National Institute for Health and Care Excellence

Draft for consultation

Ectopic pregnancy and miscarriage: diagnosis and initial management

[A] Diagnostic accuracy of ultrasound features for tubal ectopic pregnancy

NICE guideline CG154 (update)

Evidence review

December 2018

Draft for Consultation

This evidence review was developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Diagnostic accuracy of ultrasound features for tubal ectopic pregnancy

Review question

What ultrasound features are most diagnostic of a tubal ectopic pregnancy?

Introduction

Ectopic pregnancy remains the leading cause of maternal mortality in early pregnancy in the UK and early diagnosis is important to reduce this risk. Early diagnosis may also allow non-surgical treatment options, including expectant or medical management. The diagnosis of ectopic pregnancy is made using a combination of the clinical presentation, serum human chorionic gonadotrophin (hCG) levels and pelvic ultrasound scan findings.

Ultrasound features of ectopic pregnancy can vary widely between different individuals, and depend on a variety of factors, including the gestation of the pregnancy, experience of the sonographer, route of scanning (transabdominal or transvaginal) as well as features of the scan equipment. The aim of this review was to identify ultrasound scan features which have high diagnostic accuracy for the identification of ectopic pregnancy.

Summary of the protocol

Please see Table 1 for a summary of the Population, Index test, Reference test, and Outcome (PIRO) characteristics of this review.

Table 1: Summary of the protocol (PIRO table)

Population	Pregnant women presenting in early pregnancy (<13^{+0} weeks) with pain or vaginal bleeding Asymptomatic pregnant women with indeterminate features on ultrasound, or pregnancy of unknown location

Index tests	Ultrasonography with the following features:
	Uterus:
	• Empty uterus/no evidence of intrauterine pregnancy
	• Cystic areas/sacs, including any of the following:
	  ○ Pseudo-gestational sac/decidual cyst
	  ○ Cystic area inside the uterus
	  ○ Pseudo sac
	• Fluid inside the uterus
	• Heterotopic pregnancy (co-existing intrauterine and ectopic pregnancies)
	Tube and ovary:
	• Adnexal mass (yolk sac, fetal pole, fetal heartbeat)
	• Tubal ring sign (also known as bagel sign, donut sign or blob sign)
	• Adnexal cyst (simple)
	• Complex extra-adnexal mass
	Peritoneal cavity:
	• Identification of fluid/blood, including any of the following:
	  ○ Free fluid

	○ Haemoperitoneum ○ Free blood in the pelvis
Reference tests	• Surgical/histological confirmation of ectopic pregnancy • Confirmation of ectopic pregnancy on follow up ultrasound scan • Rising hCG levels with no evidence of chorionic villi on evacuation of retained products of conception (ERPC) • Suspected/confirmed ectopic pregnancy which resolved after medical treatment
Outcome	• Sensitivity • Specificity • Positive likelihood ratio (LR+) • Negative likelihood ratio (LR-) • Area under the curve (AUC)

AUC: area under the curve; ERPC: evacuation of retained products of conception; hCG: human chorionic gonadotrophin; IVF: in vitro fertilisation; LR: likelihood ratio; PUL: pregnancy of unknown location

For full details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Please see the methods section of the 2012 guideline for further details.

Methods specific to this review question are described in the review protocol in appendix A.

The use of GRADE for reviews of diagnostic test accuracy has recently been adopted by NICE, and this methodology was applied to the review. Cross-sectional diagnostic test accuracy studies were initially rated as high quality, and the rating was amended according to the risk of bias (as assessed using the QUADAS-2 checklist) inconsistency, imprecision, indirectness and other factors, in a manner analogous to intervention reviews. Imprecision was assessed according to pre-specified thresholds for sensitivity and specificity, which were identified by the guideline committee as representing clinically meaningful results. In determining these thresholds, the committee recognised that the identification of ectopic pregnancy often requires an assessment of a combination of features (including the woman's symptoms and hCG levels as well as ultrasound findings). Therefore they agreed a threshold of ≥75% for sensitivity and ≥80% for specificity would represent a very useful test. The lower threshold (representing a not useful test) was set at <50%.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Ten cohort studies were included in this review (4 prospective cohorts: Dart 2002, Malek-Mellouli 2013, Moore 2007, Sadek 1995; 6 retrospective cohorts: Ahmed 2004, Barnhart 2011, Dart 1998, Hammoud 2005, Mehta 1999, Nadim 2018).

All studies examined features seen using transvaginal ultrasonography (TVUS), and two studies additionally used transabdominal ultrasonography (TAS) (Hammoud 2005, Moore 2007).

Studies were conducted in three distinct populations of women and so the results have been analysed for these separate sub-populations:

- three studies included any women with bleeding and/or pain during the first trimester, who were referred for ultrasound (sub-population 1, all symptomatic women: Barnhart 2011, Moore 2007, Sadek 1995).
- two studies included only women with a suspected ectopic pregnancy or pregnancy of unknown location (PUL), where women with confirmed intrauterine pregnancies (IUP) were excluded from the analysis (sub-population 2, IUPs excluded: Hammoud 2005, Mehta 1999).
- five studies included women with PULs, where women with definite ectopic pregnancies and IUPs were excluded (sub-population 3, IUP and EP excluded, Ahmed 2004, Dart 1998, Dart 2002, Malek-Mellouli 2013, Nadim 2018).

Terminology used to define findings seen on the ultrasound varied across studies, and did not align precisely with terms used in the protocol. Consequently, the description given within each study was used to group like with like, and the wording in this review has been modified to reflect this:

- An adnexal mass with a gestational sac and yolk sac or fetal pole with/without fetal heartbeat is termed “adnexal ectopic”
- Sonographic findings reported as inhomogeneous mass, heterogeneous mass, or adnexal mass (no yolk sac or fetal pole visible) are termed “complex adnexal mass”

Meta-analysis of diagnostic accuracy measures for the different features identified on the ultrasound was not possible due to the small number of comparable studies (different populations, and/or different features visualised).

Studies are summarised in Table 2.

See also the literature search strategy in appendix B and study selection flowchart in appendix C.

Excluded studies

Studies not included in this systematic review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies.

Table 2: Summary of included studies

Study	Population	Index test	Reference test	Outcomes
Ahmed 2004 Retrospective cohort UK	N=77 • Women with suspected ectopic pregnancy who had diagnostic laparoscopy	TVUS	Histopathological examination was performed to confirm the diagnosis of ectopic pregnancy	• Pseudo-sac: 2x2 DTA table • Complex adnexal mass: 2x2 DTA table

Study	Population	Index test	Reference test	Outcomes
Barnhart 2011 Retrospective cohort USA	N=1880 • Women with pain or bleeding during the first trimester of pregnancy, presenting to ED • Excluded: simple viable IUP (included abnormal IUP, or IUPs that needed further gynaecological consult)	TVUS	Followed by the gynaecology service until a definitive diagnosis was made	• Adnexal mass (adnexal ectopic): 2x2 DTA table, Sensitivity, Specificity • Complex adnexal mass: 2x2 DTA table, Sensitivity, Specificity
Dart 1998 Retrospective cohort USA	N=228 • Women with symptoms (pain or bleeding) presenting to ED in first trimester • US indeterminate findings	TVUS	Visualised at laparoscopy or laparotomy and confirmed by histopathology	• Empty uterus: 2x2 DTA table and LR • Fluid inside uterus: 2x2 DTA table and LR
Dart 2002 Prospective cohort USA	N=635 • Symptomatic (pain or bleeding) presenting to ED in first trimester • US indeterminate findings	TVUS	(1) Extrauterine pregnancy visualised at laparoscopy; (2) Confirmed in patients managed with methotrexate (ectopic pregnancy confirmed with US follow-up; or hCG values that increased or plateaued after curettage)	• Empty uterus: 2x2 DTA table • Fluid inside uterus: 2x2 DTA table
Hammoud 2005 Retrospective cohort USA	N=403 • Symptomatic (pain or bleeding) in first trimester • No obvious IUP	TAS and TVUS	(1) When surgical: pathological diagnosis; (2) When medical: clinical follow up, and established sonographic criteria	• Pseudo-sac: 2x2 DTA table
Malek-Mellouli 2013 Prospective cohort Tunisia	N=94 • Suspected early pregnancy complications (PUL) • No obvious IUP • No obvious ectopic pregnancy	TVUS	Visualised at laparoscopy or laparotomy and confirmed by histopathology	• Free fluid in peritoneal cavity: AUC, Sensitivity, Specificity
Mehta 1999 Retrospective cohort USA	N=128 • Women with symptoms (pain or bleeding) in first trimester • No obvious IUP or abnormal IUP	TVUS	Medical records, clinical and sonographic follow up	• Complex adnexal mass: 2x2 DTA table • Free fluid in peritoneal cavity: 2x2 DTA table • Fluid inside uterus: 2x2 DTA table
Moore 2007	N=226 • Women with symptoms (pain or bleeding)	TAS and TVUS	Medical and operative records, clinical and	• Free fluid in peritoneal cavity:

Study	Population	Index test	Reference test	Outcomes
Prospective cohort USA	presenting to ED in first trimester		sonographic follow up	Sensitivity, Specificity, LR
Nadim 2018 Retrospective cohort Australia	N=849 • PUL or probable ectopic pregnancy • No definite ectopic pregnancy • No non-tubal ectopic pregnancy • No IUP	TVUS	(1) Visualised at laparoscopy or laparotomy and confirmed by histopathology of removed fallopian tube; (2) PULs: repeat TVUS and clinical follow up (hCG analysis) until diagnosis	• Complex adnexal mass: 2x2 DTA table, Sensitivity, Specificity, LR • Adnexal mass (adnexal ectopic): 2x2 DTA table, Sensitivity, Specificity, LR
Sadek 1995 Prospective cohort Norway	N=525 • Women with symptoms (pain or bleeding) in first trimester	TVUS	Visualised at laparoscopy or laparotomy and confirmed by histopathology	• Free fluid in peritoneal cavity: 2x2 DTA table, Sensitivity, Specificity • Complex adnexal mass: 2x2 DTA table, Sensitivity, Specificity

AUC: area under the curve; DTA: diagnostic test accuracy; ED: emergency department; IUP: intrauterine pregnancy; LR: likelihood ratio; N: number of women; PUL: pregnancy of unknown location; TAS: transabdominal sonography; TVUS: transvaginal ultrasonography; US: ultrasound

See appendix D for full evidence tables.

Quality assessment of clinical outcomes included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

A systematic review of economic literature was conducted, but no studies were identified which were applicable to this review question.

Economic model

No economic modelling was undertaken for this review.

Evidence statements

Sub-population 1. All symptomatic women (women with pain/bleeding or referred for a scan due to high risk of ectopic pregnancy)

TVUS: adnexal ectopic (adnexal mass with gestational sac and yolk sac or fetal pole +/- fetal heartbeat)

- Low quality evidence from 1 cohort study (N=1880) showed low sensitivity and high specificity to detect tubal ectopic pregnancy using the visualisation of an adnexal ectopic pregnancy with transvaginal ultrasound. The positive likelihood ratio showed this was a very useful feature: when an adnexal ectopic is visualised

there is more likely to be a tubal ectopic pregnancy. The negative likelihood ratio showed it was not a useful feature: failure to identify an adnexal ectopic does not markedly reduce the chance of having an ectopic pregnancy.

TVUS: complex adnexal mass: inhomogeneous, heterogeneous, or adnexal mass (no yolk sac or fetal pole)

- Low quality evidence from 1 cohort study (N=1880) showed low sensitivity and high specificity to detect tubal ectopic pregnancy using the visualisation of a complex adnexal mass with transvaginal ultrasound. The positive likelihood ratio showed this to be a very useful feature: when visualised, it has increased likelihood of being an ectopic pregnancy. The negative likelihood ratio showed it was not a useful feature.

TVUS: Free fluid in the pelvis

- Moderate quality evidence from 1 cohort study (N=226) showed moderate sensitivity and specificity to detect tubal ectopic pregnancy using visualisation of free fluid in the pelvis with transvaginal ultrasound. The positive and negative likelihood ratios showed this was not a useful feature.
- High quality evidence from 1 cohort study (N=525) showed high sensitivity and specificity to detect tubal ectopic pregnancy using visualisation of free fluid in the pelvis with transvaginal ultrasound. The positive and negative likelihood ratios showed this to be a very useful feature.

TAS: Free fluid in the pelvis

- Moderate quality evidence from 1 cohort study (N=241) showed low sensitivity and high specificity to detect tubal ectopic pregnancy using visualisation of free fluid in the pelvis with transabdominal ultrasound. The positive likelihood ratio showed this to be a moderately useful feature, but the negative likelihood ratio showed it was not a useful feature.

Sub-population 2. High risk of ectopic pregnancy: includes pregnancy of unknown location and ectopic pregnancy (all intrauterine pregnancies excluded)

TVUS: Pseudo-sac

- Moderate quality evidence from 1 cohort study (N=403) showed low sensitivity and high specificity to detect tubal ectopic pregnancy using visualisation of a pseudo-sac with transvaginal ultrasound. The positive and negative likelihood ratios showed this was not a useful feature.

TVUS: Intrauterine fluid

- Low quality evidence from 1 cohort study (N=128) showed low sensitivity and moderate specificity to detect tubal ectopic pregnancy using visualisation of intrauterine fluid with transvaginal ultrasound. The positive and negative likelihood ratios showed this was not a useful feature.

TVUS: Complex adnexal mass: inhomogeneous mass, heterogeneous mass, or adnexal mass (no yolk sac or fetal pole)

- Low quality evidence from 1 cohort study (N=128) showed moderate sensitivity and high specificity to detect tubal ectopic pregnancy using visualisation of a complex adnexal mass with transvaginal ultrasound. The positive likelihood ratio

showed this was a very useful feature. The negative likelihood ratio showed it was not a useful feature.

TVUS: Free fluid in the peritoneal cavity

- Low quality evidence from 1 cohort study (N=128) showed moderate sensitivity and high specificity to detect tubal ectopic pregnancy using visualisation of free fluid in the peritoneal cavity with transvaginal ultrasound. The positive likelihood ratio was not calculable (due to a specificity of 100%). The negative likelihood ratio showed that it was not a useful feature.

Sub-population 3. High risk of ectopic pregnancy: pregnancy of unknown location only (all intrauterine pregnancies and definite ectopic pregnancies excluded)

TVUS: Empty uterus

- Low quality evidence from 2 cohort studies (N=228 and N=635) showed high sensitivity and moderate specificity to detect tubal ectopic pregnancy using visualisation of an empty uterus with transvaginal ultrasound. The positive and negative likelihood ratios showed this was a not useful feature.

TVUS: Pseudo-sac

- Low quality evidence from 1 cohort study (N=77) showed low sensitivity and specificity to detect tubal ectopic pregnancy using visualisation of a pseudo-sac with transvaginal ultrasound. The positive and negative likelihood ratios showed this was a not useful feature.

TVUS: Intrauterine fluid

- Low and moderate quality evidence from 2 cohort studies (N=228 and N=635) showed low sensitivity and high specificity to detect tubal ectopic pregnancy using visualisation of intrauterine fluid with transvaginal ultrasound. The positive and negative likelihood ratios showed this was not a useful feature.

TVUS: Tubal ring sign (bagel sign)

- Low quality evidence from 1 cohort study (N=612) showed high sensitivity and specificity to detect tubal ectopic pregnancy using visualisation of the tubal ring sign with transvaginal ultrasound. The positive likelihood ratio showed this was a very useful feature. The negative likelihood ratio showed this was a moderately useful feature.

TVUS: Complex adnexal mass: inhomogeneous mass, heterogeneous mass, or adnexal mass (no yolk sac or fetal pole)

- Very low quality evidence from 1 cohort study (N=77) showed moderate sensitivity and high specificity to detect tubal ectopic pregnancy using visualisation of a complex adnexal mass with transvaginal ultrasound. The positive likelihood ratio showed this was a useful feature. The negative likelihood ratio showed this was not a useful feature.
- Moderate quality evidence from 1 cohort study (N=663) showed high sensitivity and specificity to detect tubal ectopic pregnancy using visualisation of a complex adnexal mass with transvaginal ultrasound. The positive and negative likelihood ratios showed this to be a very useful feature.

TVUS: Free fluid in the peritoneal cavity

- High quality evidence from 1 cohort study (N=94) showed low sensitivity and high specificity to detect tubal ectopic pregnancy using visualisation of free fluid in the peritoneal cavity with transvaginal ultrasound. The positive and negative likelihood ratios showed this to be not a useful feature.

Recommendations

A1. When carrying out a transvaginal ultrasound in early pregnancy, look for these signs indicating there is a tubal ectopic pregnancy:

- an adnexal mass, moving separate to the ovary[1], comprising a gestational sac containing a yolk sac, **or**
- an adnexal mass, moving separate to the ovary[1], comprising a gestational sac and fetal pole (with or without fetal heartbeat).

A2. When carrying out a transvaginal ultrasound in early pregnancy, look for these signs indicating a high probability of a tubal ectopic pregnancy:

- a complex, inhomogeneous adnexal mass, moving separate to the ovary[1], **or**
- an adnexal mass with an empty gestational sac, moving separate to the ovary[1] (also called a 'tubal ring' or 'bagel sign'[2]).

If these features are present, take into account other intrauterine and adnexal features on the scan, the woman's clinical presentation and serum hCG levels before making a diagnosis.

A3. When carrying out a transvaginal ultrasound in early pregnancy, look for these signs indicating a possible ectopic pregnancy:

- an empty uterus, **or**
- a collection of fluid within the uterine cavity (often referred to as a pseudo-sac[3]).

If these features are present, take into account other intrauterine and adnexal features on the scan, the woman's clinical presentation and serum hCG levels before making a diagnosis. (See also recommendations 1.4.23–1.4.32 on pregnancy of unknown location).

A4. When carrying out a transabdominal or transvaginal ultrasound in early pregnancy, look for a moderate to large amount of free fluid in the peritoneal cavity or Pouch of Douglas. If this is present, take into account other intrauterine and adnexal features on the scan, the woman's clinical presentation and hCG levels before making a diagnosis.

A5. When scanning women during early pregnancy, scan the adnexa as well as the uterus, even if there is an intrauterine pregnancy, to confirm there is no coexisting ectopic pregnancy.

[1] Sometimes called the 'sliding sign'.
[2] A discrete rounded thick-walled mass with a central cystic area.
[3] A pseudo-sac must be differentiated from an early intrauterine sac, which is identified by the presence of an eccentrically-located hypoechoic structure with a double decidual sign (gestational sac surrounded by two concentric echogenic rings) in the endometrium.

Rationale and impact

Why the committee made the recommendations

There was good evidence that, when seen on ultrasound, the presence of an adnexal mass with features of an early pregnancy (a gestational sac containing a yolk sac or fetal pole, with or without a heartbeat) was a reliable indicator for ectopic pregnancy.

Other features such as a complex inhomogeneous adnexal mass, adnexal mass with an empty gestational sac, empty uterus, pseudo-sac or free peritoneal fluid may indicate a suspicion of an ectopic pregnancy, but the evidence showed they are not reliable enough features on their own to diagnose an ectopic pregnancy. The committee used their knowledge and experience to recommend that other scan features, clinical presentation and serum hCG levels should therefore be used as well to confirm or rule out the diagnosis of ectopic pregnancy.

Impact of the recommendations on practice

The recommendations will not change the amount of ultrasound scanning that is carried out but will standardise practice across the NHS. By defining the features that should be used to indicate the presence of an ectopic pregnancy, or a suspicion of an ectopic pregnancy (which can then be investigated further), the diagnosis of ectopic pregnancy should be improved and so risks to women will be reduced.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the correct and timely diagnosis of an ectopic pregnancy was vital to be able to offer the most appropriate management options to women. The committee identified the positive likelihood ratio as being of use in making a diagnosis of ectopic pregnancy. Features with a high positive likelihood ratio would increase the chance of identifying an ectopic pregnancy, making the correct diagnosis more likely.

This review aimed to determine the usefulness of individual features seen on an ultrasound scan, rather than whether or not ultrasound itself is a useful tool. Therefore it was noted that the sensitivity of individual features may not be particularly high – women with an ectopic pregnancy may have a variety of different features identified on scan, and a single feature could not be expected to be present in all women. The committee also noted that, overall, it was important not to miss a diagnosis of ectopic pregnancy (high sensitivity preferable), but that this would be accomplished through the current pathway of clinical follow up where scan findings were uncertain.

In addition, the specificity of certain features appeared to be very high in some studies – as the majority of women in the study had a viable, intrauterine pregnancy that was easily identified. Therefore the number of correctly identified "true negative" test results was high.

