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Accuracy of first-trimester ultrasound in diagnosis of tubal ectopic pregnancy in the absence of an obvious extrauterine embryo: systematic review and meta-analysis

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KEYWORDS: diagnostic accuracy; ectopic; pregnancy; systematic review; ultrasound

ABSTRACT

Objectives *To determine the accuracy of ultrasound in the diagnosis of a tubal ectopic pregnancy in the absence of an obvious extrauterine embryo.*

Methods *This was a systematic review conducted in accordance with the PRISMA statement and registered with PROSPERO. We searched MEDLINE, EMBASE and The Cochrane Library for relevant citations from database inception to July 2014. Studies were selected in a two-stage process and their data extracted by two reviewers. Accuracy measures were calculated for each ultrasound sign, i.e. empty uterus, pseudosac, adnexal mass and free fluid in the pouch of Douglas, alone and in various combinations. Individual study estimates were plotted in summary receiver–operating characteristics curves and forest plots for examination of heterogeneity. The quality of included studies was assessed.*

Results *Thirty-one studies including 5858 women were selected from 19 959 citations. Following meta-analysis, an empty uterus on ultrasound was found to predict an ectopic pregnancy with a sensitivity of 81.1% (95% CI, 42.1–96.2%) and specificity of 79.5% (95% CI, 68.9–87.1%). The corresponding performance of the pseudosac, adnexal mass and free fluid were: 5.5% (95% CI, 3.3–9.0%) and 94.2% (95% CI, 75.9–98.8%); 63.5% (95% CI, 48.5–76.3%) and 91.4% (95% CI, 83.6–95.7%); and 47.2% (95% CI, 33.2–61.7%) and 92.3% (95% CI, 85.6–96.0%), respectively.*

Conclusion *Visualization of an empty uterus, adnexal mass, free fluid or a pseudosac has poor sensitivity for the diagnosis of a tubal pregnancy when an obvious extrauterine embryo is absent, but it has good specificity. We can therefore infer that ultrasound is more useful for 'ruling in' a tubal pregnancy than 'ruling out' one. However, the findings were limited by the poor quality of some included studies and heterogeneity in the index test and reference standard. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The incidence of ectopic pregnancy has risen over the last few decades. Fortunately, both maternal morbidity and mortality associated with the condition have declined during this period, largely owing to greater awareness and earlier diagnosis. Despite this, ectopic pregnancy still accounts for 3.4% of maternal mortality in the UK[1]. Early diagnosis of ectopic pregnancy is essential for reducing maternal mortality. Although diagnostic laparoscopy is considered the gold standard, it has a false-positive rate of 5% and a false-negative rate of 3–4%[2]. The advent of high-resolution transvaginal ultrasound (TVS) has revolutionized the diagnosis of ectopic pregnancy.

Unfortunately the ultrasonographic signs of ectopic pregnancy vary greatly. Diagnosis should be based on the positive visualization of an extrauterine mass rather than the inability to recognize an intrauterine pregnancy[3]. A living embryo located outside the uterus is the only pathognomonic sign of an ectopic pregnancy, but is only reported in 8–26% of ectopic pregnancies detected on TVS[2]. In the absence of an obvious ectopic pregnancy, several different ultrasonographic signs have been proposed for the detection of an ectopic pregnancy, with variable sensitivities and specificities; these include an empty uterus (i.e. one that does not contain a gestational sac, pseudosac or retained products of conception), a pseudosac, free fluid and an adnexal mass[3]. An adnexal mass separate from the ovary is non-discriminatory, with some studies reporting

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that they are seen in 89–100% of ectopic pregnancies[4,5], while others have shown that they are not evident in 15–35% of patients who are subsequently found to have an ectopic pregnancy[6]. Free fluid may be present but is also a non-specific finding, as it may be demonstrated ultrasonographically in up to 63% of ectopic pregnancies but also in 25–31% of intrauterine pregnancies[2]. A pseudosac represents a thickened decidual reaction surrounding an intrauterine collection of fluid. They occur in up to 15% of ectopic pregnancies and are a common cause of diagnostic confusion[7]. An empty uterus is another non-specific finding that occurs not only in an ectopic pregnancy but also in a very early intrauterine pregnancy, following a complete miscarriage and in non-pregnant women.

We performed a systematic review and meta-analysis of the literature to determine the accuracy of commonly described first-trimester ultrasonographic signs in the diagnosis of tubal ectopic pregnancy in the absence of a living embryo located outside the uterus, in women with or without symptoms of abdominal pain and/or vaginal bleeding in early pregnancy.

METHODS

Protocol and registration

Search methods, criteria for inclusion and outcomes were specified in advance and documented in the protocol, which was registered with PROSPERO (http://www.crd.york.ac.uk/PROSPERO) on 13 December 2012. The registration number was CRD42012003410. The systematic review was carried out in accordance with the PRISMA checklist[8].

Information sources

The following databases were searched electronically for relevant citations: MEDLINE (1951 to March 2013), EMBASE (1980 to March 2013) and The Cochrane Library (2013). We used a combination of Medical Subject Headings and text words to generate two subsets of citations, one indexing ultrasound ('ultraso*' OR 'sonograph*') and the other indexing terms related to early pregnancy location or viability ('ectopic pregnancy' OR 'tubal pregnancy' OR 'viab* pregnancy' OR 'failing pregnancy' OR 'miscarr*' OR 'abort*' OR 'intrauterine pregnancy') or ultrasonographic signs of either an intrauterine pregnancy ('gestation* sac' OR 'yolk sac' OR 'f*etal pole' OR 'intradecidual sign' OR 'double decidual sac sign' OR 'double decidual sac' OR 'double decidual sign' OR 'chorionic rim sign' OR 'chorionic rim') or an ectopic pregnancy ('empty uterus' OR 'pseudosac' OR 'free fluid' OR 'cul de sac fluid' OR 'adnexal mass' OR 'tubal ring' OR 'donut sign' OR 'doughnut sign'). These two subsets were then combined with 'AND' to generate a subset of citations relevant to the two research questions. Duplicates were removed during the process of assessing the full-text articles for eligibility. The search was last run on 3 July 2014. Further relevant papers were searched by examination of the reference lists of all included studies, reviews and other papers identified previously, and a comprehensive database of relevant articles was constructed.

