32.00 ± 4.15y) vs suction curettage under transabdominal sonography guidance (gestational sac diameter: 2.79 ± 1.50 cm. 33 cases, age:30.79 ± 4.29y)
Outcomes	Primary outcomes: • success after initial treatment • complications (including recurrence of active bleeding, pelvic infection, and hysterectomy) Secondary outcomes: • adverse effects (including chest congestion) • time to normalize β-hCG
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "using computerized randomization."

Qian 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No data available for this specific type of bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No data available for the specific type of bias, and blinding was not possible with this methodology.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No data available for this specific type of bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No data available for this specific type of bias.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias existed.

Wang 2015

Study characteristics	
Methods	Randomization using a randomization list generated by a random number generator
Participants	45 women with CSP who were haemodynamically stable and eligible for conservative treatment
Interventions	Ultrasonography-guided local injection of MTX into the gestational sac (15A, 6B. 21 cases, age: 29.52 ± 4.88y) vs UAE with local MTX injection (18A, 6B. 24 cases, age: 29.96 ± 4.14y) (A: diameter of the gestational sac ≤ 5 cm, B: diameter of the gestational sac > 5 cm) Another dose of systemic MTX (50 mg/m^2 body surface area, intramuscularly) was administered if serum β-hCG levels failed to decrease by 15% between days 4 and 7.
Outcomes	Primary outcomes: • success after initial treatment Secondary outcomes: • time to normalize β-hCG
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomized according to a randomization list, generated by a random number generator."
Allocation concealment (selection bias)	Unclear risk	No data available for this specific type of bias.

Wang 2015 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No data available for the specific type of bias, and blinding was not possible with this methodology.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No data available for this specific type of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "46 patients were recruited, only one participant was lost to follow up."
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias existed.

Zhuang 2009

Study characteristics	
Methods	Randomization using sealed and numbered envelopes, with a randomization table
Participants	72 women with CSP
Interventions	Infusion of MTX intravenously (50 mg/m^2 body surface area) (35 cases, age: 32.88 ± 0.98y) vs UAE (37 cases, age: 32.23 ± 0.65y) suction curettage performed when β-hCG decreased to < 50 mIU/mL in MTX group suction curettage performed after 24 hours in UACE group
Outcomes	Primary outcomes: • success after initial treatment • complications Secondary outcomes: • adverse effects (MTX group including abnormal liver function and severe vomiting; UAE group including fever and pain and 1 readmitted woman) • blood loss • hospital stay
Notes	Data of primary outcome (serum β-hCG level) not shown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned in a 1:1 allocation ratio using a randomization table."
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was conducted via a system of sealed and numbered envelopes."

Zhuang 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No data available for this specific type of bias, and blinding was not possible with this methodology.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No data available for this specific type of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias existed.

β-hCG: β-human chorionic gonadotropin; CSP: caesarean scar pregnancy; MTX: methotrexate; PVA: polyvinyl acetate; UACE: uterine arterial chemoembolization; UAE: uterine arterial embolization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Gu 2010	Not an RCT (involving method of non-random categorization of participants)
Li 2010	Not an RCT (via emailing the author)
Liu 2015	Not an RCT (grouping based on subjective judgement)
Peng 2015	Not an RCT (systematic approaches in the sequence generation process)
Wei 2007	Not an RCT (systematic approaches in the sequence generation process)
Wu 2014	Not an RCT (cohort study)
Yan 2007	Not an RCT (via emailing the author)
Zhuang 2008	Not an RCT (group based on subjective judgement)

RCT: randomized controlled trial.

DATA AND ANALYSES

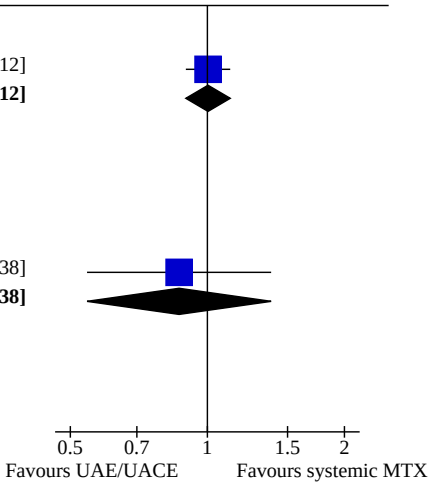
Comparison 1. UAE/UACE versus systemic MTX, both + suction curettage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Treatment success after initial treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 UAE vs systemic MTX	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.90, 1.12]
1.1.2 UACE plus MTX vs systemic MTX	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.54, 1.38]
1.2 Complications	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 UAE vs systemic MTX	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.13, 1.75]
1.2.2 UACE plus MTX vs systemic MTX	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.26, 1.48]
1.3 Adverse effects (overall)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 UAE vs systemic MTX	1	72	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.41, 6.11]
1.3.2 UACE plus MTX vs systemic MTX	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.32, 4.24]
1.4 Blood loss	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 UAE vs systemic MTX	1	72	Mean Difference (IV, Fixed, 95% CI)	-378.70 [-401.43, -355.97]
1.4.2 UACE plus MTX vs systemic MTX	1	28	Mean Difference (IV, Fixed, 95% CI)	-879.00 [-1135.23, -622.77]
1.5 Hospital stay	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.5.1 UAE vs systemic MTX	1	72	Mean Difference (IV, Fixed, 95% CI)	-27.90 [-29.44, -26.36]
1.5.2 UACE plus MTX vs systemic MTX	1	28	Mean Difference (IV, Fixed, 95% CI)	-23.00 [-27.80, -18.20]