The committee therefore focused on the likelihood ratios when considering the evidence. Features showing a high positive likelihood ratio would mean that the chance of an ectopic pregnancy being present would be considerably increased.

Similarly, a low positive likelihood ratio would reduce the clinical suspicion of an ectopic pregnancy.

The quality of the evidence

The quality of the evidence ranged from very low to high, with downgrading predominantly due to imprecision (based on the confidence intervals of both sensitivity and specificity) and concern over the risk of bias from participant flow (loss-to-follow up resulting in missing data from the final analysis).

On review of the evidence, it was noted that studies included different sub-populations of women. Some studies included all women with pain or bleeding in early pregnancy, others focused on women in whom a viable intrauterine pregnancy had been excluded. It was noted that the pre-test probability of an ectopic pregnancy differed markedly in these populations. Although an ectopic pregnancy is a relatively rare occurrence, if a viable intrauterine pregnancy cannot be seen, then the likelihood of an ectopic pregnancy is increased. Several studies reported on any woman presenting with pain or bleeding or any asymptomatic woman presenting for an ultrasound scan before 13^{+0} weeks gestation. Other studies excluded obvious IUPs (on first scan), and others excluded obvious IUPs and obvious ectopic pregnancies, so only presenting data for women with pregnancy of unknown location, or complex scan results.

Each of these populations were felt to be relevant to clinical practise, as women may undergo multiple ultrasound scans during the course of early pregnancy. For the first scan, data on all women is relevant. However, if a viable intrauterine pregnancy cannot be confirmed on this scan, then data on the “higher risk” populations becomes relevant. Therefore, the studies were separated into three distinct populations for consideration, but the quality of evidence was not downgraded for indirectness unless other concerns were noted.

The committee considered making separate recommendations for these groups of women (all women, and those at higher risk of ectopic pregnancy – in whom an intrauterine pregnancy had been excluded). However, it was felt that this may lead to a lack of clarity about how to apply the recommendations. Therefore the evidence from the different populations was considered together in order to make recommendations.

The committee discussed the age of the studies, and how the technical capabilities of ultrasound machines have improved over the last 20 years. They highlighted that the reported diagnostic accuracy for the visualisation of features in the studies pre-2000 may not reflect current practice, especially with the use of the transabdominal ultrasound in these earlier studies.

Benefits and harms

The committee noted that the evidence showed that visualisation of an adnexal mass with features of an early pregnancy (a gestational sac containing a yolk sac or fetal pole, with or without a fetal heartbeat) had a very high positive likelihood ratio for the diagnosis of ectopic pregnancy. This was entirely consistent with their clinical experience – that the identification of a mass showing such features would give a firm diagnosis. The committee did not consider that any other features could make such a definite diagnosis of an ectopic pregnancy.

However, other features were also shown to have a high positive likelihood ratio for the identification of ectopic pregnancy. Therefore, the committee agreed that these features should raise a strong suspicion of the diagnosis. These included the

presence of a complex, inhomogeneous or non-cystic adnexal mass, or the presence of an adnexal mass with an empty gestation sac (containing no yolk sac, fetal pole or fetal heartbeat) (also called a “tubal ring sign” or “bagel sign”).

The identification of a pseudosac (central intrauterine fluid) or an empty uterus were not shown to have a high positive likelihood ratio for the diagnosis of ectopic pregnancy. However, based on their clinical expertise, the committee members agreed that these features, when present, should raise suspicion of ectopic pregnancy, but women presenting with these features would require further investigation.

The presence of free fluid on ultrasound scan was noted to cause challenges in interpretation. The committee were aware that a scan finding of “free fluid” could vary between a trace of fluid identified on transvaginal scan, to a large amount of free fluid visible transabdominally. The likelihood of an ectopic pregnancy would be very different in each of these circumstances. This was reflected in the evidence, where some studies showed a high positive likelihood ratio for the diagnosis of ectopic based on the presence of free fluid, and others showed a low positive likelihood ratio. From the evidence, there was no information as to the volume of free fluid in the peritoneal cavity that was visualised, how to measure it, or how the volume could be interpreted. The committee agreed that it may be a marker of an ectopic pregnancy based on the evidence presented, but free fluid alone could not be relied upon for a diagnosis, and women presenting with only this feature would require further investigation.

When scan findings were not conclusive (a diagnosis of ectopic pregnancy could not be made nor excluded) the committee stressed the importance of using other features to help determine the likelihood of an ectopic pregnancy being present. This would include assessing the clinical presentation and serum hCG levels, rather than relying on scan features alone.

The committee were aware that, although the incidence of heterotopic pregnancy (co-existing intrauterine pregnancy and ectopic pregnancy) is rare, it is known to be increasing. There was concern that practitioners may over-rely on the presence of an intra-uterine pregnancy to exclude the possibility of an ectopic pregnancy. The committee members strongly agreed that this should not be the case, therefore made a recommendation to highlight this issue, as clinicians should scan both the uterus and adnexa for any of the physical features of a pregnancy in all possible locations.

Diagnosis of tubal ectopic pregnancy using visualisation and correct interpretation of certain ultrasound features, will result in reduced delay in treatment and management of the ectopic pregnancy. This may permit a wider range of management options, such as medical or expectant management, in addition to surgery, giving greater choice for women. Early diagnosis should also reduce maternal mortality and morbidity.

Possible harms included the uncertainty of diagnosis in cases where an ultrasound is not definitive. This may lead to unnecessary concern or follow up for women who ultimately are identified as having an intrauterine pregnancy. However, the committee considered that the risks of a missed diagnosis of ectopic pregnancy were so great that this justified the additional follow up and monitoring that may be required.

The committee noted that the majority of the evidence reflected the accuracy of transvaginal, rather than transabdominal, scanning. Transabdominal scanning was considered less accurate, with poorer resolution, particularly at a lower gestational age. However, the committee were aware that some women may decline

transvaginal scanning for a variety of reasons, and that this may put them at increased risk of an uncertain diagnosis.

The committee could not identify any obvious disadvantages to the use of certain features visualised on an ultrasound scan to make a diagnosis of ectopic pregnancy, however they acknowledged that ultrasound scan findings can be subjective, may depend on the operator experience, cannot be 100% accurate, and there will still be some false positives and false negatives.

Cost effectiveness and resource use

Ultrasound scanning is already used in women presenting to an early pregnancy unit and therefore there are no additional ultrasound costs due to these recommendations and no significant resource impact is anticipated. The committee agreed that early diagnosis of ectopic pregnancy using the visualisation of certain features on an ultrasound scan may lead to savings as it would lead to:

- Fewer visits to the hospital, clinic, or early pregnancy assessment unit to make a diagnosis
- Reduced number of blood tests (serum hCG) to make a diagnosis
- Reduced costs due to emergency admissions with ruptured ectopic pregnancies.

Overall, the committee agreed that there would be no significant resource impact from these recommendations.

Other factors the committee took into account

The committee were aware that interpretation of ultrasound findings is dependent upon the training of individuals performing the ultrasound scan and considered that each unit has to take the responsibility of having adequately trained and accredited professionals performing ultrasound scans.

The committee discussed that there may be additional factors regarding language barriers in women who did not speak English or women with learning disabilities, and therefore difficulty communicating the different degrees of certainty or uncertainty around the diagnosis of an ectopic pregnancy, and that clear information should be provided, tailored to an individual women's needs.

The committee also noted that some women, or women from conservative groups within society may avoid transvaginal ultrasound (TVUS) due to possible stigma surrounding the insertion of an object into the vagina, and thus delay a diagnosis. These factors are often highlighted in maternal mortality reports, and the committee acknowledged the importance of working towards educating and supporting women to understand their health/clinical problems and help them to understand that TVUS can be helpful in making a more accurate diagnosis, but that transabdominal ultrasound could be used in these women if necessary (although was not as effective a tool for diagnosis).

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1 Appendices

2 Appendix A: Review protocols

3 **Review protocol for evidence review question: What ultrasound features are most diagnostic of a tubal ectopic pregnancy?**

Field (based on PRISMA-P)	Content
Key area in the scope	The accuracy and interpretation of biomarkers (human chorionic gonadotrophin [hCG], progesterone) and ultrasound in diagnosis, and identifying both the location and the viability of the pregnancy
Draft review question from the previous guideline	N/A
Actual review question	What ultrasound features are most diagnostic of a tubal ectopic pregnancy?
Type of review question	Diagnostic accuracy
Objective of the review	To identify what ultrasound criteria can be used to make a diagnosis of tubal ectopic pregnancy (new evidence identified by surveillance)
Eligibility criteria – population/disease/condition/issue/domain	Pregnant women presenting in early pregnancy (<13 weeks) with pain or vaginal bleeding, (includes women with a previous history of ectopic pregnancy, pelvic inflammatory disease, pregnancy with coil in situ, women with IVF) Asymptomatic pregnant women with indeterminate features on ultrasound, or pregnancy of unknown location (when scan does not show any pregnancy)

Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Ultrasonography with the following features:
	Uterus:
	• Empty uterus / no evidence of intrauterine pregnancy
	• Cystic areas/sacs, including any of the following:
	  ○ Pseudo-gestational sac/ decidual cyst
	  ○ Cystic area inside the uterus
	  ○ Pseudo sac
	• Fluid inside the uterus
	• Heterotopic pregnancy (coexisting IUP + ectopic)

Field (based on PRISMA-P)	Content

	Tube and ovary:
	• Adnexal mass (yolk sac, fetal pole, fetal heartbeat)
	• Tubal ring sign (also known as bagel sign, donut sign or blob sign)
	• Adnexal cyst (simple)
	• Complex extra-adnexal mass
	Peritoneal cavity:
	• Identification of fluid/blood, including any of the following:
	  ○ Free fluid
	  ○ Haemoperitoneum
	  ○ Free blood in the pelvis

Eligibility criteria – comparator(s)/control or reference (gold) standard	• Surgical/histological confirmation of ectopic pregnancy • Confirmation of ectopic pregnancy on follow up ultrasound scan • Rising hCG levels with no evidence of chorionic villi on evacuation of retained products of conception (ERPC) • Suspected/confirmed ectopic pregnancy which resolved after medical treatment
Outcomes and prioritisation	• Sensitivity • Specificity • Positive likelihood ratio (LR+) • Negative likelihood ratio (LR-) • Area under the curve (AUC)
Eligibility criteria – study design	Only published full text papers in English • Cross-sectional diagnostic accuracy studies • Cohort studies (where cross-sectional data were reported therefore 2x2 table can be tabulated) Conference abstracts will only be considered if no evidence is available from full published studies

Field (based on PRISMA-P)	Content
Other exclusion criteria	• Women with pain and/or bleeding after the first trimester (13 or more completed weeks of pregnancy) • Women with tumours of the placenta (molar pregnancy or trophoblastic disease) after the initial diagnosis • Women with pain and/or bleeding unrelated to pregnancy A date cut off of 1995 will be applied due to the advances in scan technology and training of scan operators over the past 25 years. Articles before this date were considered to have very limited importance for decision making.
Proposed stratified, sensitivity/sub-group analysis, or meta-regression	Transabdominal and transvaginal scans will be analysed as separate subgroups, and data will not be combined If possible, asymptomatic women will be analysed as a subgroup
Selection process – duplicate screening/selection/analysis	Duplicate screening/ selection/ analysis will not be undertaken for this review as this question was not prioritised for it. Included and excluded studies will be cross checked with the committee and with published systematic reviews when available.
Data management (software)	A bivariate random effects model will be used to conduct pairwise meta-analysis with, for example, the metandi package in STATA. STAR will be used for bibliographies/citations, text mining, and study sifting, data extraction and quality assessment/critical appraisal.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase. Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. Date limited to 1995 onwards. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies. Key papers:

Field (based on PRISMA-P)	Content
	○ Richardson A, Gallos I, Dobson S et al. (2016) Accuracy of first-trimester ultrasound in diagnosis of tubal ectopic pregnancy in the absence of an obvious extrauterine embryo: systematic review and meta-analysis. [Review]. Ultrasound in Obstetrics & Gynecology 47:28-37. ○ Kirk E, Papageorghiou AT, Condous G, Tan L, Bora S, Bourne The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy. Hum Reprod 2007;22:2824–8 ○ 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 ○ 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. ○ 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. ○ Frates MC, Laing FC. Sonographic evaluation of ectopicpregnancy: an update. Am J Roentgenol 1995;165:251–9. ○ Benson CB, Doubilet PM, Peters HE, Frates MC. Intrauterine fluid with ectopic pregnancy: a reappraisal. J Ultrasound Med 2013;32:389–93. ○ 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. ○ 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. ○ 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. ○ Lin EP, Bhatt S, Dogra VS. Diagnostic clues to ectopic pregnancy. Radiographics 2008;28:1661–71.
Identify if an update	Not an update

Field (based on PRISMA-P)	Content
Author contacts	Developer: National Guideline Alliance NGA-enquiries@RCOG.ORG.UK
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual 2014
Search strategy – for one database	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables)
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables)
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: QUADAS –II checklist for diagnostic studies For details please see section 6.2 of Developing NICE guidelines: the manual 2014 The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual 2014
Methods for quantitative analysis – combining studies and exploring (in)consistency	**Synthesis of data:** Meta-analysis will be conducted where appropriate using STATA. **Minimally important differences** Sensitivity: ≥ 75% very useful test < 50% not a useful test Specificity: ≥ 80% very useful test < 50% not a useful test

Field (based on PRISMA-P)	Content
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual 2014.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual 2014
Rationale/context – what is known	For details please see the introduction to the evidence review
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual 2014. Staff from the NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 2
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA to develop guidelines for the NHS in England.
PROSPERO registration number	Not registered with PROSPERO

1

Appendix B: Literature search strategies

Review question search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	exp PREGNANCY, ECTOPIC/
2	((ectopic or extra uterine or extra?uterine or tub$ or ampullary or isthm$ or fimbrial or cornual or interstitial or abdom$ or ovar$ or cervi$) adj3 (pregnan$ or gestat$)).ti,ab.
3	(pregnan$ adj3 ((unknown or uncertain) adj (location$ or site$))).ti,ab.
4	PUL.ti,ab.
5	or/1-4
6	DIAGNOSIS/
7	exp DIAGNOSIS, COMPUTER-ASSISTED/
8	DIAGNOSIS, DIFFERENTIAL/
9	exp DIAGNOSTIC ERRORS/
10	EARLY DIAGNOSIS/
11	diagnos$.ti,ab.
12	or/6-11
13	(ultraso$ adj3 featur$).ti,ab.
14	(empty adj3 uterus$).ti,ab.
15	(no adj3 intrauterin$ adj3 pregnanc$).ti,ab.
16	(pseudo$ adj3 sac?).ti,ab.
17	(decidual adj3 cyst?).ti,ab.
18	(cyst$ adj3 inside adj3 uterus$).ti,ab.
19	(fluid? adj3 inside adj3 uterus$).ti,ab.
20	(heterotopic$ adj3 pregnan$).ti,ab.
21	((coexist$ or co-exist$) adj3 (intrauterin$ or IUP) adj3 (ectopic$ or EP)).ti,ab.
22	adnexal mass$.ti,ab.
23	yolk sac?.ti,ab.
24	((fetal or fetus) adj2 pole?).ti,ab.
25	((fetal or fetus) adj2 (heartbeat? or heartrate?)).ti,ab.
26	((fetal or fetus) adj2 heart adj2 (beat$ or rate?)).ti,ab.
27	(Tubal adj3 ring?).ti,ab.
28	((bagel? or donut? or doughnut? or blob?) adj3 sign?).ti,ab.
29	Adnexal cyst?.ti,ab.
30	(Identif$ adj3 (fluid? or blood$)).ti,ab.
31	(Free$ adj3 fluid?).ti,ab.
32	H?emoperitoneum.ti,ab.
33	(Free$ adj3 blood$ adj3 pelvi$).ti,ab.
34	or/13-33
35	exp ULTRASONOGRAPHY/
36	ultrasonograph$.ti,ab.
37	sonograph$.ti,ab.
38	ultrasound.ti,ab.
39	ultrasonic$.ti,ab.
40	sonogram?.ti,ab.
41	Echocardiograph$.ti,ab.
42	Echoencephalograph$.ti,ab.
43	Echograph$.ti,ab.
44	Echotomograph$.ti,ab.
45	Endosonograph$.ti,ab.
46	or/35-45
47	Positive likelihood ratio?.ti,ab.
48	LR+.ti,ab.
49	Negative likelihood ratio?.ti,ab.
50	LR-.ti,ab.
51	AREA UNDER CURVE/
52	(area? under adj2 curve?).ti,ab.
53	AUC?.ti,ab.
54	"SENSITIVITY AND SPECIFICITY"/
55	(sensitiv$ adj10 specific$).ti,ab.
56	or/47-55

#	Searches
57	exp PREGNANCY, ECTOPIC/di [Diagnosis]
58	exp PREGNANCY, ECTOPIC/dg [Diagnostic Imaging]
59	5 and 12 and 34
60	5 and 12 and 46 and 56
61	34 and 57
62	34 and 58
63	or/59-62
64	limit 63 to english language
65	limit 64 to yr="1995 -Current"
66	LETTER/
67	EDITORIAL/
68	NEWS/
69	exp HISTORICAL ARTICLE/
70	ANECDOTES AS TOPIC/
71	COMMENT/
72	CASE REPORT/
73	(letter or comment*).ti.
74	or/66-73
75	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
76	74 not 75
77	ANIMALS/ not HUMANS/
78	exp ANIMALS, LABORATORY/
79	exp ANIMAL EXPERIMENTATION/
80	exp MODELS, ANIMAL/
81	exp RODENTIA/
82	(rat or rats or mouse or mice).ti.
83	or/76-82
84	65 not 83

Databases: Embase; and Embase Classic

#	Searches
1	exp ECTOPIC PREGNANCY/
2	((ectopic or extra uterine or extra?uterine or tub$ or ampullary or isthm$ or fimbrial or cornual or interstitial or abdom$ or ovar$ or cervi$) adj3 (pregnan$ or gestat$)).ti,ab.
3	(pregnan$ adj3 ((unknown or uncertain) adj (location$ or site$))).ti,ab.
4	PUL.ti,ab.
5	or/1-4
6	*DIAGNOSIS/
7	*COMPUTER ASSISTED DIAGNOSIS/
8	*DIFFERENTIAL DIAGNOSIS/
9	exp *DIAGNOSTIC ERROR/
10	*EARLY DIAGNOSIS/
11	diagnos$.ti,ab.
12	or/6-11
13	(ultraso$ adj3 featur$).ti,ab.
14	(empty adj3 uterus$).ti,ab.
15	(no adj3 intrauterin$ adj3 pregnanc$).ti,ab.
16	(pseudo$ adj3 sac?).ti,ab.
17	(decidual adj3 cyst?).ti,ab.
18	(cyst$ adj3 inside adj3 uterus$).ti,ab.
19	(fluid? adj3 inside adj3 uterus$).ti,ab.
20	(heterotopic$ adj3 pregnan$).ti,ab.
21	((coexist$ or co-exist$) adj3 (intrauterin$ or IUP) adj3 (ectopic$ or EP)).ti,ab.
22	adnexal mass$.ti,ab.
23	yolk sac?.ti,ab.
24	((fetal or fetus) adj2 pole?).ti,ab.
25	((fetal or fetus) adj2 (heartbeat? or heartrate?)).ti,ab.
26	((fetal or fetus) adj2 heart adj2 (beat$ or rate?)).ti,ab.
27	(Tubal adj3 ring?).ti,ab.
28	((bagel? or donut? or doughnut? or blob?) adj3 sign?).ti,ab.
29	Adnexal cyst?.ti,ab.
30	(Identif$ adj3 (fluid? or blood$)).ti,ab.
31	(Free$ adj3 fluid?).ti,ab.
32	H?emoperitoneum.ti,ab.
33	(Free$ adj3 blood$ adj3 pelvi$).ti,ab.
34	or/13-33
35	exp *ECHOGRAPHY/