Study selection

Primary studies that reported original data regarding the ultrasonographic diagnosis of an ectopic pregnancy were included. Case reports and case studies in which the sample size was fewer than 10 cases were excluded owing to the high risk of bias. Commentaries, narrative reviews and letters were also excluded. There were no limitations on publication date, language or publication status.

Studies were selected in a two-stage process. First, two reviewers (A.R. and S.D.) examined independently the titles and abstracts of all citations produced by the electronic searches. The full manuscripts of citations that met the predefined selection criteria were subsequently obtained. Second, examination of the full manuscripts led to a final decision regarding inclusion or exclusion. In case of duplicates, the most recent and complete version was selected. Any disagreements concerning selection were resolved by consensus or arbitration by a third reviewer (N.R.F.).

Data collection

Two review authors (A.R. and S.D.) extracted independently the data from included studies using a data extraction form designed and pilot-tested by the authors. One author (A.R.) checked independently the extracted data. If there were data queries, the corresponding author of the study was contacted. Disagreements were resolved by consensus. The names of article authors and titles of the included studies were juxtaposed to identify duplicate publications; in case of duplicates, both articles were considered as a single study.

Data items

The following data were extracted from included studies using a standardized data extraction form, designed and pilot-tested by the authors: study characteristics (first author, year of publication, population, age group, inclusion and exclusion criteria); study methodology (study design, study period, recruitment method); details of the intervention (ultrasound approach i.e. transabdominal or transvaginal, frequency/resolution of ultrasound machine, operator; ultrasonographic feature under evaluation, i.e. pseudosac, empty uterus, free fluid, adnexal mass); outcome investigated; and quality and accuracy of the results. Accuracy data were used to construct 2×2 tables of ultrasound findings and pregnancy location.

Risk of bias in individual studies

The QUADAS-2 methodology checklist was used to assess the quality of the studies[9]. This checklist is designed to assess the quality of primary diagnostic accuracy studies, and consists of four principal domains covering patient selection, index test, reference standard and flow of

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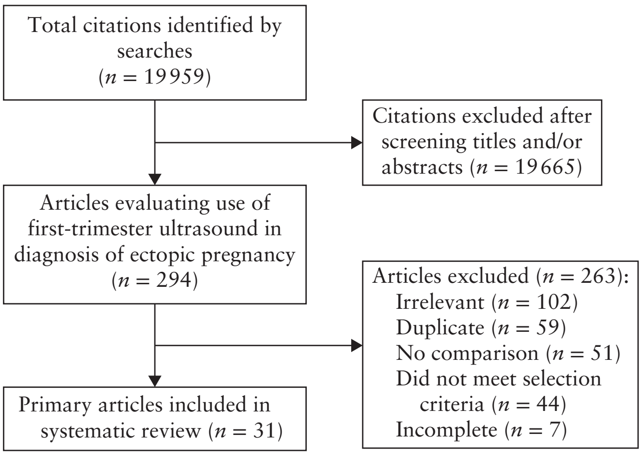

Figure 1 Flowchart summarizing selection of studies on first-trimester ultrasound signs in diagnosis of ectopic pregnancy, in absence of live extrauterine embryo.

patients through the study and timing of the index test and reference standard.

Summary measures

All results were entered into Review Manager 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2011) for producing summary tables. Accuracy measures of the various ultrasonographic signs were calculated, including sensitivity, specificity and likelihood ratios. When there were more than three studies reporting on the ultrasonographic sign, a meta-analysis was performed. Individual study estimates of sensitivities and specificities were plotted in summary receiver–operating characteristics (ROC) space and forest plots for visual examination of heterogeneity. We used the statistical package STATA version 12 (College Station, TX, USA) to meta-analyze the sensitivity and specificity of each included study using the hierarchical summary ROC (HSROC) approach[10,11]. This approach estimates the position and shape of the summary ROC curve and takes into account both within- and between-study variations. The summary ROC curve includes the pairs of sensitivity and specificity for individual studies showing the differences in precision between them, and the overall sensitivity and specificity for the test when all studies are pooled together. When the parameters of the HSROC model could not be estimated owing to a limited number of studies, it was simplified by assuming a symmetrical shape for the summary ROC curve. When only one study was available, we calculated the sensitivities, specificities, 95% CIs, likelihood ratios and pretest with post-test probabilities for that study. Post-test probabilities were calculated using the summary likelihood ratios and the median prevalence values, with their ranges as the pretest probabilities.

Risk of bias across studies

The potential impacts of publication and reporting bias were minimized by performing a comprehensive search for eligible studies and by looking for duplication of data.

RESULTS

Study selection

The search identified 19 959 potential papers. Following review of the titles and abstracts, 294 full-text papers were selected for further examination and subsequently 263 of these studies were excluded (Figure 1). Thirty-one studies[12–42], including 5858 women, met the inclusion criteria and were incorporated into the systematic review. The characteristics of the included studies are shown in Table S1.

Diagnostic accuracy of empty uterus for predicting tubal pregnancy

Thirteen cohort studies[12,16–18,20,22,23,26,33,36,37,39,40], including 2499 women in early pregnancy, evaluated the diagnostic accuracy of an empty uterus on ultrasound to predict the likelihood of an ectopic pregnancy; Figure 2 shows its sensitivity and specificity in the individual studies. The precision estimates for each of the studies and estimated sensitivity and specificity for differentiating between an ectopic and an intrauterine pregnancy are shown in Figure 3a and Table 1.

Diagnostic accuracy of pseudosac for predicting tubal pregnancy

Eight cohort studies[12,13,20,22,25,28,36,39], including 1838 women in early pregnancy, evaluated the diagnostic accuracy of a pseudosac on ultrasound to predict the likelihood of an ectopic pregnancy; Figure 2 shows its sensitivity and specificity in the individual studies. The estimated summary sensitivity and specificity for differentiating between an ectopic and an intrauterine pregnancy are shown in Figure 3b and Table 1.