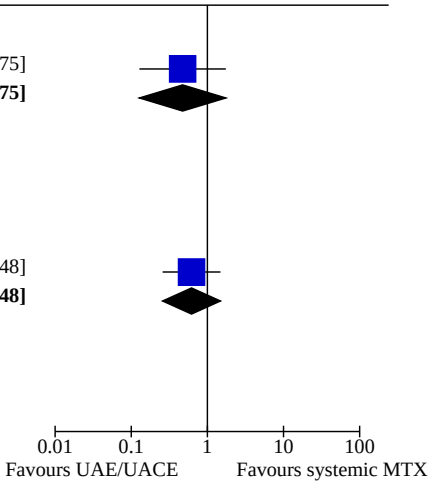
Analysis 1.1. Comparison 1: UAE/UACE versus systemic MTX, both + suction curettage, Outcome 1: Treatment success after initial treatment

Study or Subgroup	UAE/UACE Events	UAE/UACE Total	Systemic MTX Events	Systemic MTX Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 UAE vs systemic MTX						
Zhuang 2009	35	37	33	35	100.0%	1.00 [0.90 , 1.12]
Subtotal (95% CI)		**37**		**35**	**100.0%**	**1.00 [0.90 , 1.12]**
Total events:	35		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.1.2 UACE plus MTX vs systemic MTX						
Li 2011b	10	15	10	13	100.0%	0.87 [0.54 , 1.38]
Subtotal (95% CI)		**15**		**13**	**100.0%**	**0.87 [0.54 , 1.38]**
Total events:	10		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%						



Analysis 1.2. Comparison 1: UAE/UACE versus systemic MTX, both + suction curettage, Outcome 2: Complications

Study or Subgroup	UAE/UACE Events	UAE/UACE Total	Systemic MTX Events	Systemic MTX Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 UAE vs systemic MTX						
Zhuang 2009 (1)	3	37	6	35	100.0%	0.47 [0.13 , 1.75]
Subtotal (95% CI)		**37**		**35**	**100.0%**	**0.47 [0.13 , 1.75]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
1.2.2 UACE plus MTX vs systemic MTX						
Li 2011b (2)	5	15	7	13	100.0%	0.62 [0.26 , 1.48]
Subtotal (95% CI)		**15**		**13**	**100.0%**	**0.62 [0.26 , 1.48]**
Total events:	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%						



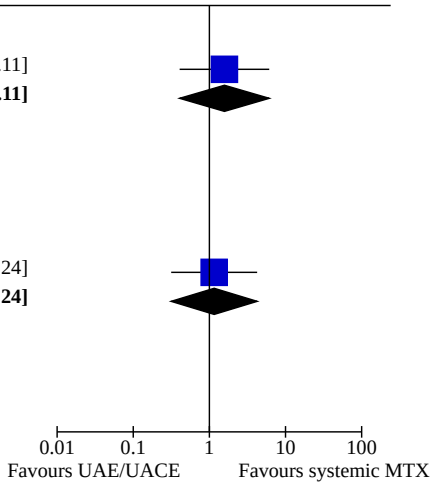
Footnotes

(1) Complications: heavy bleeding, recurrence of active bleeding, and hysterectomy

(2) Complications: hysterectomy and heavy or active uterine bleeding

Analysis 1.3. Comparison 1: UAE/UACE versus systemic MTX, both + suction curettage, Outcome 3: Adverse effects (overall)

Study or Subgroup	UAE/UACE Events	UAE/UACE Total	Systemic MTX Events	Systemic MTX Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 UAE vs systemic MTX						
Zhuang 2009 (1)	5	37	3	35	100.0%	1.58 [0.41 , 6.11]
Subtotal (95% CI)		**37**		**35**	**100.0%**	**1.58 [0.41 , 6.11]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.3.2 UACE plus MTX vs systemic MTX						
Li 2011b (2)	4	15	3	13	100.0%	1.16 [0.32 , 4.24]
Subtotal (95% CI)		**15**		**13**	**100.0%**	**1.16 [0.32 , 4.24]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.75), I² = 0%						



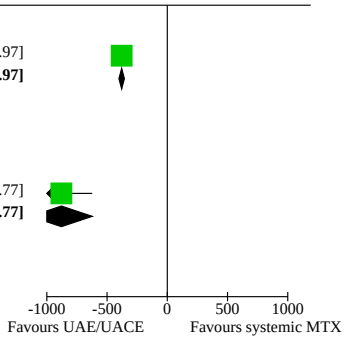
Footnotes

(1) Included: abnormal liver function, severe vomiting, fever, pain and readmission

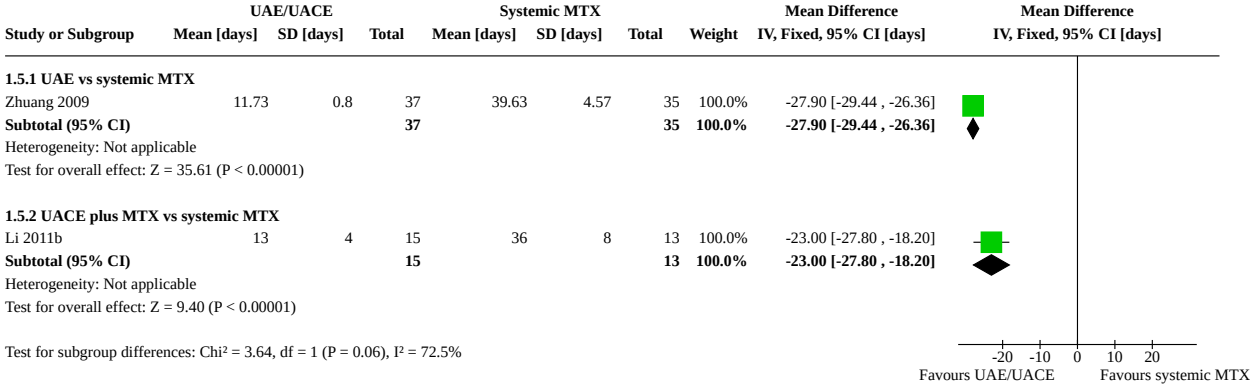
(2) Included: mild increase in liver enzymes, mild vomiting, and moderate abdominal or pelvic pain.