#	Searches
36	ultrasonograph$.ti,ab.
37	sonograph$.ti,ab.
38	ultrasound.ti,ab.
39	ultrasonic$.ti,ab.
40	sonogram?.ti,ab.
41	Echocardiograph$.ti,ab.
42	Echoencephalograph$.ti,ab.
43	Echograph$.ti,ab.
44	Echotomograph$.ti,ab.
45	Endosonograph$.ti,ab.
46	or/35-45
47	Positive likelihood ratio?.ti,ab.
48	LR+.ti,ab.
49	Negative likelihood ratio?.ti,ab.
50	LR-.ti,ab.
51	AREA UNDER THE CURVE/
52	(area? under adj2 curve?).ti,ab.
53	AUC?.ti,ab.
54	"SENSITIVITY AND SPECIFICITY"/
55	(sensitiv$ adj10 specific$).ti,ab.
56	or/47-55
57	exp *ECTOPIC PREGNANCY/di [Diagnosis]
58	5 and 12 and 34
59	5 and 12 and 46 and 56
60	34 and 57
61	or/58-60
62	limit 61 to english language
63	limit 62 to yr="1995 -Current"
64	letter.pt. or LETTER/
65	note.pt.
66	editorial.pt.
67	CASE REPORT/ or CASE STUDY/
68	(letter or comment*).ti.
69	or/64-68
70	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
71	69 not 70
72	ANIMAL/ not HUMAN/
73	NONHUMAN/
74	exp ANIMAL EXPERIMENT/
75	exp EXPERIMENTAL ANIMAL/
76	ANIMAL MODEL/
77	exp RODENT/
78	(rat or rats or mouse or mice).ti.
79	or/71-78
80	63 not 79

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

#	Searches
1	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees
2	((ectopic or extra uterine or extra*uterine or tub* or ampullary or isthm* or fimbrial or cornual or interstitial or abdom* or ovar* or cervi*) near/3 (pregnan* or gestat*)):ti,ab
3	(pregnan* near/3 ((unknown or uncertain) near/1 (location* or site*))):ti,ab
4	PUL:ti,ab
5	#1 or #2 or #3 or #4
6	MeSH descriptor: [DIAGNOSIS] this term only
7	MeSH descriptor: [DIAGNOSIS, COMPUTER-ASSISTED] explode all trees
8	MeSH descriptor: [DIAGNOSIS, DIFFERENTIAL] this term only
9	MeSH descriptor: [DIAGNOSTIC ERRORS] explode all trees
10	MeSH descriptor: [EARLY DIAGNOSIS] this term only
11	diagnos*:ti,ab
12	#6 or #7 or #8 or #9 or #10 or #11
13	(ultraso* near/3 featur*):ti,ab
14	(empty near/3 uterus*):ti,ab
15	(no near/3 intrauterin* near/3 pregnanc*):ti,ab
16	(pseudo* near/3 sac*):ti,ab

#	Searches
17	(decidual near/3 cyst*):ti,ab
18	(cyst* near/3 inside near/3 uterus*):ti,ab
19	(fluid* near/3 inside near/3 uterus*):ti,ab
20	(heterotopic* near/3 pregnan*):ti,ab
21	((coexist* or co-exist*) near/3 (intrauterin* or IUP) near/3 (ectopic* or EP)):ti,ab
22	"adnexal mass*":ti,ab
23	"yolk sac*":ti,ab
24	((fetal or fetus) near/2 pole*):ti,ab
25	((fetal or fetus) near/2 (heartbeat* or heartrate*)):ti,ab
26	((fetal or fetus) near/2 heart near/2 (beat* or rate*)):ti,ab
27	(Tubal near/3 ring*):ti,ab
28	((bagel* or donut* or doughnut* or blob*) near/3 sign*):ti,ab
29	"Adnexal cyst*":ti,ab
30	(Identif* near/3 (fluid* or blood*)):ti,ab
31	(Free* near/3 fluid*):ti,ab
32	(Hemoperitoneum or Haemoperitoneum):ti,ab
33	(Free* near/3 blood* near/3 pelvi*):ti,ab
34	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
35	MeSH descriptor: [ULTRASONOGRAPHY] explode all trees
36	ultrasonograph*:ti,ab
37	sonograph*:ti,ab
38	ultrasound:ti,ab
39	ultrasonic*:ti,ab
40	sonogram*:ti,ab
41	Echocardiograph*:ti,ab
42	Echoencephalograph*:ti,ab
43	Echograph*:ti,ab
44	Echotomograph*:ti,ab
45	Endosonograph*:ti,ab
46	#35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45
47	"Positive likelihood ratio*":ti,ab
48	"Negative likelihood ratio*":ti,ab
49	LR*:ti,ab
50	MeSH descriptor: [AREA UNDER CURVE] this term only
51	("area* under" near/2 curve*):ti,ab
52	AUC*:ti,ab
53	MeSH descriptor: [SENSITIVITY AND SPECIFICITY] this term only
54	(sensitiv* near/10 specific*):ti,ab
55	#47 or #48 or #49 or #50 or #51 or #52 or #53 or #54
56	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees and with qualifier(s): [Diagnosis - DI]
57	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees and with qualifier(s): [Diagnostic imaging - DG]
58	#5 and #12 and #34
59	#5 and #12 and #46 and #55
60	#34 and #56
61	#34 and #57
62	#58 or #59 or #60 or #61 Publication Year from 1995 to 2018

Health economics search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.

#	Searches
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	exp PREGNANCY, ECTOPIC/
23	((ectopic or extra uterine or extra?uterine or tub$ or ampullary or isthm$ or fimbrial or cornual or interstitial or abdom$ or ovar$ or cervi$) adj3 (pregnan$ or gestat$)).ti,ab.
24	(pregnan$ adj3 ((unknown or uncertain) adj (location$ or site$))).ti,ab.
25	PUL.ti,ab.
26	or/22-25
27	DIAGNOSIS/
28	exp DIAGNOSIS, COMPUTER-ASSISTED/
29	DIAGNOSIS, DIFFERENTIAL/
30	exp DIAGNOSTIC ERRORS/
31	EARLY DIAGNOSIS/
32	diagnos$.ti,ab.
33	or/27-32
34	(ultraso$ adj3 featur$).ti,ab.
35	(empty adj3 uterus$).ti,ab.
36	(no adj3 intrauterin$ adj3 pregnanc$).ti,ab.
37	(pseudo$ adj3 sac?).ti,ab.
38	(decidual adj3 cyst?).ti,ab.
39	(cyst$ adj3 inside adj3 uterus$).ti,ab.
40	(fluid? adj3 inside adj3 uterus$).ti,ab.
41	(heterotopic$ adj3 pregnan$).ti,ab.
42	((coexist$ or co-exist$) adj3 (intrauterin$ or IUP) adj3 (ectopic$ or EP)).ti,ab.
43	adnexal mass$.ti,ab.
44	yolk sac?.ti,ab.
45	((fetal or fetus) adj2 pole?).ti,ab.
46	((fetal or fetus) adj2 (heartbeat? or heartrate?)).ti,ab.
47	((fetal or fetus) adj2 heart adj2 (beat$ or rate?)).ti,ab.
48	(Tubal adj3 ring?).ti,ab.
49	((bagel? or donut? or doughnut? or blob?) adj3 sign?).ti,ab.
50	Adnexal cyst?.ti,ab.
51	(Identif$ adj3 (fluid? or blood$)).ti,ab.
52	(Free$ adj3 fluid?).ti,ab.
53	H?emoperitoneum.ti,ab.
54	(Free$ adj3 blood$ adj3 pelvi$).ti,ab.
55	or/34-54
56	exp ULTRASONOGRAPHY/
57	ultrasonograph$.ti,ab.
58	sonograph$.ti,ab.
59	ultrasound.ti,ab.
60	ultrasonic$.ti,ab.
61	sonogram?.ti,ab.
62	Echocardiograph$.ti,ab.
63	Echoencephalograph$.ti,ab.
64	Echograph$.ti,ab.
65	Echotomograph$.ti,ab.
66	Endosonograph$.ti,ab.
67	or/56-66
68	Positive likelihood ratio?.ti,ab.
69	LR+.ti,ab.
70	Negative likelihood ratio?.ti,ab.
71	LR-.ti,ab.
72	AREA UNDER CURVE/
73	(area? under adj2 curve?).ti,ab.
74	AUC?.ti,ab.
75	"SENSITIVITY AND SPECIFICITY"/
76	(sensitiv$ adj10 specific$).ti,ab.
77	or/68-76
78	exp PREGNANCY, ECTOPIC/di [Diagnosis]
79	exp PREGNANCY, ECTOPIC/dg [Diagnostic Imaging]
80	26 and 33 and 55
81	26 and 33 and 67 and 77
82	55 and 78

#	Searches
83	55 and 79
84	or/80-83
85	limit 84 to english language
86	limit 85 to yr="1995 -Current"
87	LETTER/
88	EDITORIAL/
89	NEWS/
90	exp HISTORICAL ARTICLE/
91	ANECDOTES AS TOPIC/
92	COMMENT/
93	CASE REPORT/
94	(letter or comment*).ti.
95	or/87-94
96	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
97	95 not 96
98	ANIMALS/ not HUMANS/
99	exp ANIMALS, LABORATORY/
100	exp ANIMAL EXPERIMENTATION/
101	exp MODELS, ANIMAL/
102	exp RODENTIA/
103	(rat or rats or mouse or mice).ti.
104	or/97-103
105	86 not 104
106	21 and 105

Databases: Embase; and Embase Classic

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	exp ECTOPIC PREGNANCY/
19	((ectopic or extra uterine or extra?uterine or tub$ or ampullary or isthm$ or fimbrial or cornual or interstitial or abdom$ or ovar$ or cervi$) adj3 (pregnan$ or gestat$)).ti,ab.
20	(pregnan$ adj3 ((unknown or uncertain) adj (location$ or site$))).ti,ab.
21	PUL.ti,ab.
22	or/18-21
23	*DIAGNOSIS/
24	*COMPUTER ASSISTED DIAGNOSIS/
25	*DIFFERENTIAL DIAGNOSIS/
26	exp *DIAGNOSTIC ERROR/
27	*EARLY DIAGNOSIS/
28	diagnos$.ti,ab.
29	or/23-28
30	(ultraso$ adj3 featur$).ti,ab.
31	(empty adj3 uterus$).ti,ab.
32	(no adj3 intrauterin$ adj3 pregnanc$).ti,ab.
33	(pseudo$ adj3 sac?).ti,ab.
34	(decidual adj3 cyst?).ti,ab.
35	(cyst$ adj3 inside adj3 uterus$).ti,ab.
36	(fluid? adj3 inside adj3 uterus$).ti,ab.
37	(heterotopic$ adj3 pregnan$).ti,ab.
38	((coexist$ or co-exist$) adj3 (intrauterin$ or IUP) adj3 (ectopic$ or EP)).ti,ab.
39	adnexal mass$.ti,ab.

#	Searches
40	yolk sac?.ti,ab.
41	((fetal or fetus) adj2 pole?).ti,ab.
42	((fetal or fetus) adj2 (heartbeat? or heartrate?)).ti,ab.
43	((fetal or fetus) adj2 heart adj2 (beat$ or rate?)).ti,ab.
44	(Tubal adj3 ring?).ti,ab.
45	((bagel? or donut? or doughnut? or blob?) adj3 sign?).ti,ab.
46	Adnexal cyst?.ti,ab.
47	(Identif$ adj3 (fluid? or blood$)).ti,ab.
48	(Free$ adj3 fluid?).ti,ab.
49	H?emoperitoneum.ti,ab.
50	(Free$ adj3 blood$ adj3 pelvi$).ti,ab.
51	or/30-50
52	exp *ECHOGRAPHY/
53	ultrasonograph$.ti,ab.
54	sonograph$.ti,ab.
55	ultrasound.ti,ab.
56	ultrasonic$.ti,ab.
57	sonogram?.ti,ab.
58	Echocardiograph$.ti,ab.
59	Echoencephalograph$.ti,ab.
60	Echograph$.ti,ab.
61	Echotomograph$.ti,ab.
62	Endosonograph$.ti,ab.
63	or/52-62
64	Positive likelihood ratio?.ti,ab.
65	LR+.ti,ab.
66	Negative likelihood ratio?.ti,ab.
67	LR-.ti,ab.
68	AREA UNDER THE CURVE/
69	(area? under adj2 curve?).ti,ab.
70	AUC?.ti,ab.
71	"SENSITIVITY AND SPECIFICITY"/
72	(sensitiv$ adj10 specific$).ti,ab.
73	or/64-72
74	exp *ECTOPIC PREGNANCY/di [Diagnosis]
75	22 and 29 and 51
76	22 and 29 and 63 and 73
77	51 and 74
78	or/75-77
79	limit 78 to english language
80	limit 79 to yr="1995 -Current"
81	letter.pt. or LETTER/
82	note.pt.
83	editorial.pt.
84	CASE REPORT/ or CASE STUDY/
85	(letter or comment*).ti.
86	or/81-85
87	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
88	86 not 87
89	ANIMAL/ not HUMAN/
90	NONHUMAN/
91	exp ANIMAL EXPERIMENT/
92	exp EXPERIMENTAL ANIMAL/
93	ANIMAL MODEL/
94	exp RODENT/
95	(rat or rats or mouse or mice).ti.
96	or/88-95
97	80 not 96
98	17 and 97

Database: Cochrane Central Register of Controlled Trials

#	Searches
1	MeSH descriptor: [ECONOMICS] this term only
2	MeSH descriptor: [VALUE OF LIFE] this term only
3	MeSH descriptor: [COSTS AND COST ANALYSIS] explode all trees
4	MeSH descriptor: [ECONOMICS, HOSPITAL] explode all trees
5	MeSH descriptor: [ECONOMICS, MEDICAL] explode all trees

#	Searches
6	MeSH descriptor: [RESOURCE ALLOCATION] explode all trees
7	MeSH descriptor: [ECONOMICS, NURSING] this term only
8	MeSH descriptor: [ECONOMICS, PHARMACEUTICAL] this term only
9	MeSH descriptor: [FEES AND CHARGES] explode all trees
10	MeSH descriptor: [BUDGETS] explode all trees
11	budget*:ti,ab
12	cost*:ti,ab
13	(economic* or pharmaco?economic*):ti,ab
14	(price* or pricing*):ti,ab
15	(financ* or fee or fees or expenditure* or saving*):ti,ab
16	(value near/2 (money or monetary)):ti,ab
17	resourc* allocat*:ti,ab
18	(fund or funds or funding* or funded):ti,ab
19	(ration or rations or rationing* or rationed):ti,ab
20	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees
22	((ectopic or extra uterine or extra*uterine or tub* or ampullary or isthm* or fimbrial or cornual or interstitial or abdom* or ovar* or cervi*) near/3 (pregnan* or gestat*)):ti,ab
23	(pregnan* near/3 ((unknown or uncertain) near/1 (location* or site*))):ti,ab
24	PUL:ti,ab
25	#21 or #22 or #23 or #24
26	MeSH descriptor: [DIAGNOSIS] this term only
27	MeSH descriptor: [DIAGNOSIS, COMPUTER-ASSISTED] explode all trees
28	MeSH descriptor: [DIAGNOSIS, DIFFERENTIAL] this term only
29	MeSH descriptor: [DIAGNOSTIC ERRORS] explode all trees
30	MeSH descriptor: [EARLY DIAGNOSIS] this term only
31	diagnos*:ti,ab
32	#26 or #27 or #28 or #29 or #30 or #31
33	(ultraso* near/3 featur*):ti,ab
34	(empty near/3 uterus*):ti,ab
35	(no near/3 intrauterin* near/3 pregnanc*):ti,ab
36	(pseudo* near/3 sac*):ti,ab
37	(decidual near/3 cyst*):ti,ab
38	(cyst* near/3 inside near/3 uterus*):ti,ab
39	(fluid* near/3 inside near/3 uterus*):ti,ab
40	(heterotopic* near/3 pregnan*):ti,ab
41	((coexist* or co-exist*) near/3 (intrauterin* or IUP) near/3 (ectopic* or EP)):ti,ab
42	"adnexal mass*":ti,ab
43	"yolk sac*":ti,ab
44	((fetal or fetus) near/2 pole*):ti,ab
45	((fetal or fetus) near/2 (heartbeat* or heartrate*)):ti,ab
46	((fetal or fetus) near/2 heart near/2 (beat* or rate*)):ti,ab
47	(Tubal near/3 ring*):ti,ab
48	((bagel* or donut* or doughnut* or blob*) near/3 sign*):ti,ab
49	"Adnexal cyst*":ti,ab
50	(Identif* near/3 (fluid* or blood*)):ti,ab
51	(Free* near/3 fluid*):ti,ab
52	(Hemoperitoneum or Haemoperitoneum):ti,ab
53	(Free* near/3 blood* near/3 pelvi*):ti,ab
54	#33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53
55	MeSH descriptor: [ULTRASONOGRAPHY] explode all trees
56	ultrasonograph*:ti,ab
57	sonograph*:ti,ab
58	ultrasound:ti,ab
59	ultrasonic*:ti,ab
60	sonogram*:ti,ab
61	Echocardiograph*:ti,ab
62	Echoencephalograph*:ti,ab
63	Echograph*:ti,ab
64	Echotomograph*:ti,ab
65	Endosonograph*:ti,ab
66	#55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65
67	"Positive likelihood ratio*":ti,ab
68	"Negative likelihood ratio*":ti,ab
69	LR*:ti,ab
70	MeSH descriptor: [AREA UNDER CURVE] this term only
71	("area* under" near/2 curve*):ti,ab
72	AUC*:ti,ab
73	MeSH descriptor: [SENSITIVITY AND SPECIFICITY] this term only

#	Searches
74	(sensitiv* near/10 specific*):ti,ab
75	#67 or #68 or #69 or #70 or #71 or #72 or #73 or #74
76	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees and with qualifier(s): [Diagnosis - DI]
77	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees and with qualifier(s): [Diagnostic imaging - DG]
78	#25 and #32 and #54
79	#25 and #32 and #66 and #75
80	#54 and #76
81	#54 and #77
82	#78 or #79 or #80 or #81 Publication Year from 1995 to 2018
83	#20 and #82

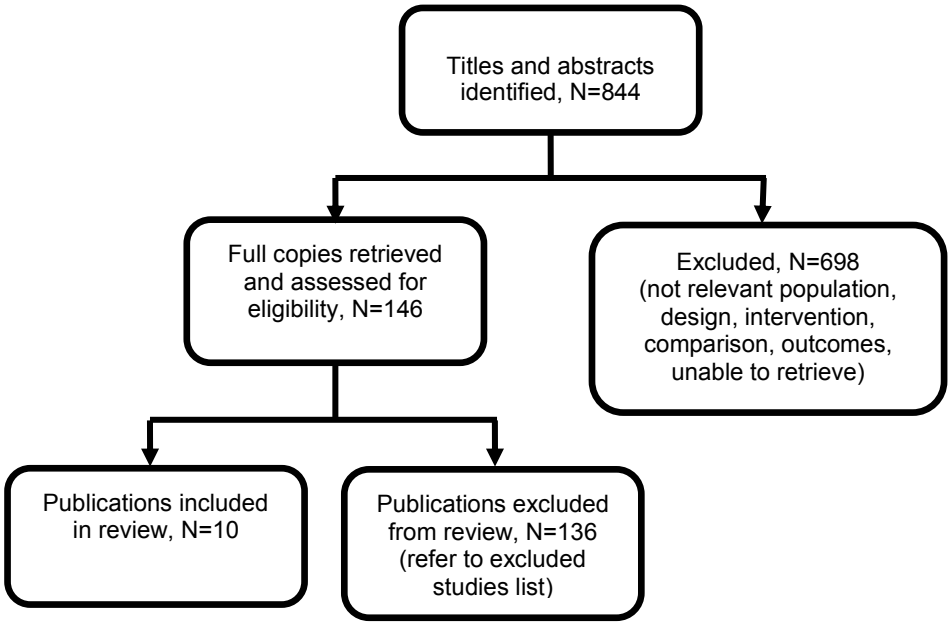
Databases: Health Technology Assessment; and NHS Economic Evaluation Database