Diagnostic accuracy of adnexal mass for predicting tubal pregnancy

Twenty-one cohort studies[12,14–17,19,23,24,26–30,32–37,41,42], including 2787 women in early pregnancy, evaluated the diagnostic accuracy of an adnexal mass for predicting the likelihood of an ectopic pregnancy; Figure 2 shows its sensitivity and specificity in the individual studies. The precision estimates for each of the studies and estimated sensitivity and specificity for differentiating between an ectopic and an intrauterine pregnancy are shown in Figure 3c and Table 1.

Diagnostic accuracy of free fluid for predicting tubal pregnancy

Nineteen cohort studies[12,14,19,21,23,24,26,28–34,36–38,41,42] including 3232 women in early pregnancy, evaluated the diagnostic accuracy of free fluid to predict the likelihood of an ectopic pregnancy; Figure 4 shows its sensitivity and specificity in the individual studies. The precision estimates for each of the studies and estimated sensitivity

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Study	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)	Sensitivity (95% CI)	Specificity (95% CI)
Empty uterus						
Achiron (1987)[12]	17	1	12	31	0.59 (0.39, 0.76)	0.97 (0.84, 1.00)
Cacciatore (1988)[18]	12	7	29	52	0.29 (0.16, 0.46)	0.88 (0.77, 0.95)
Cacciatore (1989)[16]	4	4	35	57	0.10 (0.03, 0.24)	0.93 (0.84, 0.98)
Cacciatore (1990)[17]	5	14	63	118	0.07 (0.02, 0.16)	0.89 (0.83, 0.94)
Dart (1998)[39]	25	69	7	127	0.78 (0.60, 0.91)	0.65 (0.58, 0.71)
Dart (2002)[22]	21	78	3	53	0.88 (0.68, 0.97)	0.40 (0.32, 0.49)
Dart (2002)[20]	36	223	10	366	0.78 (0.64, 0.89)	0.62 (0.58, 0.66)
Dashefsky (1988)[23]	18	9	0	26	1.00 (0.81, 1.00)	0.74 (0.57, 0.88)
Huter (1990)[26]	10	4	196	55	0.05 (0.02, 0.09)	0.93 (0.84, 0.98)
Nyberg (1988)[40]	42	43	6	120	0.88 (0.75, 0.95)	0.74 (0.66, 0.80)
Russell (1993)[33]	19	16	0	88	1.00 (0.82, 1.00)	0.85 (0.76, 0.91)
Tongsong (1992)[37]	65	24	0	78	1.00 (0.94, 1.00)	0.76 (0.67, 0.84)
Tongsong (1993)[36]	105	44	0	52	1.00 (0.97, 1.00)	0.54 (0.44, 0.64)
Pseudosac						
Achiron (1987)[12]	0	1	29	31	0.00 (0.00, 0.12)	0.97 (0.84, 1.00)
Ahmed (2004)[13]	3	14	50	10	0.06 (0.01, 0.16)	0.42 (0.22, 0.63)
Dart (2002)[22]	3	53	21	78	0.13 (0.03, 0.32)	0.60 (0.51, 0.68)
Dart (1998)[39]	4	26	28	170	0.13 (0.04, 0.29)	0.87 (0.81, 0.91)
Dart (2002)[20]	6	121	40	468	0.13 (0.05, 0.26)	0.79 (0.76, 0.83)
Hammoud (2005)[25]	8	2	249	141	0.03 (0.01, 0.06)	0.99 (0.95, 1.00)
Mahony (1985)[28]	2	0	33	46	0.06 (0.01, 0.19)	1.00 (0.92, 1.00)
Tongsong (1993)[36]	3	0	102	96	0.03 (0.01, 0.08)	1.00 (0.96, 1.00)
Adnexal mass						
Achiron (1987)[12]	1	2	28	30	0.03 (0.00, 0.18)	0.94 (0.79, 0.99)
Aleem (1990)[14]	17	16	3	22	0.85 (0.62, 0.97)	0.58 (0.41, 0.74)
Braffman (1994)[15]	30	16	35	188	0.46 (0.34, 0.59)	0.92 (0.88, 0.95)
Cacciatore (1989)[16]	27	1	12	60	0.69 (0.52, 0.83)	0.98 (0.91, 1.00)
Cacciatore (1990)[17]	63	1	5	131	0.93 (0.84, 0.98)	0.99 (0.96, 1.00)
Chambers (1990)[19]	32	13	21	66	0.60 (0.46, 0.74)	0.84 (0.74, 0.91)
Dashefsky (1988)[23]	12	2	6	7	0.67 (0.41, 0.87)	0.78 (0.40, 0.97)
Gabrielli (1992)[24]	41	8	1	17	0.98 (0.87, 1.00)	0.68 (0.46, 0.85)
Huter (1990)[26]	43	18	163	41	0.21 (0.16, 0.27)	0.69 (0.56, 0.81)
Kivikoski (1990)[27]	21	6	4	3	0.84 (0.64, 0.95)	0.33 (0.07, 0.70)
Mahony (1985)[28]	19	10	16	36	0.54 (0.37, 0.71)	0.78 (0.64, 0.89)
Mehta (1999)[29]	25	1	17	85	0.60 (0.43, 0.74)	0.99 (0.94, 1.00)
Nyberg (1988)[41]	19	0	7	58	0.73 (0.52, 0.88)	1.00 (0.94, 1.00)
Nyberg (1991)[30]	35	6	33	75	0.51 (0.39, 0.64)	0.93 (0.85, 0.97)
Romero (1988)[32]	38	21	35	126	0.52 (0.40, 0.64)	0.86 (0.79, 0.91)
Russell (1993)[33]	9	4	10	12	0.47 (0.24, 0.71)	0.75 (0.48, 0.93)
Sadek (1995)[34]	43	2	10	470	0.81 (0.68, 0.91)	1.00 (0.98, 1.00)
Shapiro (1988)[35]	20	1	2	2	0.91 (0.71, 0.99)	0.67 (0.09, 0.99)
Tongsong (1992)[37]	10	3	55	21	0.15 (0.08, 0.26)	0.88 (0.68, 0.97)
Tongsong (1993)[36]	90	7	15	89	0.86 (0.78, 0.92)	0.93 (0.86, 0.97)
Weckstein (1985)[42]	10	0	16	11	0.38 (0.20, 0.59)	1.00 (0.72, 1.00)

