



BJOG

An International Journal of
Obstetrics and Gynaecology



Royal College of
Obstetricians &
Gynaecologists

Diagnosis and Management of Ectopic Pregnancy

Green-top Guideline No. 21

RCOG/AEPU Joint Guideline | November 2016

Please cite this paper as: Elson CJ, Salim R, Potdar N, Chetty M, Ross JA, Kirk Ej on behalf of the Royal College of Obstetricians and Gynaecologists. Diagnosis and management of ectopic pregnancy. *BJOG* 2016;123:e15–e55.



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Diagnosis and Management of Ectopic Pregnancy

This guideline replaces *The Management of Tubal Pregnancy*, which was published in 2004.

Executive summary of recommendations

Diagnosis of ectopic pregnancy

How is a tubal pregnancy diagnosed?

What are the ultrasound criteria?

Transvaginal ultrasound is the diagnostic tool of choice for tubal ectopic pregnancy. [New 2016]

B

Tubal ectopic pregnancies should be positively identified, if possible, by visualising an adnexal mass that moves separate to the ovary. [New 2016]

D

What biochemical investigations should be carried out?

A serum progesterone level is not useful in predicting ectopic pregnancy. [New 2016]

B

A serum beta-human chorionic gonadotrophin (β -hCG) level is useful for planning the management of an ultrasound visualised ectopic pregnancy. [New 2016]

C

How is a cervical pregnancy diagnosed?

What are the ultrasound criteria?

The following ultrasound criteria may be used for the diagnosis of cervical ectopic pregnancy: an empty uterus, a barrel-shaped cervix, a gestational sac present below the level of the internal cervical os, the absence of the 'sliding sign' and blood flow around the gestational sac using colour Doppler. [New 2016]

D

What biochemical investigations should be carried out?

A single serum β -hCG should be carried out at diagnosis. [New 2016]

D

How is a caesarean scar pregnancy diagnosed?

What are the ultrasound criteria?

Clinicians should be aware that ultrasound is the primary diagnostic modality, using a transvaginal approach supplemented by transabdominal imaging if required. [New 2016]

D

Defined criteria for diagnosing caesarean scar pregnancy on transvaginal scan have been described. [New 2016]

D

Magnetic resonance imaging (MRI) can be used as a second-line investigation if the diagnosis is equivocal and there is local expertise in the MRI diagnosis of caesarean scar pregnancies. [New 2016]

D

What biochemical investigations should be carried out?

No biochemical investigations are needed routinely. [New 2016]



How is an interstitial pregnancy diagnosed?

What are the ultrasound criteria?

The following ultrasound scan criteria may be used for the diagnosis of interstitial pregnancy: empty uterine cavity, products of conception/gestational sac located laterally in the interstitial (intramural) part of the tube and surrounded by less than 5 mm of myometrium in all imaging planes, and presence of the 'interstitial line sign'. [New 2016]

D

Sonographic findings in two-dimension can be further confirmed using three-dimensional ultrasound, where available, to avoid misdiagnosis with early intrauterine or angular (implantation in the lateral angles of the uterine cavity) pregnancy. [New 2016]

D

Supplementation with MRI can also be helpful in the diagnosis of interstitial pregnancy. [New 2016]

D

What biochemical investigations should be carried out?

A single serum β -hCG should be carried out at diagnosis to help with management. In some cases, a repeat serum β -hCG in 48 hours may be useful in deciding further management. [New 2016]



How is a cornual pregnancy diagnosed?

What are the ultrasound criteria?

The following ultrasound scan criteria may be used for the diagnosis of cornual pregnancy: visualisation of a single interstitial portion of fallopian tube in the main uterine body, gestational sac/products of conception seen mobile and separate from the uterus and completely surrounded by myometrium, and a vascular pedicle adjoining the gestational sac to the unicornuate uterus. [New 2016]

D

What biochemical investigations should be carried out?

A single serum β -hCG should be carried out at diagnosis to help with management. In some cases, a repeat serum β -hCG in 48 hours may be useful in deciding further management. [New 2016]

✓

How is an ovarian pregnancy diagnosed?

What are the ultrasound criteria?

There are no specific agreed criteria for the ultrasound diagnosis of ovarian ectopic pregnancy. [New 2016]

D

What biochemical investigations should be carried out?

A single serum β -hCG should be carried out at diagnosis to help with management. In some cases, a repeat serum β -hCG in 48 hours may be useful in deciding further management. [New 2016]

✓

How is an abdominal pregnancy diagnosed?

What are the ultrasound criteria?

Defined ultrasound criteria can be used to diagnose an abdominal pregnancy. [New 2016]

D

MRI can be a useful diagnostic adjunct in advanced abdominal pregnancy and can help to plan the surgical approach. [New 2016]

D

What biochemical investigations should be carried out?

A high index of suspicion is based upon an elevated serum β -hCG level in combination with ultrasound findings. [New 2016]

D

How is heterotopic pregnancy diagnosed?

What are the ultrasound criteria?

A heterotopic pregnancy is diagnosed when the ultrasound findings demonstrate an intrauterine pregnancy and a coexisting ectopic pregnancy. [New 2016]

D

What biochemical investigations should be carried out?

A serum β -hCG level is of limited value in diagnosing heterotopic pregnancy. [New 2016]

D

Management options

What are the surgical, pharmacological or conservative treatment options for tubal pregnancy?

A laparoscopic surgical approach is preferable to an open approach.

A

In the presence of a healthy contralateral tube, salpingectomy should be performed in preference to salpingotomy. [New 2016]

B

In women with a history of fertility-reducing factors (previous ectopic pregnancy, contralateral tubal damage, previous abdominal surgery, previous pelvic inflammatory disease), salpingotomy should be considered. [New 2016]

C

If a salpingotomy is performed, women should be informed about the risk of persistent trophoblast with the need for serum β -hCG level follow-up. They should also be counselled that there is a small risk that they may need further treatment in the form of systemic methotrexate or salpingectomy.



Systemic methotrexate may be offered to suitable women with a tubal ectopic pregnancy. It should never be given at the first visit, unless the diagnosis of ectopic pregnancy is absolutely clear and a viable intrauterine pregnancy has been excluded. [New 2016]

B

Expectant management is an option for clinically stable women with an ultrasound diagnosis of ectopic pregnancy and a decreasing β -hCG level initially less than 1500 iu/l.

B

What are the surgical, pharmacological or conservative treatment options for cervical pregnancy?

Medical management with methotrexate can be considered for cervical pregnancy. [New 2016]

D

Surgical methods of management are associated with a high failure rate and should be reserved for those women suffering life-threatening bleeding. [New 2016]

D

What are the surgical, pharmacological or conservative treatment options for caesarean scar pregnancy?

Women diagnosed with caesarean section scar pregnancies should be counselled that such pregnancies are associated with severe maternal morbidity and mortality. [New 2016]

D

Medical and surgical interventions with or without additional haemostatic measures should be considered in women with first trimester caesarean scar pregnancy. [New 2016]

D

There is insufficient evidence to recommend any one specific intervention over another for caesarean scar pregnancy, but the current literature supports a surgical rather than medical approach as the most effective. [New 2016]

D

What are the surgical, pharmacological or conservative treatment options for interstitial pregnancy?

Nonsurgical management is an acceptable option for stable interstitial pregnancies. [New 2016]

D

Expectant management is only suitable for women with low or significantly falling β-hCG levels in whom the addition of methotrexate may not improve the outcome. [New 2016]

D

A pharmacological approach using methotrexate has been shown to be effective, although, there is insufficient evidence to recommend local or systemic approach. [New 2016]

D

Surgical management by laparoscopic cornual resection or salpingotomy is an effective option. [New 2016]

D

Alternative surgical techniques could include hysteroscopic resection under laparoscopic or ultrasound guidance. [New 2016]

D

There is insufficient evidence on safety and complications in future pregnancies to recommend other nonsurgical methods. [New 2016]

D

What are the surgical, pharmacological or conservative treatment options for cornual pregnancy?

Cornual pregnancies should be managed by excision of the rudimentary horn via laparoscopy or laparotomy. [New 2016]

D

What are the surgical, pharmacological or conservative treatment options for ovarian pregnancy?

Definitive surgical treatment is preferred if laparoscopy is required to make the diagnosis of ovarian ectopic pregnancy. [New 2016]

D

Systemic methotrexate can be used to treat ovarian ectopic pregnancy when the risk of surgery is high, or postoperatively in the presence of persistent residual trophoblast or persistently raised β-hCG levels. [New 2016]

D

What are the surgical, pharmacological or conservative treatment options for abdominal pregnancy?

Laparoscopic removal is an option for treatment of early abdominal pregnancy. [New 2016]

D

Possible alternative treatment methods would be systemic methotrexate with ultrasound-guided fetocide. [New 2016]

D

Advanced abdominal pregnancy should be managed by laparotomy. [New 2016]

D

What are the surgical, pharmacological or conservative treatment options for heterotopic pregnancy?

The intrauterine pregnancy must be considered in the management plan. [New 2016]

B

Methotrexate should only be considered if the intrauterine pregnancy is nonviable or if the woman does not wish to continue with the pregnancy. [New 2016]

D

Local injection of potassium chloride or hyperosmolar glucose with aspiration of the sac contents is an option for clinically stable women. [New 2016]

D

Surgical removal of the ectopic pregnancy is the method of choice for haemodynamically unstable women and is also an option for haemodynamically stable women. [New 2016]

D

Expectant management is an option in heterotopic pregnancies where the ultrasound findings are of a nonviable pregnancy. [New 2016]

D

Do rhesus D (RhD)-negative women with an ectopic pregnancy require anti-D immunoglobulin?

Offer anti-D prophylaxis as per national protocol to all RhD-negative women who have surgical removal of an ectopic pregnancy, or where bleeding is repeated, heavy or associated with abdominal pain. [New 2016]

D

What are the long-term fertility prospects following an ectopic pregnancy?

In the absence of a history of subfertility or tubal pathology, women should be advised that there is no difference in the rate of fertility, the risk of future tubal ectopic pregnancy or tubal patency rates between the different management methods. [New 2016]

D

Women with a previous history of subfertility should be advised that treatment of their tubal ectopic pregnancy with expectant or medical management is associated with improved reproductive outcomes compared with radical surgery. [New 2016]

C

Women receiving methotrexate for the management of tubal ectopic pregnancy can be advised that there is no effect on ovarian reserve. [New 2016]

D

Women undergoing treatment with uterine artery embolisation and systemic methotrexate for nontubal ectopic pregnancies can be advised that live births have been reported in subsequent pregnancies. [New 2016]

D

Women undergoing laparoscopic management of ovarian pregnancies can be advised that their future fertility prospects are good. [New 2016]

D

What support and counselling should be offered to women undergoing treatment for ectopic pregnancy?

Women should be advised, whenever possible, of the advantages and disadvantages associated with each approach used for the treatment of ectopic pregnancy, and should participate fully in the selection of the most appropriate treatment.

D

Women should be made aware of how to access support via patient support groups, such as the Ectopic Pregnancy Trust, or local bereavement counselling services. [New 2016]

D

Muscle relaxation training may be of use to women undergoing treatment for ectopic pregnancy with methotrexate. [New 2016]

C

It is recommended that women treated with methotrexate wait at least 3 months before trying to conceive again. [New 2016]

D

Service and training

What is the most appropriate setting for management of women with an ectopic pregnancy?

Providers of early pregnancy care should provide a 7-day early pregnancy assessment service with direct access for women referred by general practitioners and accident and emergency departments, i.e. along current NHS recommendations. Available facilities for the management of suspected ectopic pregnancy should include diagnostic and therapeutic algorithms, transvaginal ultrasound and serum β-hCG estimations.

✓

Women should have access to all appropriate management options for their ectopic pregnancy. If local facilities do not provide all options, then clear referral pathways should exist to allow them to access appropriate care. [New 2016]

✓

What are the training implications for those managing women with ectopic pregnancy?

Clinicians undertaking the surgical management of ectopic pregnancy must have received appropriate training. Laparoscopic surgery requires appropriate equipment and trained theatre staff.

✓

Clinicians undertaking ultrasound for the diagnosis of ectopic pregnancy must have received appropriate training. [New 2016]

✓

Clinicians undertaking medical management via ultrasound-guided needle techniques must have received appropriate training. [New 2016]



If clinicians undertaking surgical management of ectopic pregnancy cannot carry out the full range of surgical procedures, appropriately experienced support must be available if necessary. [New 2016]



Virtual reality simulators can be used as a training tool for salpingectomy. [New 2016]



1. Purpose and scope

The purpose of this guideline is to provide evidence-based guidance on the diagnosis and management of ectopic pregnancies. This guideline will cover the following ectopic pregnancies: tubal, cervical, caesarean scar, interstitial, cornual, ovarian, abdominal and heterotopic. The diagnosis and management of pregnancy of unknown location (PUL) will not be covered.

The management of PUL is discussed in the National Institute for Health and Care Excellence (NICE) guideline.¹

2. Introduction and background epidemiology

An ectopic pregnancy is any pregnancy implanted outside of the endometrial cavity. In the UK, the incidence is approximately 11/1000 pregnancies, with an estimated 11 000 ectopic pregnancies diagnosed each year.² The incidence of ectopic pregnancy in women attending early pregnancy units is 2–3%.^{3,4} Unfortunately, women still die from ectopic pregnancy, with six maternal deaths reported between 2006 and 2008. However, the case fatality rate has decreased over recent years, suggesting that earlier diagnosis and treatment may have made an impact.²

Risk factors for ectopic pregnancy include tubal damage following surgery or infection, smoking and in vitro fertilisation.^{5–9} However, the majority of women with an ectopic pregnancy have no identifiable risk factor.

3. Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing Royal College of Obstetricians and Gynaecologists (RCOG) Green-top Guidelines. MEDLINE, EMBASE and the Cochrane Library were searched. The search was restricted to articles published between 1995 and July 2015 and limited to humans and the English language. The databases were searched using the relevant Medical Subject Headings (MeSH) terms and this was combined with a keyword search. Search terms included ‘ectopic pregnancy’, ‘tubal pregnancy’, ‘interstitial pregnancy’, ‘cornual pregnancy’, ‘cervical pregnancy’, ‘caesarean scar pregnancy’, ‘ovarian pregnancy’, ‘abdominal pregnancy’, ‘heterotopic pregnancy’, ‘pregnancy of unknown location’ and ‘extrauterine pregnancy’. The National Guideline Clearinghouse, NICE Evidence Search and Trip were also searched for relevant guidelines. Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and annotated as ‘good practice points’ (GPP).

Further information about the assessment of evidence and the grading of recommendations may be found in Appendix I.

4. Diagnosis of ectopic pregnancy

4.1 How is a tubal pregnancy diagnosed?

4.1.1 What are the ultrasound criteria?

Transvaginal ultrasound is the diagnostic tool of choice for tubal ectopic pregnancy.

B

Tubal ectopic pregnancies should be positively identified, if possible, by visualising an adnexal mass that moves separate to the ovary.

D

The majority of tubal ectopic pregnancies should be visualised on transvaginal ultrasound. Transvaginal ultrasound has reported sensitivities of 87.0–99.0% and specificities of 94.0–99.9% for the diagnosis of ectopic pregnancy.^{3,10–13} The majority of ectopic pregnancies will be visualised on the initial ultrasound examination.^{14–18} The remainder will initially be classified as a PUL. Not all ectopic pregnancies initially classified as a PUL are ‘missed’ on the initial scan. Some of these ectopic pregnancies are just too small and too early in the disease process to be visualised on the initial ultrasound examination.¹⁹ Laparoscopy is no longer the gold standard for diagnosis. False-negative laparoscopies (3.0–4.5%) have been reported when the procedure is performed too early in the development of an ongoing ectopic pregnancy.^{20,21}

Evidence level 2++

An inhomogeneous or noncystic adnexal mass is the most common finding in around 50–60% of cases.^{4,10,12,13,19} An empty extrauterine gestational sac will be present in around 20–40% of cases.^{4,10,19} While an extrauterine gestational sac containing a yolk sac and/or embryonic pole that may or may not have cardiac activity will be present in around 15–20% of cases.^{4,10,19}

There is no specific endometrial appearance or thickness to support a diagnosis of tubal ectopic pregnancy. In up to 20% of cases, a collection of fluid may be seen within the uterine cavity, classically referred to as a ‘pseudosac’.^{22–24} The key is to distinguish this from an early intrauterine gestational sac. The intradecidual and double decidual signs can be used to diagnose an early intrauterine pregnancy. The intradecidual sign is described as a fluid collection with an echogenic rim located ‘within a markedly thickened decidua on one side of the uterine cavity’.²⁵ The double decidual sign is described as an intrauterine fluid collection surrounded by ‘two concentric echogenic rings’.²⁶ However, in practice, it can be very difficult to distinguish a ‘pseudosac’ which is just a collection of fluid in the endometrial cavity from an early intrauterine sac. The presence of a ‘pseudosac’ alone cannot be used to diagnose an ectopic pregnancy and in fact, a small anechoic cystic structure is more likely to be an early sac rather than a ‘pseudosac’. A study²⁷ has shown that a woman with a positive pregnancy test, an intrauterine smooth-walled anechoic cystic structure and no adnexal mass has a 0.02% probability of ectopic pregnancy, while the probability of intrauterine pregnancy in such a patient is 99.98%.

Evidence level 3

Free fluid is often seen on ultrasound, but is not diagnostic of ectopic pregnancy. A small amount of anechoic fluid in the pouch of Douglas may be found in both intrauterine and ectopic pregnancies. Echogenic fluid has been reported in 28–56% of ectopic pregnancies.^{28,29} It may signify tubal rupture, but most commonly is due to blood leaking from the fimbrial end of the fallopian tube.

4.1.2 What biochemical investigations should be carried out?

A serum progesterone level is not useful in predicting ectopic pregnancy.

B

A serum beta-human chorionic gonadotrophin (β -hCG) level is useful for planning the management of an ultrasound visualised ectopic pregnancy.

C

A meta-analysis³⁰ has confirmed that a single β -hCG level cannot be used in isolation to predict an ectopic pregnancy.

Evidence level 1-

There is a common misconception that a single low serum β -hCG level (e.g. less than 1000 iu/l) means that an ectopic pregnancy is unlikely. However, this is a false assumption and in modern practice many ectopic pregnancies have a β -hCG value below this level.³¹

Evidence level 2+

The initial serum β -hCG level is a key prognostic indicator for the success of conservative management (expectant and medical) in cases of ultrasound visualised tubal ectopic pregnancies.³²

Evidence level 2-

4.2 How is a cervical pregnancy diagnosed?

4.2.1 What are the ultrasound criteria?

The following ultrasound criteria may be used for the diagnosis of cervical ectopic pregnancy: an empty uterus, a barrel-shaped cervix, a gestational sac present below the level of the internal cervical os, the absence of the 'sliding sign' and blood flow around the gestational sac using colour Doppler.

D

Cervical pregnancies are rare, accounting for less than 1% of all ectopic gestations.³³ Defined criteria have been described for diagnosing cervical ectopic pregnancies.^{34,35}

The following ultrasound criteria have been described in the diagnosis of cervical ectopic pregnancy:

1. Empty uterine cavity.
2. A barrel-shaped cervix.
3. A gestational sac present below the level of the internal cervical os.
4. The absence of the 'sliding sign'.
5. Blood flow around the gestational sac using colour Doppler.

Evidence level 3

The 'sliding sign' enables cervical ectopic pregnancies to be distinguished from miscarriages that are within the cervical canal. When pressure is applied to the cervix using the probe, in a miscarriage, the gestational sac slides against the endocervical canal, but it does not in an implanted cervical pregnancy.³⁴

4.2.2 What biochemical investigations should be carried out?

A single serum β-hCG should be carried out at diagnosis.

D

Evidence level 3

A single serum β-hCG carried out at the time of ultrasound diagnosis is useful in deciding management options. A serum β-hCG level greater than 10 000 iu/l is associated with a decreased chance of successful methotrexate treatment.³⁶

4.3 How is a caesarean scar pregnancy diagnosed?

4.3.1 What are the ultrasound criteria?

Clinicians should be aware that ultrasound is the primary diagnostic modality, using a transvaginal approach supplemented by transabdominal imaging if required.

D

D

Defined criteria for diagnosing caesarean scar pregnancy on transvaginal scan have been described.

Magnetic resonance imaging (MRI) can be used as a second-line investigation if the diagnosis is equivocal and there is local expertise in the MRI diagnosis of caesarean scar pregnancies.

D

Caesarean scar pregnancy is defined as implantation into the myometrial defect occurring at the site of the previous uterine incision. The prevalence of caesarean scar pregnancy is estimated to be approximately 1 in 2000 pregnancies and these pregnancies may be ongoing potentially viable pregnancies or miscarriages within the scar.³⁷

The diagnostic criteria described for diagnosing caesarean scar implantation on transvaginal ultrasound include:

1. Empty uterine cavity.³⁸
2. Gestational sac or solid mass of trophoblast located anteriorly at the level of the internal os embedded at the site of the previous lower uterine segment caesarean section scar.³⁹
3. Thin or absent layer of myometrium between the gestational sac and the bladder.^{38,40}
4. Evidence of prominent trophoblastic/placental circulation on Doppler examination.⁴¹
5. Empty endocervical canal.³⁸

Evidence level 3

Thirteen percent of reported cases of caesarean scar pregnancy were misdiagnosed as intrauterine or cervical pregnancies at presentation.⁴² The true prevalence of caesarean scar pregnancies is likely to be somewhat higher than estimated in the literature as some cases will end in the first trimester, either by miscarriage or termination, and go unreported and undiagnosed. There is a spectrum of severity

associated with pregnancies implanted into caesarean section scars and the natural history is uncertain. Vial et al.⁴³ proposed that there are two different types of pregnancies implanted in a caesarean scar: the first type progressing into the uterine cavity as the gestational sac grows and develops, so with the potential to reach a viable gestational age, but with the risk of massive bleeding from the implantation site; and the second with progression deeper towards the serosal surface of the uterus with the risk of first trimester rupture and haemorrhage. Given that there are also varying appearances of caesarean section scars on the uterus and that placental development evolves over time as the pregnancy progresses, all of these factors can cause difficulty in the diagnosis of caesarean scar pregnancy. The diagnostic criteria have not been subject to validation and are derived from descriptive case series,^{38–44} so to minimise the risk of false-positive diagnosis, we recommend that all nonemergency cases of suspected scar pregnancy are referred to a regional centre to confirm the diagnosis.

Evidence level 3

The MRI features of caesarean scar pregnancy are essentially the same as those described on ultrasound, but ultrasound is more readily available and cheaper.^{44,45}

4.3.2 What biochemical investigations should be carried out?

No biochemical investigations are needed routinely.



A serum β-hCG level may be useful as a baseline prior to monitoring if conservative treatment is contemplated, but it does not have a role in the diagnosis of caesarean scar pregnancy.

4.4 How is an interstitial pregnancy diagnosed?

4.4.1 What are the ultrasound criteria?

The following ultrasound scan criteria may be used for the diagnosis of interstitial pregnancy: empty uterine cavity, products of conception/gestational sac located laterally in the interstitial (intramural) part of the tube and surrounded by less than 5 mm of myometrium in all imaging planes, and presence of the ‘interstitial line sign’.



Sonographic findings in two-dimension can be further confirmed using three-dimensional ultrasound, where available, to avoid misdiagnosis with early intrauterine or angular (implantation in the lateral angles of the uterine cavity) pregnancy.



Supplementation with MRI can also be helpful in the diagnosis of interstitial pregnancy.



Interstitial pregnancy occurs when the ectopic pregnancy implants in the interstitial part of the fallopian tube. The reported incidence varies between 1.0% and 6.3% of ectopic pregnancies.^{46–48} The interstitial part of the fallopian tube is about 1–2 cm in length and traverses the muscular myometrium of the uterine wall, opening via the tubal ostium into the uterine cavity.⁴⁹

Evidence level 3

Ultrasound criteria have been described for the diagnosis of interstitial pregnancy.⁵⁰ These include:

1. Empty uterine cavity.
2. Products of conception/gestational sac located laterally in the interstitial (intramural) part of the tube and surrounded by less than 5 mm of myometrium in all imaging planes.
3. The ‘interstitial line sign’, which is a thin echogenic line extending from the central uterine cavity echo to the periphery of the interstitial sac. The ‘interstitial line sign’ has been shown to have a sensitivity of 80% and a specificity of 98% for the diagnosis of interstitial ectopic pregnancy.⁵¹

Evidence level 3

In the three-dimensional coronal view of the uterus, a connection between the endometrial cavity and interstitial part of the tube can be visualised.^{52,53}

On MRI examination, a gestational sac-like structure is seen lateral to the cornua surrounded by the myometrium. The presence of the intact junctional zone (endomyometrial junction) between the uterine cavity and the gestational sac-like structure also supports the diagnosis.^{54,55}

4.4.2 What biochemical investigations should be carried out?

A single serum β-hCG should be carried out at diagnosis to help with management. In some cases, a repeat serum β-hCG in 48 hours may be useful in deciding further management.



At presentation, based on clinical symptoms and ultrasound scan, if there is suspicion of interstitial pregnancy, a single serum β-hCG should be carried out. This does not contribute to the diagnosis, but can be useful in deciding management options, such as surgical, medical or expectant treatment. The overall decision regarding management options depends upon clinical presentation, size of the interstitial pregnancy, presence of fetal cardiac activity and the serum β-hCG level. In some cases with a small interstitial pregnancy identified on an ultrasound scan, a repeat serum β-hCG in 48 hours may be helpful in deciding management options.

4.5 How is a cornual pregnancy diagnosed?

4.5.1 What are the ultrasound criteria?

The following ultrasound scan criteria may be used for the diagnosis of cornual pregnancy: visualisation of a single interstitial portion of fallopian tube in the main uterine body, gestational sac/products of conception seen mobile and separate from the uterus and completely surrounded by myometrium, and a vascular pedicle adjoining the gestational sac to the unicornuate uterus.

D

One of the initial reports⁵⁶ defined cornual pregnancy as being ‘in one horn of a bicornuate uterus, or, by extension of meaning, in one lateral half of a uterus of bifid tendency’. Subsequently, the two terms ‘interstitial’ and ‘cornual’ pregnancy have been used synonymously by some authors,^{57,58} while others have advocated the original definition of implantation in the congenitally abnormal uterus.^{59–61}

Evidence level 3

Defined in this way, cornual pregnancy is the rarest form of ectopic pregnancy with a reported incidence of 1 in 76 000 pregnancies.⁶¹ The following ultrasound scan criteria described in the literature can be used for the diagnosis of cornual pregnancy:⁶²

1. Visualisation of a single interstitial portion of fallopian tube in the main uterine body.
2. Gestational sac/products of conception seen mobile and separate from the uterus and completely surrounded by myometrium.
3. A vascular pedicle adjoining the gestational sac to the unicornuate uterus.

Evidence level 3

4.5.2 What biochemical investigations should be carried out?

A single serum β -hCG should be carried out at diagnosis to help with management. In some cases, a repeat serum β -hCG in 48 hours may be useful in deciding further management. 

Based on clinical symptoms and ultrasound scan, if there is suspicion of cornual pregnancy, single serum β -hCG is useful for planning management. The overall decision regarding management options (surgical, medical or expectant treatment) depends upon the clinical presentation, size of the cornual pregnancy and the serum β -hCG level. In some cases with a small cornual pregnancy identified on an ultrasound scan, a repeat serum β -hCG in 48 hours may be helpful in deciding management options.

4.6 How is an ovarian pregnancy diagnosed?

4.6.1 What are the ultrasound criteria?

There are no specific agreed criteria for the ultrasound diagnosis of ovarian ectopic pregnancy. 