#	Searches
1	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees
2	((ectopic or extra uterine or extra*uterine or tub* or ampullary or isthm* or fimbrial or cornual or interstitial or abdom* or ovar* or cervi*) near/3 (pregnan* or gestat*)):ti,ab
3	(pregnan* near/3 ((unknown or uncertain) near/1 (location* or site*))):ti,ab
4	PUL:ti,ab
5	#1 or #2 or #3 or #4
6	MeSH descriptor: [DIAGNOSIS] this term only
7	MeSH descriptor: [DIAGNOSIS, COMPUTER-ASSISTED] explode all trees
8	MeSH descriptor: [DIAGNOSIS, DIFFERENTIAL] this term only
9	MeSH descriptor: [DIAGNOSTIC ERRORS] explode all trees
10	MeSH descriptor: [EARLY DIAGNOSIS] this term only
11	diagnos*:ti,ab
12	#6 or #7 or #8 or #9 or #10 or #11
13	(ultraso* near/3 featur*):ti,ab
14	(empty near/3 uterus*):ti,ab
15	(no near/3 intrauterin* near/3 pregnanc*):ti,ab
16	(pseudo* near/3 sac*):ti,ab
17	(decidual near/3 cyst*):ti,ab
18	(cyst* near/3 inside near/3 uterus*):ti,ab
19	(fluid* near/3 inside near/3 uterus*):ti,ab
20	(heterotopic* near/3 pregnan*):ti,ab
21	((coexist* or co-exist*) near/3 (intrauterin* or IUP) near/3 (ectopic* or EP)):ti,ab
22	"adnexal mass*":ti,ab
23	"yolk sac*":ti,ab
24	((fetal or fetus) near/2 pole*):ti,ab
25	((fetal or fetus) near/2 (heartbeat* or heartrate*)):ti,ab
26	((fetal or fetus) near/2 heart near/2 (beat* or rate*)):ti,ab
27	(Tubal near/3 ring*):ti,ab
28	((bagel* or donut* or doughnut* or blob*) near/3 sign*):ti,ab
29	"Adnexal cyst*":ti,ab
30	(Identif* near/3 (fluid* or blood*)):ti,ab
31	(Free* near/3 fluid*):ti,ab
32	(Hemoperitoneum or Haemoperitoneum):ti,ab
33	(Free* near/3 blood* near/3 pelvi*):ti,ab
34	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
35	MeSH descriptor: [ULTRASONOGRAPHY] explode all trees
36	ultrasonograph*:ti,ab
37	sonograph*:ti,ab
38	ultrasound:ti,ab
39	ultrasonic*:ti,ab
40	sonogram*:ti,ab
41	Echocardiograph*:ti,ab
42	Echoencephalograph*:ti,ab
43	Echograph*:ti,ab
44	Echotomograph*:ti,ab
45	Endosonograph*:ti,ab
46	#35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45
47	"Positive likelihood ratio*":ti,ab
48	"Negative likelihood ratio*":ti,ab
49	LR*:ti,ab
50	MeSH descriptor: [AREA UNDER CURVE] this term only
51	("area* under" near/2 curve*):ti,ab
52	AUC*:ti,ab

#	Searches
53	MeSH descriptor: [SENSITIVITY AND SPECIFICITY] this term only
54	(sensitiv* near/10 specific*):ti,ab
55	#47 or #48 or #49 or #50 or #51 or #52 or #53 or #54
56	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees and with qualifier(s): [Diagnosis - DI]
57	MeSH descriptor: [PREGNANCY, ECTOPIC] explode all trees and with qualifier(s): [Diagnostic imaging - DG]
58	#5 and #12 and #34
59	#5 and #12 and #46 and #55
60	#34 and #56
61	#34 and #57
62	#58 or #59 or #60 or #61 Publication Year from 1995 to 2018

Appendix C: Clinical evidence study selection

Figure 1: Flow diagram of clinical article selection for diagnostic accuracy of ultrasound features for tubal ectopic pregnancy review



Appendix D: Clinical evidence tables

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Ahmed, Ahmed A., Tom, Brian D. M., Calabrese, Peter, Ectopic pregnancy diagnosis and the pseudo-sac, Fertility and Sterility, 81, 1225-8, 2004

Ref Id

875655

Country/ies where the study was carried out

UK

Study type

Retrospective cohort study</td>
<td>Sample size

n=77 who had diagnostic laparoscopy for suspected ectopic pregnancy

Characteristics

Not reported

Inclusion Criteria

• Patients with suspected ectopic pregnancy who had diagnostic laparoscopy for confirmation.
• hCG>2000iu/L with no intrauterine or extrauterine pregnancy
• presence of heterogeneous adnexal mass or</td>
<td>Tests

Data recorded: patient history, examination, hCG level, transvaginal ultrasound (TVUS) findings, laparoscopy findings, final diagnosis. Histopathological examination was performed to confirm the diagnosis of ectopic pregnancy</td>
<td>Methods

Retrospective review of a series of cases. Review of theatre records.</td>
<td>Results

UTERUS: PSEUDOSAC
Pseudosac: any reported sac within the uterine cavity in the absence of a double decidual sac or a yolk sac
<table>
<tr><td></td><td>US pseudosac</td><td>US no pseudosac</td><td>total</td></tr>
<tr><td>ectopic pregnancy +</td><td>3</td><td>50</td><td>53</td></tr>
<tr><td>ectopic pregnancy -</td><td>14</td><td>10</td><td>24</td></tr>
<tr><td>total</td><td>17</td><td>60</td><td>77</td></tr>
</table>
TUBE & OVARY: COMPLEX ADNEXAL MASS
Heterogeneous adnexal mass
<table>
<tr><td></td><td>US adnexal mass</td><td>US no adnexal mass</td><td>total</td></tr>
<tr><td>ectopic pregnancy +</td><td>34</td><td>19</td><td>53</td></tr>
<tr><td>ectopic pregnancy -</td><td>3</td><td>21</td><td>24</td></tr>
</table>
</td>
<td>Limitations

Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? No – 13/90 women who underwent laparoscopy for possible ectopic pregnancy were excluded.
2. Was a case-control design avoided? yes
3. Did the study avoid inappropriate exclusions? Unclear – the authors specify inclusion criteria, including an hCG level of >2000IU/L, adnexal mass or suboptimal rise in hCG. 13/90</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study Impact of ultrasound finding of pseudosac (uterine sac without double decidual ring or yolk sac) on management of possible ectopic pregnancy **Study dates** Jan 1997 - Jan 2000 **Source of funding** Not reported	an adnexal ring by TVUS • suboptimal rise (<50%) of hCG over 48 hours in the absence of an intrauterine sac if absolute level <2000iu/L **Exclusion Criteria** • patients who had diagnostic laparoscopy for exclusion of heterotopic pregnancy, or based on clinical suspicion alone (not US or hCG assessment for ectopic pregnancy) • haemodynamically unstable			total 37 40 77	women undergoing laparoscopy for suspected ectopic pregnancy were excluded, but the specific reasons are not stated. **Could the selection of patients have introduced bias?** **RISK: HIGH** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard? unclear

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					2. If a threshold was used, was it pre-specified? yes **Could the conduct or interpretation of the index test have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **DOMAIN 3: REFERENCE STANDARD** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? Yes - Histopathological examination was performed to confirm the diagnosis.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					2. Were the reference standard results interpreted without knowledge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **DOMAIN 4: FLOW AND TIMING** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? unclear 2. Did all patients receive a reference standard? yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>3. Did patients receive the same reference standard? yes
4. Were all patients included in the analysis? yes

Could the patient flow have introduced bias? RISK: LOW

Other information</td></tr>
<tr><td>Full citation

Barnhart, Kurt T., Fay, Courtney A., Suescum, Maria, Sammel, Mary D., Appleby, Dina, Shaunik, Alka, Dean, Anthony J., Clinical factors affecting the accuracy of ultrasonography in symptomatic first-trimester pregnancy, Obstetrics and Gynecology,</td><td>Sample size

n=2058 (178 lost to follow up) --> n=1880
n=739 women identified as having an ultrasound diagnosis in any one of the five categories other than indeterminate

Characteristics

mean age: 26 years (range 13–48 years)
mean parity: 1.3 (range 0–9)

Inclusion Criteria</td><td>Tests

Index test: transvaginal ultrasound (TVUS)
Reference standard: patient followed by the gynaecology service until a definitive diagnosis was made or the patient was lost to follow-up</td><td>Methods

All patients received a transvaginal ultrasonography (TV US) that was reviewed and interpreted by a board-certified radiologist.
US diagnoses were classified:

1. definite intrauterine pregnancy (visualization of a gestational sac with a yolk sac, embryo, or both);</td><td>Results

TUBE & OVARY: ADNEXAL MASS
<u>definite ectopic pregnancy:</u> extrauterine gestational sac with yolk sac, embryo or both Sensitivity 13.2 (9.9–17) Specificity 99.9 (99.6–100)
<table><tr><td></td><td>US "definite ectopic"</td><td>US no "definite ectopic"</td><td>total</td></tr><tr><td>ectopic pregnancy +</td><td>50</td><td>330</td><td>380</td></tr><tr><td>ectopic pregnancy -</td><td>1</td><td>1499</td><td>1500</td></tr><tr><td>total</td><td>51</td><td>1829</td><td>1880</td></tr></table>TUBE & OVARY: COMPLEX ADNEXAL MASS</td><td>Limitations

Risk of bias assessed using QUADAS-II
DOMAIN 1: PATIENT SELECTION
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? Yes - all women presenting to the emergency department with first-trimester pain, bleeding, or both
2. Was a case-control design avoided? yes</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>117, 299-306, 2011

Ref Id

875697

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study

Evaluate factors associated with accuracy of initial ultrasonography in patients with symptomatic first-trimester pregnancy (for diagnosis of EP)</td>
<td>Need for acute gynaecological consultation after TVUS
all women presenting to the emergency department with first-trimester pain, bleeding, or both and one or more of:

• an indeterminate ultrasonography (no definite intrauterine pregnancy or ectopic pregnancy);
• an abnormal intrauterine pregnancy;
• an ectopic pregnancy that was not immediately admitted for operative management;
• an intrauterine pregnancy requiring gynaecologic evaluation</td>
<td></td>
<td>2. probable intrauterine pregnancy (intrauterine echogenic sac-like structure without visualization of a yolk sac or embryo);
3. definite ectopic pregnancy (extrauterine gestational sac with yolk sac, embryo or both);
4. probable ectopic pregnancy (inhomogeneous adnexal mass or extrauterine sac-like structure without identification of a yolk sac or embryo);
5. nondiagnostic or pregnancy of unknown location (no evidence of either ectopic pregnancy or intrauterine pregnancy);</td>
<td><u>probable ectopic pregnancy:</u>
inhomogeneous adnexal mass or extrauterine sac-like structure without identification of a yolk sac or embryo:
Sensitivity 42.1 (36.7–47.7) Specificity 98.1 (97.2–98.7)
<table>
<tr><td></td><td>US "probable ectopic pregnancy"</td><td>US no "probable ectopic pregnancy"</td><td>total</td></tr>
<tr><td>ectopic pregnancy+</td><td>139</td><td>241</td><td>380</td></tr>
<tr><td>ectopic pregnancy-</td><td>29</td><td>1471</td><td>1500</td></tr>
<tr><td>total</td><td>168</td><td>1711</td><td>1880</td></tr>
</table>
</td>
<td>3. Did the study avoid inappropriate exclusions? yes

Could the selection of patients have introduced bias?
RISK: LOW
B. CONCERNS REGARDING APPLICABILITY
Is there concern that the included patients do not match the review question? CONCERN: LOW

DOMAIN 2: INDEX TESTS
A. RISK OF BIAS

1. Were the index test results interpreted without knowledge of the results of the reference standard? yes
2. If a threshold was used, was it pre-specified? yes

Could the conduct or interpretation of the index test have</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates August 1999 - Sept 2007 **Source of funding** Not reported	**Exclusion Criteria** None reported		6. nonviable intrauterine pregnancy (ultrasound evidence of a fetal death, anembryonic gestation, or retained products of conception) Final diagnosis defined as: 1. visualised intrauterine pregnancy: intrauterine gestational sac with yolk sac or embryo; 2. ectopic pregnancy: visualised extrauterine gestational sac with yolk sac or embryo or nonvisualised ectopic pregnancy: no products of conception on uterine evacuation or		**introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **DOMAIN 3: REFERENCE STANDARD** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes - follow up until definitive diagnosis 2. Were the reference standard results interpreted without knowledge of the results of the index test? no - ultrasound findings were communicated to the emergency department attending before

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
			confirmed with surgical pathologic specimens and a rise in postoperative quantitative hCG concentration); 3. spontaneous miscarriage: identification of products of conception on uterine evacuation or complete resolution of hCG from the serum		gynaecology consultation **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **DOMAIN 4: FLOW AND TIMING** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? unclear 2. Did all patients receive a reference standard? unclear - reportedly followed up until definitive diagnosis of IUP, EP, or miscarriage,

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>not clear what was used for diagnosis
3. Did patients receive the same reference standard? unclear - not clear what was used for diagnosis
4. Were all patients included in the analysis? No, 178 women were lost to follow up.

Could the patient flow have introduced bias? RISK: UNCLEAR

Other information</td></tr>
<tr><td>Full citation

Dart,R., Howard,K., Subclassification of indeterminate pelvic ultrasonograms: stratifying the risk of ectopic pregnancy, Academic Emergency</td><td>Sample size

n=248 patients were identified. n=20 patients were excluded because a final diagnosis could not be determined n=228 used in analysis

Characteristics

Not reported</td><td>Tests

Index test: transvaginal ultrasound
Reference test: An extrauterine pregnancy visualised at laparoscopy or laparotomy and confirmed at pathology.</td><td>Methods

Ultrasonography was performed using either an Acuson 128 (Acuson, Mountain View, CA) or an ATL Ultramark 9 HDI (Advanced Technologies Laboratories, Bothell, WA) scanner. All transvaginal probes used a 5-MHz transducer</td><td>Results

Total confirmed ectopic pregnancy=32/228

UTERUS: EMPTY UTERUS
<u>Empty uterus:</u> Empty endometrial cavity with or without a thickened endometrium
ectopic pregnancy n=25/94; LR= 2.2 (95%CI 1.1-5.0)<table><tr><td></td><td>US empty uterus</td><td>US no empty uterus</td><td>total</td></tr><tr><td>ectopic pregnancy +</td><td>25</td><td>7</td><td>32</td></tr></table></td><td>Limitations

Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? Yes - retrospective review was made of consecutive ED patients presenting</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Medicine, 5, 313-319, 1998

Ref Id

91148

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study

To determine whether the subclassification of indeterminate ultrasound readings can identify patients who are at differing risk for ectopic pregnancy</td>
<td>Inclusion Criteria

first-trimester pregnant women who presented with abdominal pain and/or bleeding who received pelvic ultrasonography:

• positive serum hCG
• a transvaginal ultrasound examination performed during the ED visit that was read as indeterminate (i.e., it was neither diagnostic for an IUP nor suggestive of an ectopic pregnancy)

Exclusion Criteria

• post dilatation and evacuation procedure,
• recently delivered a baby,</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>ectopic pregnancy -</td><td>69</td><td>127</td><td>196</td></tr>
<tr><td>total</td><td>94</td><td>134</td><td>228</td></tr>
</table>

UTERUS: FLUID INSIDE UTERUS
<u>Nonspecific fluid</u>: Anechoic intrauterine fluid collection <10 mm mean diameter without an echogenic border
ectopic pregnancy=4/30; LR=1.0 (95%CI 0.32-3.1)
<table>
<tr><td></td><td>US nonspecific fluid</td><td>US no nonspecific fluid</td><td>total</td></tr>
<tr><td>ectopic pregnancy+</td><td>4</td><td>28</td><td>32</td></tr>
<tr><td>ectopic pregnancy-</td><td>26</td><td>170</td><td>196</td></tr>
<tr><td>total</td><td>30</td><td>198</td><td>228</td></tr>
</table>
</td>
<td>with abdominal pain/bleeding and positive B-hCG
2. Was a case-control design avoided? yes
3. Did the study avoid inappropriate exclusions? Yes

Could the selection of patients have introduced bias?
RISK: LOW

B. CONCERNS REGARDING APPLICABILITY
Is there concern that the included patients do not match the review question? CONCERN: LOW

<u>DOMAIN 2: INDEX TESTS</u>
A. RISK OF BIAS

1. Were the index test results interpreted without knowledge of the results of the reference standard? yes</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates August 1991 - December 1994 **Source of funding** Not reported	• final diagnosis that could not be definitively determined. TVUS showing definite IUP or suggestive of ectopic pregnancy: • diagnostic for an IUP: presence of an intrauterine gestational sac with a clearly visible yolk sac or fetal pole with or without a fetal heart beat. • suggestive of ectopic pregnancy: an extrauterine sac with or without a fetal pole or yolk sac, a complex mass discrete from the ovary, and the presence of a moderate to large amount of anechoic fluid or any amount of fluid with echogenic components (the				2. If a threshold was used, was it pre-specified? yes **Could the conduct or interpretation of the index test have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	presence of echogenic components is suggestive of clotted blood) in the cul-de-sac or abdomen.				results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? yes 4. Were all patients included in the final

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>analysis? No - 20 patients (8%) were excluded because a final diagnosis could not be determined

Could the patient flow have introduced bias? RISK: HIGH

Other information</td></tr>
<tr><td>Full citation

Dart, Robert Gerard, Burke, Garett, Dart, Linda, Subclassification of indeterminate pelvic ultrasonography: prospective evaluation of the risk of ectopic pregnancy, Annals of Emergency Medicine, 39, 382-8, 2002

Ref Id</td><td>Sample size

n=780, n=145 lost to follow up
n=635 for analysis

Characteristics

Not reported

Inclusion Criteria

• first trimester pregnant women with abdominal pain or vaginal bleeding
• positive hCG test result,
• a transvaginal ultrasonographic</td><td>Tests

Index: TVUS
Reference test: EP diagnosed by (1) Extrauterine pregnancy visualized at laparoscopy; (2) in patients managed with methotrexate, either identification of an ectopic pregnancy at follow-up ultrasonographic examination or hCG values that increase or plateau in patients after curettage and without evidence of chorionic villi at pathology</td><td>Methods

Ultrasonographic examinations were performed with an Acuson 128 (Acuson, Mountain View, CA) or an ATL Ultramark 9 HDI (Advanced Technologies Laboratories, Bothell, WA) scanner. The Acuson machine used a 5-MHz transvaginal transducer. The Ultramark machine allowed the operator to adjust the frequency of the transvaginal</td><td>Results

UTERUS: EMPTY UTERUS
<u>Empty uterus:</u> Empty endometrial cavity with or without a thickened endometrium.
<table><tr><td></td><td>US empty uterus</td><td>US no empty uterus</td><td>total</td></tr><tr><td>ectopic pregnancy+</td><td>36</td><td>10</td><td>46</td></tr><tr><td>ectopic pregnancy-</td><td>223</td><td>366</td><td>589</td></tr><tr><td>total</td><td>259</td><td>376</td><td>635</td></tr></table>
UTERUS: FLUID INSIDE UTERUS
<u>Nonspecific fluid:</u> Anechoic intrauterine fluid collection of <10mm in mean sac diameter without an echogenic border</td><td>Limitations

Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? Yes – consecutive emergency department patients in the first trimester of pregnancy with a chief complaint of abdominal pain or vaginal bleeding and who had an indeterminate transvaginal</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>875765

Country/ies where the study was carried out

USA

Study type

Prospective cohort study

Aim of the study

Determine the frequency of ectopic pregnancy among subclasses of indeterminate ultrasonographic examinations

Study dates

1 January 1995 - 31 August 2000</td>
<td>examination performed during the ED visit that was classified as indeterminate (ie, it was neither diagnostic of an IUP nor suggestive or diagnostic of an ectopic pregnancy)

Exclusion Criteria

• patient recently delivered or passed definite products of conception at home or in the ED;
• patient was after a dilatation and evacuation (D&E) procedure;
• patient was lost to follow-up

TVUS that was diagnostic of IUP or suspected/diagnosed ectopic pregnancy:</td>
<td></td>
<td>transducer from 5 to 10 MHz</td>
<td>
<table>
<tr><td></td><td>US nonspecific fluid</td><td>US no nonspecific fluid</td><td>total</td></tr>
<tr><td>ectopic pregnancy+</td><td>6</td><td>40</td><td>46</td></tr>
<tr><td>ectopic pregnancy-</td><td>121</td><td>468</td><td>589</td></tr>
<tr><td>total</td><td>127</td><td>508</td><td>635</td></tr>
</table>
</td>
<td>ultrasonographic examination at the time of the ED visit
2. Was a case-control design avoided? yes
3. Did the study avoid inappropriate exclusions? Yes

Could the selection of patients have introduced bias?
RISK: LOW

B. CONCERNS REGARDING APPLICABILITY
Is there concern that the included patients do not match the review question? CONCERN: LOW

<u>DOMAIN 2: INDEX TESTS</u>
A. RISK OF BIAS

1. Were the index test results interpreted without knowledge of the results of the reference standard? yes</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding Supported by an institutional seed grant from Boston Medical Center	• TVUS diagnostic of an IUP: presence of an intrauterine gestational sac containing a clearly defined yolk sac or fetal pole. • TVUS suggestive or diagnostic of an ectopic pregnancy: visualisation of a complex adnexal mass separate from the ovary, identification of an extrauterine sac-like structure with or without a yolk sac or fetal pole, or identification of a moderate to large amount of anechoic fluid or any echogenic fluid in the cul de sac.				2. If a threshold was used, was it pre-specified? yes **Could the conduct or interpretation of the index test have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **DOMAIN 3: REFERENCE STANDARD** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>4. Were all patients included in the analysis? No 145/780 (18.6%) women were lost to follow up and therefore excluded from the analysis.