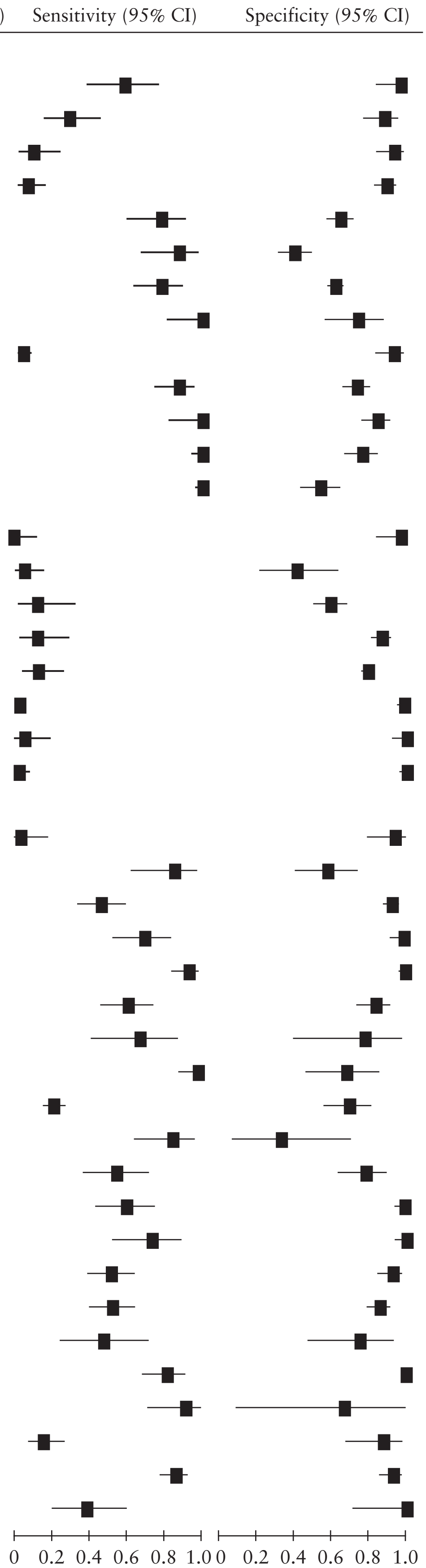

Figure 2 Forest plot of performance of an empty uterus, pseudosac and an adnexal mass seen on ultrasound for predicting ectopic pregnancy. Only first author of each study is given. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

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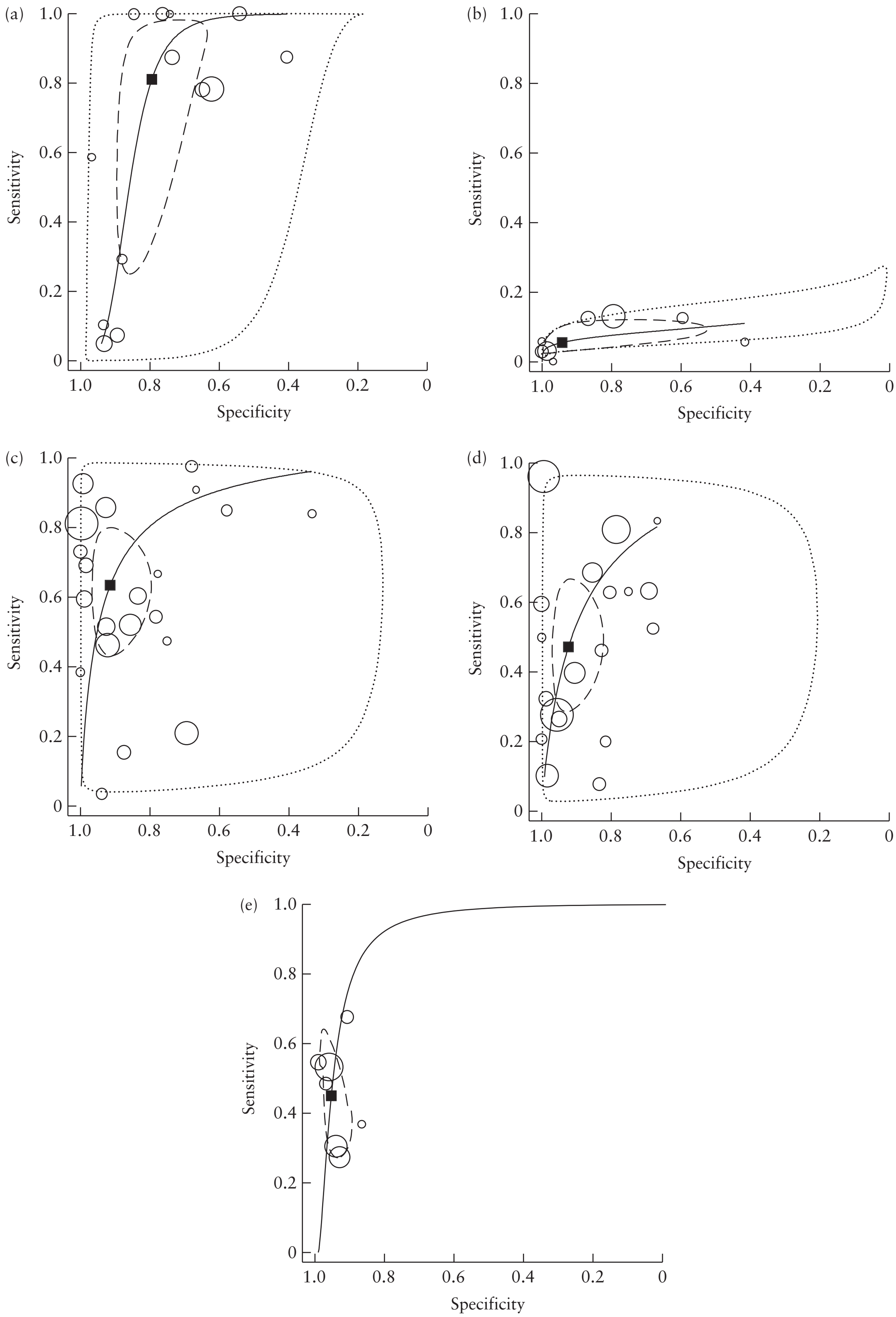

Figure 3 Summary receiver–operating characteristics (ROC) plots of the ability of an empty uterus (a), pseudosac (b), adnexal mass (c), free fluid (d) and the combination of an adnexal mass and free fluid (e) to predict ectopic pregnancy. ○, Study estimate; ——, hierarchical summary ROC curve; .... , 95% prediction region; ■, summary point; — —, 95% confidence region.