D

Findings suggestive of an ovarian ectopic pregnancy on transvaginal ultrasound with an empty uterus are a wide echogenic ring with an internal anechoic area on the ovary. A yolk sac or embryo is seen less commonly.^{63,64} It is not possible to separate the cystic structure or gestational sac from the ovary on gentle palpation (negative sliding organ sign). The corpus luteum should be identified separate from the suspected ovarian pregnancy. Colour Doppler may aid detection of a fetal heart pulsation within the ovary. A complex echogenic adnexal mass with free fluid in the pouch of Douglas can represent a ruptured ovarian ectopic pregnancy.

Evidence level 3

As it can be difficult to distinguish ovarian ectopic pregnancies from corpus luteal cysts, tubal ectopic pregnancy stuck to the ovary, a second corpus luteum, ovarian germ cell tumours and other ovarian pathologies, diagnosis is usually confirmed surgically and histologically.

4.6.2 What biochemical investigations should be carried out?

A single serum β -hCG should be carried out at diagnosis to help with management. In some cases, a repeat serum β -hCG in 48 hours may be useful in deciding further management.



Evidence level 3

Ovarian ectopic pregnancy can be difficult to diagnose with certainty preoperatively, so the diagnosis should be considered whenever ultrasound findings are suspicious. After surgical treatment, the histopathology result will confirm the diagnosis of ovarian ectopic pregnancy.^{65,66}

4.7 How is an abdominal pregnancy diagnosed?

4.7.1 What are the ultrasound criteria?

Defined ultrasound criteria can be used to diagnose an abdominal pregnancy.



MRI can be a useful diagnostic adjunct in advanced abdominal pregnancy and can help to plan the surgical approach.

The following ultrasound criteria have been suggested by Gerli et al.⁶⁷ as being diagnostic of an early abdominal pregnancy:

1. Absence of an intrauterine gestational sac.
2. Absence of both an evident dilated tube and a complex adnexal mass.
3. A gestational cavity surrounded by loops of bowel and separated from them by peritoneum.
4. A wide mobility similar to fluctuation of the sac, particularly evident with pressure of the transvaginal probe toward the posterior cul-de-sac.

Evidence level 3

In a clinically stable patient where abdominal pregnancy is identified or strongly suspected on ultrasound, MRI can help to confirm the diagnosis and to identify placental implantation over vital structures, such as major blood vessels or bowel.⁶⁸ This can help to guide perioperative considerations, such as the surgical team, blood products, preoperative angiographic embolisation, bowel preparation and insertion of ureteral catheters. Ultrasound and/or MRI can be used to precisely map the location of the placenta prior to laparotomy so as to avoid incising the placenta and the associated risk of uncontrollable haemorrhage.⁶⁹

4.7.2 What biochemical investigations should be carried out?

A high index of suspicion is based upon an elevated serum β -hCG level in combination with ultrasound findings.



An early abdominal pregnancy is usually diagnosed at laparoscopy during investigation for a persistently elevated serum β -hCG level.⁷⁰

4.8 How is heterotopic pregnancy diagnosed?

4.8.1 What are the ultrasound criteria?

A heterotopic pregnancy is diagnosed when the ultrasound findings demonstrate an intrauterine pregnancy and a coexisting ectopic pregnancy.

Heterotopic pregnancy should be considered in all women presenting after assisted reproductive technologies, in women with an intrauterine pregnancy complaining of persistent pelvic pain and in those women with a persistently raised β -hCG level following miscarriage or termination of pregnancy.^{50,71}

D

Evidence level 3

4.8.2 What biochemical investigations should be carried out?

A serum β -hCG level is of limited value in diagnosing heterotopic pregnancy.

D

A higher than expected level of serum β -hCG in relation to gestational age may be suspicious of heterotopic gestations, although, the presence of a complete or partial mole must also be considered. However, in a case series⁷² of 20 heterotopic pregnancies following assisted reproductive technology, the mean β -hCG level at the time of pregnancy test was no higher than in nonheterotopic pregnancies.

Evidence level 3

5. Management options

5.1 What are the surgical, pharmacological or conservative treatment options for tubal pregnancy?

A laparoscopic surgical approach is preferable to an open approach.

A

In the presence of a healthy contralateral tube, salpingectomy should be performed in preference to salpingotomy.

B

In women with a history of fertility-reducing factors (previous ectopic pregnancy, contralateral tubal damage, previous abdominal surgery, previous pelvic inflammatory disease), salpingotomy should be considered.

C

If a salpingotomy is performed, women should be informed about the risk of persistent trophoblast with the need for serum β -hCG level follow-up. They should also be counselled that there is a small risk that they may need further treatment in the form of systemic methotrexate or salpingectomy.

✓

Systemic methotrexate may be offered to suitable women with a tubal ectopic pregnancy. It should never be given at the first visit, unless the diagnosis of ectopic pregnancy is absolutely clear and a viable intrauterine pregnancy has been excluded.

B

Expectant management is an option for clinically stable women with an ultrasound diagnosis of ectopic pregnancy and a decreasing β -hCG level initially less than 1500 iu/l.

B

5.1.1 Surgical management

The majority of tubal ectopic pregnancies are managed surgically. Laparoscopy is preferable to laparotomy due to its many advantages, such as shorter operation time, less intraoperative blood loss, shorter hospital stay, lower cost, lower analgesic requirements and less adhesion formation.^{73–75} Evidence, however, suggests that there is no difference in terms of health benefits between laparoscopy and laparotomy, including the key outcome of subsequent successful pregnancy.¹

A multicentre randomised controlled trial (RCT) on 446 women with a laparoscopically confirmed tubal ectopic pregnancy and a healthy contralateral tube⁷⁶ has found that the cumulative ongoing pregnancy rate was 60.7% after salpingotomy and 56.2% after salpingectomy. Persistent trophoblast occurred more frequently in the salpingotomy group (14 [7%] versus 1 [less than 1%]; relative risk [RR] 15.0, 95% CI 2.0–113.4). Repeat ectopic pregnancy occurred in 18 women (8%) in the salpingotomy group and 12 (5%) in the salpingectomy group (RR 1.6, 95% CI 0.8–3.3). It was concluded that in women with a tubal ectopic pregnancy and a healthy contralateral tube, salpingotomy does not significantly improve fertility prospects compared with salpingectomy.

Evidence level 1+

Higher rates of subsequent intrauterine pregnancy have been found if salpingotomy is performed rather than salpingectomy in women with a history of fertility-reducing factors (previous ectopic pregnancy, contralateral tubal damage, previous abdominal surgery, previous pelvic inflammatory disease). One study⁷⁷ found subsequent intrauterine pregnancy rates of 75% with salpingotomy and 40% with salpingectomy in such women. However, subsequent intrauterine pregnancy rates were greater than 90% in both groups in women without fertility-reducing factors.

Evidence level 2-

Persistent trophoblast is detected by the failure of serum β -hCG levels to fall as expected after initial treatment. It is primarily a problem occurring after salpingotomy rather than following salpingectomy. Although, even in the presence of persistent trophoblast, β -hCG levels may return uneventfully to normal,⁷⁸ this provides the rationale for following women with serial β -hCG measurements after treatment and administering methotrexate if levels plateau or start to rise. NICE¹ recommends that women undergoing salpingotomy have a serum β -hCG level taken 7 days after surgery and then weekly until a negative result is obtained.

Evidence level 3

Studies have reported persistent trophoblast rates of 3.9–11.0% after salpingotomy.^{79–82} Factors that have been suggested as increasing the risk of developing persistent trophoblast include higher preoperative serum β -hCG levels, a rapid preoperative rise in serum β -hCG and larger tubal masses. However, there is no convincing evidence for this and, at present, no definitive risk factors have been identified for predicting it after salpingotomy.⁸²

5.1.2 Pharmacological management

Methotrexate at a dose of 50 mg/m² has been widely used as a single dose instead of a repeat surgical procedure, although, no formal comparative studies have been performed. The use of prophylactic methotrexate at the time of laparoscopic salpingotomy has also been reported and in one randomised trial,⁸³ when compared with simple salpingotomy alone, there was a significant reduction in the rate of persistent trophoblast (1.9% versus 14.5%; RR 0.13, 95% CI 0.02–0.97).

Evidence level 1-

Systemic methotrexate is the most commonly used drug for the pharmacological treatment of tubal ectopic pregnancy. RCTs comparing methotrexate with laparoscopic surgery^{84,85} have shown methotrexate to be equally successful to surgery in certain cases of tubal ectopic pregnancy.

Evidence level I—

While it can be given in a multiple dose regimen, methotrexate is most commonly given as a single intramuscular dose of 50 mg/m² (see Appendix II).⁸⁶ Serum β-hCG levels are measured on days 4 and 7 post methotrexate. If the β-hCG level decreases by more than 15% between days 4 and 7, β-hCG levels are then measured weekly until less than 15 iu/l. If the level does not decrease by 15%, a repeat transvaginal ultrasound should be considered to exclude ectopic fetal cardiac activity and the presence of significant haemoperitoneum. Consideration may then be given to administration of a second dose of methotrexate.⁸⁶

Overall, success rates of single-dose methotrexate for tubal ectopic pregnancy range from 65–95%, with 3–27% of women requiring a second dose.⁸⁷ Success rates vary considerably due to different inclusion criteria. In the review by Kirk et al.,⁸⁷ some studies included PULs and presumed, but did not sonically visualise, ectopic pregnancies. Other studies⁸⁷ have included cases with already decreasing serum β-hCG levels that would have certainly resolved without any intervention. The largest single study to date⁸⁸ has been on 559 cases of ectopic pregnancy, where the success of methotrexate was found to be 90.7% (507/559).

There are a number of predictors of success:

- **Initial serum β-hCG level**

Success rates are higher with lower β-hCG levels. Success rates of 81–98% have been reported if serum β-hCG levels are less than 1000 iu/l, compared with only 38% if β-hCG levels are greater than 5000 iu/l.^{32,89,90}

Evidence level 3

- **Ultrasound appearance of the ectopic pregnancy**

The presence of a yolk sac, fetal pole and/or fetal cardiac activity are significant predictors of failure.^{32,88,91–93} Success rates are higher when no gestational sac is visualised.

- **Pretreatment changes in serum β-hCG levels**

The smaller the increase in β-hCG level prior to administration of methotrexate, the higher the chance of successful medical management. A β-hCG increase of up to 11–20% over 48 hours prior to the administration of methotrexate has been associated with higher rates of success.^{89,94}

- **Decrease in β-hCG levels from day 1 to day 4 after methotrexate**

Success rates of 88–100% have been reported if the serum β-hCG level decreases from day 1 to day 4 post administration of methotrexate, compared with only 42–62% if the serum β-hCG level increases.^{95,96}

During treatment with methotrexate women should be advised to avoid alcohol and folate-containing vitamins.⁸⁶

There are adverse effects, which include marrow suppression, pulmonary fibrosis, nonspecific pneumonitis, liver cirrhosis, renal failure and gastric ulceration. The most common adverse effects are excessive flatulence and bloating due to intestinal gas formation, a transient mild elevation in liver enzymes and stomatitis.⁹⁷ The contraindications to methotrexate are listed in Appendix III.

A good candidate for methotrexate has the following characteristics:

- haemodynamic stability
- low serum β-hCG, ideally less than 1500 iu/l but can be up to 5000 iu/l
- no fetal cardiac activity seen on ultrasound scan
- certainty that there is no intrauterine pregnancy
- willingness to attend for follow-up
- no known sensitivity to methotrexate.

NICE¹ recommends that methotrexate should be the first-line management for women who are able to return for follow-up and who have:

- no significant pain
- an unruptured ectopic pregnancy with a mass smaller than 35 mm with no visible heartbeat
- a serum β-hCG between 1500 and 5000 iu/l
- no intrauterine pregnancy (as confirmed on ultrasound scan).

Evidence level 3

However, before administering methotrexate, it is essential that the diagnosis of ectopic pregnancy is correct. As the majority of ectopic pregnancies are visualised as inhomogeneous masses, it is prudent to repeat the serum β-hCG in such cases in 48 hours. In the event of the serum β-hCG dropping, then expectant management may be appropriate. Should the serum β-hCG be rising at a rate that may be consistent with a viable intrauterine pregnancy, then a repeat scan to check the diagnosis before administering methotrexate is advisable. There are many well-documented cases of women with intrauterine pregnancies treated for suspected ectopic pregnancy with methotrexate.⁹⁸ Methotrexate should, therefore, never be given at the first visit, unless the diagnosis of ectopic pregnancy is absolutely clear and a viable intrauterine pregnancy has been excluded.⁹⁹

5.1.3 Expectant management

Expectant management is a reasonable option for appropriately selected and counselled women. They must be willing and able to attend for follow-up, have minimal pain, and have low or declining serum β-hCG levels. Reported success rates range from 57–100% and are very dependent on case selection.¹⁰⁰

Evidence level 3

Success rates are inversely proportional to serum β -hCG levels, with lower success rates associated with higher initial serum β -hCG levels. One study¹⁰¹ reported success rates of 96% with serum β -hCG levels of less than 175 iu/l and 66% if serum β -hCG levels were 175–1500 iu/l. Other studies^{102,103} have reported success rates of 80–90% if the serum β -hCG levels are less than 1000 iu/l and 60–67% if β -hCG levels are less than 2000 iu/l.

A prospective observational study⁴ on women with tubal ectopic pregnancies found that over 30% of them could be successfully managed expectantly: 146/333 ectopic pregnancies were managed expectantly with a success rate of 71.2% (104/146). Selection criteria for expectant management were clinical stability with no abdominal pain, no evidence of significant haemoperitoneum on ultrasound scan, an ectopic pregnancy measuring less than 30 mm in mean diameter with no evidence of embryonic cardiac activity, a serum β -hCG level of less than 1500 iu/l and the woman's consent. All women were followed up until the serum β -hCG level was less than 20 iu/l. The protocol was individualised in each case, so that the interval of repeat β -hCG tests varied between 2 and 7 days. Expectant management was discontinued if the woman opted out, had significant pain, or if the serum β -hCG level showed a sustained increase or increased to greater than 2000 iu/l during follow-up.

Evidence level 2+

A decreasing serum β -hCG level is also a good predictor of success. One study⁸⁹ proposed that the pretreatment β -hCG ratio (serum β -hCG at 48 hours/serum β -hCG at 0 hours) could be used to predict the likely success of expectant and medical management. It was found that if the β -hCG ratio is less than 0.8, expectant management is likely to succeed. The overall success rate of expectant management in this study was 72%.