Could the patient flow have introduced bias? RISK: HIGH

Other information</td></tr>
<tr><td>Full citation

Hammoud, Ahmad O., Hammoud, Ihab, Bujold, Emmanuel, Gonik, Bernard, Diamond, Michael P., Johnson, Samuel C., The role of sonographic endometrial patterns and endometrial thickness in the differential</td><td>Sample size

n=441; 38/441 lost to follow up; final n=403

Characteristics

mean age: 27.9 ± 6.7 years

Inclusion Criteria

abdominal pain and/or vaginal bleeding in the first trimester and a positive pregnancy test</td><td>Tests

Index tests: TVUS and TAS
Reference test: pathologic diagnosis when surgery was performed; when m edical treatment was used, final ectopic pregnancy diagnosis was based on a combination of clinical evaluation, hormone studies, and established sonographic criteria for ectopic pregnancy that included the presence of a complex extra ovarian adnexal mass</td><td>Methods

All ultrasound examinations were performed with both TAS and TVUS technique</td><td>Results

UTERUS: PSEUDO-GESTATIONAL SAC
<table><tr><td></td><td>US pseudosac</td><td>US no pseudosac</td><td>total</td></tr><tr><td>ectopic pregnancy+</td><td>8</td><td>249</td><td>257</td></tr><tr><td>ectopic pregnancy-</td><td>2</td><td>144</td><td>146</td></tr><tr><td>total</td><td>10</td><td>393</td><td>403</td></tr></table>This is a combined value for TAS + TVUS</td><td>Limitations

Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? Yes - retrospective study included all patients who were referred to the Radiology Department for pelvic ultrasonography who had abdominal</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
diagnosis of ectopic pregnancy, American Journal of Obstetrics and Gynecology, 192, 1370-5, 2005 **Ref Id** 875852 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** examine the usefulness of the endometrial trilaminar patter n and thickness in the diagnosis of ectopic pregnancy	**Exclusion Criteria** • unstable condition • required urgent surgical intervention that precluded an ultrasound study • visible IUP on emergency department scan				pain and/or vaginal bleeding in the first trimester and a positive pregnancy test 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? Yes – excluded patients whose condition was unstable and who needed urgent surgical intervention that precluded an ultrasound study **Could the selection of patients have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **DOMAIN 2: INDEX TESTS** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates July 1999 - July 2003 **Source of funding** Not reported					1. Were the index test results interpreted without knowledge of the results of the reference standard? yes 2. If a threshold was used, was it pre-specified? yes **Could the conduct or interpretation of the index test have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW (com bined use of TAS and TVUS considered) **DOMAIN 3: REFERENCE STANDARD** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					1. Is the reference standard likely to correctly classify the target condition? Yes – pathologic confirmation or combination of clinical evaluation, hormone studies, and established sonographic criteria 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					DOMAIN 4: FLOW AND TIMING **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? no - surgery or clinical follow up after treatment 4. Were all patients included in the analysis? No, 38 women were lost to follow up and excluded from the analysis. **Could the patient flow have introduced bias? RISK: HIGH** **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Malek-Mellouli, Monia, Oumara, Maina, Ben Amara, Fethi, Zouch, Ons, Neji, Khaled, Reziga, Hedi, Prediction of ectopic pregnancy in early pregnancy of unknown location, La Tunisie medicale, 91, 27-32, 2013 **Ref Id** 875961 **Country/ies where the study was carried out** Tunisia **Study type** Prospective cohort study	**Sample size** n=2675, of which n=94 were PUL (used in analysis) Normal intrauterine pregnancy was diagnosed in 1990 women (74%), miscarriage in 513 (19%) and ectopic pregnancy in 78 women **Characteristics** • previous history of ectopic pregnancy n=5 • previous history of miscarriage n=27 • previous history of caesarean section n=19 **Inclusion Criteria** • suspected early pregnancy complications, who had been referred for an ultrasound scan	**Tests** Index tests: TVS Reference test: confirmed with laparoscopy and histological examination of the biopsy specimens	**Methods** All women underwent a transvaginal ultrasound examination with a 7.5 MHz probe (logic 400 pro series, GE ultrasound Europe; beethovenstrasse 239, 42665 solingin, Germany). Ectopic pregnancy: heterogeneous mass seen in the adnexal region adjacent to the ovary, a mass with a hyper echogenic ring around the gestational sac in the adnexal region, or the presence of an embryo with or without a heart beat in the adnexal region accompanied by raised serum levels of hCG	**Results** ectopic pregnancy=40/94; IUP=18/94; miscarriage of IUP=17/94; spontaneous resolution=19/94 **PERITONEAL CAVITY: FREE FLUID** **Free fluid in pouch of Douglas** AUC: 0.60 Sensitivity: 0.26 95%CI (0.14-0.42) Specificity: 0.94 95%CI (0.84-0.99)	**Limitations** **Risk of bias assessed using QUADAS-II** **DOMAIN 1: PATIENT SELECTION** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes 2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias?** **RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW - women with PUL only **DOMAIN 2: INDEX TESTS** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study identify diagnostic parameters which are predictive of ectopic pregnancies in women with early pregnancies of unknown location (PUL) **Study dates** August 2007 - February 2009 **Source of funding** Not reported	by their general practitioners or the hospital consultant in the emergency department • pregnancy of unknown location (PUL) **Exclusion Criteria** • visualisation of any evidence of an intrauterine pregnancy, • identification of an adnexal mass thought to be an ectopic pregnancy, or blood in the pouch of Douglas on the initial scan, • visualisation of products of conception through the speculum • clinically unstable patients • women with an acute abdomen				1. Were the index test results interpreted without knowledge of the results of the reference standard? yes 2. If a threshold was used, was it pre-specified? yes **Could the conduct or interpretation of the index test have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>standard? yes - those included in 2x2 (PUL only)
3. Did patients receive the same reference standard? yes
4. Were all patients included in the analysis? yes

Could the patient flow have introduced bias? RISK: LOW

Other information</td></tr>
<tr><td>Full citation

Mehta,T.S., Levine,D., McArdle,C.R., Lack of sensitivity of endometrial thickness in predicting the presence of an ectopic pregnancy, Journal of Ultrasound in</td><td>Sample size

n=676 referred with clinical suspicion of ectopic pregnancy; n=548 excluded with IUP or abnormal IUP; n=128 analysed

Characteristics

mean age: 31.0 years (range 19 to 44 years)</td><td>Tests

Index test: TVUS
Reference test: medical records, clinical and sonographic follow up</td><td>Methods

Static sonographic images were reviewed for endometrial thickness, presence or absence of fluid within the endometrial cavity, presence of an adnexal mass, and presence of a moderate or large amount of free fluid</td><td>Results

TUBE & OVARY: COMPLEX ADNEXAL MASS (adnexal mass with sac/fetal pole/fetal heart beat may have been included too)
<u>Extraovarian adnexal mass</u><table><tr><td></td><td>US mass</td><td>US no mass</td><td>total</td></tr><tr><td>ectopic pregnancy+</td><td>25</td><td>17</td><td>42</td></tr><tr><td>ectopic pregnancy-</td><td>1</td><td>85</td><td>86</td></tr><tr><td>total</td><td>26</td><td>102</td><td>128</td></tr></table></td><td>Limitations

Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? Yes – sonographic images from all women attending with suspicion of EP (positive pregnancy</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Medicine, 18, 117-122, 1999

Ref Id

91697

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study

evaluate endometrial thickness measurements of all patients who were examined with clinical suspicion of ectopic pregnancy

Study dates</td>
<td>Inclusion Criteria

clinical suspicion of ectopic pregnancy (positive pregnancy test with symptoms of pain or bleeding, or both)

Exclusion Criteria

normal IUP or abnormal IUP on TVUS</td>
<td></td>
<td></td>
<td>PERITONEAL CAVITY: FREE FLUID
<u>Moderate or large amount of free fluid</u>
<table>
<tr><th></th><th>US free fluid</th><th>US no free fluid</th><th>total</th></tr>
<tr><td>ectopic pregnancy+</td><td>25</td><td>17</td><td>42</td></tr>
<tr><td>ectopic pregnancy-</td><td>0</td><td>86</td><td>86</td></tr>
<tr><td>total</td><td>25</td><td>103</td><td>128</td></tr>
</table>
UTERUS: FLUID INSIDE THE UTERUS
<u>Endometrial fluid</u>
<table>
<tr><th></th><th>US endometrial fluid</th><th>US no endometrial fluid</th><th>total</th></tr>
<tr><td>ectopic pregnancy+</td><td>11</td><td>31</td><td>42</td></tr>
<tr><td>ectopic pregnancy-</td><td>41</td><td>45</td><td>86</td></tr>
<tr><td>total</td><td>52</td><td>76</td><td>128</td></tr>
</table>
</td>
<td>test with symptoms of pain or bleeding, or both) were assessed without knowledge of pregnancy outcome
2. Was a case-control design avoided? yes
3. Did the study avoid inappropriate exclusions? Yes - patients with sonographic evidence of normal or abnormal IUP were excluded (n=548/676 excluded for IUP)

Could the selection of patients have introduced bias?
RISK: LOW

B. CONCERNS REGARDING APPLICABILITY
Is there concern that the included patients do not match the review question? CONCERN: LOW

<u>DOMAIN 2: INDEX TESTS</u></td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
1 January 1993 - 31 December 1995 **Source of funding** Not reported					**A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard? Yes – images assessed without knowledge of pregnancy outcome 2. If a threshold was used, was it pre-specified? yes **Could the conduct or interpretation of the index test have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **DOMAIN 3: REFERENCE STANDARD** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					1. Is the reference standard likely to correctly classify the target condition? Yes – by surgery, by negative findings on dilatation and curettage with abnormally rising hCG levels, by sonographic demonstration of an adnexal mass separate from the ovary without an IUP, or by a combination of these methods 2. Were the reference standard results interpreted without knowledge of the results of the index test? unclear **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? unclear 2. Did all patients receive a reference standard? Yes 3. Did patients receive the same reference standard? No - by one or more of: surgery, negative findings on dilatation and curettage with abnormally rising hCG levels, sonographic demonstration of an adnexal mass separate from the ovary without an IUP

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					4. Were all patients included in the analysis? Unclear – only those with transvaginal sonograms, adequate clinical follow up and determination of serum hCG within 24 hours were included. It is not stated how many exclusions (if any) this led to. **Could the patient flow have introduced bias? RISK: UNCLEAR** **Other information**
Full citation Moore, Chris, Todd, William M., O'Brien, Elizabeth, Lin, Henry, Free fluid in Morison's pouch on bedside ultrasound predicts need	**Sample size** n=242; n=241 had TAS (n=90 IUP; n=150 no definite IUP, n=1 ectopic pregnancy) Subsequent TVS pelvic US was performed by the Department of Radiology during the initial patient visit on n=226 patients	**Tests** Index test: TAS and TVS in some cases. Pelvic US result was classified as intrauterine pregnancy (IUP) or no definitive IUP, and fluid in the cul-de-sac was classified as present or absent Reference test: radiology US and/or operative	**Methods** Bedside transabdominal US was performed using a B-K Medical Hawk XDI ultrasound scanner (B-K Medical, Herlev, Denmark). The US was recorded on S-VHS videotape	**Results** confirmed ectopic pregnancy: n=28/242 **PERITONEAL CAVITY: FREE FLUID** **<u>Free fluid in the pelvis</u>** • emergency room TAS: free fluid seen n=23/241: Sensitivity 39% 95%CI (29, 59); Specificity 94% 95%CI (90, 97); LR+ 7.0 95%CI (3.4, 14) • radiology-performed TVS: free fluid seen n=69/226: Sensitivity 53% (36, 69);	**Limitations** **Risk of bias assessed using QUADAS-II** **<u>DOMAIN 1: PATIENT SELECTION</u>** **A. RISK OF BIAS** 1. Was a consecutive or random sample of patients enrolled? yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
for operative intervention in suspected ectopic pregnancy, Academic emergency medicine : official journal of the Society for Academic Emergency Medicine, 14, 755-8, 2007 **Ref Id** 875992 **Country/ies where the study was carried out** USA **Study type** Prospective cohort study **Aim of the study** prospectively determine if emergency	**Characteristics** Not reported **Inclusion Criteria** female patients with positive pregnancy test results who presented in the first trimester with abdominal pain and/or vaginal bleeding and for whom the emergency physician intended to obtain imaging or consultation **Exclusion Criteria** • declined enrolment • found not to be pregnant • data form was not filled out	findings - operative records, online medical records, and/or telephone conversations		Specificity 74% (67, 80); LR+ 2.0 (1.4, 3.0)	2. Was a case-control design avoided? yes 3. Did the study avoid inappropriate exclusions? yes **Could the selection of patients have introduced bias?** **RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the included patients do not match the review question? CONCERN: LOW **<u>DOMAIN 2: INDEX TESTS</u>** **A. RISK OF BIAS** 1. Were the index test results interpreted without knowledge of the results of the reference standard? yes 2. If a threshold was used, was it pre-specified? yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
physician-performed transabdominal pelvic ultrasonography (TAS) with determination of free abdominal fluid in the hepatorenal space predicted the need for operative intervention **Study dates** February 2003 - January 2004 **Source of funding** Not reported					**Could the conduct or interpretation of the index test have introduced bias?** **RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **DOMAIN 3: REFERENCE STANDARD** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretation**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					have introduced bias? RISK: LOW **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes - those included in 2x2 (PUL only) 3. Did patients receive the same reference standard? yes - operative/surgical 4. Were all patients included in the analysis? yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Could the patient flow have introduced bias?
RISK: LOW

Other information</td></tr>
<tr><td>Full citation

Nadim, B., Infante, F., Lu, C., Sathasivam, N., Condous, G., Morphological ultrasound types known as 'blob' and 'bagel' signs should be reclassified from suggesting probable to indicating definite tubal ectopic pregnancy, Ultrasound in obstetrics & gynecology : the official journal of the</td><td>Sample size

n=849 analysed

Characteristics

Age (ectopic pregnancy cohort) 30.6 ± 5.6 years
Gestational age (ectopic pregnancy cohort) 39.9 ± 11.7 days

Inclusion Criteria

probable ectopic pregnancy (inhomogeneous adnexal mass (‘blob’ sign) or extrauterine sac-like structure (‘bagel’ sign)) or a pregnancy of unknown</td><td>Tests

Index test: TVUS
Reference test: gold standard for the diagnosis of tubal ectopic pregnancy was histopathological confirmation of chorionic villi in the removed Fallopian tube. Women with a PUL were followed up by repeat TVUS and quantitative hCG analysis until a final diagnosis was reached.</td><td>Methods

TVS was performed by a clinical fellow using a Medison X8 or Medison Accuvix V20 Prestige (Samsung Medison, Seoul, South Korea) ultrasound system, equipped with a 4–9-MHz transvaginal probe.</td><td>Results

probable ectopic pregnancy: n=240/849 (n=174/240 blob sign; 66/240 bagel sign)
PUL: n=609/849 (EP=47/609; 24/47 blob sign, 19/47 bagel sign, 4/47 gestational sac with embryo/yolk sac)

TUBE & OVARY: COMPLEX ADNEXAL MASS
<u>blob sign:</u> Sensitivity 89.8% (82.2–94.4); Specificity 99.5% (98.5–99.8); LR+ 169.1 (54.6–523.8); LR- 0.103 (0.057–0.185)
<table><tr><td></td><td>US blob</td><td>US no blob</td><td>total</td></tr><tr><td>ectopic pregnancy+</td><td>88</td><td>10</td><td>98</td></tr><tr><td>ectopic pregnancy-</td><td>3</td><td>562</td><td>565</td></tr><tr><td>total</td><td>91</td><td>572</td><td>663</td></tr></table>
TUBE & OVARY: ADNEXAL MASS
<u>bagel sign:</u> Sensitivity 83.3% (70.4–91.3); specificity 99.6% (98.7–99.9); LR+ 235.0 (58.6–942.8); LR- 0.167 (0.089–0.315)</td><td>Limitations

Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? yes
2. Was a case-control design avoided? yes
3. Did the study avoid inappropriate exclusions? unclear - 101 women with blob sign underwent surgery, and they present results for these, but not for the 97 other women with blobs, who were managed conservatively; bag</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>International Society of Ultrasound in Obstetrics and Gynecology, 51, 543-549, 2018

Ref Id

876001

Country/ies where the study was carried out

Australia

Study type

Retrospective cohort study

Aim of the study

determine whether specific ultrasound markers (inhomogeneous adnexal mass (‘blob’ sign) or extrauterine sac-like structure</td>
<td>location (PUL), i.e. with no signs of extra- or intrauterine pregnancy (IUP), at their first TVS

Exclusion Criteria

• definite tubal ectopic pregnancy
• IUP
• non-tubal ectopic pregnancy</td>
<td></td>
<td></td>
<td>
<table>
<tr><th></th><th>US bagel</th><th>US no bagel</th><th>total</th></tr>
<tr><td>ectopic pregnancy+</td><td>40</td><td>8</td><td>48</td></tr>
<tr><td>ectopic pregnancy-</td><td>2</td><td>562</td><td>564</td></tr>
<tr><td>total</td><td>42</td><td>570</td><td>612</td></tr>
</table>
TUBE & OVARY: ADNEXAL MASS
<u>gestational sac with embryo "definite ectopic pregnancy":</u> Sensitivity 84.0% (64.3–92.7); Specificity 99.9% (99.2–100); LR+ 930.3 (57.9–14 937.7); LR- 0.173 (0.075–0.401)
<table>
<tr><th></th><th>US "definite ectopic pregnancy"</th><th>US no "definite ectopic pregnancy"</th><th>total</th></tr>
<tr><td>ectopic pregnancy+</td><td>21</td><td>4</td><td>25</td></tr>
<tr><td>ectopic pregnancy-</td><td>0</td><td>562</td><td>562</td></tr>
<tr><td>total</td><td>21</td><td>566</td><td>587</td></tr>
</table>
</td>
<td>el sign – only 50/85 had surgery

Could the selection of patients have introduced bias?
RISK: UNCLEAR
B. CONCERNS REGARDING APPLICABILITY
Is there concern that the included patients do not match the review question?
CONCERN: LOW

<u>DOMAIN 2: INDEX TESTS</u>
A. RISK OF BIAS

1. Were the index test results interpreted without knowledge of the results of the reference standard? yes
2. If a threshold was used, was it pre-specified? yes

Could the conduct or interpretation of the index test have introduced bias?
RISK: LOW</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
('bagel' sign)) can be used to predict a definite tubal ectopic pregnancy **Study dates** November 2006 - June 2016 **Source of funding** Not reported					**B. CONCERNS REGARDING APPLICABILITY** Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW **<u>DOMAIN 3: REFERENCE STANDARD</u>** **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias? RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **<u>DOMAIN 4: FLOW AND TIMING</u>** **A. RISK OF BIAS** 1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? no - operative/surgical or repeat US and clinical follow up. Those who did not have the same reference standard (ie treated conservatively) were excluded 4. Were all patients included in the analysis? Yes.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Could the patient flow have introduced bias?
RISK: HIGH

Other information</td></tr>
<tr><td>Full citation

Sadek,A.L., Schiotz,H.A., Transvaginal sonography in the management of ectopic pregnancy, Acta Obstetricia et Gynecologica Scandinavica, 74, 293-296, 1995

Ref Id

65458

Country/ies where the study was carried out

Norway</td><td>Sample size

n=525 women referred with abdominal pain and/or vaginal bleeding in the first trimester of pregnancy were evaluated by TVUS

Characteristics

• mean age 31 years (range 23-43)
• duration of amenorrhoea 6.5 weeks (range 4-12)

Inclusion Criteria

All patients referred with amenorrhoea, abdominal pain and/or</td><td>Tests

Index test: TVUS
Reference test: If ectopic pregnancy was suspected, treated laparoscopically with linear salpingostomy or salpingectomy using diathermy technique; all tubal or uterine material and abdominal fluid was examined histologically.</td><td>Methods

sonographic examination was performed by a gynaecologist as part of the initial evaluation with the patient in the lithotomy position using a 5 MHz vaginal transducer (General Electric 3200 or Aloka SSD-650)</td><td>Results

ectopic pregnancy was suspected when the pregnancy test was positive and TVUS showed (a) empty uterus or pseudosac, and (b) free pelvic fluid and/or a tubal mass
suspected ectopic pregnancy n=57; confirmed ectopic pregnancy n=53