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Table 1 Summary estimates for each ultrasonographic (US) sign for predicting tubal ectopic pregnancy

US sign	Studies (n)	Women (n)	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	LR+ (95% CI)	LR− (95% CI)	Pre- and post-test probability (range) (%) Pretest	Post-test if test positive	Post-test if test negative
EU	13	2499	81.1 (42.1–96.2)	79.5 (68.9–87.1)	3.95 (2.70–5.77)	0.24 (0.06–0.94)	29.6 (7.2–77.7)	62 (60–65)	9 (8–11)
PS	8	1838	5.5 (3.3–9.0)	94.2 (75.9–98.8)	0.96 (0.26–3.48)	1.00 (0.93–1.08)	31.6 (7.2–68.8)	12 (8–16)	35 (34–35)
AM	21	2787	63.5 (48.5–76.3)	91.4 (83.6–95.7)	7.39 (3.63–15.05)	0.40 (0.27–0.59)	39.4 (24.2–88.0)	83 (80–85)	21 (19–22)
FF	19	3232	47.2 (33.2–61.7)	92.3 (85.6–96.0)	6.12 (3.08–12.18)	0.57 (0.43–0.76)	30.7 (5.19–77.7)	73 (70–76)	20 (19–21)
AM and FF	7	1023	45 (34–56)	96 (93–98)	12.0 (5.9–24.1)	0.57 (0.46–0.71)	54.3 (33.2–77.7)	93 (90–96)	40 (38–42)
AM and PS	1	265	2.9 (1.1–6.2)	100 (93.4–100)	∞	0.97 (0.95–0.99)	77.7	100	22.8
FF and PS	1	265	3.9 (1.7–7.5)	96.6 (88.3–99.5)	1.15 (0.25–5.25)	0.99 (0.94–1.05)	77.7	80.0	22.3
AM, FF and PS	1	265	5.8 (3.1–10.0)	100 (93.9–100)	∞	0.94 (0.91–0.97)	77.7	100	23.3

AM, adnexal mass; EU, empty uterus; FF, free fluid; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PS, pseudosac.

and specificity for differentiating between an ectopic and an intrauterine pregnancy are shown in Figure 3d and Table 1.

Diagnostic accuracy of the combination of adnexal mass and free fluid for predicting tubal pregnancy

Seven cohort studies[19,26,28,32,33,36,37], including 1023 women in early pregnancy, evaluated the diagnostic accuracy of the combination of an adnexal mass and free fluid to predict the likelihood of an ectopic pregnancy; Figure 4 shows the sensitivity and specificity of this combination in the individual studies. The precision estimates for each of the studies and estimated sensitivity and specificity for differentiating between an ectopic and an intrauterine pregnancy are shown in Figure 3e and Table 1.

Diagnostic accuracy of the combination of a pseudosac and adnexal mass for predicting tubal pregnancy

One cohort study[26], including 265 women in early pregnancy, evaluated the diagnostic accuracy of the combination of an adnexal mass and pseudosac to predict the likelihood of an ectopic pregnancy; Figure 4 and Table 1 show the sensitivity and specificity of this combination for predicting an ectopic pregnancy.

Diagnostic accuracy of the combination of a pseudosac and free fluid for predicting tubal pregnancy

One cohort study[26], including 265 women in early pregnancy, evaluated the diagnostic accuracy of the combination of free fluid and a pseudosac to predict the likelihood of an ectopic pregnancy; Figure 4 and Table 1 show the sensitivity and specificity of this combination for predicting an ectopic pregnancy.

Diagnostic accuracy of the combination of a pseudosac, adnexal mass and free fluid for predicting tubal pregnancy

One cohort study[26], including 265 women in early pregnancy, evaluated the diagnostic accuracy of the combination of a pseudosac, adnexal mass and free fluid to predict the likelihood of an ectopic pregnancy; Figure 4 and Table 1 show the sensitivity and specificity of this combination of ultrasonographic features for predicting an ectopic pregnancy.

Risk of bias within studies

The risk of bias and applicability concerns of studies based on QUADAS-2 are summarized in Figure 5 (the assessment of each individual study is presented in Table 2). The quality of most of the included studies was considered mediocre. Eight studies[13,21,23,25,26,33,39,41] were retrospective in nature, 10 were small (including fewer than 100 participants)[12–14,23,24,27,28,35,41,42] and 22 were undertaken more than 20 years ago[12,14–19,23,24,26–28,30–33,36–38,40–42]. Many studies did not describe fully the methods of patient selection, hence it is unclear whether the selection of patients could have introduced bias[12,14,16,18,19,24,27,30–32,35–38,40,41]. One study included only women who underwent surgery for suspected ectopic pregnancy[26] and three studies included women who were at particularly high risk of ectopic pregnancy as they had risk factors for, as well as symptoms suggestive of, ectopic pregnancy[23,27,35].