Analysis 1.4. Comparison 1: UAE/UACE versus systemic MTX, both + suction curettage, Outcome 4: Blood loss

Study or Subgroup	UAE/UACE Mean [mL]	UAE/UACE SD [mL]	UAE/UACE Total	Systemic MTX Mean [mL]	Systemic MTX SD [mL]	Systemic MTX Total	Weight	Mean Difference IV, Fixed, 95% CI [mL]
1.4.1 UAE vs systemic MTX								
Zhuang 2009	36.93	6.01	37	415.63	68.37	35	100.0%	-378.70 [-401.43 , -355.97]
Subtotal (95% CI)			**37**			**35**	**100.0%**	**-378.70 [-401.43 , -355.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 32.65 (P < 0.00001)								
1.4.2 UACE plus MTX vs systemic MTX								
Li 2011b	73	20	15	952	471	13	100.0%	-879.00 [-1135.23 , -622.77]
Subtotal (95% CI)			**15**			**13**	**100.0%**	**-879.00 [-1135.23 , -622.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.72 (P < 0.00001)								
Test for subgroup differences: Chi² = 14.53, df = 1 (P = 0.0001), I² = 93.1%								



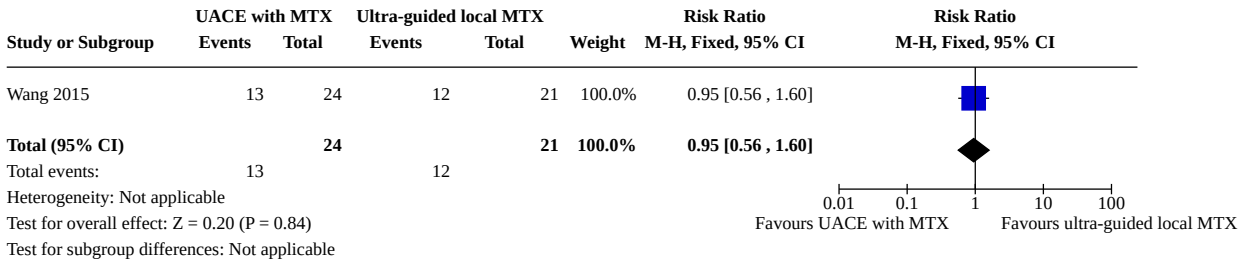
Analysis 1.5. Comparison 1: UAE/UACE versus systemic MTX, both + suction curettage, Outcome 5: Hospital stay



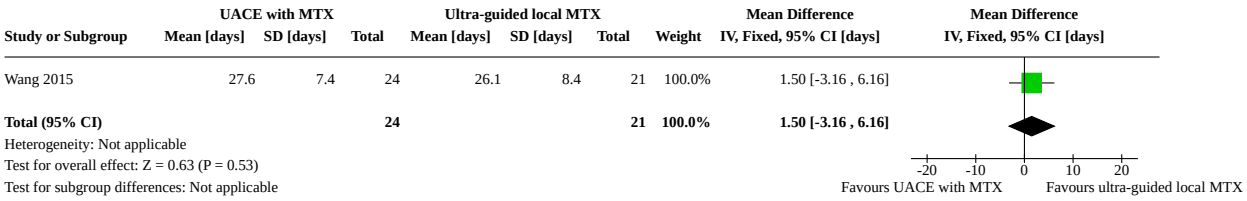
Comparison 2. UACE plus MTX versus ultrasonography-guided local MTX injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Treatment success after initial treatment	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.56, 1.60]
2.2 Time to normalize β-hCG	1	45	Mean Difference (IV, Fixed, 95% CI)	1.50 [-3.16, 6.16]
2.3 Adverse effects (overall)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.40, 1.92]

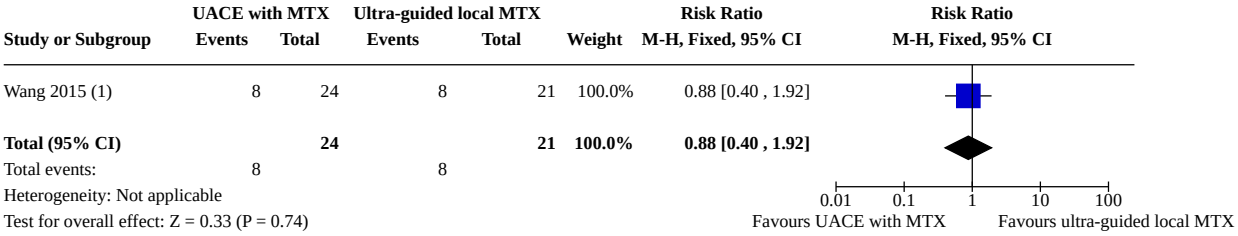
Analysis 2.1. Comparison 2: UACE plus MTX versus ultrasonography-guided local MTX injection, Outcome 1: Treatment success after initial treatment



Analysis 2.2. Comparison 2: UACE plus MTX versus ultrasonography-guided local MTX injection, Outcome 2: Time to normalize β-hCG



Analysis 2.3. Comparison 2: UACE plus MTX versus ultrasonography-guided local MTX injection, Outcome 3: Adverse effects (overall)