• empty uterus n=48/57
• pseudosac n=5/57
• tubal mass n=45/57
• free pelvic fluid n=54/57

PERITONEAL CAVITY: FREE FLUID
<u>Free pelvic fluid:</u> Sensitivity 96.2%; Specificity 99.4%; PPV 94.4% (51/54); NPV 99.6% (469/471)
<table><tr><td></td><td>US free fluid</td><td>US no free fluid</td><td>total</td></tr><tr><td>ectopic pregnancy+</td><td>51</td><td>2</td><td>53</td></tr><tr><td>ectopic pregnancy-</td><td>3</td><td>469</td><td>472</td></tr></table></td><td>Limitations

Risk of bias assessed using QUADAS-II
<u>DOMAIN 1: PATIENT SELECTION</u>
A. RISK OF BIAS

1. Was a consecutive or random sample of patients enrolled? yes
2. Was a case-control design avoided? yes
3. Did the study avoid inappropriate exclusions? yes

Could the selection of patients have introduced bias?
RISK: LOW
B. CONCERNS REGARDING APPLICABILITY</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Study type

Prospective cohort study

Aim of the study

evaluate the role of transvaginal sonography (TVUS) in the early diagnosis of symptomatic EP and its influence in facilitating laparoscopic management

Study dates

January 1990 - January 1993

Source of funding

Not reported</td>
<td>vaginal bleeding with positive pregnancy test

Exclusion Criteria

Not reported</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>total</td><td>54</td><td>471</td><td>525</td></tr>
</table>

TUBE & OVARY: COMPLEX ADNEXAL MASS
<u>Tubal mass:</u> Sensitivity 81.1%; Specificity 99.6%; PPV 95.6% (43/45); NPV 97.9% (470/480)
<table>
<tr><td></td><td>US tubal mass</td><td>US no tubal mass</td><td>total</td></tr>
<tr><td>ectopic pregnancy+</td><td>43</td><td>10</td><td>53</td></tr>
<tr><td>ectopic pregnancy-</td><td>2</td><td>470</td><td>472</td></tr>
<tr><td>total</td><td>45</td><td>480</td><td>525</td></tr>
</table>
</td>
<td>Is there concern that the included patients do not match the review question?
CONCERN: LOW

<u>DOMAIN 2: INDEX TESTS</u>
A. RISK OF BIAS

1. Were the index test results interpreted without knowledge of the results of the reference standard? yes
2. If a threshold was used, was it pre-specified? yes

Could the conduct or interpretation of the index test have introduced bias?
RISK: LOW
B. CONCERNS REGARDING APPLICABILITY
Is there concern that the index test, its conduct, or interpretation differ from the review question? CONCERN: LOW</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					DOMAIN 3: REFERENCE STANDARD **A. RISK OF BIAS** 1. Is the reference standard likely to correctly classify the target condition? yes 2. Were the reference standard results interpreted without knowledge of the results of the index test? yes **Could the reference standard, its conduct, or its interpretation have introduced bias?** **RISK: LOW** **B. CONCERNS REGARDING APPLICABILITY** Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW **DOMAIN 4: FLOW AND TIMING** **A. RISK OF BIAS**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					1. Was there appropriate interval between index tests and reference standard? yes 2. Did all patients receive a reference standard? yes 3. Did patients receive the same reference standard? yes - operative/surgical 4. Were all patients included in the analysis? Yes **Could the patient flow have introduced bias? RISK: LOW** **Other information**

Appendix E: Forest plots

There are no forest plots for this evidence review as no meta-analysis was performed.

Appendix F:GRADE tables

Table 3: All symptomatic women (women with pain/bleeding or referred for a scan due to high risk of ectopic pregnancy)

Number of studies (author)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
TVUS: adnexal ectopic (Adnexal mass with gestational sac and yolk sac or fetal pole +/- fetal heartbeat)									
1 (Barnhart 2011)[1]	1880	Serious risk of bias[2]	No serious inconsistency	Serious[3]	No serious imprecision	0.13 (0.10 to 0.17)	1.00 (1.00 to 1.00)	197.37 (27.35 to 1424.15) 0.87 (0.84 to 0.90)	LOW ⊕⊕⊖⊖
TVUS: Complex adnexal mass: inhomogenous mass, heterogeneous mass, or adnexal mass (no yolk sac or fetal pole)									
1 (Barnhart 2011)[1]	1880	Serious risk of bias[2]	No serious inconsistency	Serious[3]	No serious imprecision	0.42 (0.37 to 0.48)	0.98 (0.97 to 0.99)	18.92 (12.89 to 27.78) 0.65 (0.60 to 0.70)	LOW ⊕⊕⊖⊖
TVUS: Free fluid in the pelvis									
1 (Moore 2007)[4]	226	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	0.53 (0.36 to 0.69)	0.74 (0.67 to 0.80)	2.0 (1.4 to 3.0) 0.63 (0.42 to 0.93)	MODERATE ⊕⊕⊕⊖
1 (Sadek 1995)[6]	525	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.96 (0.87 to 1.00)	0.99 (0.98 to 1.00)	151.40 (48.94 to 468.32) 0.04 (0.01 to 0.15)	HIGH ⊕⊕⊕⊕
TAS: Free fluid in the pelvis									
1 (Moore 2007)[4]	241	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[7]	0.39	0.94	7.0 (3.4 to 14)	MODERATE ⊕⊕⊕⊖

Number of studies (author)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95% CI)	Specificity (95% CI)	Effect size LR+ (95% CI) LR- (95% CI)	Quality of the evidence (GRADE)
						(0.29 to 0.59)	(0.90 to 0.97)	0.65 (0.48 to 0.87)	

CI: confidence interval; EP: ectopic pregnancy; IUP: intrauterine pregnancy; IVF: in vitro fertilisation; LR+: positive likelihood ratio; LR-: negative likelihood ratio; MID: minimally important difference; NGA: National Guideline Alliance; TAS: transabdominal ultrasound; TVUS: transvaginal ultrasound
1 Additional data calculated by the NGA technical team: LR using RevMan 5.3 calculator and vassarstats online calculator (http://vassarstats.net/clin1.html)
2 The quality of the evidence was downgraded by 1 level as there was an unclear risk of bias in the participant flow
3 The quality of the evidence was downgraded by 1 level as the study excluded simple viable IUPs (included abnormal, unclear, or IUP with need for further gynaecological consult), therefore a higher risk population
4 Additional data calculated by the NGA technical team: LR- using RevMan 5.3 calculator and vassarstats online calculator (http://vassarstats.net/clin1.html)
5 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crosses 0.50: protocol-specified MID thresholds for sensitivity are 0.50 and 0.75
6 Additional data calculated by the NGA technical team: 95% CI for sensitivity and specificity using RevMan5.3 calculator, and LR using vassarstats online calculator (http://vassarstats.net/clin1.html)
7 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crosses 0.50: protocol-specified MID thresholds for sensitivity are 0.50 and 0.75

Table 4: High risk of ectopic pregnancy: includes PUL and ectopic pregnancy (all IUPs excluded)

Number of studies (author)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Effect size LR+ (95%CI) LR- (95%CI)	Quality of the evidence (GRADE)
TVUS: Pseudosac									
1 (Hammoud 2005)[1]	403	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	0.03 (0.01 to 0.06)	0.99 (0.95 to 1.00)	2.27 (0.49 to 10.56) 0.98 (0.96 to 1.00)	MODERATE ⊕⊕⊕⊖
TVUS: Intrauterine fluid									
1 (Mehta 1999)[1]	128	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Serious[4]	0.26 (0.14 to 0.42)	0.52 (0.41 to 0.63)	0.55 (0.32 to 0.96) 1.41 (1.15 to 1.72)	LOW ⊕⊕⊖⊖
TVUS: Complex adnexal mass: inhomogeneous mass, heterogeneous mass, or adnexal mass (no yolk sac or fetal pole)									
1 (Mehta 1999)[1,5]	128	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Serious[6]	0.60 (0.43 to 0.74)	0.99 (0.94 to 1.00)	51.19 (7.18 to 365.03) 0.41 (0.28 to 0.60)	LOW ⊕⊕⊖⊖
TVUS: Free fluid in peritoneal cavity									
1 (Mehta 1999)[1]	128	Serious risk of bias[3]	No serious inconsistency	No serious indirectness	Serious[6]	0.60 (0.43 to 0.74)	1.00 (0.96 to 1.00)	Not calculable[7] 0.40 (0.28 to 0.58)	LOW ⊕⊕⊖⊖

CI: confidence interval; EP: ectopic pregnancy; IUP: intrauterine pregnancy; LR+: positive likelihood ratio; LR-: negative likelihood ratio; MID: minimally important difference; NGA: National Guideline Alliance; PUL: pregnancy of unknown location; TVUS: transvaginal ultrasound

1 Additional data calculated by the NGA technical team: sensitivity and specificity using RevMan 5.3 calculator, and LR using vassarstats online calculator (http://vassarstats.net/clin1.html)

2 The quality of the evidence was downgraded by 1 level due to an unclear risk of bias in participant flow, as 8.6% of women were excluded from the final analysis due to loss to follow up.

3 The quality of the evidence was downgraded by 1 level due to an unclear risk of bias in participant flow – there was an unclear interval between the index test and reference standard, patients received different reference standards and participants were excluded if there was insufficient clinical or sonographic follow up, or no serum hCG measurement within 24 hours of the scan.

4 The quality of the evidence was downgraded by 1 level as the 95% CI for specificity crosses 0.50: protocol-specified MID thresholds for specificity are 0.50 and 0.80

5 Study may have included adnexal masses with additional features (such as yolk sac and/or fetal pole) – described only as adnexal mass

6 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crosses 0.50: protocol-specified MID thresholds for sensitivity are 0.50 and 0.77
7 Positive likelihood ratio (LR+) not calculable as specificity is 1.00 (100%)

Table 5: High risk of ectopic pregnancy: PULs only – excluded all IUPs and definite ectopic pregnancy

Number of studies (author)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Effect size LR+ (95%CI) LR- (95%CI)	AUC (95% CI)	Quality of the evidence (GRADE)
TVUS: Empty uterus										
1 (Dart 1998)[1]	228	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	Serious[3]	0.78 (0.60 to 0.91)	0.65 (0.58 to 0.71)	2.22 (1.1-5.0) 0.34 (0.17 to 0.65)	-	LOW ⊕⊕⊖⊖
1 (Dart 2002)[4]	635	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious[3]	0.78 (0.64 to 0.89)	0.62 (0.58 to 0.66)	2.07 (1.72 to 2.48) 0.35 (0.20 to 0.61)	-	LOW ⊕⊕⊖⊖
TVUS: Pseudosac										
1 (Ahmed 2004)[4]	77	Serious risk of bias[6]	No serious inconsistency	No serious indirectness	Serious[7]	0.06 (0.01 to 0.16)	0.42 (0.22 to 0.63)	0.10 (0.03 to 0.31) 2.26 (1.89 to 2.71)	-	LOW ⊕⊕⊖⊖
TVUS: Intrauterine fluid										
1 (Dart 1998)[1]	228	Serious risk of bias[2]	No serious inconsistency	No serious indirectness	No serious imprecision	0.13 (0.04 to 0.29)	0.87 (0.81 to 0.91)	1.0 (0.32 to 3.1) 1.01 (0.88 to 1.15)	-	MODERATE ⊕⊕⊕⊖
1 (Dart 2002)[4]	635	Serious risk of bias[5]	No serious inconsistency	No serious indirectness	Serious[8]	0.13 (0.05 to 0.26)	0.80 (0.76 to 0.83)	0.63 (0.29 to 1.36) 1.09 (0.98 to 1.23)	-	LOW ⊕⊕⊖⊖
TVUS: Tubal ring sign (bagel sign)										
1 (Nadim 2018)[9]	612	Serious[10]	No serious inconsistency	No serious indirectness	Serious[3]	0.83 (0.70 to 0.91)	1.00 (0.99 to 1.00)	235.0 (58.6 to 942.8)	-	LOW ⊕⊕⊖⊖

Number of studies (author)	Number of women	Risk of bias	Inconsistency	Indirectness	Imprecision	Sensitivity (95%CI)	Specificity (95%CI)	Effect size LR+ (95%CI) LR- (95%CI)	AUC (95% CI)	Quality of the evidence (GRADE)
								0.167 (0.089 to 0.315)		
TVUS: Complex adnexal mass: inhomogeneous mass, heterogeneous mass, or adnexal mass (no yolk sac or fetal pole)										
1 (Ahmed 2004)[4]	77	Serious risk of bias[6]	No serious inconsistency	No serious indirectness	Very serious[11]	0.64 (0.50 to 0.77)	0.88 (0.68 to 0.97)	5.13 (1.75 to 15.07) 0.41 (0.28 to 0.59)	-	VERY LOW ⊕⊖⊖⊖
1 (Nadim 2018)[9]	663	Serious[10]	No serious inconsistency	No serious indirectness	No serious imprecision	0.90 (0.82 to 0.94)	1.00 (0.99 to 1.00)	169.1 (54.6 to 523.8) 0.103 (0.057 to 0.185)	-	MODERATE ⊕⊕⊕⊖
TVUS: Free fluid in peritoneal cavity										
1 (Malek-Mellouli 2013)[12]	94	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	0.26 (0.14 to 0.42)	0.94 (0.84 to 0.99)	4.5 (1.32 to 15.30) [13] 0.79 (0.66 to 0.95) [13]	0.60	HIGH ⊕⊕⊕⊕

AUC: area under the curve; CI: confidence interval; EP: ectopic pregnancy; IUP: intrauterine pregnancy; LR+: positive likelihood ratio; LR-: negative likelihood ratio; MID: minimally important difference; NGA: National Guideline Alliance; PUL: pregnancy of unknown location; TVUS: transvaginal ultrasound
1 Additional data calculated by the NGA technical team: sensitivity and specificity using RevMan 5,3 calculator, and LR- using vassarstats online calculator (http://vassarstats.net/clin1.html)
2 The quality of the evidence was downgraded by 1 level due to high risk of bias in participant flow: 8% of women were excluded from the analysis as the reference standard was not available (lost to follow up before a final diagnosis was made)
3 The quality of the evidence was downgraded by 1 level as the 95% CI for sensitivity crosses 0.75: protocol-specified MID thresholds for sensitivity are 0.50 and 0.75
4 Additional data calculated by the NGA technical team: sensitivity and specificity using RevMan 5.3 calculator, and LR using vassarstats online calculator (http://vassarstats.net/clin1.html)
5 The quality of the evidence was downgraded by 1 level due to a high risk of bias in participant flow: 18% of participants were excluded from the final analysis as they were lost to follow up (reference standard was not available)
6 The quality of the evidence was downgraded by 1 level due to a high risk of bias in participant selection, as 13/90 women undergoing laparoscopy for suspected ectopic pregnancy were excluded
7 The quality of the evidence was downgraded by 1 level as the 95% CI for specificity crosses 0.50: protocol-specified MID thresholds for specificity are 0.50 and 0.80
8 The quality of the evidence was downgraded by 1 level as the 95% CI for specificity crosses 0.80: protocol-specified MID thresholds for specificity are 0.50 and 0.80
9 Study excluded definite EP and IUP, and non-tubal pregnancy (additional exclusion to other studies)

10 The quality of the evidence was downgraded by 1 level due to possible selection bias (women were excluded if they had conservative management instead of surgery and histological confirmation)
11 The quality of the evidence was downgraded by 2 levels as the 95% CI for sensitivity crosses 0.75 (protocol-specified MID thresholds for sensitivity are 0.50 and 0.75), and for specificity crosses 0.80 (protocol-specified MID thresholds for specificity are 0.50 and 0.80)
12 Additional data calculated by the NGA technical team: LR using vassarstats online calculator (http://vassarstats.net/clin1.html)
13 Values back-calculated by the NGA technical team using RevMan 5.3 calculator and vasserstats online calculator (http://vassarstats.net/clin1.html) from reported sensitivity and specificity in the study. Unable to extract original data for 2x2 DTA table

Appendix G: Economic evidence study selection

Figure 2: Flow diagram of economic evidence study selection

Appendix H: Economic evidence tables

No economic evidence was identified for this review question.

Appendix I: Health economic evidence profiles

No economic evidence was identified for this review question.

Appendix J: Health economic analysis

No health economic analysis was conducted for this review question.

Appendix K: Excluded studies

Clinical studies

Study	Reason for Exclusion
Abeia, A., Assefa, G., Diagnostic performance of transvesical ultrasound in clinically suspected ectopic pregnancy in a public and tertiary,hospital setup, Ethiopian Medical Journal, 51, 49-57, 2013	Diagnostic accuracy using US for EP, but no diagnostic detail on characteristics - frequency reported of some
Abrahamson,L., Newton,W., What is the optimal protocol for diagnosis of ectopic pregnancy?, Journal of Family Practice, 50, 570-, 2001	Short overview of a study - no usable data
Achanna,S., Har,W.Y., Predictive value of transabdominal ultrasonography in the diagnosis of ectopic pregnancy, Biomedical Research, 13, 85-3, 2002	Diagnostic accuracy using US for EP, but no diagnostic detail on characteristics - frequency reported of each
Adhikari, Srikar, Blaivas, Michael, Lyon, Matthew, Diagnosis and management of ectopic pregnancy using bedside transvaginal ultrasonography in the ED: a 2-year experience, The American journal of emergency medicine, 25, 591-6, 2007	Sonographer experience
Ali, J., Lotfi, G., Retrospective cross-sectional analysis of diagnosis criteria and management outcomes for patients diagnosed with caesarean scar pregnancy (CSP) at a single tertiary center, Gynecological Surgery, 13, S352, 2016	Full text is an abstract
Al-Memar, M., Bobdiwala, S., Madhra, M., Cock, B. D., Calster, B. V., Bottomley, C., Horne, A., Bourne, T., The potential value of activin B and fibronectin as biomarkers to predict outcome in pregnancies of unknown location and first trimester viability, BJOG: An International Journal of Obstetrics and Gynaecology, 123, 241, 2016	Full text is an abstract
Al-Memar, M., Bobdiwala, S., Madhra, M., Saso, S., De Cock, B., Van Calster, B., Brown, J. K., Mukri, F., Bottomley, C., Papageorghiou, A., Timmerman, D., Horne, A. W., Bourne, T., The potential value of activin B and fibronectin for the triage of pregnancies of unknown location and prediction of first trimester viability, Australasian Journal of Ultrasound in Medicine, 2018	Not diagnostic for US - accuracy of biomarkers only
Ankum, W. M., Van der Veen, F., Hamerlynck, J. V., Lammes, F. B., Suspected ectopic pregnancy. What to do when human chorionic gonadotropin levels are below the discriminatory zone, Journal of Reproductive Medicine, 40, 525-8, 1995	Diagnostic accuracy using US for EP, but no diagnostic detail on US features. Focus on a treatment pathway/ protocol/ algorithm
Asaravala, M., Wang, R., Hensley, B., Neilson, J., Jacoby, V., Stein, J., Does the finding of	Full text is an abstract

Study	Reason for Exclusion
gestational sac on point of care ultrasound decrease the risk of ectopic pregnancy?, Academic Emergency Medicine, 20, S254, 2013	
Atri, M., Leduc, C., Gillett, P., Bret, P. M., Reinhold, C., Kintzen, G., Aldis, A. E., Thibodeau, M., Role of endovaginal sonography in the diagnosis and management of ectopic pregnancy, Radiographics, 16, 755-74; discussion 775, 1996	Narrative overview
Atri, Mostafa, Ectopic pregnancy versus corpus luteum cyst revisited: best Doppler predictors, Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine, 22, 1181-4, 2003	Not diagnostic accuracy
Atri, Mostafa, Valenti, David A., Bret, Patrice M., Gillett, Peter, Effect of transvaginal sonography on the use of invasive procedures for evaluating patients with a clinical diagnosis of ectopic pregnancy, Journal of clinical ultrasound : JCU, 31, 1-8, 2003	Diagnostic accuracy using US for EP, but no diagnostic detail on characteristics - frequency reported of some. Focus on different eras of sonography
Banu, S. A., Khatun, S., Shamsuddin, L., Assesment of adnexal masses by transvaginal sonography and serum CA125 assay in pre- and postmenopausal women, Bangladesh Journal of Obstetrics and Gynecology, 24, 56-62, 2009	Diagnostic accuracy of type of adnexal mass - not ectopic pregnancy
Barnhart, Kurt T., Casanova, Bruno, Sammel, Mary D., Timbers, Kelly, Chung, Karine, Kulp, J. L., Prediction of location of a symptomatic early gestation based solely on clinical presentation, Obstetrics and Gynecology, 112, 1319-26, 2008	Diagnostic accuracy of different decision models (for management)
Barnhart,K.T., Simhan,H., Kamelle,S.A., Diagnostic accuracy of ultrasound above and below the beta-hCG discriminatory zone, Obstetrics and Gynecology, 94, 583-587, 1999	Diagnostic accuracy using US HCG for EP, but no detail on US characteristics used in diagnosis
Basak, S., Van Roon, Y., Ghosh, B., Sriemevan, A., Diagnosis and management of pregnancy of unknown location (PUL): The completed audit cycle, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 560-561, 2013	Full text is an abstract
Bayyarapu, Vijaya B., Gundabattula, Sirisha R., Diagnosis and Management of 'Cornual' Pregnancies from 2002 to 2015 at a Tertiary Referral Centre in South India: Insights from Introspection, Journal of obstetrics and gynaecology of India, 67, 414-420, 2017	Does not look at tubal EP
Benacerraf,B.R., Shipp,T.D., Bromley,B., Does the 10-MHz transvaginal transducer improve the diagnostic certainty that an intrauterine fluid collection is a true gestational sac?, Journal of Clinical Ultrasound, 27, 374-377, 1999	Comparison in diagnostic accuracy of different US frequencies. Not characteristics of ectopic pregnancy