The degree of blinding in the studies was also unclear. The majority of studies did not state explicitly whether the ultrasound images were interpreted without knowledge of the final diagnosis (reference standard result). Four studies did not clearly define the ultrasonographic feature under surveillance[12,25,40,42] and in those studies that did

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Study	TP (*n*)	FP (*n*)	FN (*n*)	TN (*n*)	Sensitivity (95% CI)	Specificity (95% CI)
Free fluid						
Achiron (1987)[12]	6	0	23	32	0.21 (0.08, 0.40)	1.00 (0.89, 1.00)
Aleem (1990)[14]	4	7	16	31	0.20 (0.06, 0.44)	0.82 (0.66, 0.92)
Bateman (1990)[38]	11	1	23	73	0.32 (0.17, 0.51)	0.99 (0.93, 1.00)
Chambers (1990)[19]	14	4	39	75	0.26 (0.15, 0.40)	0.95 (0.88, 0.99)
Dart (2002)[21]	16	22	42	481	0.28 (0.17, 0.41)	0.96 (0.93, 0.97)
Dashefsky (1988)[23]	15	3	3	6	0.83 (0.59, 0.96)	0.67 (0.30, 0.93)
Gabrielli (1992)[24]	22	8	20	17	0.52 (0.36, 0.68)	0.68 (0.46, 0.85)
Huter (1990)[26]	21	1	185	58	0.10 (0.06, 0.15)	0.98 (0.91, 1.00)
Mahony (1985)[28]	22	9	13	37	0.63 (0.45, 0.79)	0.80 (0.66, 0.91)
Mehta (1999)[29]	25	0	17	86	0.60 (0.43, 0.74)	1.00 (0.96, 1.00)
Nyberg (1988)[41]	12	10	14	48	0.46 (0.27, 0.67)	0.83 (0.71, 0.91)
Nyberg (1991)[30]	43	25	25	56	0.63 (0.51, 0.75)	0.69 (0.58, 0.79)
Rempen (1988)[31]	17	82	4	301	0.81 (0.58, 0.95)	0.79 (0.74, 0.83)
Romero (1988)[32]	29	14	44	133	0.40 (0.28, 0.52)	0.90 (0.85, 0.95)
Russell (1993)[33]	12	4	7	12	0.63 (0.38, 0.84)	0.75 (0.48, 0.93)
Sadek (1995)[34]	51	3	2	469	0.96 (0.87, 1.00)	0.99 (0.98, 1.00)
Tongsong (1992)[37]	5	4	60	20	0.08 (0.03, 0.17)	0.83 (0.63, 0.95)
Tongsong (1993)[36]	72	14	33	82	0.69 (0.59, 0.77)	0.85 (0.77, 0.92)
Weckstein (1985)[42]	13	0	13	11	0.50 (0.30, 0.70)	1.00 (0.72, 1.00)
Adnexal mass and free fluid						
Chambers (1990)[19]	29	0	24	79	0.55 (0.40, 0.68)	1.00 (0.95, 1.00)
Huter (1990)[26]	63	3	143	56	0.31 (0.24, 0.37)	0.95 (0.86, 0.99)
Mahony (1985)[28]	17	1	18	45	0.49 (0.31, 0.66)	0.98 (0.88, 1.00)
Romero (1988)[32]	20	9	53	138	0.27 (0.18, 0.39)	0.94 (0.89, 0.97)
Russell (1993)[33]	7	2	12	14	0.37 (0.16, 0.62)	0.88 (0.62, 0.98)
Tongsong (1992)[37]	44	2	21	22	0.68 (0.55, 0.79)	0.92 (0.73, 0.99)
Tongsong (1993)[36]	56	3	49	93	0.53 (0.43, 0.63)	0.97 (0.91, 0.99)
Pseudosac and adnexal mass						
Huter (1990)[26]	6	0	200	59	0.03 (0.01, 0.06)	1.00 (0.94, 1.00)
Pseudosac and free fluid						
Huter (1990)[26]	8	2	198	57	0.04 (0.02, 0.08)	0.97 (0.88, 1.00)
Pseudosac, adnexal mass and free fluid						
Huter (1990)[26]	12	0	194	59	0.06 (0.03, 0.10)	1.00 (0.94, 1.00)

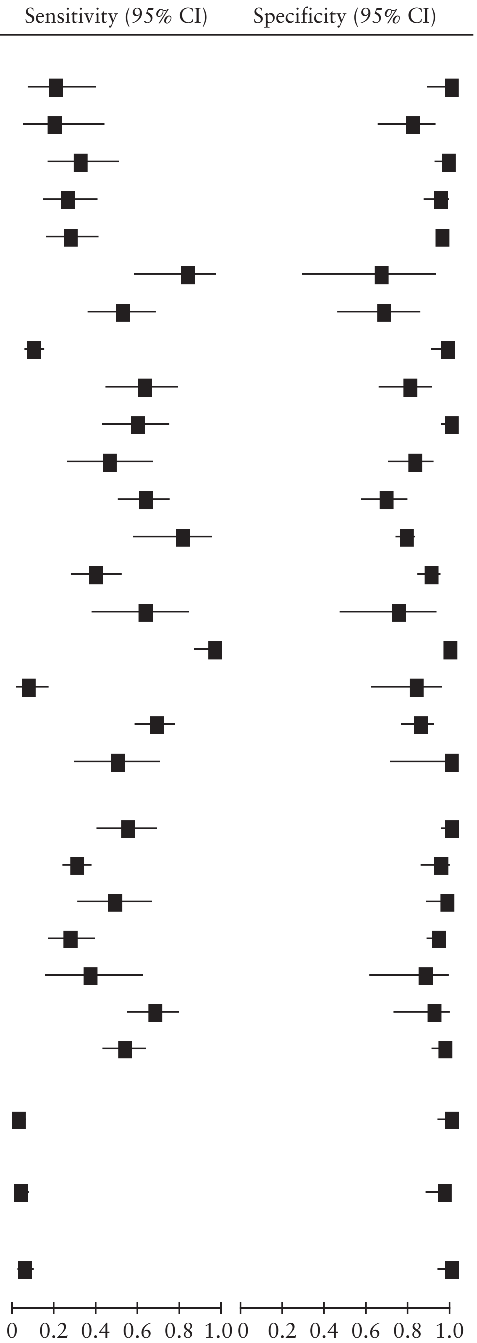

Figure 4 Forest plot of performance of free fluid, combination of an adnexal mass and free fluid, combination of a pseudosac and an adnexal mass, combination of a pseudosac and free fluid and combination of a pseudosac, adnexal mass and free fluid, seen on ultrasound, for predicting ectopic pregnancy. Only first author of each study is given. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

give a clear definition there were often considerable differences between the studies. For example, the study by Braffman *et al.*[15] considered only complex adnexal masses, while the study by Aleem *et al.*[14] included both complex and cystic masses. Similarly, for free fluid, some studies considered merely the presence or absence of free fluid[12,14,23,24,26,31,32,34,37,38] while others tried to quantify its volume[28,29,41], and two studies included the appearance of the fluid on ultrasound rather than the volume in its definition[19,36]. Some of the older studies utilized transabdominal ultrasound only[12,18,32,37] and the ultrasound approach was not stated in others[13,19,28–30,40–42], hence their results may not be applicable to current practice.