Footnotes

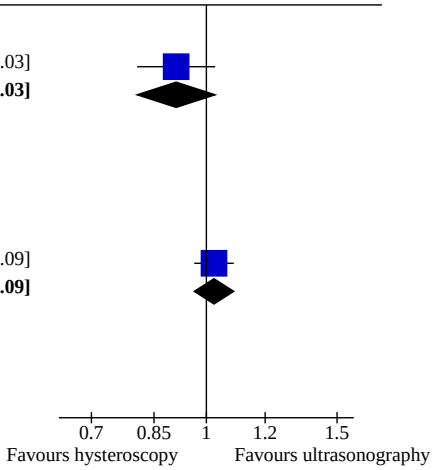
(1) Described in paper as 'failed treatment'

Comparison 3. Suction curettage under hysteroscopy versus under ultrasonography

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Treatment success after initial treatment	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1.1 Suction curettage after UAE	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.81, 1.03]
3.1.2 Suction curettage after UACE	1	92	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.09]
3.2 Complications	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.2.1 Suction curettage after UAE	1	66	Risk Ratio (M-H, Fixed, 95% CI)	4.00 [0.47, 33.91]
3.2.2 Suction curettage after UACE	1	92	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.72]
3.3 Adverse effects (overall)	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3.1 Suction curettage after UAE	1	66	Odds Ratio (M-H, Fixed, 95% CI)	3.09 [0.12, 78.70]
3.3.2 Suction curettage after UACE	1	92	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Time to normalize β-hCG	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.4.1 Suction curettage after UAE	1	66	Mean Difference (IV, Fixed, 95% CI)	4.03 [-1.79, 9.85]
3.4.2 Suction curettage after UACE	1	92	Mean Difference (IV, Fixed, 95% CI)	0.84 [-1.90, 3.58]

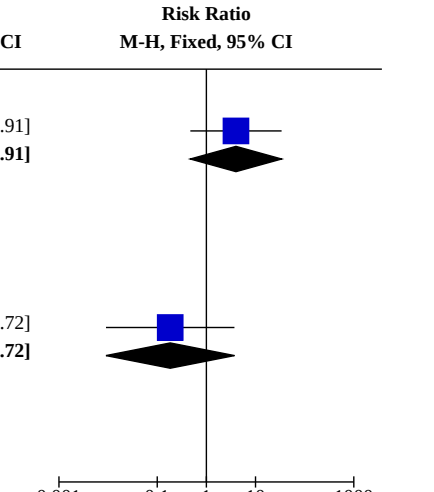
Analysis 3.1. Comparison 3: Suction curettage under hysteroscopy versus under ultrasonography, Outcome 1: Treatment success after initial treatment

Study or Subgroup	Hysteroscopy Events	Hysteroscopy Total	Ultrasonography Events	Ultrasonography Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Suction curettage after UAE						
Qian 2015	30	33	33	33	100.0%	0.91 [0.81 , 1.03]
Subtotal (95% CI)		**33**		**33**	**100.0%**	**0.91 [0.81 , 1.03]**
Total events:	30		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						
3.1.2 Suction curettage after UACE						
Li 2016	48	48	43	44	100.0%	1.02 [0.96 , 1.09]
Subtotal (95% CI)		**48**		**44**	**100.0%**	**1.02 [0.96 , 1.09]**
Total events:	48		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
Test for subgroup differences: Chi² = 2.88, df = 1 (P = 0.09), I² = 65.3%						



Analysis 3.2. Comparison 3: Suction curettage under hysteroscopy versus under ultrasonography, Outcome 2: Complications

Study or Subgroup	Hysteroscopy Events	Hysteroscopy Total	Ultrasonography Events	Ultrasonography Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Suction curettage after UAE						
Qian 2015 (1)	4	33	1	33	100.0%	4.00 [0.47 , 33.91]
Subtotal (95% CI)		**33**		**33**	**100.0%**	**4.00 [0.47 , 33.91]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.27 (P = 0.20)						
3.2.2 Suction curettage after UACE						
Li 2016 (2)	0	48	2	44	100.0%	0.18 [0.01 , 3.72]
Subtotal (95% CI)		**48**		**44**	**100.0%**	**0.18 [0.01 , 3.72]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Test for subgroup differences: Chi² = 2.68, df = 1 (P = 0.10), I² = 62.6%						