One question that is often raised is whether there is a benefit in giving methotrexate rather than managing expectantly. A multicentre RCT¹⁰⁴ was performed to assess the treatment success rate of systemic methotrexate compared with expectant management in women with an ectopic pregnancy or a PUL with low or plateauing serum β -hCG levels (less than 1500 iu/l and less than 2000 iu/l for ectopic pregnancy and PUL, respectively). They found that there was no difference in the primary treatment success rate of single-dose methotrexate versus expectant management, with success rates of 31/41 (76%) and 19/32 (59%), respectively. However, the majority of the cases were PULs with only 15 (15/73; 21%) visualised ectopic pregnancies included.

Evidence level 1+

5.2 What are the surgical, pharmacological or conservative treatment options for cervical pregnancy?

Medical management with methotrexate can be considered for cervical pregnancy.

D

Surgical methods of management are associated with a high failure rate and should be reserved for those women suffering life-threatening bleeding.

D

Early, accurate diagnosis is the key factor in the conservative management of cervical pregnancies. Gestational age less than 12^{+0} weeks, absence of fetal cardiac activity and lower serum β -hCG levels are associated with more successful conservative management.^{105,106} A variety of methods have been

Evidence level 2-

described in the literature (dilatation and curettage, systemic methotrexate, local injection with potassium chloride or methotrexate).¹⁰⁷ A retrospective review¹⁰⁸ of 62 cases of cervical ectopic pregnancy estimated the efficacy of systemic methotrexate administration in the treatment of cervical ectopic pregnancy to be approximately 91%. There was, however, no standard protocol of methotrexate used and successful cases required surgical debulking or local injection with methotrexate in addition to systemic therapy. Gestational age more than 9⁺⁰ weeks, β-hCG levels greater than 10 000 iu/l, crown–rump length greater than 10 mm and fetal cardiac activity were shown to be associated with a higher risk of primary failure of the treatment of cervical ectopic pregnancy with systemic methotrexate. In addition, combination therapy with intra-amniotic injection seemed to increase the chance of successful treatment in this retrospective study.

Evidence level 2

A number of adjunctive methods to control haemorrhage in the treatment of cervical ectopic pregnancy have been described; these include uterine artery ligation and uterine artery embolisation (UAE).¹⁰⁹

Case series¹¹⁰ report success with these methods in combination with intracervical or systemic methotrexate, but the number of cases reported are small and associated complications include infection, uterine infarction, sciatic nerve injury, and necrosis of the bladder or rectum.

Traditionally, cervical ectopic pregnancies were managed with dilatation and curettage with additional measures designed to reduce the amount of haemorrhage.¹⁰⁷ However, rates of excessive bleeding necessitating hysterectomy were high and therefore, its use should be restricted to those women for whom alternative measures are unsuitable.³⁴

Evidence level 3

More recently, a small case series¹¹¹ of five women with cervical ectopic pregnancies treated with hysteroscopic resection and UAE has been described. None of the women required blood transfusion or additional techniques. However, UAE is associated with complications and there have been no long-term follow-up studies of these women.

5.3 What are the surgical, pharmacological or conservative treatment options for caesarean scar pregnancy?

Women diagnosed with caesarean section scar pregnancies should be counselled that such pregnancies are associated with severe maternal morbidity and mortality.

D

Medical and surgical interventions with or without additional haemostatic measures should be considered in women with first trimester caesarean scar pregnancy.

D

There is insufficient evidence to recommend any one specific intervention over another for caesarean scar pregnancy, but the current literature supports a surgical rather than medical approach as the most effective.

D

To date, there are 35 cases of ongoing caesarean section scar pregnancies that were diagnosed in the first trimester where the women chose to continue with the pregnancy.^{112–115} There were 27 live births and 22 pregnancies ended with emergency hysterectomy, at gestational ages ranging from 15 to 38 weeks,

Evidence level 3

due to haemorrhage and morbidly adherent placentas. There have also been numerous small case series and case reports⁴² of intra-abdominal rupture and severe vaginal haemorrhage at the point of diagnosis or following intervention. There were six maternal deaths due to haemorrhage in women with a history of caesarean section in the 2006–08 Centre for Maternal and Child Enquiries report,¹¹⁶ although, the site of implantation was not always identified.

There have been very few small randomised studies of the treatment of caesarean scar pregnancy.¹¹⁷ As expected for an uncommon condition, the body of evidence otherwise consists of case series and reviews thereof.^{37,39,40,118–120} There has been one systematic review of studies reporting outcomes on five or more patients.¹²¹

Primary medical treatment consists of using methotrexate, which may be administered by local injection into the gestational sac under ultrasound guidance or systemically by intramuscular injection. Local injection seems to be a more effective means of terminating the pregnancy.⁴⁰ The disadvantage of using medical treatment is that the trophoblast remains in situ; there is a risk of haemorrhage as the retained, often very vascular, placental tissue degenerates, so some authors have advocated using suction evacuation in addition to methotrexate to hasten resolution and reduce the risk of unpredictable haemorrhage in the follow-up period.¹²² Surgical treatment consists of either evacuation of the pregnancy (using suction or hysteroscopic resection)¹²³ or excision of the pregnancy as an open,¹²⁴ laparoscopic¹²⁵ or transvaginal procedure.^{126,127} Suction evacuation is probably the most frequently described procedure and has been combined with cervical cerclage, Foley catheter insertion or UAE as additional haemostatic measures.^{39,117,128–130} Excisional techniques have the advantage of incorporating a repair of the scar, but these procedures are technically more difficult and invasive, and it is not known whether scar repair reduces the risk of recurrent caesarean scar pregnancy or scar rupture in future pregnancies.

Evidence level 3

Expectant management may be suitable for women with small, nonviable scar pregnancies and may be considered if the pregnancy is partially implanted into the scar and grows into the uterine cavity, provided that the woman is counselled regarding the associated potential risks, haemorrhage and morbidly adherent placentation, and she declines termination of the pregnancy.^{114,119}

The management of ongoing second trimester scar pregnancies is challenging with a high risk of maternal morbidity and hysterectomy whichever approach is taken. In these cases, the risk of surgical intervention must be balanced with the risks of allowing the pregnancy to continue with the aim of reaching a potentially viable gestational age. Women with such pregnancies should have a care package put in place for morbidly adherent placenta, with a plan for emergency intervention should haemorrhage or rupture occur.^{131,132}

5.4 *What are the surgical, pharmacological or conservative treatment options for interstitial pregnancy?*

Nonsurgical management is an acceptable option for stable interstitial pregnancies.

D

Expectant management is only suitable for women with low or significantly falling β-hCG levels in whom the addition of methotrexate may not improve the outcome.

D

A pharmacological approach using methotrexate has been shown to be effective, although, there is insufficient evidence to recommend local or systemic approach.

D

Surgical management by laparoscopic cornual resection or salpingotomy is an effective option.

D

Alternative surgical techniques could include hysteroscopic resection under laparoscopic or ultrasound guidance.

D

There is insufficient evidence on safety and complications in future pregnancies to recommend other nonsurgical methods.

D

The likely success of conservative management is determined by the initial level of serum β -hCG.¹³³ The options for conservative management include expectant management or a pharmacological approach using local or systemic methotrexate.

In a case series of 42 women with interstitial pregnancy,¹³³ women with a successful outcome following expectant and medical management¹³⁴ were found to have lower levels of initial β -hCG than those that were unsuccessful (3216 iu/l versus 15 900 iu/l; $P < 0.05$). A success rate of 89.5% was found in another case series of 19 women managed expectantly.¹³⁴

No complications were reported in an observational study¹³⁵ of 17 women diagnosed with interstitial pregnancy and treated with systemic methotrexate 50 mg/m², while another study¹³³ reported adverse effects in 40% of women who received systemic methotrexate. In an Australian case series¹³⁶ of 13 interstitial pregnancies, a single-dose intravenous methotrexate and oral folinic acid rescue regimen was shown to be successful (91% success rate). Other described methods include transvaginal ultrasound-guided aspiration of the exocoelomic fluid from the gestational sac, followed by intrasaccular injection of 25 mg of methotrexate with/without 0.2–0.4 mEq of potassium chloride.¹³⁷ This is reported to have a 91% success rate, with the advantages of fewer adverse effects and the ability to perform embryocide at the same time if required. The disadvantage is that it is a technically more challenging procedure. Embryocide has been shown to improve the success rate of the procedure.^{36,92,137}

Evidence level 3

Various endoscopic approaches have been reported, such as electrocauterisation, endoloop application or the encircling suture before evacuation of the conceptus.¹³⁸ Moon et al.¹³⁹ described a technique of using highly diluted vasopressin for haemostasis during laparoscopic surgery (1 ampoule [20 U] of vasopressin diluted in 1000 ml of normal saline [1000-fold] and 150–250 ml [0.02 U/ml] of diluted vasopressin injected in the uterus below the interstitial pregnancy). Others have reported laparoscopic haemostatic suturing techniques¹⁴⁰ and laparoscopic resection using the ‘purse-string’ technique.¹⁴¹

Successful hysteroscopic resection of interstitial pregnancies under laparoscopic vision and ultrasound guidance has also been reported.¹⁴² In a small case series¹⁴³ ($n = 3$) the technique of ultrasound-guided dilatation and evacuation using polypectomy forceps, followed by single-dose systemic methotrexate, was described.

Other reported nonsurgical techniques include selective UAE used in conjunction with methotrexate to reduce haemorrhage.¹⁴⁴⁻¹⁴⁶ The disadvantages with this technique are uncertainty about the safety and complications in future pregnancies. In a case of a 12-week interstitial pregnancy with failed systemic methotrexate,¹⁴⁷ successful treatment was reported with use of intra-amniotic injection of etoposide, a topoisomerase II inhibitor used in the treatment of gestational trophoblastic disease.

Evidence level 3

5.5 What are the surgical, pharmacological or conservative treatment options for cornual pregnancy?

Cornual pregnancies should be managed by excision of the rudimentary horn via laparoscopy or laparotomy.

D

Conservative, laparoscopic and open surgical methods of management have all been described. There are several reported cases of methotrexate and potassium chloride injection prior to later laparoscopic rudimentary horn excision.¹⁴⁸ However, to avoid recurrence, excision of the rudimentary horn seems to be the best approach. The laparoscopic technique is safe, but attention needs to be paid to the possibility of urinary tract anomalies, which can be associated with unicornuate uteri. The technique involves excision of the fibrous band that attaches the rudimentary horn to the unicornuate uterus with removal of the rudimentary horn through the secondary port.¹⁴⁹

Evidence level 3

5.6 What are the surgical, pharmacological or conservative treatment options for ovarian pregnancy?

Definitive surgical treatment is preferred if laparoscopy is required to make the diagnosis of ovarian ectopic pregnancy.

D

Systemic methotrexate can be used to treat ovarian ectopic pregnancy when the risk of surgery is high, or postoperatively in the presence of persistent residual trophoblast or persistently raised β -hCG levels.

D

Minimal access surgery is now the treatment of choice for ovarian ectopic pregnancy. Removal of the gestational products by enucleation or wedge resection (in the presence of a large ectopic mass) is preferred.¹⁵⁰ Enucleating the products of conception bluntly from the ovary minimises damage to the surrounding ovarian tissue. Haemostasis can be achieved by electrocautery or suturing. Oophorectomy is occasionally required when there is coexisting ipsilateral ovarian pathology or excessive bleeding.¹⁵⁰

Evidence level 3

A number of successful and unsuccessful attempts have been made to treat ovarian ectopic pregnancy with systemic methotrexate. In one series,¹⁵¹ there was a failure rate of 40% using methotrexate alone. However, all the cases successfully treated with methotrexate were diagnosed laparoscopically. There are no defined selection criteria, or treatment or follow-up regimens.

5.7 What are the surgical, pharmacological or conservative treatment options for abdominal pregnancy?

Laparoscopic removal is an option for treatment of early abdominal pregnancy.

D

Possible alternative treatment methods would be systemic methotrexate with ultrasound-guided fetocide.

D

Advanced abdominal pregnancy should be managed by laparotomy.

D

Laparoscopic treatment is a safe and effective option for the management of abdominal pregnancy when the diagnosis is made early and the site of implantation does not involve a vascular area. Laparoscopic management has been associated with reduced operative time, blood loss and length of hospital stay when compared with laparotomy.¹⁵²

Very few cases of nonsurgical management of early abdominal pregnancy have been reported. These include cases managed with intramuscular methotrexate alone and in combination with intrasaccular injection with methotrexate.^{137,153}

Methotrexate has also been used as an adjunctive treatment to surgery.⁷⁰

Evidence level 3

Advanced abdominal pregnancy is associated with significant maternal and fetal morbidity and mortality,¹⁵⁴ and once diagnosed, a laparotomy should be undertaken promptly.^{68,152} The surgical approach should be planned to avoid incision of the placenta. The placenta may be left in situ if the vascular attachment involves major vessels or vital structures, and spontaneous resorption awaited.¹⁵⁵ Preserving the placenta (or ‘its retention’) is associated with significant morbidity (ileus, bowel obstruction, fistula formation, haemorrhage, peritonitis), but the mortality is lower than with its removal.¹⁵⁶ Adjuvant treatments with methotrexate¹⁵⁷ and selective arterial embolisation¹⁵² have been described.

5.8 What are the surgical, pharmacological or conservative treatment options for heterotopic pregnancy?

The intrauterine pregnancy must be considered in the management plan.

B

Methotrexate should only be considered if the intrauterine pregnancy is nonviable or if the woman does not wish to continue with the pregnancy.

D

Local injection of potassium chloride or hyperosmolar glucose with aspiration of the sac contents is an option for clinically stable women.

D

Surgical removal of the ectopic pregnancy is the method of choice for haemodynamically unstable women and is also an option for haemodynamically stable women.

D

Expectant management is an option in heterotopic pregnancies where the ultrasound findings are of a nonviable pregnancy.