Eleven studies did not define clearly the reference standard[12–15,23,31,32,34,35,37,42] and in the majority of studies it was unclear whether the results of the reference standard were interpreted without knowledge of the index test. One study clearly stated that the results of the ultrasound were known at the time of surgery and were often an important factor in the decision-making process, which could have introduced bias[26]. Patient

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Table 2 Quality assessment of included studies in the systematic review using quality assessment of diagnostic accuracy studies (QUADAS-2)

	Risk of bias				*Applicability concerns*		
Study	*Patient selection*	*Index test*	*Reference standard*	*Flow and timing*	*Patient selection*	*Index test*	*Reference standard*
Achiron (1987)[12]	Unclear	Unclear	Unclear	Low	Unclear	Low	Low
Ahmed (2004)[13]	Low	Low	Unclear	Low	Low	Low	Low
Aleem (1990)[14]	Unclear	Low	Unclear	Low	Low	Low	Low
Bateman (1990)[38]	Unclear	Low	Low	Low	Unclear	Low	Low
Braffman (1994)[15]	Low	Low	Unclear	Low	Low	Low	Low
Cacciatore (1988)[18]	Unclear	Low	Low	Low	Low	Low	Low
Cacciatore (1989)[16]	Unclear	Low	Low	Low	Low	Low	Low
Cacciatore (1990)[17]	Low	Low	Low	Low	Low	Low	Low
Chambers (1990)[19]	Unclear	Low	Low	Low	Unclear	Low	Low
Dart (1998)[39]	Low	Low	Low	Low	Low	Low	Low
Dart (2002)[22]	Low	Low	Low	Low	Low	Low	Low
Dart (2002)[20]	Low	Low	Low	Low	Low	Low	Low
Dart (2002)[21]	Low	Low	Low	Low	Low	Low	Low
Dashefsky (1988)[23]	Low	Low	Unclear	Low	Low	Low	Low
Gabrielli (1992)[24]	Unclear	Low	Low	Low	Low	Low	Low
Hammoud (2005)[25]	Low	Unclear	Low	Low	Low	Low	Low
Huter (1990)[26]	Low	Unclear	High	Low	High	Low	Low
Kivikoski (1990)[27]	Unclear	Low	Low	Low	Low	Low	Low
Mahony (1985)[28]	Low	Low	Low	Low	Low	Low	Low
Mehta (1999)[29]	Low	Low	Low	Low	Low	Low	Low
Nyberg (1988)[40]	Unclear	Low	Low	Low	Low	High	Low
Nyberg (1988)[41]	Unclear	Low	Low	Low	Low	Low	Low
Nyberg (1991)[30]	Unclear	Low	Low	Low	Low	Low	Low
Rempen (1988)[31]	Unclear	Low	Unclear	Low	Unclear	Low	Low
Romero (1988)[32]	Unclear	Low	Unclear	Low	Low	Low	Low
Russell (1993)[33]	Low	Low	Low	Low	Low	Low	Low
Sadek (1995)[34]	Low	Low	Unclear	Low	Low	Low	Low
Shapiro (1988)[35]	Unclear	Low	Unclear	Low	Low	Low	Low
Tongsong (1992)[37]	Unclear	Low	Unclear	Low	Low	Low	Low
Tongsong (1993)[36]	Unclear	Low	Low	Low	Low	Low	Low
Weckstein (1985)[42]	Low	Unclear	Unclear	Low	Low	High	Low

Only the first author of each study is given.

Table 3 Summary estimates for an empty uterus (EU), adnexal mass (AM) and free fluid (FF) on ultrasound (US) for predicting tubal ectopic pregnancy, using only high-quality studies

US sign	*Studies (n)*	*Women (n)*	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*	*LR+ (95% CI)*	*LR− (95% CI)*
EU	5	1341	75.8 (31.4–95.5)	71.0 (52.6–84.4)	2.61 (1.49–4.58)	0.34 (0.09–1.35)
AM	4	444	67.3 (42.6–85.1)	94.9 (74.3–99.2)	13.3 (1.73–102.0)	0.34 (0.16–0.74)
FF	4	805	52.3 (35.9–68.2)	93.5 (74.4–98.6)	8.09 (1.87–35.10)	0.51 (0.36–0.72)

LR+, positive likelihood ratio; LR−, negative likelihood ratio.

flow was considered to be appropriate in all the studies.

Eight studies had a low risk of bias across all seven domains[17,20–22,28,29,33,39] (Table 2). Subgroup analysis using only these high-quality studies was performed and the estimated summary sensitivities and specificities and positive and negative likelihood ratios of an empty uterus, adnexal mass and free fluid on ultrasound to differentiate between an ectopic pregnancy and an intrauterine pregnancy are illustrated in Table 3.

DISCUSSION

Summary of evidence

Our systematic review and meta-analysis summarizes the diagnostic accuracy of commonly used ultrasonographic signs for predicting a tubal ectopic pregnancy, and shows that when an obvious extrauterine pregnancy is not present, the ultrasonographic findings of an empty uterus, a pseudosac, an adnexal mass and/or free fluid have poor sensitivity for identifying a tubal pregnancy. However, the presence of these features on ultrasound has good specificity for predicting an ectopic pregnancy, especially when found in combination. We can therefore infer that these ultrasound features are more useful for 'ruling in' a tubal ectopic pregnancy, than for 'ruling out' one.