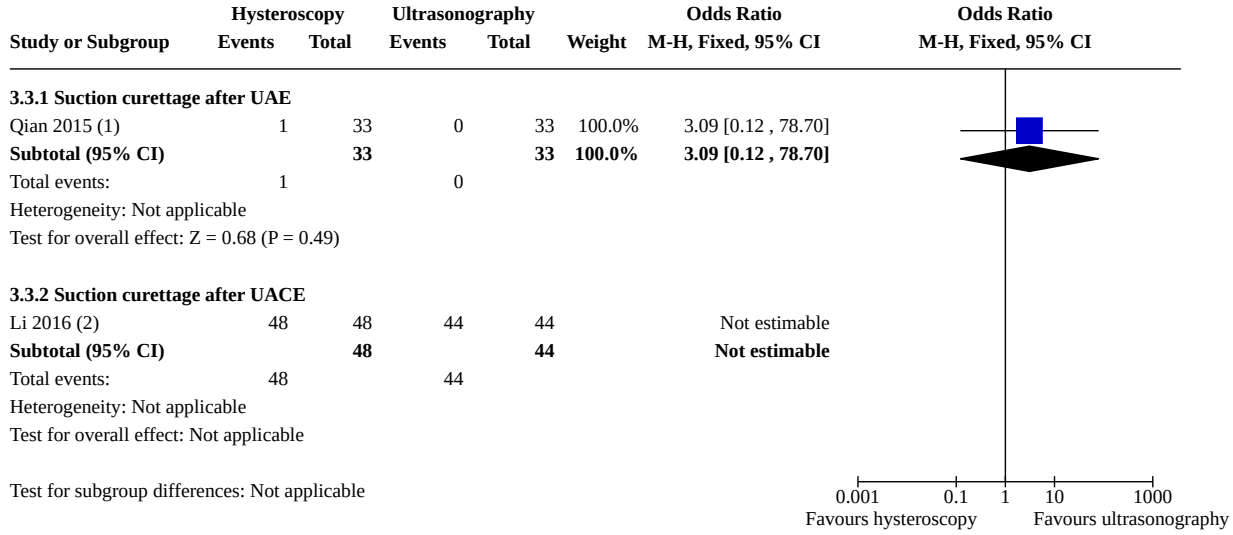


Footnotes

(1) Complications: recurrence of active bleeding, pelvic infection and hysterectomy

(2) Complications: heavy bleeding, uterine perforation, pelvic infection, incomplete abortion and uterine adhesion

Analysis 3.3. Comparison 3: Suction curettage under hysteroscopy versus under ultrasonography, Outcome 3: Adverse effects (overall)

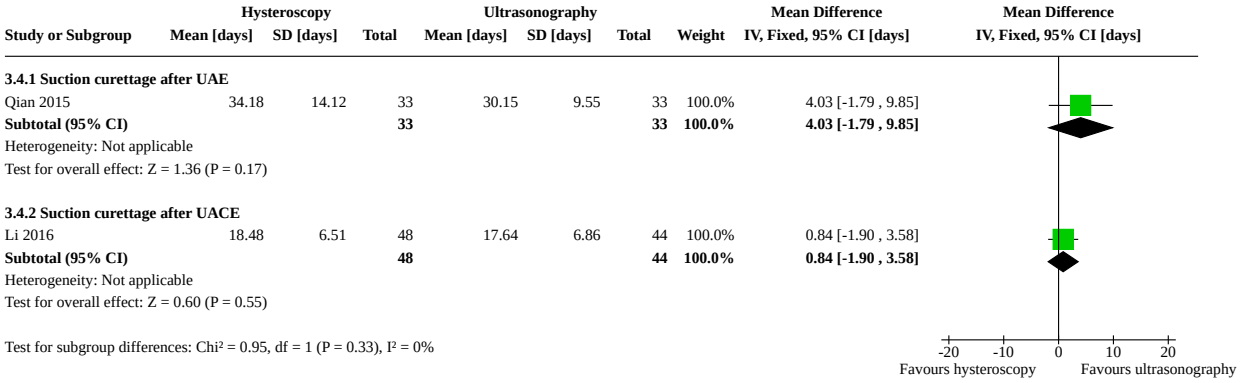


Footnotes

(1) Included: chest congestion

(2) Included: low fever (37.3–38.5 °C) and abdominal pain

Analysis 3.4. Comparison 3: Suction curettage under hysteroscopy versus under ultrasonography, Outcome 4: Time to normalize β-hCG



ADDITIONAL TABLES

Table 1. Incidence of non-tubal ectopic pregnancy in all ectopic pregnancies

Type	Incidence (%)
Abdominal	0.3–1.4
Caesarean scar	6.1
Cervical	< 1
Cornual	1.7–2.1

Table 1. Incidence of non-tubal ectopic pregnancy in all ectopic pregnancies *(Continued)*

Ovarian	1–6

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility (CGF) Group Specialised Register search strategy

PROCITE platform

Searched 12 December 2019

Keywords CONTAINS "ectopic pregnancies" or "ectopic pregnancy" or "ectopic pregnancy-outcome" or "ectopic pregnancy rate" or "ectopic rate" or "caesarean scar pregnancy" or Title CONTAINS "ectopic pregnancies" or "ectopic pregnancy" or "ectopic pregnancy-outcome" or "ectopic pregnancy rate" or "ectopic rate" or "caesarean scar pregnancy"

(263 records)