D

The management approach adopted for heterotopic pregnancy should incorporate the prognosis of the intrauterine pregnancy and the wishes of the woman regarding its final outcome.¹⁵⁸

Evidence level 2++

Methotrexate is not an option for the treatment of women with a heterotopic pregnancy who have a viable intrauterine pregnancy or wish to continue with the pregnancy. Methotrexate, therefore, needs to be given only with very careful consideration, as even local injection will affect the intrauterine pregnancy.¹⁵⁹ In women with a viable pregnancy who do not wish to continue with the pregnancy, the Abortion Act regulations will apply.

Evidence level 4

Medical management using local injection of hyperosmolar glucose into the extrauterine sac, or potassium chloride into either the fetal pole if possible or the sac if not, alongside aspiration of the sac contents, minimises the risks posed to the coexisting intrauterine pregnancy by surgical approaches. Ultrasound follow-up is necessary in these women to ensure resolution of the ectopic pregnancy as β-hCG levels cannot be used. This approach has been described for interstitial, caesarean scar and cervical heterotopic pregnancies.^{160,161}

Evidence level 3

In those women presenting with heterotopic pregnancy who are haemodynamically unstable, surgical management should be carried out.¹⁶² In those haemodynamically stable women with an easily accessible ectopic pregnancy, such as a tubal, cervical or interstitial heterotopic pregnancy, surgical removal is also an option.^{163,164} Care should be taken at the time of laparoscopy to avoid cannulation or manipulation of the uterus.^{165,166}

Expectant management of an interstitial heterotopic pregnancy in a symptom-free woman with ultrasound evidence that the interstitial pregnancy was not ongoing has been described.^{167,168}

6. Do rhesus D (RhD)-negative women with an ectopic pregnancy require anti-D immunoglobulin?

Offer anti-D prophylaxis as per national protocol to all RhD-negative women who have surgical removal of an ectopic pregnancy, or where bleeding is repeated, heavy or associated with abdominal pain.

D

Alloimmunisation has been reported following ectopic pregnancy and 25% of cases of ruptured tubal ectopic pregnancy are associated with a significant number of fetal cells in the maternal circulation.¹⁶⁹

Evidence level 2-

However, there are no studies evaluating the use of anti-D prophylaxis in women with an ectopic pregnancy.

Women who undergo surgical management of ectopic pregnancy may be at higher risk of sensitisation due to mixing of fetal and maternal blood.¹

There is a paucity of evidence regarding the risk of alloimmunisation associated with medical and expectant management of ectopic pregnancy. However, the risk of mixing of fetal and maternal blood following conservative or medical management is thought to be low.¹ NICE¹ recommend only offering anti-D prophylaxis to those undergoing surgical management, but this is contrary to the British Committee for Standards in Haematology guidance.¹⁷⁰

Evidence level 4

7. What are the long-term fertility prospects following an ectopic pregnancy?

In the absence of a history of subfertility or tubal pathology, women should be advised that there is no difference in the rate of fertility, the risk of future tubal ectopic pregnancy or tubal patency rates between the different management methods.

D

Women with a previous history of subfertility should be advised that treatment of their tubal ectopic pregnancy with expectant or medical management is associated with improved reproductive outcomes compared with radical surgery.

C

Women receiving methotrexate for the management of tubal ectopic pregnancy can be advised that there is no effect on ovarian reserve.

D

Women undergoing treatment with UAE and systemic methotrexate for nontubal ectopic pregnancies can be advised that live births have been reported in subsequent pregnancies.

D

Women undergoing laparoscopic management of ovarian pregnancies can be advised that their future fertility prospects are good.

D

Several studies comparing surgical methods, medical and surgical management, and surgical and expectant management have confirmed that there are no statistical differences in the rate of recurrent ectopic pregnancy, with most long-term follow-up studies quoting a rate of around 18.5%.^{171,172}

Evidence level 1+

There is no difference in the tubal patency rates as examined by hysterosalpingography in women whose tubal ectopic pregnancies were managed expectantly or medically in the ipsilateral tube, or among those managed expectantly, medically or surgically in the contralateral tube.¹⁷³

Evidence level 2-

In women with a history of subfertility, especially those over the age of 35 years, radical surgery has been shown to be associated with lower rates of subsequent intrauterine pregnancy compared with conservative surgical or medical management.^{77,174}

RCTs have found that future fertility outcomes are no different for women managed with medical treatment, conservative or radical surgery,¹⁷⁵ or conservative versus radical surgery.¹⁷¹ Other case series¹⁷² have also shown no difference in future fertility with expectant management versus radical surgery.

Evidence level 1-

Several studies^{176–178} have examined various measures of ovarian reserve following medical management of tubal ectopic pregnancy and concluded that there is no effect on antimüllerian hormone, antral follicle counts or ovarian responsiveness. There is some evidence that if fertility treatment is recommended within 180 days of methotrexate, the oocyte yield is lower, but the study size was small.¹⁷⁹

A small case series¹⁸⁰ looking at the future fertility of women undergoing treatment with UAE and systemic methotrexate for nontubal ectopics found that in the 12 women who tried to conceive following treatment, 83% conceived and 58% had a live birth.

Evidence level 3

The future fertility outcomes of women undergoing laparoscopic surgery for ovarian ectopic pregnancy were examined in a small case series¹⁸¹ which showed that 100% went on to conceive again with 83% achieving a live birth.

8. What support and counselling should be offered to women undergoing treatment for ectopic pregnancy?

Women should be advised, whenever possible, of the advantages and disadvantages associated with each approach used for the treatment of ectopic pregnancy, and should participate fully in the selection of the most appropriate treatment.

D

Women should be made aware of how to access support via patient support groups, such as the Ectopic Pregnancy Trust, or local bereavement counselling services.

D

Muscle relaxation training may be of use to women undergoing treatment for ectopic pregnancy with methotrexate.

C

It is recommended that women treated with methotrexate wait at least 3 months before trying to conceive again.

D

The psychological impact of early pregnancy loss may seriously affect a significant proportion of women, their partners and families.^{182,183}

Evidence level 2-

Plans for follow-up should be clearly recorded in the discharge letter from the early pregnancy clinic. Women should be provided with written information concerning their treatment options, follow-up, and the availability of local and national support services.¹⁸⁴

A study looking at psychological outcomes⁸⁵ has suggested that there is little difference when comparing surgical and medical methods of managing ectopic pregnancy.

Around half of women with an ectopic pregnancy suffer a significant grief reaction, with those women without a child scoring higher on the perinatal grief score.¹⁸⁵ Patient support may also be of benefit for women in their subsequent pregnancies whom are more likely to be anxious about their pregnancy outcome.¹⁸⁶

Evidence level 3

An RCT¹⁸⁷ of women undergoing methotrexate treatment for ectopic pregnancy given adjuvant muscle relaxation training using the Bernstein and Borkovec technique¹⁸⁸ showed that those women in the muscle relaxation group had less anxiety and improved health-related quality of life on discharge from hospital than the control group who had had no adjuvant muscle relaxation.

Evidence level 1–

The manufacturers of methotrexate recommend a 3-month window after use before conception due to the length of time that it may remain present in some organs and because of concern for subsequent pregnancy and fetal development. A small cohort study¹⁸⁹ which examined the malformation rate in those women who conceived within 3 months of methotrexate exposure showed a higher than expected major malformation rate. However, conception within 3 months of methotrexate should not be considered an indication for a termination.¹⁹⁰

Evidence level 2–

9. Service and training

9.1 What is the most appropriate setting for management of women with an ectopic pregnancy?

Providers of early pregnancy care should provide a 7-day early pregnancy assessment service with direct access for women referred by general practitioners and accident and emergency departments, i.e. along current NHS recommendations. Available facilities for the management of suspected ectopic pregnancy should include diagnostic and therapeutic algorithms, transvaginal ultrasound and serum β-hCG estimations.



Women should have access to all appropriate management options for their ectopic pregnancy. If local facilities do not provide all options, then clear referral pathways should exist to allow them to access appropriate care.



In line with NICE recommendations from guidelines on the management of early pregnancy complications and RCOG study groups,^{1,182} women with suspected ectopic pregnancy should be managed in dedicated early pregnancy clinics.

Ideally, these clinics should be sited in a dedicated area with appropriate staffing and should be available on a daily basis, 7 days a week. If the facility to refer women for attendance within 24 hours is not available, then there should be the facility to refer women to attend elsewhere for specialist clinical assessment and scanning, that is the gynaecology ward or accident and emergency with specialist gynaecology support.^{1,191}

Evidence level 4

Laparoscopic salpingotomy is not part of the core training of gynaecologists and a survey suggested that 51% of trainees did not possess the skills necessary to perform salpingotomy if needed.¹⁹² Services must be designed so that appropriate support is available from senior staff trained in all surgical techniques.

Given that caesarean scar pregnancy is uncommon, potentially difficult to diagnose and has many different treatment options, clinically stable women should be managed by a multidisciplinary team with expertise in this area.

9.2 *What are the training implications for those managing women with ectopic pregnancy?*

Clinicians undertaking the surgical management of ectopic pregnancy must have received appropriate training. Laparoscopic surgery requires appropriate equipment and trained theatre staff.



Clinicians undertaking ultrasound for the diagnosis of ectopic pregnancy must have received appropriate training.



Clinicians undertaking medical management via ultrasound-guided needle techniques must have received appropriate training.



If clinicians undertaking surgical management of ectopic pregnancy cannot carry out the full range of surgical procedures, appropriately experienced support must be available if necessary.



Virtual reality simulators can be used as a training tool for salpingectomy.



Clinical staff should be trained as required by the RCOG curriculum or equivalent to undertake both the open and laparoscopic management of ectopic pregnancy.¹⁹³ This should include the safe use of monopolar and bipolar diathermy. They should also be supported with suitable efficient modern equipment to facilitate safe surgery.

Evidence level 4

Staff using ultrasound for the diagnosis of ectopic pregnancy should have completed the RCOG ultrasound module in intermediate ultrasound of early pregnancy complications or be able to show equivalent training.

Completion of the RCOG Advanced Training Skills Module in acute gynaecology and early pregnancy does not cover independent competency in ultrasound-guided needle techniques. Clinicians undertaking such techniques should be able to provide evidence of training and a log of ongoing cases and complications thereof.

Ideally, the operating clinician should have the skills to carry out the appropriate surgical treatment, i.e. salpingectomy and salpingotomy. If they do not, then there should be on-call support available should other procedures be necessary and to provide on-the-job training.

Studies have shown that virtual reality simulators offer realistic training for surgical procedures, such as salpingectomy.^{194,195}

Evidence level 3

10. Recommendations for future research

- The need for anti-D in women with nontubal ectopic pregnancies.
- Methotrexate for the treatment of ovarian ectopic pregnancy.
- Long-term fertility following management of nontubal ectopic pregnancies.
- Diagnostic test studies for interstitial and caesarean scar pregnancies.
- The long-term behaviour of pregnancies implanted at, in or into the caesarean scar.
- Optimal management of caesarean scar pregnancy.
- Validation studies of expectant management of ectopic pregnancy.
- Novel biomarkers to predict success from methotrexate or expectant management.
- Understanding the psychological impact of ectopic pregnancy and its treatment.
- Multidose versus single-dose methotrexate in nontubal ectopic pregnancies.

11. Auditable topics

- Proportion of tubal ectopic pregnancies identified on initial scan (90%).
- Negative laparoscopy rate following an ultrasound diagnosis of tubal ectopic pregnancy (0%).
- Proportion of women with ectopic pregnancy offered all relevant management options (100%).
- Percentage of women suitable for laparoscopic management of ectopic pregnancy managed laparoscopically (100%).
- Number of cases where methotrexate given for a false-positive diagnosis of ectopic pregnancy (0%).
- Number of nonemergency cases having surgery between 8 p.m and 8 a.m. (0%).
- Percentage of women provided with information containing support group details (100%).

12. Useful links and support groups

- Association of Early Pregnancy Units [www.earlypregnancy.org.uk].
- The Ectopic Pregnancy Trust [www.ectopic.org.uk].
- Infertility Network UK [www.infertilitynetworkuk.com].
- Miscarriage Association [www.miscarriageassociation.org.uk].
- Royal College of Obstetricians and Gynaecologists. *An ectopic pregnancy: Information for you*. London: RCOG; 2010 [<https://www.rcog.org.uk/en/patients/patient-leaflets/ectopic-pregnancy/>].

References

1. National Institute for Health and Care Excellence. *Ectopic pregnancy and miscarriage. diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage*. NICE clinical guideline 154. Manchester: NICE; 2012.
2. O'Herlihy C; Centre for Maternal and Child Enquiries. Deaths in early pregnancy. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011;118 Suppl 1:81–4.
3. Kirk E, Papageorgiou AT, Condous G, Tan L, Bora S, Bourne T. The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy. *Hum Reprod* 2007;22:2824–8.
4. Mavrellos D, Nicks H, Jamil A, Hoo W, Jauniaux E, Jurkovic D. Efficacy and safety of a clinical protocol for expectant management of selected women diagnosed with a tubal ectopic pregnancy. *Ultrasound Obstet Gynecol* 2013;42:102–7.
5. Ankum WM, Mol BW, Van der Veen F, Bossuyt PM. Risk factors for ectopic pregnancy: a meta-analysis. *Fertil Steril* 1996;65:1093–9.
6. Tay JI, Moore J, Walker JJ. Ectopic pregnancy. *West J Med* 2000;173:131–4.
7. Bouyer J, Coste J, Shojaei T, Pouly JL, Fernandez H, Gerbaud L, et al. Risk factors for ectopic pregnancy: a comprehensive analysis based on a large case-control, population-based study in France. *Am J Epidemiol* 2003;157:185–94.