Study	Reason for Exclusion
Benson, Carol B., Doubilet, Peter M., Peters, Hope E., Frates, Mary C., Intrauterine fluid with ectopic pregnancy: a reappraisal, Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine, 32, 389-93, 2013	No diagnostic outcomes available
Bignardi, Tommaso, Alhamdan, Dalya, Condous, George, Is ultrasound the new gold standard for the diagnosis of ectopic pregnancy?, Seminars in ultrasound, CT, and MR, 29, 114-20, 2008	Narrative review
Birkhahn, Robert H., Gaeta, Theodore J., Van Deusen, Shawn K., Tloczkowski, John, The ability of traditional vital signs and shock index to identify ruptured ectopic pregnancy, American Journal of Obstetrics and Gynecology, 189, 1293-6, 2003	Diagnostic accuracy of shock index and heart rate, not US
Bixby, Sarah, Tello, Richard, Kuligowska, Ewa, Presence of a yolk sac on transvaginal sonography is the most reliable predictor of single-dose methotrexate treatment failure in ectopic pregnancy, Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine, 24, 591-8, 2005	Accuracy of model for assessing whether a certain treatment would work in cases of ectopic pregnancy
Blaivas, Michael, Lyon, Matthew, Reliability of adnexal mass mobility in distinguishing possible ectopic pregnancy from corpus luteum cysts, Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine, 24, 599-605, 2005	Not reliant on US for diagnosis - based on adnexal mass mobility
Bottomley, C., Van Belle, V., Pexsters, A., Papageorghiou, A. T., Mukri, F., Kirk, E., Van Huffel, S., Timmerman, D., Bourne, T., A model and scoring system to predict outcome of intrauterine pregnancies of uncertain viability, Ultrasound in Obstetrics & Gynecology, 37, 588-95, 2011	Diagnostic accuracy of a model determining viability of pregnancy
Cacciatore,B., Korhonen,J., Stenman,U.H., Ylostalo,P., Transvaginal sonography and serum hCG in monitoring of presumed ectopic pregnancies selected for expectant management, Ultrasound in Obstetrics and Gynecology, 5, 297-300, 1995	Descriptive - incidence of certain ectopic characteristics in cohort, and diagnostic accuracy for HCG not US
Chama,C.M., Obed,J.Y., Ekanem,I.A., Transvaginal ultrasound scan versus laparoscopy in the diagnosis of suspected ectopic pregnancy, Journal of Obstetrics and Gynaecology, 21, 184-186, 2001	Diagnostic accuracy using US for EP, but no diagnostic detail on US features - frequency reported of each
Chen, P. C., Sickler, G. K., Dubinsky, T. J., Maklad, N., Jacobi, R. L., Weaver, J. E., Sonographic detection of echogenic fluid and	Diagnostic accuracy of hemoperitoneum, not tubal EP

Study	Reason for Exclusion
correlation with culdocentesis in the evaluation of ectopic pregnancy, AJR. American Journal of Roentgenology, 170, 1299-302, 1998	
Chen, Z. Y., Liu, J. H., Liang, K., Liang, W. X., Ma, S. H., Zeng, G. J., Xiao, S. Y., He, J. G., The diagnostic value of a multivariate logistic regression analysis model with transvaginal power Doppler ultrasonography for the prediction of ectopic pregnancy, Journal of International Medical Research, 40, 184-93, 2012	Diagnostic accuracy of prediction model based on endometrial thickness
Chew,S., Anandakumar,C., Vanaja,K., Wong,Y.C., Chia,D., Ratnam,S.S., The role of transvaginal ultrasonography and colour Doppler imaging in the detection of ectopic pregnancy, Journal of Obstetrics and Gynaecology Research, 22, 455-460, 1996	Cannot extract data for US features of EP, only for overall US diagnosis of EP
Col-Madendag, Ilknur, Madendag, Yusuf, Kanat-Pektas, Mine, Danisman, Nuri, Can sonographic endometrial pattern be an early indicator for tubal ectopic pregnancy and related tubal rupture?, Archives of Gynecology and Obstetrics, 281, 189-94, 2010	Diagnostic accuracy of logistic model based on endometrial pattern
Comstock, Christine, Huston, Kathleen, Lee, Wesley, The ultrasonographic appearance of ovarian ectopic pregnancies, Obstetrics and Gynecology, 105, 42-5, 2005	Not diagnostic accuracy - case review of 6 ovarian ectopic pregnancies
Condous, G., Kirk, E., Lu, C., Van Huffel, S., Gevaert, O., De Moor, B., De Smet, F., Timmerman, D., Bourne, T., Diagnostic accuracy of varying discriminatory zones for the prediction of ectopic pregnancy in women with a pregnancy of unknown location, Ultrasound in Obstetrics & Gynecology, 26, 770-5, 2005	Diagnostic accuracy of serum HCG and progesterone
Condous, G., Van Calster, B., Kirk, E., Haider, Z., Timmerman, D., Van Huffel, S., Bourne, T., Prediction of ectopic pregnancy in women with a pregnancy of unknown location, Ultrasound in Obstetrics & Gynecology, 29, 680-7, 2007	Accuracy of logistic models for prediction of EP based on HCG
Condous, George, Okaro, Emeka, Khalid, Asma, Lu, Chuan, Van Huffel, Sabine, Timmerman, D., Bourne, Tom, The accuracy of transvaginal ultrasonography for the diagnosis of ectopic pregnancy prior to surgery, Human reproduction (Oxford, England), 20, 1404-9, 2005	Diagnostic accuracy using US for EP, but no diagnostic detail on US features - frequency reported of each
Crochet, J. R., Bastian, L. A., Chireau, M. V., Does this woman have an ectopic pregnancy? The rational clinical examination systematic review, JAMA - Journal of the American Medical Association, 309, 1722-1729, 2013	SR with MA includes data that does not adhere to the protocol - pre-1995. Included studies checked for inclusion/exclusion
Dart,R., Kaplan,B., Ortiz,L., Cloherty,J., Lavoie,T., Normal intrauterine pregnancy is	Not diagnostic accuracy

Study	Reason for Exclusion
unlikely in emergency department patients with either menstrual days > 38 days or beta-hCG > 3,000 mIU/mL, but without a gestational sac on ultrasonography, Academic Emergency Medicine, 4, 967-971, 1997	
Dart,R.G., Dart,L., Mitchell,P., Berty,C., The predictive value of endometrial stripe thickness in patients with suspected ectopic pregnancy who have an empty uterus at ultrasonography, Academic Emergency Medicine, 6, 602-609, 1999	Diagnostic accuracy based on endometrial stripe thickness and hCG
Dart,R.G., Mitterando,J., Dart,L.M., Rate of change of serial beta-human chorionic gonadotropin values as a predictor of ectopic pregnancy in patients with indeterminate transvaginal ultrasound findings, Annals of Emergency Medicine, 34, 703-710, 1999	Not diagnostic accuracy
Devarajan, S. D., Balachandren, N. B., Ramalingam, K. R., Fleming, D. F., Shankar, M., Diagnosis of ectopic pregnancy: Is ultrasound a reliable tool?, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 543, 2013	Full text is an abstract
Dhiman, Pooja, Senthilkumar, G. P., Rajendiran, Soundravally, Sivaraman, K., Soundararaghavan, S., Kulandhasamy, Maheshwari, Serum activin B concentration as predictive biomarker for ectopic pregnancy, Clinical biochemistry, 49, 609-12, 2016	Diagnostic of serum markers, not US
Dilbaz, S., Guvendag Guven, E. S., Yildirim, B., Gelisen, O., Karcaaltincaba, D., Kurtaran, V., Haberal, A., Is it necessary to operate on all women with an acute abdomen following medical treatment of tubal ectopic pregnancy?, Journal of Obstetrics and Gynaecology, 30, 496-500, 2010	Efficacy of treatment in ectopic cohorts. Not diagnostic accuracy of US
Dogra, Vikram, Paspulati, Raj Mohan, Bhatt, Shweta, First trimester bleeding evaluation, Ultrasound Quarterly, 21, 69-4, 2005	Narrative review
Drobny,J., Sonography in the management of symptomatic pregnancies of unknown location, Bratislavske lekarske listy, 109, 254-259, 2008	Cannot extract usable data. Diagnostic accuracy using US for ectopic pregnancy overall, and reports frequency of some US characteristics, but no diagnostic accuracy for those features
Durham,B., Lane,B., Burbridge,L., Balasubramaniam,S., Mateer,J., Pelvic ultrasound performed by emergency physicians for the detection of ectopic pregnancy in complicated first-trimester pregnancies, Annals of Emergency Medicine, 29, 338-347, 1997	Cannot extract data for separate features seen by US as categorised by protocol (sums complex and simple adnexal mass)
Ellaithy, Mohamed, Abdelaziz, Ahmed, Hassan, Mahmoud Fathy, Outcome prediction in pregnancies of unknown location using endometrial thickness measurement: is this of	Diagnostic accuracy using endometrial thickness

Study	Reason for Exclusion
real clinical value?, European journal of obstetrics, gynecology, and reproductive biology, 168, 68-74, 2013	
Erol, Onur, Suren, Dinc, Karaca, Mehmet, Sezer, Cem, Ultrasonography for the prediction of extension of trophoblastic infiltration into the tubal wall in ampullary pregnancy, Ginekologia polska, 86, 16-20, 2015	Diagnostic accuracy for assessing depth of infiltration into tubal wall
Farren, J., Kirk, E., Mitchell, H., Sayasneh, A., Condous, G., Stalder, C., Bourne, T., The characteristics of 671 cases of tubal ectopic pregnancy, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 539, 2013	Full text is an abstract
Fauconnier, Arnaud, Mabrouk, Ali, Salomon, Laurent J., Bernard, Jean-Pierre, Ville, Yves, Ultrasound assessment of haemoperitoneum in ectopic pregnancy: derivation of a prediction model, World journal of emergency surgery : WJES, 2, 23, 2007	Diagnostic accuracy to predict haemoperitoneum, using confirmed ectopic pregnancy as cohort
Fistouris, J., Bergh, C., Strandell, A., Classification of pregnancies of unknown location according to four different hCG-based protocols, Human Reproduction, 31, 2203-11, 2016	Diagnostic accuracy based on change in hCG level
Florio, Pasquale, Severi, Filiberto Maria, Bocchi, Caterina, Luisi, Stefano, Mazzini, Massimo, Danero, Secondo, Torricelli, Michela, Petraglia, Felice, Single serum activin a testing to predict ectopic pregnancy, The Journal of clinical endocrinology and metabolism, 92, 1748-53, 2007	Diagnostic accuracy using serum biomarkers: hCG, progesterone, and activin A
Frates, M. C., Visweswaran, A., Laing, F. C., Comparison of tubal ring and corpus luteum echogenicities: a useful differentiating characteristic, Journal of Ultrasound in Medicine, 20, 27-31; quiz 33, 2001	Not diagnostic accuracy - echogenicity of difference characteristics
Frates, Mary C., Doubilet, Peter M., Peters, Hope E., Benson, Carol B., Adnexal sonographic findings in ectopic pregnancy and their correlation with tubal rupture and human chorionic gonadotropin levels, Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine, 33, 697-703, 2014	Not diagnostic accuracy for ectopic pregnancy
Frates,M.C., Laing,F.C., Sonographic evaluation of ectopic pregnancy: An update, American Journal of Roentgenology, 165, 251-259, 1995	Narrative review
Fukami, Tatsuya, Emoto, Makoto, Tamura, Riko, Kawarabayashi, Tatsuhiko, Sonographic findings of transvaginal color Doppler ultrasound in ectopic pregnancy, Journal of medical ultrasonics (2001), 33, 37-42, 2006	Not diagnostic accuracy

Study	Reason for Exclusion
Gracia,C.R., Barnhart,K.T., Diagnosing ectopic pregnancy: decision analysis comparing six strategies, Obstetrics and Gynecology, 97, 464-470, 2001	Assessment of decision algorithms - order of assessment/treatment
Guvendag Guven, E. S., Dilbaz, S., Dilbaz, B., Guven, S., Sahin Ozdemir, D., Haberal, A., Serum biochemistry correlates with the size of tubal ectopic pregnancy on sonography, Ultrasound in Obstetrics & Gynecology, 28, 826-30, 2006	Not diagnostic accuracy - correlation between serum biomarkers and US
Hajenius, P. J., Mol, B. W., Ankum, W. M., van der Veen, F., Bossuyt, P. M., Lammes, F. B., Suspected ectopic pregnancy: expectant management in patients with negative sonographic findings and low serum hCG concentrations, Early Pregnancy, 1, 258-62, 1995	Diagnostic accuracy using US for ectopic pregnancy, but no diagnostic detail on characteristics - frequency reported of each
Harvey, S., Gillespie, M., McMurray, C., Robb, H., Mackay, V., A retrospective case note analysis of the diagnostic effectiveness of a single transvaginal scan in detecting ectopic pregnancy, BJOG: An International Journal of Obstetrics and Gynaecology, 123, 235, 2016	Full text is an abstract
Hertzberg,B.S., Kliewer,M.A., Paulson,E.K., Ovarian cyst rupture causing hemoperitoneum: imaging features and the potential for misdiagnosis, Abdominal Imaging, 24, 304-308, 1999	Data not available to calculate diagnostic accuracy
Hinney,B., Bertagnoli,C., Tobler-Sommer,M., Osmers,R., Wuttke,W., Kuhn,W., Diagnosis of early ectopic pregnancy by measurement of the maternal serum to cul-de-sac fluid beta-hCG ratio, Ultrasound in Obstetrics and Gynecology, 5, 260-266, 1995	Diagnostic accuracy using ratio of maternal serum (hCG) to cul-de-sac fluid (taken via US-guided puncture system)
Hoffmann, Beatrice, Nurnberg, Dieter, Westergaard, Mary C., Focus on abnormal air: diagnostic ultrasonography for the acute abdomen, European journal of emergency medicine : official journal of the European Society for Emergency Medicine, 19, 284-91, 2012	Narrative review
Hourani, Roula, Hachem, Kamal, Haddad-Zebouni, Soha, Mansour, Fersan, Elhage, Abdo, Checrallah, Antoine, Ghossain, Michel A., The multiple ultrasound patterns of ectopic pregnancy, Le Journal medical libanais. The Lebanese medical journal, 56, 27-34, 2008	Narrative overview
Hsu,C.Y., Jeng,C.J., Lin,S.Y., Wang,Y.L., Wu,J.J., Wang,K.G., Impact of ultrasonography on the management of tubal pregnancy: Current status, Journal of Medical Ultrasound, 4, 33-38, 1996	Incidence of characteristics - no diagnostic accuracy data

Study	Reason for Exclusion
Huang, K. S., Tsai, Y. S., Jan, Y. T., Yang, F. S., Retrospective image observation of ectopic pregnancy on computed tomography in the emergency condition: How useful is adnexal ring sign?, Chinese Journal of Radiology (Taiwan), 41, 7-12, 2016	Use of CT not US
Hung,F.Y., Jeng,C.J., Hsieh,F.J., Yang,Y.C., Su,T.H., Wang,K.G., Transvaginal sonographic features of cervical pregnancy, Journal of Medical Ultrasound, 5, 95-100, 1997	Not diagnostic accuracy for ectopic pregnancy. Cohort diagnosed and treated for cervical ectopic pregnancy (not tubal ectopic pregnancy) using US
Ignacio, Elizabeth A., Hill, Michael C., Ultrasound of the acute female pelvis, Ultrasound Quarterly, 19, 86-10, 2003	Narrative review
Jakiel,G., Wieczorek,P., Bokiniec,M., Bakalczuk,S., Ectopic pregnancy diagnosis in very high risk patients, Ginekologia Polska, 69, 575-579, 1998	Diagnostic accuracy using US for ectopic pregnancy, but no diagnostic detail on characteristics - frequency reported of some
Jilian, S., Jiale, Q., Junmei, W., Jiamin, L., Haili, L., Application value of transvaginal ultrasound combined with abdominal ultrasonography in the diagnosis of ectopic pregnancy, Biomedical Research (India), 28, 9358-9361, 2017	Cohort already had confirmed ectopic pregnancy. Diagnostic accuracy using US for ectopic pregnancy, but no diagnostic detail on US features - frequency reported of each
Kahyaoglu, Serkan, Turgay, Inci, Gocmen, Muhammed, Sut, Necdet, Batioglu, Sertac, A new predictive scoring system including shock index for unruptured tubal pregnancy patients, European journal of obstetrics, gynecology, and reproductive biology, 126, 99-103, 2006	Predicting whether a treatment would work. Diagnostic accuracy using Shock Index (ratio of HR to SBP) instead of US
Kaplan, B. C., Dart, R. G., Moskos, M., Kuligowska, E., Chun, B., Hamid, M. A., Northern, K., Schmidt, J., Kharwadkar, A., Ectopic pregnancy: Prospective study with improved diagnostic accuracy, Annals of Emergency Medicine, 28, 10-17, 1996	Diagnostic accuracy using US for ectopic pregnancy, but no usable diagnostic detail on US features (data cannot be separated for individual features as per protocol)
Karakus, S., Yildiz, C., Akkar, O., Sancakdar, E., Ulger, D., Cetin, A., The significance of the neutrophil-to-lymphocyte ratio in differantial diagnosis of ectopic pregnancy and miscarriage, International Journal of Clinical and Experimental Medicine, 9, 11327-11333, 2016	Diagnostic accuracy based on biomarkers and biochemistry only
Kemp, B., Funk, A., Rath, W., Doppler sonographic criteria for viability in ectopic pregnancy in correlation with histology, International Journal of Gynaecology & Obstetrics, 54, 179-81, 1996	Brief/short communication
Kirk, E., Bottomley, C., Bourne, T., Diagnosing ectopic pregnancy and current concepts in the management of pregnancy of unknown location, Human Reproduction Update, 20, 250-61, 2014	Narrative overview
Kirk, Emma, Bourne, Tom, Diagnosis of ectopic pregnancy with ultrasound, Best practice &	Narrative overview