Appendix 2. CENTRAL Register of Studies ONLINE (CRSO) search strategy

Web platform

Searched 12 December 2019

#1 MESH DESCRIPTOR Pregnancy, Ectopic EXPLODE ALL TREES 159

#2 (cornual adj3 pregnanc*):TI,AB,KY 1

#3 (heterotopic adj3 pregnanc*):TI,AB,KY 2

#4 (ectopic adj3 pregnanc*):TI,AB,KY 639

#5 (abdomin* adj3 pregnanc*):TI,AB,KY 33

#6 (extrauterine adj3 pregnanc*):TI,AB,KY 8

#7 (interstitial adj3 pregnanc*):TI,AB,KY 2

#8 (cervi* adj3 pregnanc*):TI,AB,KY 188

#9 (ovar* adj3 pregnanc*):TI,AB,KY 888

#10 (cesarean scar adj3 pregnanc*):TI,AB,KY 23

#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 1778

#12 MESH DESCRIPTOR Hysteroscopy EXPLODE ALL TREES 382

#13 MESH DESCRIPTOR Laparoscopy EXPLODE ALL TREES 5347

#14 MESH DESCRIPTOR Hysterectomy EXPLODE ALL TREES 1722

#15 MESH DESCRIPTOR Uterine Artery Embolization EXPLODE ALL TREES 47

#16 MESH DESCRIPTOR Dilatation and Curettage EXPLODE ALL TREES 357

#17 MESH DESCRIPTOR Salpingectomy EXPLODE ALL TREES 44

#18 MESH DESCRIPTOR Salpingostomy EXPLODE ALL TREES 39

#19 MESH DESCRIPTOR Methotrexate EXPLODE ALL TREES 3756

#20 MESH DESCRIPTOR Potassium Chloride EXPLODE ALL TREES 319

#21 MESH DESCRIPTOR Sodium Chloride EXPLODE ALL TREES 2453

#22 (expectant management):TI,AB,KY 619

#23 (wait adj1 see):TI,AB,KY 182

#24 (watchful wait*):TI,AB,KY 708

#25 (medical treatment*):TI,AB,KY 5430

#26 (medical therap*):TI,AB,KY 4355

#27 (hysteroscop* or laparoscop*):TI,AB,KY 19570

#28 hysterectom*:TI,AB,KY 5845

#29 (uterine artery emboli?ation or UAE):TI,AB,KY 552

#30 (Dilatation adj3 Curettage):TI,AB,KY 364

#31 (High-intensity focused ultraso*):TI,AB,KY 219

#32 Methotrexate:TI,AB,KY 10515

#33 (Potassium Chloride):TI,AB,KY 840

#34 (Sodium Chloride):TI,AB,KY 7972

#35 (sac adj3 aspirat*):TI,AB,KY 0

#36 (open surg*):TI,AB,KY 2381

#37 (conservative treatment*):TI,AB,KY 4560

#38 (conservative management):TI,AB,KY 937

#39 embryocide*:TI,AB,KY 0

#40 (hyperosmolar glucose):TI,AB,KY 13

#41 (crystalline trichosanthin):TI,AB,KY 0

#42 (Salpingostom* or salpingectom*):TI,AB,KY 293

#43 MESH DESCRIPTOR High-Intensity Focused Ultrasound Ablation EXPLODE ALL TREES 66

#44 (ultrasound ablation):TI,AB,KY 72

#45 MESH DESCRIPTOR Laparotomy EXPLODE ALL TREES 714

#46 laparotom*:TI,AB,KY 3142

#47 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 61887

#48 #11 AND #47 427

Appendix 3. MEDLINE search strategy

Ovid platform

Searched from 1946 to 12 December 2019

1 pregnancy, ectopic/ or exp pregnancy, abdominal/ or pregnancy, heterotopic/ (11763)
2 (cornual adj3 pregnanc$).tw. (304)
3 (heterotopic adj3 pregnanc$).tw. (641)
4 ectopic pregnanc$.tw. (9946)
5 (abdomin$ adj3 pregnanc$).tw. (1832)
6 (extrauterine adj3 pregnanc$).tw. (1302)
7 (interstitial adj3 pregnanc$).tw. (629)

8 (cervi$ adj3 pregnanc$).tw. (2678)
9 (ovar$ adj3 pregnanc$).tw. (2879)
10 (cesarean scar adj3 pregnanc$).tw. (454)
11 or/1-10 (21375)
12 exp hysteroscopy/ or laparoscopy/ or hand-assisted laparoscopy/ (87508)
13 exp hysterectomy/ or uterine artery embolization/ (30831)
14 exp "Dilatation and Curettage"/ (3036)
15 Methotrexate/ (37195)
16 Potassium Chloride/ (17780)
17 Sodium Chloride/ (58018)
18 expectant management.tw. (2467)
19 (wait adj1 see).tw. (5)
20 medical treatment.tw. (44126)
21 medical therap$.tw. (29916)
22 (hysteroscop$ or laparoscop$).tw. (126734)
23 hysterectom$.tw. (35236)
24 uterine artery emboli?ation.tw. (1667)
25 (Dilatation and Curettage).tw. (1366)
26 High-intensity focused ultrasound.tw. (2795)
27 Methotrexate.tw. (39821)
28 Potassium Chloride.tw. (6061)
29 Sodium Chloride.tw. (16652)
30 sac aspiration.tw. (25)
31 high-intensity focused ultrasound ablation/ or laparotomy/ (20142)
32 open surg$.tw. (23722)
33 conservative treatment.tw. (28616)
34 conservative management.tw. (14395)
35 embryocide$.tw. (10)
36 hyperosmolar glucose.tw. (72)
37 crystalline trichosanthin.tw. (1)
38 or/12-37 (461512)
39 11 and 38 (5837)
40 randomized controlled trial.pt. (495635)
41 controlled clinical trial.pt. (93449)
42 randomized.ab. (462685)
43 randomised.ab. (92495)
44 placebo.tw. (208784)
45 clinical trials as topic.sh. (189357)
46 randomly.ab. (322897)
47 trial.ti. (209094)
48 (crossover or cross-over or cross over).tw. (82695)
49 or/40-48 (1318313)
50 exp animals/ not humans.sh. (4648880)
51 49 not 50 (1213123)
52 39 and 51 (266)

Appendix 4. Embase search strategy

Ovid platform

Searched from 1980 to 12 December 2019

1 exp ectopic pregnancy/ (17716)
2 (cornual adj3 pregnanc$).tw. (500)
3 (heterotopic adj3 pregnanc$).tw. (877)
4 ectopic pregnanc$.tw. (12257)
5 (abdomin$ adj3 pregnanc$).tw. (1627)
6 (extrauterine adj3 pregnanc$).tw. (852)
7 (interstitial adj3 pregnanc$).tw. (676)
8 (cervi$ adj3 pregnanc$).tw. (2828)
9 (ovar$ adj3 pregnanc$).tw. (2882)
10 (cesarean scar adj3 pregnanc$).tw. (684)
11 or/1-10 (24654)