8. Shaw JL, Oliver E, Lee KF, Entrican G, Jabbour HN, Critchley HO, et al. Cotinine exposure increases Fallopian tube PROKR1 expression via nicotinic AChR α -7: a potential mechanism explaining the link between smoking and tubal ectopic pregnancy. *Am J Pathol* 2010;177:2509–15.
9. Shaw JL, Wills GS, Lee KF, Horner PJ, McClure MO, Abrahams VM, et al. *Chlamydia trachomatis* infection increases fallopian tube PROKR2 via TLR2 and NF κ B activation resulting in a microenvironment predisposed to ectopic pregnancy. *Am J Pathol* 2011;178:253–60.
10. Condous G, Okaro E, Khalid A, Lu C, Van Huffel S, Timmerman D, et al. The accuracy of transvaginal ultrasonography for the diagnosis of ectopic pregnancy prior to surgery. *Hum Reprod* 2005;20:1404–9.
11. Atri M, Valenti DA, Bret PM, Gillett P. Effect of transvaginal sonography on the use of invasive procedures for evaluating patients with a clinical diagnosis of ectopic pregnancy. *J Clin Ultrasound* 2003;31:1–8.
12. Braffman BH, Coleman BG, Ramchandani P, Arger PH, Nodine CF, Dinsmore BJ, et al. Emergency department screening for ectopic pregnancy: a prospective US study. *Radiology* 1994;190:797–802.
13. Shalev E, Yarom I, Bustan M, Weiner E, Ben-Shlomo I. Transvaginal sonography as the ultimate diagnostic tool for the management of ectopic pregnancy: experience with 840 cases. *Fertil Steril* 1998;69:62–5.
14. Hahlin M, Thorburn J, Bryman I. The expectant management of early pregnancies of uncertain site. *Hum Reprod* 1995;10:1223–7.
15. Banerjee S, Aslam N, Zosmer N, Woelfer B, Jurkovic D. The expectant management of women with early pregnancy of unknown location. *Ultrasound Obstet Gynecol* 1999;14:231–6.
16. Banerjee S, Aslam N, Woelfer B, Lawrence A, Elson J, Jurkovic D. Expectant management of early pregnancies of unknown location: a prospective evaluation of methods to predict spontaneous resolution of pregnancy. *BJOG* 2001;108:158–63.
17. Condous G, Van Calster B, Kirk E, Haider Z, Timmerman D, Van Huffel S, et al. Prediction of ectopic pregnancy in women with a pregnancy of unknown location. *Ultrasound Obstet Gynecol* 2007;29:680–7.
18. Kirk E, Condous G, Van Calster B, Van Huffel S, Timmerman D, Bourne T. Rationalizing the follow-up of pregnancies of unknown location. *Hum Reprod* 2007;22:1744–50.
19. Kirk E, Daemen A, Papageorghiou AT, Bottomley C, Condous G, De Moor B, et al. Why are some ectopic pregnancies characterized as pregnancies of unknown location at the initial transvaginal ultrasound examination? *Acta Obstet Gynecol Scand* 2008;87:1150–4.
20. Li TC, Tristram A, Hill AS, Cooke ID. A review of 254 ectopic pregnancies in a teaching hospital in the Trent Region, 1977–1990. *Hum Reprod* 1991;6:1002–7.
21. Atri M, Leduc C, Gillett P, Bret PM, Reinhold C, Kintzen G, et al. Role of endovaginal sonography in the diagnosis and management of ectopic pregnancy. *Radiographics* 1996;16:755–74.
22. Marks WM, Filly RA, Callen PW, Laing FC. The decidual cast of ectopic pregnancy: a confusing ultrasonographic appearance. *Radiology* 1979;133:451–4.
23. Frates MC, Laing FC. Sonographic evaluation of ectopic pregnancy: an update. *Am J Roentgenol* 1995;165:251–9.
24. Benson CB, Doubilet PM, Peters HE, Frates MC. Intrauterine fluid with ectopic pregnancy: a reappraisal. *J Ultrasound Med* 2013;32:389–93.
25. Yeh HC, Goodman JD, Carr L, Rabinowitz JG. Intradecidual sign: a US criterion of early intrauterine pregnancy. *Radiology* 1986;161:463–7.
26. Bradley WG, Fiske CE, Filly RA. The double sac sign of early intrauterine pregnancy: use in exclusion of ectopic pregnancy. *Radiology* 1982;143:223–6.
27. Doubilet PM, Benson CB. Double sac sign and intradecidual sign in early pregnancy: interobserver reliability and frequency of occurrence. *J Ultrasound Med* 2013;32:1207–14.
28. Fleischer AC, Pennell RG, McKee MS, Worrell JA, Keefe B, Herbert CM, et al. Ectopic pregnancy: features at transvaginal sonography. *Radiology* 1990;174:375–8.
29. Nyberg DA, Hughes MP, Mack LA, Wang KY. Extrauterine findings of ectopic pregnancy of transvaginal US: importance of echogenic fluid. *Radiology* 1991;178:823–6.
30. van Mello NM, Mol F, Opmeer BC, Ankum WM, Barnhart K, Coomarasamy A, et al. Diagnostic value of serum β -hCG on the outcome of pregnancy of unknown location: a systematic review and meta-analysis. *Hum Reprod Update* 2012;18:603–17.
31. Condous G, Kirk E, Lu C, Van Huffel S, Gevaert O, De Moor B, et al. Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location. *Ultrasound Obstet Gynecol* 2005;26:770–5.
32. Potter MB, Lepine LA, Jamieson DJ. Predictors of success with methotrexate treatment of tubal ectopic pregnancy at Grady Memorial Hospital. *Am J Obstet Gynecol* 2003;188:1192–4.
33. Ushakov FB, Elchalal U, Aceman PJ, Schenker JG. Cervical pregnancy: past and future. *Obstet Gynecol Surv* 1997;52:45–59.
34. Jurkovic D, Hackett E, Campbell S. Diagnosis and treatment of early cervical pregnancy: a review and a report of two cases treated conservatively. *Ultrasound Obstet Gynecol* 1996;8:373–80.
35. Timor-Tritsch IE, Monteagudo A, Mandeville EO, Peisner DB, Anaya GP, Pirrone EC. Successful management of viable cervical pregnancy by local injection of methotrexate guided by transvaginal ultrasonography. *Am J Obstet Gynecol* 1994;170:737–9.
36. Hung TH, Shau WY, Hsieh TT, Hsu JJ, Soong YK, Jeng CJ. Prognostic factors for an unsatisfactory primary methotrexate treatment of cervical pregnancy: a quantitative review. *Hum Reprod* 1998;13:2636–42.
37. Rotas MA, Haberman S, Levgor M. Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. *Obstet Gynecol* 2006;107:1373–81.
38. Godin PA, Bassil S, Donnez J. An ectopic pregnancy developing in a previous caesarian section scar. *Fertil Steril* 1997;67:398–400.
39. Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. First-trimester diagnosis and management of pregnancies implanted into the lower uterine segment Cesarean section scar. *Ultrasound Obstet Gynecol* 2003;21:220–7.
40. Timor-Tritsch IE, Monteagudo A, Santos R, Tsymbal T, Pineda G, Arslan AA. The diagnosis, treatment, and follow-up of cesarean scar pregnancy. *Am J Obstet Gynecol* 2012;207:4.e1–13.
41. Seow KM, Hwang JL, Tsai YL. Ultrasound diagnosis of a pregnancy in a Cesarean section scar. *Ultrasound Obstet Gynecol* 2001;18:547–9.
42. Timor-Tritsch IE, Monteagudo A. Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. *Am J Obstet Gynecol* 2012;207:14–29.
43. Vial Y, Petignat P, Hohlfeld P. Pregnancy in a cesarean scar. *Ultrasound Obstet Gynecol* 2000;16:592–3.
44. Osborn DA, Williams TR, Craig BM. Cesarean scar pregnancy: sonographic and magnetic resonance imaging findings, complications, and treatment. *J Ultrasound Med* 2012;31:1449–56.

45. Peng P, Gui T, Liu X, Chen W, Liu Z. Comparative efficacy and safety of local and systemic methotrexate injection in cesarean scar pregnancy. *Ther Clin Risk Manag* 2015;11:137–42.
46. Felmus LB, Pedowitz P. Interstitial pregnancy. A survey of 45 cases. *Am J Obstet Gynecol* 1953;66:1271–9.
47. Eddy CA, Pauerstein CJ. Anatomy and physiology of the fallopian tube. *Clin Obstet Gynecol* 1980;23:1177–93.
48. Tulandi T, Saleh A. Surgical management of ectopic pregnancy. *Clin Obstet Gynecol* 1999;42:31–8; quiz 55–6.
49. Moore KL, Dalley AF, Agur AM. *Clinically Oriented Anatomy*, 6th ed. Baltimore, MD: Lippincott Williams & Wilkins, 2010.
50. Lin EP, Bhatt S, Dogra VS. Diagnostic clues to ectopic pregnancy. *Radiographics* 2008;28:1661–71.
51. Ackerman TE, Levi CS, Dashefsky SM, Holt SC, Lindsay DJ. Interstitial line: sonographic finding in interstitial (cornual) ectopic pregnancy. *Radiology* 1993;189:83–7.
52. Araujo Júnior E, Zanforlin Filho SM, Pires CR, Guimarães Filho HA, Massagué AA, Nardozza LM, et al. Three-dimensional transvaginal sonographic diagnosis of early and asymptomatic interstitial pregnancy. *Arch Gynecol Obstet* 2007;275:207–10.
53. Rastogi R, Meena GL, Rastogi N, Rastogi V. Interstitial ectopic pregnancy: A rare and difficult clinicosonographic diagnosis. *J Hum Reprod Sci* 2008;1:81–2.
54. Filastre M, Dechaud H, Lesnik A, Taourel P. Interstitial pregnancy: role of MRI. *Eur Radiol* 2005;15:93–5.
55. Tamai K, Koyama T, Togashi K. MR features of ectopic pregnancy. *Eur Radiol* 2007;17:3236–46.
56. Johnston LW, Moir JC. A case of angular pregnancy complicated by gas-gangrene infection of the uterus. *J Obstet Gynaecol Br Emp* 1952;59:85–7.
57. Maher PJ, Grimwade JC. Cornual pregnancy-diagnosis before rupture a report of 2 cases. *Aust N Z J Obstet Gynaecol* 1982;22:172–4.
58. Ng S, Hamontri S, Chua I, Chern B, Siow A. Laparoscopic management of 53 cases of cornual ectopic pregnancy. *Fertil Steril* 2009;92:448–52.
59. Lau S, Tulandi T. Conservative medical and surgical management of interstitial ectopic pregnancy. *Fertil Steril* 1999;72:207–15.
60. Alves JA, Alves NG, Alencar Júnior CA, Feitosa FE, da Silva Costa F. Term angular pregnancy: successful expectant management. *J Obstet Gynaecol Res* 2011;37:641–4.
61. Nahum GG. Rudimentary uterine horn pregnancy. The 20th-century worldwide experience of 588 cases. *J Reprod Med* 2002;47:151–63.
62. Mavrellos D, Sawyer E, Helmy S, Holland TK, Ben-Nagi J, Jurkovic D. Ultrasound diagnosis of ectopic pregnancy in the non-communicating horn of a unicornuate uterus (cornual pregnancy). *Ultrasound Obstet Gynecol* 2007;30:765–70.
63. Comstock C, Huston K, Lee W. The ultrasonographic appearance of ovarian ectopic pregnancies. *Obstet Gynecol* 2005;105:42–5.
64. Shiao CS, Hsieh CL, Chang MY. Primary ovarian pregnancy. *Int J Gynaecol Obstet* 2007;96:127.
65. Bontis J, Grimbizis G, Tarlatzis BC, Miliaras D, Bili H. Intrafollicular ovarian pregnancy after ovulation induction/intrauterine insemination: pathophysiological aspects and diagnostic problems. *Hum Reprod* 1997;12:376–8.
66. Sergent F, Mauger-Tinlot F, Gravier A, Verspyck E, Marpeau L. [Ovarian pregnancies: revaluation of diagnostic criteria]. *J Gynecol Obstet Biol Reprod (Paris)* 2002;31:741–6. French.
67. Gerli S, Rossetti D, Baiocchi G, Clerici G, Unfer V, Di Renzo GC. Early ultrasonographic diagnosis and laparoscopic treatment of abdominal pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2004;113:103–5.
68. Worley KC, Hnat MD, Cunningham FG. Advanced extrauterine pregnancy: diagnostic and therapeutic challenges. *Am J Obstet Gynecol* 2008;198:e1–7.
69. Aliyu LD, Ashimi AO. A multicentre study of advanced abdominal pregnancy: a review of six cases in low resource settings. *Eur J Obstet Gynecol Reprod Biol* 2013;170:33–8.
70. Poole A, Haas D, Magann EF. Early abdominal ectopic pregnancies: a systematic review of the literature. *Gynecol Obstet Invest* 2012;74:249–60.
71. Li XH, Ouyang Y, Lu GX. Value of transvaginal sonography in diagnosing heterotopic pregnancy after *in-vitro* fertilization with embryo transfer. *Ultrasound Obstet Gynecol* 2013;41:563–9.
72. Marcus SF, Macnamee M, Brinsden P. Heterotopic pregnancies after *in-vitro* fertilization and embryo transfer. *Hum Reprod* 1995;10:1232–6.
73. Vermesh M, Silva PD, Rosen GF, Stein AL, Fossum GT, Sauer MV. Management of unruptured ectopic gestation by linear salpingostomy: a prospective, randomized clinical trial of laparoscopy versus laparotomy. *Obstet Gynecol* 1989;73:400–4.
74. Lundorff P, Thorburn J, Hahlin M, Källfelt B, Lindblom B. Laparoscopic surgery in ectopic pregnancy. A randomized trial versus laparotomy. *Acta Obstet Gynecol Scand* 1991;70:343–8.
75. Gray DT, Thorburn J, Lundorff P, Strandell A, Lindblom B. A cost-effectiveness study of a randomised trial of laparoscopy versus laparotomy for ectopic pregnancy. *Lancet* 1995;345:1139–43.
76. Mol F, van Mello NM, Strandell A, Strandell K, Jurkovic D, Ross J, et al.; European Surgery in Ectopic Pregnancy (ESEP) study group. Salpingotomy versus salpingectomy in women with tubal pregnancy (ESEP study): an open-label, multicentre, randomised controlled trial. *Lancet* 2014;383:1483–9.
77. Becker S, Solomayer E, Hornung R, Kurek R, Banys M, Aydeniz B, et al. Optimal treatment for patients with ectopic pregnancies and a history of fertility-reducing factors. *Arch Gynecol Obstet* 2011;283:41–5.
78. Kelly RW, Martin SA, Strickler RC. Delayed hemorrhage in conservative surgery for ectopic pregnancy. *Am J Obstet Gynecol* 1979;133:225–6.
79. Yao M, Tulandi T. Current status of surgical and nonsurgical management of ectopic pregnancy. *Fertil Steril* 1997;67:421–33.
80. Sowter MC, Frappell J. The role of laparoscopy in the management of ectopic pregnancy. *Reviews in gynaecological practice* 2002;2:73–82.
81. Hajenius PJ, Mol BW, Ankum WM, van der Veen F, Bossuyt PM, Lammes FB. Clearance curves of serum human chorionic gonadotrophin for the diagnosis of persistent trophoblast. *Hum Reprod* 1995;10:683–7.
82. Lund CO, Nilas L, Bangsgaard N, Ottesen B. Persistent ectopic pregnancy after linear salpingotomy: a non-predictable complication to conservative surgery for tubal gestation. *Acta Obstet Gynecol Scand* 2002;81:1053–9.
83. Graczykowski JW, Mishell DR Jr. Methotrexate prophylaxis for persistent ectopic pregnancy after conservative treatment by salpingostomy. *Obstet Gynecol* 1997;89:118–22.
84. Saraj AJ, Wilcox JG, Najmabadi S, Stein SM, Johnson MB, Paulson RJ. Resolution of hormonal markers of ectopic gestation: a randomized trial comparing single-dose intramuscular methotrexate with salpingostomy. *Obstet Gynecol* 1998;92:989–94.
85. Sowter MC, Farquhar CM, Petrie KJ, Gudex G. A randomised trial comparing single dose systemic methotrexate and laparoscopic surgery for the treatment of unruptured tubal pregnancy. *BJOG* 2001;108:192–203.
86. Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. *Obstet Gynecol* 1991;77:754–7.