Study	Reason for Exclusion
research. Clinical obstetrics & gynaecology, 23, 501-8, 2009	
Kirk, Emma, Daemen, Anneleen, Papageorghiou, Aris T., Bottomley, Cecilia, Condous, George, De Moor, Bart, Timmerman, Dirk, Bourne, Tom, Why are some ectopic pregnancies characterized as pregnancies of unknown location at the initial transvaginal ultrasound examination?, Acta Obstetricia et Gynecologica Scandinavica, 87, 1150-4, 2008	Not diagnostic accuracy - comparison of characteristics of women with PUL or ectopic pregnancy
Kirk, Emma, Papageorghiou, Aris T., Condous, George, Tan, Linda, Bora, Shabana, Bourne, Tom, The diagnostic effectiveness of an initial transvaginal scan in detecting ectopic pregnancy, Human reproduction (Oxford, England), 22, 2824-8, 2007	Overall ectopic pregnancy data show discrepancies between text and table - cannot extract accurate data. Cannot separate tubal and non-tubal ectopic pregnancies
Laing, F. C., Brown, D. L., Price, J. F., Teeger, S., Wong, M. L., Intradecidual sign: is it effective in diagnosis of an early intrauterine pregnancy?, Radiology, 204, 655-60, 1997	Focus on sensitivity and specificity of different classes of sonographer: fellow, resident, student, attending sonographer
Lavie,O., Boldes,R., Neuman,M., Rabinovitz,R., Algur,N., Beller,U., Ultrasonographic "endometrial three-layer" pattern: a unique finding in ectopic pregnancy, Journal of Clinical Ultrasound, 24, 179-183, 1996	Diagnostic accuracy using endometrial three-layer pattern
Leiserowitz, Gary S., Xing, Guibo, Cress, Rosemary, Brahmbhatt, Bhoomi, Dalrymple, John L., Smith, Lloyd H., Adnexal masses in pregnancy: how often are they malignant?, Gynecologic oncology, 101, 315-21, 2006	Incidence of malignant masses during pregnancy - not diagnostic for ectopic pregnancy
Li, X. H., Ouyang, Y., Lu, G. X., Value of transvaginal sonography in diagnosing heterotopic pregnancy after in-vitro fertilization with embryo transfer, Ultrasound in Obstetrics & Gynecology, 41, 563-9, 2013	Diagnostic accuracy using US for heterotopic pregnancy (incorrect reference standard)
Lin, Edward P., Bhatt, Shweta, Dogra, Vikram S., Diagnostic clues to ectopic pregnancy, Radiographics : a review publication of the Radiological Society of North America, Inc, 28, 1661-71, 2008	Not diagnostic accuracy - narrative overview and teaching points
Lipscomb, Gary H., Gomez, Isabel G., Givens, Vanessa M., Meyer, Norman L., Bran, Derita F., Yolk sac on transvaginal ultrasound as a prognostic indicator in the treatment of ectopic pregnancy with single-dose methotrexate, American Journal of Obstetrics and Gynecology, 200, 338.e1-4, 2009	Risk factors for treatment success/failure - not diagnostic accuracy
Loubeyre, Pierre, Patel, Seema, Copercini, Michele, Petignat, Patrick, Dallenbach, Patrick, Dubuisson, Jean Bernard, Role of sonography in the diagnostic workup of ovarian and adnexal masses except in pregnancy and during ovarian	Diagnostic overview for ovarian and adnexal masses not in pregnancy

Study	Reason for Exclusion
stimulation, Journal of clinical ultrasound : JCU, 40, 424-32, 2012	
Louis-Sylvestre,C., Morice,P., Chapron,C., Dubuisson,J.B., The role of laparoscopy in the diagnosis and management of heterotopic pregnancies, Human Reproduction, 12, 1100-1102, 1997	Heterotopic pregnancy case reports (not diagnostic accuracy)
Majeed, H., Bor, P., The diagnostic value of the presence of pelvic fluid in the cul-de-sac in women with pregnancy of unknown location, Acta Obstetricia et Gynecologica Scandinavica, 91, 110, 2012	Full text is an abstract
Malik, S. A., Malik, S., Maqbool, A., Comparison of transabdominal and transvaginal sonography in the diagnosis of ectopic pregnancy, Pakistan Journal of Medical and Health Sciences, 4, 22-27, 2010	Diagnostic accuracy using US for ectopic pregnancy, but no diagnostic detail on characteristics - frequency reported of some
Mateer,J.R., Valley,V.T., Aiman,E.J., Phelan,M.B., Thoma,M.E., Kefer,M.P., Outcome analysis of a protocol including bedside endovaginal sonography in patients at risk for ectopic pregnancy, Annals of Emergency Medicine, 27, 283-289, 1996	Not diagnostic accuracy for ectopic pregnancy - incidence of ruptured ectopic pregnancy when using bedside US in ED
Mathlouthi, N., Slimani, O., Fatnassi, A., Ben Temime, R., Makhlouf, T., Attia, L., Chachia, A., Ultrasound diagnosis of ectopic pregnancy: Prospective study about 200 cases, Tunisie Medicale, 91, 254-257, 2013	Full text in French
McCord,M.L., Muram,D., Buster,J.E., Arheart,K.L., Stovall,T.G., Carson,S.A., Single serum progesterone as a screen for ectopic pregnancy: Exchanging specificity and sensitivity to obtain optimal test performance, Fertility and Sterility, 66, 513-516, 1996	Diagnostic accuracy of serum progesterone
McRae,A., Edmonds,M., Murray,H., Diagnostic accuracy and clinical utility of emergency department targeted ultrasonography in the evaluation of first-trimester pelvic pain and bleeding: A systematic review, Canadian Journal of Emergency Medicine, 11, 355-364, 2009	SR with no MA (narrative review). Diagnostic accuracy for IUP, not ectopic pregnancy. Included studies checked for relevance
Miller, V. I., Coughlin, B. F., Pregnancy and abdominal pain: Value of ultrasound in diagnosis, Emergency Radiology, 3, 118-125, 1996	Ectopic pregnancy not listed as gynaecological pathology with diagnostic data
Mol, B. W., Hajenius, P. J., Ankum, W. M., Bossuyt, P. M., van der Veen, F., Screening for ectopic pregnancy in symptom-free women at increased risk, Obstetrics & Gynecology, 89, 704-7, 1997	Distribution of ectopic pregnancy per risk factor (not characteristic seen on US)

Study	Reason for Exclusion
Mol, B. W., Hajenius, P. J., Engelsbel, S., Ankum, W. M., van der Veen, F., Hemrika, D. J., Bossuyt, P. M., Are gestational age and endometrial thickness alternatives for serum human chorionic gonadotropin as criteria for the diagnosis of ectopic pregnancy?, Fertility & Sterility, 72, 643-5, 1999	Diagnostic accuracy of gestational age and endometrial stripe thickness compared to serum hCG
Moon, Min Hoan, Lee, Young Ho, Lim, Kyung Taek, Yang, Jae Hyug, Park, Seong Ho, Outcome prediction for treatment of tubal pregnancy using an intramuscular methotrexate protocol, Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine, 27, 1461-7, 2008	Not diagnostic accuracy - presence of different characteristics to predict whether a certain treatment would be successful
Nahar, M. N., Quddus, M. A., Sattar, A., Shirin, M., Khatun, A., Ahmed, R., Sultana, F., Comparison of transvaginal and transabdominal ultrasonography in the diagnosis of ectopic pregnancy, Bangladesh Medical Research Council Bulletin, 39, 104-8, 2013	Diagnostic accuracy using US for ectopic pregnancy, but no diagnostic detail on US features - only overall accuracy presented for US ability to identify ectopic pregnancy
Naseem, Iram, Bari, Vaqar, Nadeem, Naila, Multiple parameters in the diagnosis of ectopic pregnancy, JPMA. The Journal of the Pakistan Medical Association, 55, 74-6, 2005	Diagnostic accuracy using US for ectopic pregnancy (TAS followed by TVS), but no diagnostic detail on US features - frequency reported for some. Unable to extract relevant data for diagnostic on US features
Panelli, Danielle M., Phillips, Catherine H., Brady, Paula C., Incidence, diagnosis and management of tubal and nontubal ectopic pregnancies: a review, Fertility research and practice, 1, 15, 2015	Narrative overview
Pereira,P.P., Cabar,F.R., Schultz,R., Zugaib,M., Association between ultrasound findings and extent of trophoblastic invasion into the tubal wall in ampullary pregnancy, Ultrasound in Obstetrics and Gynecology, 33, 472-476, 2009	Cohort already diagnosed with ectopic pregnancy (not diagnostic accuracy). Study examines depth of trophoblastic infiltration into wall
Perriera, Lisa, Reeves, Matthew F., Ultrasound criteria for diagnosis of early pregnancy failure and ectopic pregnancy, Seminars in reproductive medicine, 26, 373-82, 2008	Narrative overview
Platek,D.N., Henderson,C.E., Goldberg,G.L., The management of a persistent adnexal mass in pregnancy, American Journal of Obstetrics and Gynecology, 173, 1236-1240, 1995	Not ectopic pregnancy - relates to treatment pathway for adnexal mass during pregnancy
Polena, V., Huchon, C., Ramos, C. V., Rouzier, R., Dumont, A., Fauconnier, A., Non-invasive tools for the diagnosis of potentially life-threatening gynaecological emergencies: A Systematic Review, PLoS ONE, 10, e0114189, 2015	Diagnostic accuracy using Tranabdominal US for: haemoperitoneum; TVS for: Pelvic inflammatory disease, haemoperitoneum, complicated ectopic (one paper - Sadek 1995 using echogenic fluid - included elsewhere)
Popowski, Thomas, Huchon, Cyrille, Toret-Labeeuw, Flavy, Chantry, Anne A., Aegerter, Philippe, Fauconnier, Arnaud, Hemoperitoneum	Cohort of ectopic pregnancies without haemodynamic shock only (confirmed

Study	Reason for Exclusion
assessment in ectopic pregnancy, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 116, 97-100, 2012	surgically). Characteristics used to predict volume of haemoperitoneum before surgery
Ramanan,R.V., Gajaraj,J., Ectopic pregnancy--the leash sign. A new sign on transvaginal Doppler ultrasound, Acta Radiologica, 47, 529-535, 2006	Feature described not in the protocol
Rempen,A., The shape of the endometrium evaluated with three-dimensional ultrasound: an additional predictor of extrauterine pregnancy, Human Reproduction, 13, 450-454, 1998	US Diagnosis of IUP/ ectopic pregnancy /SA using shape of the endometrium, endometrial thickness, endometrial echoes
Richardson, A., Gallos, I., Dobson, S., Campbell, B. K., Coomarasamy, A., Raine-Fenning, N., Accuracy of first-trimester ultrasound in diagnosis of tubal ectopic pregnancy in the absence of an obvious extrauterine embryo: systematic review and meta-analysis, Ultrasound in Obstetrics & Gynecology, 47, 28-37, 2016	SR includes multiple pre-1995 (does not adhere to protocol). Unable to use MA/pooled/summary statistics. Included studies (1995 onwards) checked for relevance
Richardson, A., Gallos, I., Dobson, S., Campbell, B. K., Coomarasamy, A., Raine-Fenning, N., Accuracy of first-trimester ultrasound in diagnosis of intrauterine pregnancy prior to visualization of the yolk sac: a systematic review and meta-analysis, Ultrasound in Obstetrics & Gynecology, 46, 142-9, 2015	Diagnostic accuracy of IUP (not ectopic pregnancy)
Richardson, A., Hopkisson, J., Campbell, B., Raine-Fenning, N., Use of double decidual sac sign to confirm intrauterine pregnancy location prior to sonographic visualization of embryonic contents, Ultrasound in Obstetrics & Gynecology, 49, 643-648, 2017	Diagnostic accuracy for IUP (not ectopic pregnancy)
Rogers, R. G., Kammerer-Doak, D., Miller, M., Byrn, F., Conway, S., Hall, R., A comparison of ultrasound and surgical findings in suspected ectopic pregnancy, Journal of Diagnostic Medical Sonography, 16, 60-64, 2000	Cohort already had surgically confirmed and treated ectopic pregnancy (retrospective analysis of US features). Reporting on location of adnexal mass during surgery
Roghaei, Ma, Sabet, F, Mohamadi, K, Diagnostic accuracy of serum activin A in detection of ectopic pregnancy, Journal of research in medical sciences, 17, 378-381, 2012	Diagnostic accuracy of serum Activin A for ectopic pregnancy
Scaldarella, L. O., Carbone, L., Mazzarella, A., Ricciardi, D., Chiacchio, G., Valentino, A., Mancino, D., Ciccarelli, G. T., Tolino, A., Retrospective study on 43 patients with diagnosis of ectopic pregnancy, Giornale Italiano di Ostetricia e Ginecologia, 35, 419-426, 2013	Initial cohort already had ectopic pregnancy diagnosis. Study about identifying best treatment pathway for ectopic pregnancy
Segal,S., Mercado,R., Rivnay,B., Ectopic pregnancy early diagnosis markers, Minerva Ginecologica, 62, 49-62, 2010	Narrative overview

Study	Reason for Exclusion
Seo, Mi Rang, Choi, Joong Sub, Bae, Jaeman, Lee, Won Moo, Eom, Jeong Min, Lee, Eunhyun, Keum, Jihyun, Preoperative diagnostic clues to ovarian pregnancy: retrospective chart review of women with ovarian and tubal pregnancy, Obstetrics & gynecology science, 60, 462-468, 2017	Not diagnostic accuracy. Study examines characteristics in Ovarian pregnancy and Tubal pregnancy.
Shah, Anish A., Grotegut, Chad A., Likes, Creighton E., 3rd, Miller, Michael J., Walmer, David K., Heterotopic cervical pregnancy treated with transvaginal ultrasound-guided aspiration resulting in cervical site varices within the myometrium, Fertility and Sterility, 91, 934.e19-22, 2009	Case report of heterotopic cervical pregnancy
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, Fertility and Sterility, 69, 62-65, 1998	Diagnostic accuracy using US for ectopic pregnancy, but no diagnostic detail on characteristics - frequency reported of some
Shetty, Vishma H., Gowda, Some, Muralidhar, Lakshmidevi, Role of ultrasonography in diagnosis of ectopic pregnancy with clinical analysis and management in tertiary care hospital, Journal of obstetrics and gynaecology of India, 64, 354-7, 2014	Diagnostic accuracy using US for ectopic pregnancy, but no diagnostic detail on characteristics - frequency reported of some
Stein, J. C., Wang, R., Adler, N., Goldstein, R., McAlpine, I., Won, G., Jacoby, V., Kohn, M., Evaluation of ectopic pregnancy with bedside ultrasound by emergency physicians: A meta-analysis, Annals of Emergency Medicine, 54, S69, 2009	Full text is an abstract
Stein, John C., Wang, Ralph, Adler, Naomi, Boscardin, John, Jacoby, Vanessa L., Won, Gloria, Goldstein, Ruth, Kohn, Michael A., Emergency physician ultrasonography for evaluating patients at risk for ectopic pregnancy: a meta-analysis, Annals of Emergency Medicine, 56, 674-83, 2010	SR with MA includes pre-1995 studies, cannot use pooled result. Only uses overall ectopic pregnancy diagnostic accuracy/summary statistic, not accuracy of individual features. Included studies checked for relevance
Stein, Marjorie W., Ricci, Zina J., Novak, Leon, Roberts, Jeffrey H., Koenigsberg, Mordecai, Sonographic comparison of the tubal ring of ectopic pregnancy with the corpus luteum, Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine, 23, 57-62, 2004	Not diagnostic accuracy. Comparison of characteristics in ectopic pregnancy and corpus luteum (echogenicity, presence of free fluid, endometrial wall thickness)
Teixeira, Joao L. G., Rabaioli, Paola, Savaris, Ricardo F., Sensitivity and specificity of a urinary screening test used in an emergency setting to detect abnormal first trimester pregnancies, American Journal of Obstetrics and Gynecology, 212, 58.e1-5, 2015	US used as reference standard to assess diagnostic accuracy of urinary screening test in ED

Study	Reason for Exclusion
Timor-Tritsch, Ilan E., Monteagudo, Ana, Cali, Giuseppe, El Refaey, Hazem, Kaelin Agten, Andrea, Arslan, Alan A., Easy sonographic differential diagnosis between intrauterine pregnancy and cesarean delivery scar pregnancy in the early first trimester, American Journal of Obstetrics and Gynecology, 215, 225.e1-7, 2016	US to differentiate between Caesarean scar pregnancy and IUP
Tong, Stephen, Skubisz, Monika M., Horne, Andrew W., Molecular diagnostics and therapeutics for ectopic pregnancy, Molecular Human Reproduction, 21, 126-35, 2015	Narrative overview of biomarkers for diagnosis of ectopic pregnancy
Turan, C., Ugur, M., Dogan, M., Ekici, E., Vicdan, K., Gokmen, O., Transvaginal sonographic findings of chronic ectopic pregnancy, European Journal of Obstetrics, Gynecology, & Reproductive Biology, 67, 115-9, 1996	Cohort confirmed as having chronic ectopic pregnancy. Description of characteristics related to chronic ectopic pregnancy
Turkmen, G. G., Karcaaltincaba, D., Isik, H., Fidanci, V., Kaayalp, D., Timur, H., Batioglu, S., Does adenosine deaminase activity play a role in the early diagnosis of ectopic pregnancy?, Journal of Obstetrics & Gynaecology, 36, 347-50, 2016	Diagnostic accuracy of enzyme adenosine deaminase for ectopic pregnancy
Van Mello, N. M., Mol, F., Ankum, W. M., Van Der Veen, F., Barnhart, K., Mol, B. W., Hajenius, P. J., Predictive value of serum hCG on the outcome of pregnancy of unknown location: A systematic review and meta-analysis, Journal of Reproductive Immunology, 90, 181, 2011	Full text is an abstract
Verhaegen, J., Gallos, I. D., Van Mello, N. M., Abdel-Aziz, M., Takwoingi, Y., Harb, H., Deeks, J. J., Mol, B. W. J., Coomarasamy, A., Accuracy of a single progesterone test to predict early pregnancy outcome in women with pain or bleeding: A meta-analysis of cohort studies, BJOG: An International Journal of Obstetrics and Gynaecology, 1), 550-551, 2013	Full text is an abstract
Wachsberg, R. H., Karimi, S., Sonographic endometrial three-layer pattern in symptomatic first-trimester pregnancy: not diagnostic of ectopic pregnancy, Journal of Clinical Ultrasound, 26, 199-201, 1998	Diagnostic accuracy of endometrial three layer pattern for ectopic pregnancy
Wachsberg,R.H., Karimi,S., Chorionic rim sign on transvaginal sonography: Unrealiable of intrauterine pregnancy, Journal of Women's Imaging, 3, 60-62, 2001	Not diagnostic accuracy. Retrospective (unblinded) review of confirmed ectopic pregnancy cohort only
Wherry,K.L., Dubinsky,T.J., Waitches,G.M., Richardson,M.L., Reed,S., Low-resistance endometrial arterial flow in the exclusion of ectopic pregnancy revisited, Journal of Ultrasound in Medicine, 20, 335-342, 2001	Diagnostic accuracy using endometrial blood flow

Study	Reason for Exclusion
Willrich, M. A. V., Baumann, N. A., Tolan, N. V., Klee, G. G., Brown, D., Coddington, C. C., Evaluation of a discriminatory zone for serum Beta-human chorionic gonadotropin (betahCG) in early pregnancy, Clinical Chemistry, 60, S208-S209, 2014	Full text is an abstract
Wong,T.W., Lau,C.C., Yeung,A., Lo,L., Tai,C.M., Efficacy of transabdominal ultrasound examination in the diagnosis of early pregnancy complications in an emergency department, Journal of Accident and Emergency Medicine, 15, 155-158, 1998	Cannot extract diagnostic accuracy data for specific features seen on US - combination of features
Yadav, Poonam, Singla, Anshuja, Sidana, Anu, Suneja, Amita, Vaid, Neelam B., Evaluation of sonographic endometrial patterns and endometrial thickness as predictors of ectopic pregnancy, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 136, 70-75, 2017	Diagnostic accuracy using endometrial pattern. n=2/100 for pseudogestational sac.
Yakasai, I. A., Bappa, L. A., Diagnosis and management of adnexal masses in pregnancy, Journal of Surgical Technique and Case Report, 4, 79-85, 2012	Management techniques after diagnosis of an adnexal mass. Narrative overview
Young, Lee, Barnard, Cecilia, Lewis, Elisabeth, Jones, Matthew, Furlan, Jana, Karatasiou, Angela, Necas, Martin, The diagnostic performance of ultrasound in the detection of ectopic pregnancy, The New Zealand medical journal, 130, 17-22, 2017	Diagnostic accuracy using US for ectopic pregnancy, but no mention of characteristics seen on US
Yuri, M., Buzzi, J., Young, E., Diradourian, M., Isa, L., Garcia, B., Kenny, A., Our experience in ovarian ectopic pregnancy: Ultrasound, clinical and therapeutical correlation, Human Reproduction, 30, 2015	Full text is an abstract
Yuri, M., Marconi, G., Diradourian, M., Vilela, M., Kenny, A., Young, E., Buzzi, J., Early diagnosis in ovarian pregnancy. Ultrasound, clinical and therapeutical correlation, International Journal of Gynecology and Obstetrics, 119, S524, 2012	Full text is an abstract
Zaki,Z.M.S., Bahar,A.M., Ectopic pregnancy. Diagnosis using transabdominal ultrasound and a qualitative serum hCG test. Five years' experience in the Middle East, Journal of Obstetrics and Gynaecology, 15, 157-160, 1995	Diagnostic accuracy using US for ectopic pregnancy, but no diagnostic detail on characteristics - frequency reported of some

Economic studies

No economic evidence was identified for this review question.

Appendix L:Research recommendations

No research recommendations were made for this review question.