12 exp hysteroscopy/ (11521)
13 exp laparoscopy/ or exp hand assisted laparoscopy/ (151525)
14 exp hysterectomy/ or exp abdominal hysterectomy/ (66893)
15 exp uterine artery embolization/ (3546)
16 exp curettage/ (12543)
17 "Dilatation and Curettage".tw. (1421)
18 exp methotrexate/ (164785)
19 potassium chloride/ (24218)
20 sodium chloride/ (172253)
21 exp conservative treatment/ (545564)
22 expectant management.tw. (3664)
23 (wait adj1 see).tw. (15)
24 medical treatment.tw. (61737)
25 medical therap$.tw. (45496)
26 (hysteroscop$ or laparoscop$).tw. (202457)
27 hysterectom$.tw. (52580)
28 uterine artery emboli?ation.tw. (2683)
29 (Dilatation and Curettage).tw. (1554)
30 High-intensity focused ultrasound.tw. (3997)
31 Methotrexate.tw. (62532)
32 Potassium Chloride.tw. (6376)
33 Sodium Chloride.tw. (17647)
34 sac aspiration.tw. (20)
35 exp high intensity focused ultrasound/ (5266)
36 exp laparotomy/ (73782)
37 open surg$.tw. (36210)
38 conservative treatment.tw. (35831)
39 conservative management.tw. (19782)
40 embryocide$.tw. (10)
41 hyperosmolar glucose.tw. (79)
42 crystalline trichosanthin.tw. (1)
43 or/12-42 (1381398)
44 11 and 43 (10377)
45 Clinical Trial/ (949432)
46 Randomized Controlled Trial/ (576494)
47 exp randomization/ (85116)
48 Single Blind Procedure/ (37225)
49 Double Blind Procedure/ (164383)
50 Crossover Procedure/ (61279)
51 Placebo/ (329309)
52 Randomi?ed controlled trial$.tw. (216303)
53 Rct.tw. (34912)
54 random allocation.tw. (1950)
55 randomly allocated.tw. (33705)
56 allocated randomly.tw. (2480)
57 (allocated adj2 random).tw. (807)
58 Single blind$.tw. (23682)
59 Double blind$.tw. (196984)
60 ((treble or triple) adj blind$).tw. (1056)
61 placebo$.tw. (293710)
62 prospective study/ (565394)
63 or/45-62 (2106769)
64 case study/ (65626)
65 case report.tw. (386274)
66 abstract report/ or letter/ (1070162)
67 or/64-66 (1512139)
68 63 not 67 (2055003)
69 44 and 68 (809)

Appendix 5. PsycINFO search strategy

Ovid platform

Searched from 1806 to 12 December 2019

1 (cornual adj3 pregnanc$).tw. (1)
2 (heterotopic adj3 pregnanc$).tw. (1)
3 ectopic pregnanc$.tw. (97)
4 (abdomin$ adj3 pregnanc$).tw. (9)
5 (extrauterine adj3 pregnanc$).tw. (3)
6 (cervi$ adj3 pregnanc$).tw. (13)
7 (ovar$ adj3 pregnanc$).tw. (40)
8 (cesarean scar adj3 pregnanc$).tw. (0)
9 or/1-8 (156)
10 exp Surgery/ (69481)
11 exp Hysterectomy/ (441)
12 exp Drug Therapy/ or exp Induced Abortion/ (145074)
13 expectant management.tw. (30)
14 (wait adj1 see).tw. (2)
15 medical treatment.tw. (6116)
16 medical therap$.tw. (1427)
17 (hysteroscop$ or laparoscop$).tw. (503)
18 hysterectom$.tw. (811)
19 uterine artery emboli?ation.tw. (4)
20 (Dilatation and Curettage).tw. (11)
21 High-intensity focused ultrasound.tw. (10)
22 Methotrexate.tw. (352)
23 Potassium Chloride.tw. (332)
24 Sodium Chloride.tw. (957)
25 sac aspiration.tw. (0)
26 open surg$.tw. (95)
27 conservative treatment.tw. (287)
28 conservative management.tw. (149)
29 embryocide$.tw. (0)
30 hyperosmolar glucose.tw. (0)
31 crystalline trichosanthin.tw. (0)
32 or/10-31 (217544)
33 9 and 32 (36)
34 random.tw. (56898)
35 control.tw. (435200)
36 double-blind.tw. (22534)
37 clinical trials/ (11506)
38 placebo/ (5429)
39 exp Treatment/ (1023681)
40 or/34-39 (1412737)
41 33 and 40 (35)

Appendix 6. CINAHL search strategy

Ovid platform

Searched from 1961 to 12 December 2019

#	Query	Results
S56	S41 AND S55	229
S55	S42 OR S43 or S44 or S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54	1,363,333
S54	TX allocat* random*	11,181

(Continued)

S53	(MH "Quantitative Studies")	23,926
S52	(MH "Placebos")	11,504
S51	TX placebo*	60,127
S50	TX random* allocat*	11,181
S49	(MH "Random Assignment")	56,448
S48	TX randomi* control* trial*	179,148
S47	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	1,038,136
S46	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	249
S45	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	249
S44	TX clinic* n1 trial*	254,707
S43	PT Clinical trial	86,318
S42	(MH "Clinical Trials+")	270,305
S41	S11 AND S40	1,621
S40	S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39	120,857
S39	TX laparotomy	7,133
S38	TX (hyperosmolar glucose)	12
S37	TX embryocide*	1
S36	TX (conservative management)	4,101
S35	TX (conservative treatment)	6,871
S34	TX (open surg*)	9,564
S33	(MM "Laparotomy")	1,172
S32	TX sac aspiration	17
S31	TX Sodium Chloride	7,215
S30	TX Potassium Chloride	1,011
S29	TX Methotrexate	7,669
S28	TX (High-intensity focused ultrasound)	574

(Continued)