87. Kirk E, Condous G, Bourne T. The non-surgical management of ectopic pregnancy. *Ultrasound Obstet Gynecol* 2006;27:91–100.
88. Lipscomb GH, Gomez IG, Givens VM, Meyer NL, Bran DF. Yolk sac on transvaginal ultrasound as a prognostic indicator in the treatment of ectopic pregnancy with single-dose methotrexate. *Am J Obstet Gynecol* 2009;200:338.e1–4.
89. Kirk E, Van Calster B, Condous G, Papageorghiou AT, Gevaert O, Van Huffel S, et al. Ectopic pregnancy: using the β -hCG ratio to select women for expectant or medical management. *Acta Obstet Gynecol Scand* 2011;90:264–72.
90. Dudley PS, Heard MJ, Sangi-Haghpeykar H, Carson SA, Buster JE. Characterizing ectopic pregnancies that rupture despite treatment with methotrexate. *Fertil Steril* 2004;82:1374–8.
91. Trio D, Strobelt N, Picciolo C, Lapinski RH, Ghidini A. Prognostic factors for successful expectant management of ectopic pregnancy. *Fertil Steril* 1995;63:469–72.
92. Lipscomb GH, McCord ML, Stovall TG, Huff G, Portera SG, Ling FW. Predictors of success of methotrexate treatment in women with tubal ectopic pregnancies. *N Engl J Med* 1999;341:1974–8.
93. Bixby S, Tello R, Kuligowska E. Presence of a yolk sac on transvaginal sonography is the most reliable predictor of single-dose methotrexate treatment failure in ectopic pregnancy. *J Ultrasound Med* 2005;24:591–8.
94. da Costa Soares R, Elito J Jr, Camano L. Increment in β -hCG in the 48-h period prior to treatment: a new variable predictive of therapeutic success in the treatment of ectopic pregnancy with methotrexate. *Arch Gynecol Obstet* 2008;278:319–24.
95. Nguyen Q, Kapitz M, Downes K, Silva C. Are early human chorionic gonadotropin levels after methotrexate therapy a predictor of response in ectopic pregnancy? *Am J Obstet Gynecol* 2010;202:630.e1–5.
96. Skubisz MM, Li J, Wallace EM, Tong S. Decline in hCG levels between days 0 and 4 after a single dose of methotrexate for ectopic pregnancy predicts treatment success: a retrospective cohort study. *BJOG* 2011;118:1665–8.
97. Lipscomb GH. Medical management of ectopic pregnancy. *Clin Obstet Gynecol* 2012;55:424–32.
98. Doubilet PM, Benson CB, Bourne T, Blaivas M; Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy. Diagnostic criteria for nonviable pregnancy early in the first trimester. *N Engl J Med* 2013;369:1443–51.
99. Bourne T, Barnhart K, Benson CB, Brosens J, Van Calster B, Condous G, et al. NICE guidance on ectopic pregnancy and miscarriage restricts access and choice and may be clinically unsafe. *BMJ* 2013;346:f197.
100. Craig LB, Khan S. Expectant management of ectopic pregnancy. *Clin Obstet Gynecol* 2012;55:461–70.
101. Elson J, Tailor A, Banerjee S, Salim R, Hillaby K, Jurkovic D. Expectant management of tubal ectopic pregnancy: prediction of successful outcome using decision tree analysis. *Ultrasound Obstet Gynecol* 2004;23:552–6.
102. Shalev E, Peleg D, Tsabari A, Romano S, Bustan M. Spontaneous resolution of ectopic tubal pregnancy: natural history. *Fertil Steril* 1995;63:15–9.
103. Cohen MA, Sauer MV. Expectant management of ectopic pregnancy. *Clin Obstet Gynecol* 1999;42:48–54.
104. van Mello NM, Mol F, Verhoeve HR, van Wely M, Adriaanse AH, Boss EA, et al. Methotrexate or expectant management in women with an ectopic pregnancy or pregnancy of unknown location and low serum hCG concentrations? A randomized comparison. *Hum Reprod* 2013;28:60–7.
105. Spitzer D, Steiner H, Graf A, Zajc M, Staudach A. Conservative treatment of cervical pregnancy by curettage and local prostaglandin injection. *Hum Reprod* 1997;12:860–6.
106. Cosin JA, Bean M, Grow D, Wiczlyk H. The use of methotrexate and arterial embolization to avoid surgery in a case of cervical pregnancy. *Fertil Steril* 1997;67:1169–71.
107. Benson CB, Doubilet PM. Strategies for conservative treatment of cervical ectopic pregnancy. *Ultrasound Obstet Gynecol* 1996;8:371–2.
108. Kung FT, Chang SY. Efficacy of methotrexate treatment in viable and nonviable cervical pregnancies. *Am J Obstet Gynecol* 1999;181:1438–44.
109. Trambert JJ, Einstein MH, Banks E, Frost A, Goldberg GL. Uterine artery embolization in the management of vaginal bleeding from cervical pregnancy: a case series. *J Reprod Med* 2005;50:844–50.
110. Fylstra DL, Coffey MD. Treatment of cervical pregnancy with cerclage, curettage and balloon tamponade. A report of three cases. *J Reprod Med* 2001;46:71–4.
111. Scutiero G, Nappi L, Matteo M, Balzano S, Macarini L, Greco P. Cervical pregnancy treated by uterine artery embolisation combined with office hysteroscopy. *Eur J Obstet Gynecol Reprod Biol* 2013;166:104–6.
112. Timor-Tritsch IE, Khatib N, Monteagudo A, Ramos J, Berg R, Kovács S. Cesarean scar pregnancies: experience of 60 cases. *J Ultrasound Med* 2015;34:601–10.
113. Cheng LY, Wang CB, Chu LC, Tseng CW, Kung KT. Outcomes of primary surgical evacuation during the first trimester in different types of implantation in women with cesarean scar pregnancy. *Fertil Steril* 2014;102:1085–90.e2.
114. Michaels AY, Washburn EE, Pocius KD, Benson CB, Doubilet PM, Carusi DA. Outcome of cesarean scar pregnancies diagnosed sonographically in the first trimester. *J Ultrasound Med* 2015;34:595–9.
115. Zosmer N, Fuller J, Shaikh H, Johns J, Ross JA. Natural history of early first-trimester pregnancies implanted in Cesarean scars. *Ultrasound Obstet Gynecol* 2015;46:367–75.
116. Centre for Maternal and Child Enquiries (CMACE). Saving Mothers' Lives: reviewing maternal deaths to make motherhood safer: 2006–08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011;118 Suppl 1:1–203.
117. Zhuang Y, Huang L. Uterine artery embolization compared with methotrexate for the management of pregnancy implanted within a cesarean scar. *Am J Obstet Gynecol* 2009;201:152.e1–3.
118. Ash A, Smith A, Maxwell D. Caesarean scar pregnancy. *BJOG* 2007;114:253–63.
119. Litwicka K, Greco E. Caesarean scar pregnancy: a review of management options. *Curr Opin Obstet Gynecol* 2011;23:415–21.
120. Uysal F, Uysal A, Adam G. Cesarean scar pregnancy: diagnosis, management, and follow-up. *J Ultrasound Med* 2013;32:1295–300.
121. Birch Petersen K, Hoffmann E, Rifbjerg Larsen C, Nielsen HS. Cesarean scar pregnancy: a systematic review of treatment studies. *Fertil Steril* 2016;105:958–67.
122. Wu R, Klein MA, Mahboob S, Gupta M, Katz DS. Magnetic resonance imaging as an adjunct to ultrasound in evaluating cesarean scar ectopic pregnancy. *J Clin Imaging Sci* 2013;3:16.
123. Yang Q, Piao S, Wang G, Wang Y, Liu C. Hysteroscopic surgery of ectopic pregnancy in the cesarean section scar. *J Minim Invasive Gynecol* 2009;16:432–6.
124. Halperin R, Schneider D, Mendlovic S, Pansky M, Herman A, Maymon R. Uterine-preserving emergency surgery for cesarean scar pregnancies: another medical solution to an iatrogenic problem. *Fertil Steril* 2009;91:2623–7.