S27	TX (Dilatation and Curettage)	814
S26	TX (uterine artery emboli?ation)	994
S25	TX hysterectom*	10,490
S24	TX (hysteroscop* or laparoscop*)	34,538
S23	TX medical therap*	19,973
S22	TX medical treatment	22,335
S21	TX (wait N1 see)	475
S20	TX expectant management	949
S19	(MM "Sodium Chloride")	1,358
S18	(MM "Potassium Chloride")	145
S17	(MM "Methotrexate")	2,319
S16	(MM "Dilatation and Curettage")	367
S15	(MH "Uterine Artery Embolization")	516
S14	(MM "Hysterectomy") OR (MM "Hysterectomy, Vaginal")	3,852
S13	(MM "Laparoscopy") OR (MM "Surgery, Laparoscopic")	14,762
S12	(MM "Hysteroscopy")	959
S11	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10	4,582
S10	TX (cesarean scar N3 pregnanc*)	297
S9	TX (ovar* N3 pregnanc*)	452
S8	TX (cervi* N3 pregnanc*)	723
S7	TX (interstitial N3 pregnanc*)	158
S6	TX (extrauterine N3 pregnanc*)	52
S5	TX (abdomin* N3 pregnanc*)	441
S4	TX (ectopic pregnanc*)	3,190
S3	TX (heterotopic N3 pregnanc*)	172
S2	TX (cornual N3 pregnanc*)	99
S1	(MM "Pregnancy, Ectopic") OR (MM "Pregnancy, Heterotopic")	1,909

Appendix 7. CBM search strategy

Web platform

Searched from 1978 to 12 December 2019

1 Mesh:Pregnancy, Ectopic/All Trees/AL/DH/DT/NU/PC/QL/RH/RT/SU/TH/XL/ZD/ZH/ZJ/ZL

2 (Cervical Pregnancy) or (Cervical Pregnancies) or (Pregnancy, cervical) -limitation:Clinical Trials; Randomized Controlled Trials; Multicenter Studies

3 (Cesarean Scar Pregnancy) or (Cesarean Scar Pregnancies) or (Pregnancy, Cesarean Scar) -limitation:Clinical Trials; Randomized Controlled Trials; Multicenter Studies

4 (Interstitial Pregnancy) or (Interstitial Pregnancies) or (Pregnancy, Interstitial)-limitation:Clinical Trials; Randomized Controlled Trials; Multicenter Studies

5 (Cornual Pregnancy) or (Cornual Pregnancies) or (Pregnancy, Cornual)-limitation:Clinical Trials; Randomized Controlled Trials; Multicenter Studies

6 (Ovarian Pregnancy) or (Ovarian Pregnancies) or (Pregnancy, Ovarian)-limitation:Clinical Trials; Randomized Controlled Trials; Multicenter Studies

7 (Abdominal Pregnancy) or (Abdominal Pregnancies) or (Pregnancy, Abdominal)-limitation:Clinical Trials; Randomized Controlled Trials; Multicenter Studies

8 (Non-tubal Pregnancy) or (Non-tubal Pregnancies) or (Pregnancy, Non-tubal)-limitation:Clinical Trials; Randomized Controlled Trials; Multicenter Studies

9 (Unusual Located Pregnancy) or (Unusual Located Pregnancies) or (Pregnancy, Unusual Located)-limitation:Clinical Trials; Randomized Controlled Trials; Multicenter Studies

10 #8 or #9

11 # 1 and # 2

12 # 1 and # 3

13 # 1 and # 4

14 # 1 and # 5

15 # 1 and # 6

16 # 1 and # 7

17 # 1 and # 10

18 #11 or # 12 or # 13 or # 14 or # 15 or # 16 or #17

HISTORY

Protocol first published: Issue 7, 2014
Review first published: Issue 7, 2020

Date	Event	Description
16 July 2014	Amended	Name of author Shiyuan Yang incorrect in published protocol

CONTRIBUTIONS OF AUTHORS

YL: screened titles and abstracts, retrieved and examined the full texts, selected studies, assessed risk of bias.

HZ: screened titles and abstracts, retrieved and examined the full texts, selected studies.

YH: extracted data, assessed risk of bias.

LS: extracted data.

JF: resolved disagreements on selection of studies.

WH: resolved disagreements on data extraction and management.

All review authors contributed to the review development.

DECLARATIONS OF INTEREST

HZ, YH, LS, JF, WH, QW, and SY had no conflicts to declare.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There was a change of authorship. Qiushi Wang, Shiyuan Yang, and Taixiang Wu contributed to the protocol (Shen 2014), but not the review. Ying Long and Yuanyuan Hu joined the team at the review stage.

Data were too few for review authors to conduct planned subgroup and sensitivity analyses, or to construct a funnel plot to assess reporting bias.

We have removed reference to interstitial pregnancy (included in the protocol) as this is a tubal pregnancy and thus does not meet this review's inclusion criteria.

One comparison between different surgical methods was added to the review.

We added the following definition of treatment success: 'a steady decline in serum β-hCG to normal levels by the initial treatment, coupled with a lack of major complications (including massive acute bleeding, recurrence of active bleeding, incomplete abortion and hysterectomy)'.

We added a secondary outcome: 'time to normalise β-hCG'.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortifacient Agents, Nonsteroidal [administration & dosage] [adverse effects]; Bias; Cesarean Section; Chemoembolization, Therapeutic [adverse effects]; Cicatrix [complications]; Confidence Intervals; Dilatation and Curettage [adverse effects] [methods]; Hysteroscopy; Methotrexate [administration & dosage] [adverse effects]; Pregnancy, Ectopic [*therapy]; Randomized Controlled Trials as Topic; Sample Size; Ultrasonography, Interventional; Uterine Artery; Uterine Artery Embolization [adverse effects]; Vacuum Curettage

MeSH check words

Female; Humans; Pregnancy