125. Wang HY, Zhang J, Li YN, Wei W, Zhang DW, Lu YQ, et al. Laparoscopic management or laparoscopy combined with transvaginal management of type II cesarean scar pregnancy. *J SLS* 2013;17:263–72.
126. He M, Chen MH, Xie HZ, Yao SZ, Zhu B, Feng LP, et al. Transvaginal removal of ectopic pregnancy tissue and repair of uterine defect for caesarean scar pregnancy. *BJOG* 2011;118:1136–9.
127. Le A, Shan L, Xiao T, Zhuo R, Xiong H, Wang Z. Transvaginal surgical treatment of cesarean scar ectopic pregnancy. *Arch Gynecol Obstet* 2013;287:791–6.
128. Jurkovic D, Ben-Nagi J, Ofilli-Yebovi D, Sawyer E, Helmy S, Yazbek J. Efficacy of Shirodkar cervical suture in securing hemostasis following surgical evacuation of Cesarean scar ectopic pregnancy. *Ultrasound Obstet Gynecol* 2007;30:95–100.
129. Zhang XB, Zhong YC, Chi JC, Shen JL, Qiu XX, Xu JR, et al. Caesarean scar pregnancy: treatment with bilateral uterine artery chemoembolization combined with dilation and curettage. *J Int Med Res* 2012;40:1919–30.
130. Jurkovic D, Knez J, Appiah A, Farahani L, Mavrelos D, Ross JA. Surgical treatment of Cesarean scar ectopic pregnancy: efficacy and safety of ultrasound-guided suction curettage. *Ultrasound Obstet Gynecol* 2016;47:511–17.
131. Smith A, Ash A, Maxwell D. Sonographic diagnosis of cesarean scar pregnancy at 16 weeks. *J Clin Ultrasound* 2007;35:212–15.
132. Timor-Tritsch IE, Monteagudo A, Cali G, Vintzileos A, Viscarello R, Al-Khan A, et al. Cesarean scar pregnancy is a precursor of morbidly adherent placenta. *Ultrasound Obstet Gynecol* 2014;44:346–53.
133. Cassik P, Ofilli-Yebovi D, Yazbek J, Lee C, Elson J, Jurkovic D. Factors influencing the success of conservative treatment of interstitial pregnancy. *Ultrasound Obstet Gynecol* 2005;26:279–82.
134. Poon LC, Emmanuel E, Ross JA, Johns J. How feasible is expectant management of interstitial ectopic pregnancy? *Ultrasound Obstet Gynecol* 2014;43:317–21.
135. Jermy K, Thomas J, Doo A, Bourne T. The conservative management of interstitial pregnancy. *BJOG* 2004;111:1283–8.
136. Tang A, Baartz D, Khoo SK. A medical management of interstitial ectopic pregnancy: a 5-year clinical study. *Aust N Z J Obstet Gynaecol* 2006;46:107–11.
137. Andrés MP, Campillos JM, Lapresta M, Lahoz I, Crespo R, Tobajas J. Management of ectopic pregnancies with poor prognosis through ultrasound guided intrasacular injection of methotrexate, series of 14 cases. *Arch Gynecol Obstet* 2012;285:529–33.
138. Moon HS, Choi YJ, Park YH, Kim SG. New simple endoscopic operations for interstitial pregnancies. *Am J Obstet Gynecol* 2000;182:114–21.
139. Moon HS, Kim SG, Park GS, Choi JK, Koo JS, Joo BS. Efficacy of bleeding control using a large amount of highly diluted vasopressin in laparoscopic treatment for interstitial pregnancy. *Am J Obstet Gynecol* 2010;203:30.e1–6.
140. Huang MC, Su TH, Lee MY. Laparoscopic management of interstitial pregnancy. *Int J Gynaecol Obstet* 2005;88:51–2.
141. Cucinella G, Rotolo S, Calagna G, Granese R, Agrusa A, Perino A. Laparoscopic management of interstitial pregnancy: the “purse-string” technique. *Acta Obstet Gynecol Scand* 2012;91:996–9.
142. Katz DL, Barrett JP, Sanfilippo JS, Badway DM. Combined hysteroscopy and laparoscopy in the treatment of interstitial pregnancy. *Am J Obstet Gynecol* 2003;188:1113–4.
143. Wright SD, Busbridge RC, Gard GB. A conservative and fertility preserving treatment for interstitial ectopic pregnancy. *Aust N Z J Obstet Gynaecol* 2013;53:211–3.
144. Ophir E, Singer-Jordan J, Oettinger M, Odeh M, Tendler R, Feldman Y, et al. Uterine artery embolization for management of interstitial twin ectopic pregnancy: case report. *Hum Reprod* 2004;19:1774–7.
145. Deruelle P, Lucot JP, Lions C, Robert Y. Management of interstitial pregnancy using selective uterine artery embolization. *Obstet Gynecol* 2005;106:1165–7.
146. Gong W, Li X, Ren H, Han C, Li Y, Wu Z. Superselective uterine arterial embolization combined with transcatheter intra-arterial methotrexate infusion in 40 cases with fallopian tube ectopic pregnancy. *Clin Exp Obstet Gynecol* 2013;40:222–6.
147. Chen CL, Wang PH, Chiu LM, Yang ML, Hung JH. Successful conservative treatment for advanced interstitial pregnancy. A case report. *J Reprod Med* 2002;47:424–6.
148. Park JK, Dominguez CE. Combined medical and surgical management of rudimentary uterine horn pregnancy. *J SLS* 2007;11:119–22.
149. Sönmezler M, Taskin S, Atabekoglu C, Güngör M, Ünlü C. Laparoscopic management of rudimentary uterine horn pregnancy: case report and literature review. *J SLS* 2006;10:396–9.
150. Joseph RJ, Irvine LM. Ovarian ectopic pregnancy: aetiology, diagnosis, and challenges in surgical management. *J Obstet Gynaecol* 2012;32:472–4.
151. Su WH, Cheung SM, Chang SP, Chang WH, Cheng MH. Is ovarian pregnancy a medical illness? Methotrexate treatment failure and rescue by laparoscopic removal. *Taiwan J Obstet Gynecol* 2008;47:471–3.
152. Shaw SW, Hsu JJ, Chueh HY, Han CM, Chen FC, Chang YL, et al. Management of primary abdominal pregnancy: twelve years of experience in a medical centre. *Acta Obstet Gynecol Scand* 2007;86:1058–62.
153. Cobellis L, Stradella L, Messalli EM. Contribution to the choice of therapy in abdominal pregnancy. *Panminerva Med* 2000;42:159–61.
154. Nkusu Nunyalulendo D, Einterz EM. Advanced abdominal pregnancy: case report and review of 163 cases reported since 1946. *Rural Remote Health* 2008;8:1087.
155. Sunday-Adeoye I, Twomey D, Egwuatu EV, Okonta PI. A 30-year review of advanced abdominal pregnancy at the Mater Misericordiae Hospital, Afikpo, southeastern Nigeria (1976–2006). *Arch Gynecol Obstet* 2011;283:19–24.
156. Opare-Addo HS, Deganus S. Advanced abdominal pregnancy: a study of 13 consecutive cases seen in 1993 and 1994 at Komfo Anokye Teaching Hospital, Kumasi, Ghana. *Afr J Reprod Health* 2000;4:28–39.
157. Dubinsky TJ, Guerra F, Gormaz G, Maklad N. Fetal survival in abdominal pregnancy: a review of 11 cases. *J Clin Ultrasound* 1996;24:513–17.
158. Talbot K, Simpson R, Price N, Jackson SR. Heterotopic pregnancy. *J Obstet Gynaecol* 2011;31:7–12.
159. Habana A, Dokras A, Giraldo JL, Jones EE. Cornual heterotopic pregnancy: contemporary management options. *Am J Obstet Gynecol* 2000;182:1264–70.
160. Wang Y, Ma CH, Qiao J, Chen XN, Liu P. Efficacy of local aspiration in the conservative treatment of live interstitial pregnancy coexisting with live intrauterine pregnancy after in vitro fertilization and embryo transfer. *Chin Med J (Engl)* 2012;125:1345–8.
161. Gungor Ugurlucan F, Bastu E, Dogan M, Kalelioglu I, Alanya S, Has R. Management of cesarean heterotopic pregnancy with transvaginal ultrasound-guided potassium chloride injection and gestational sac aspiration, and review of the literature. *J Minim Invasive Gynecol* 2012;19:671–3.

162. Cengiz H, Kaya C, Ekin M, Karakaş S, Yasar L. Is laparoscopic surgery safe in patients with an elevated shock index due to ruptured ectopic pregnancy? *Clin Exp Obstet Gynecol* 2013;40:418–20.
163. Moragianni VA, Hamar BD, McArdle C, Ryley DA. Management of a cervical heterotopic pregnancy presenting with first-trimester bleeding: case report and review of the literature. *Fertil Steril* 2012; 98:89–94.
164. Qin L, Li S, Tan S. Laparoscopic loop ligature for selective therapy in heterotopic interstitial and intrauterine pregnancy following in-vitro fertilization and embryo transfer. *Int J Gynaecol Obstet* 2008;101:80–1.
165. Louis-Sylvestre C, Morice P, Chapron C, Dubuisson JB. The role of laparoscopy in the diagnosis and management of heterotopic pregnancies. *Human Reprod* 1997;12:1100–2.
166. Pschera H, Kandemir S. Laparoscopic treatment of heterotopic pregnancies: benefits, complications and safety aspects. *J Turkish German Gynecol Assoc* 2005;6:90–4.
167. Fernandez H, Lelaidier C, Doumerc S, Fournet P, Olivennes F, Frydman R. Nonsurgical treatment of heterotopic pregnancy: a report of six cases. *Fertil Steril* 1993;60:428–32.
168. Wang YL, Yang TS, Chang SP, Ng HT. Heterotopic pregnancy after GIFT managed with expectancy: a case report. *Zhonghua Yi Xue Za Zhi (Taipei)* 1996;58:218–22.
169. Hartwell EA. Use of Rh immune globulin: ASCP practice parameter. American Society of Clinical Pathologists. *Am J Clin Pathol* 1998;110:281–92.
170. Qureshi H, Massey E, Kirwan D, Davies T, Robson S, White J, et al.; British Society for Haematology. BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn. *Transfus Med* 2014;24:8–20.
171. van Mello NM, Mol F. Salpingotomy versus salpingectomy in women with tubal ectopic pregnancy, a randomised controlled trial. *Hum Reprod* 2012;27 Suppl 2:ii73–4.
172. Helmy S, Sawyer E, Ofili-Yebovi D, Yazbek J, Ben Nagi J, Jurkovic D. Fertility outcomes following expectant management of tubal ectopic pregnancy. *Ultrasound Obstet Gynecol* 2007;30:988–93.
173. Elito Junior J, Han KK, Camano L. Tubal patency following surgical and clinical treatment of ectopic pregnancy. *Sao Paulo Med J* 2006;124:264–6.
174. de Bennetot M, Rabischong B, Aublet-Cuvelier B, Belard F, Fernandez H, Bouyer J, et al. Fertility after tubal ectopic pregnancy: results of a population-based study. *Fertil Steril* 2012;98:1271–6.e1–3.
175. Fernandez H, Capmas P, Lucot JP, Resch B, Panel P, Bouyer J; GROG. Fertility after ectopic pregnancy: the DEMETER randomized trial. *Hum Reprod* 2013;28:1247–53.
176. Oriol B, Barrio A, Pacheco A, Serna J, Zuzuarregui JL, Garcia-Velasco JA. Systemic methotrexate to treat ectopic pregnancy does not affect ovarian reserve. *Fertil Steril* 2008;90:1579–82.
177. Boots CE, Gustofson RL, Feinberg EC. Does methotrexate administration for ectopic pregnancy after in vitro fertilization impact ovarian reserve or ovarian responsiveness? *Fertil Steril* 2013;100:1590–3.
178. Singer T, Kofinas J, Huang JY, Elias R, Schattman GL, Rosenwaks Z. Anti mullerian hormone serum levels and reproductive outcome are not affected by neither methotrexate nor laparoscopic salpingectomy for the treatment of ectopic pregnancy in IVF patients. *J Minim Invasive Gynecol* 2011;18 Suppl 1:S46.
179. McLaren JF, Burney RO, Milki AA, Westphal LM, Dahan MH, Lathi RB. Effect of methotrexate exposure on subsequent fertility in women undergoing controlled ovarian stimulation. *Fertil Steril* 2009;92:515–9.
180. Krissi H, Hiersch L, Stolovitch N, Nitke S, Wiznitzer A, Peled Y. Outcome, complications and future fertility in women treated with uterine artery embolization and methotrexate for non-tubal ectopic pregnancy. *Eur J Obstet Gynecol Reprod Biol* 2014;182:172–6.
181. Sagiv R, Debby A, Keidar R, Kerner R, Golan A. Laparoscopic conservative treatment of ovarian pregnancy and subsequent fertility outcome. *J Gynecol Surg* 2014;30:12–14.
182. 33rd RCOG Study Group. Recommendations arising from the 33rd RCOG Study Group: Problems in Early Pregnancy – Advances in Diagnosis and Management. In: Grudzinskas JG, O'Brien PM, editors. *Problems in Early Pregnancy: Advances in Diagnosis and Management*. London: RCOG Press; 1997. p. 327–31.
183. Engelhard IM, van den Hout MA, Arntz A. Posttraumatic stress disorder after pregnancy loss. *Gen Hosp Psychiatry* 2001;23:62–6.
184. Deepa J, Oladimeji O, Funlayo O. Factors that determine patient satisfaction after surgical treatment of ectopic pregnancy: improving the patient journey! *Eur J Obstet Gynecol Reprod Biol* 2014;178:60–5.
185. Purandare N, Ryan G, Ciprike V, Trevisan J, Sheehan J, Geary M. Grieving after early pregnancy loss - a common reality. *Ir Med J* 2012;105:326–8.
186. Lamb EH. The impact of previous perinatal loss on subsequent pregnancy and parenting. *J Perinat Educ* 2002;11:33–40.
187. Pan L, Zhang J, Li L. Effects of progressive muscle relaxation training on anxiety and quality of life of inpatients with ectopic pregnancy receiving methotrexate treatment. *Res Nurs Health* 2012;35:376–82.
188. Bernstein DA, Borkovec TD. *Progressive relaxation training: A Manual for the Helping Profession*. Champaign, IL: Research Press, 1973.
189. Lagarde L, Bernarnd-Phalippon N, Carlier P, Phelipot-Lates S, Perault-Pochate MC, Bourneau-Martin D. Pregnancy outcomes after preconceptual exposure to methotrexate for ectopic pregnancy. Abstracts of the 19th Annual Meeting of French Society of Pharmacology and Therapeutics, 36th Pharmacovigilance Meeting, 16th APNET Seminar, 13th CHU CIC Meeting, 21–23 April 2015, Caen, France. Abstract CO-011.
190. Hackmon R, Sakaguchi S, Koren G. Effect of methotrexate treatment of ectopic pregnancy on subsequent pregnancy. *Can Fam Physician* 2011;57:37–9.
191. Royal College of Obstetricians and Gynaecologists. *Standards for Gynaecology: Report of a Working Party*. London: RCOG Press; 2008.
192. Bharathan R, Merritt S, Ahmed H. Laparoscopic tubal surgery for ectopic pregnancy: trainees' perspective in the UK. *Gynecol Surg* 2012;9:223–9.
193. Royal College of Obstetricians and Gynaecologists. *Core Module 16: Early Pregnancy Care*. London: RCOG; 2013. [https://www.rcog.org.uk/globalassets/documents/careers-and-training/core-curriculum/2013-05-16_core_module_16.pdf].
194. Hessel M, Buzink SN, Schoot D, Jakimowicz JJ. Face and construct validity of the SimSurgery SEP VR simulator for salpingectomy in case of ectopic pregnancy. *J Gynecol Surg* 2012;28:411–17.
195. Aggarwal R, Tully A, Grantcharov T, Larsen CR, Miskry T, Farthing A, et al. Virtual reality simulation training can improve technical skills during laparoscopic salpingectomy for ectopic pregnancy. *BJOG* 2006;113:1382–7.

Appendix I: Explanation of guidelines and evidence levels

Clinical guidelines are: ‘systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions’. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No.1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at <http://www.rcog.org.uk/green-top-development>). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels	Grades of recommendations
I++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias	A At least one meta-analysis, systematic review or RCT rated as I++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as I+, directly applicable to the target population and demonstrating overall consistency of results
I+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias	B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as I++ or I+
I– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	C A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
2++ High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
2+ Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal	
2– Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	
3 Non-analytical studies, e.g. case reports, case series	
4 Expert opinion	
	Good practice point
	 Recommended best practice based on the clinical experience of the guideline development group

Appendix II: Single-dose protocol for intramuscular methotrexate

Day	Therapy
1	Serum β -hCG, U&E, LFTs, FBC, blood group, 50 mg/m ² intramuscular methotrexate
4	Serum β -hCG
7	Serum β -hCG <ul style="list-style-type: none">● If β-hCG decrease less than 15% days 4–7, for repeat TVS & methotrexate 50 mg/m² if still fulfils criteria for medical management.● If β-hCG decrease greater than 15% days 4–7, for repeat β-hCG weekly until levels less than 15 iu/l.

Abbreviations: **β -hCG** beta-human chorionic gonadotrophin; **FBC** full blood count; **LFTs** liver function tests; **TVS** transvaginal scan; **U&E** urea and electrolytes.

Adapted from Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. *Obstet Gynecol* 1991;77:754–7.

Appendix III: Contraindications to methotrexate

- Haemodynamic instability
- Presence of an intrauterine pregnancy
- Breastfeeding
- If unable to comply with follow-up
- Known sensitivity to methotrexate
- Chronic liver disease
- Pre-existing blood dyscrasia
- Active pulmonary disease
- Immunodeficiency
- Peptic ulcer disease

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All RCOG guidance developers are asked to declare any conflicts of interest. A statement summarising any conflicts of interest for this guideline is available from:

<https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg21>.

The final version is the responsibility of the Guidelines Committee of the RCOG.

The review process will commence in 2019, unless otherwise indicated.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.