Strengths and weaknesses of the study

We conducted a prospective and extensive systematic search of electronic databases using a predefined protocol that has been published. The high number of included studies in our meta-analysis for an empty uterus, the

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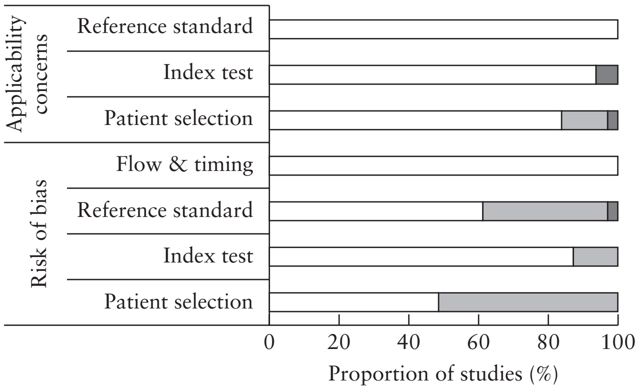

Figure 5 Summary of methodological quality of studies, according to quality assessment of diagnostic accuracy studies (QUADAS-2) tool. Proportions of studies with low (□), unclear (▩) or high (■) risk of bias or applicability concerns are shown.

presence of an adnexal mass and free fluid strengthened the power of these conclusions and enabled us to define the diagnostic accuracy of these signs in confirming an ectopic pregnancy with relative precision. Our findings for the presence of a pseudosac and various different combinations of ultrasonographic features were, however, limited by the small number of included studies.

An additional strength is that we performed an assessment of quality of the included studies. The quality of most of the included studies was mediocre. The risk of bias and concerns regarding the applicability of the results to current practice were generally low or unclear, with only three studies[26,40,42] having a high risk of bias or substantial applicability concerns in one or two domains only. In addition, we conducted subgroup analysis using results from the eight high-quality studies (with a low risk of bias across all seven QUADAS-2 domains).

The main limitation of our study is that the prevalence of an ectopic pregnancy varied considerably between the studies. This is most probably a reflection of the different inclusion criteria of the studies; for example, one study included only women who underwent a diagnostic laparoscopy for suspicion of an ectopic pregnancy[26]. Clearly the prevalence of an ectopic pregnancy in this study will be higher than in those that included only women with a positive urinary pregnancy test[31,41] or in those that included women with symptoms of abdominal pain and/or vaginal bleeding[12,13,17,18,24,25,28,29,34,36,37,40,42]. Studies that included women with risk factors for ectopic pregnancy[23,27,35] and those that included symptomatic pregnant women with indeterminate ultrasound scans[14–16,20–22,30,33,39] are also likely to have a different prevalence of ectopic pregnancy. In clinical practice it is essential to know how a particular test result predicts the risk of abnormality in the population being evaluated. Sensitivities and specificities do not describe how a particular test result predicts the risk of abnormality. The benefit of using likelihood ratios over sensitivity and specificity measures is that they can be used to calculate the probability of abnormality, while adapting for varying *a-priori* probabilities for the chance of abnormality from different contexts. It is essential therefore that the prevalence of an ectopic pregnancy in individual early pregnancy assessment/emergency gynecology units is known before likelihood ratios are applied.

While a subgroup analysis based on the level of risk would be interesting and useful clinically, unfortunately it was not possible to perform in this meta-analysis, as only one study included women at high risk of an ectopic pregnancy and only three studies included women at low risk of an ectopic pregnancy. All other studies included women at intermediate risk, and it was not possible to stratify the population further.

A further limitation of our study is the wide variation in sensitivity and specificity between studies reporting on the same ultrasonographic sign. For example, the sensitivity of an adnexal mass for predicting an ectopic pregnancy ranged from 3.6% in the study by Achiron *et al.*[12] to 97.6% in the study by Gabrielli *et al.*[24], and specificity ranged from 33.3% in the study by Kivikoski *et al.*[27] to 100% in the studies by Nyberg *et al.*[41], Sadek and Schiotz[34] and Weckstein *et al.*[42]. Similarly for free fluid, the sensitivity ranged from 7.7% in the study by Tongsong *et al.*[37] to 96.2% in the study by Sadek and Schiotz[34] and the specificity ranged from 66.7% in the study by Dashefsky *et al.*[23] to 100% in the studies by Achiron *et al.*[12], Mehta *et al.*[29] and Weckstein *et al.*[42]. This is probably because of the considerable heterogeneity between the studies involving different populations of women, different ultrasound approaches and different definitions of the signs under evaluation.

This review demonstrates that a pseudosac is a rare ultrasonographic finding in early pregnancy and is usually absent in women with an ectopic pregnancy. However, when present, it is highly suggestive of an ectopic pregnancy. Although some experts may disagree[3], many find it difficult to differentiate a gestational sac from a pseudosac prior to the development of a yolk sac or fetal pole. Several different ultrasonographic signs have been proposed to aid in the differentiation, including the intradecidual, double decidual sac and chorionic rim signs, but a recent review[43] concluded that while the presence of these signs increases substantially the probability that a pregnancy is intrauterine, their absence does not exclude the diagnosis of an intrauterine pregnancy, and a negative test result cannot be relied upon to guide clinical practice. Furthermore, none of these signs was as accurate in confirming the location of an intrauterine pregnancy as was the presence of a yolk sac hence, in the absence of further research, they concluded that it would be advisable to wait until a yolk sac is visualized before confirming that a pregnancy is definitely intrauterine. While a true pseudosac, highly suggestive of an ectopic pregnancy, is a relatively rare ultrasonographic finding in early pregnancy, an empty gestational sac, indicative of an early or failing intrauterine pregnancy, is much more common. It would be preferable to differentiate between these potential diagnoses as early as possible, as doing so would reduce anxiety for women and also prevent unnecessary

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investigations for those with an intrauterine pregnancy and minimize morbidity and mortality, permit earlier, potentially less invasive intervention and possibly preserve future fertility in women with an ectopic pregnancy. Therefore this review strengthens the need for a definitive test accuracy study following recommended guidelines to establish standards for the accurate confirmation of an intrauterine pregnancy prior to the development of a yolk sac, or more specifically, the differentiation between an early gestational sac and a pseudosac[44].

In conclusion, this review is the first to collate comprehensively evidence of the accuracy of various ultrasonographic features to accurately confirm the presence of an ectopic pregnancy in the absence of a live extrauterine embryo. When an obvious extrauterine pregnancy is not present, the commonly used ultrasound features have poor sensitivity for identifying a tubal pregnancy, but they have good specificity. We can therefore infer ultrasound features are more useful for ruling in a tubal ectopic pregnancy, than for ruling one out. The findings are limited by the small number and poor quality of the included studies and by the considerable variation in index test and reference standard among the different studies.

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SUPPORTING INFORMATION ON THE INTERNET

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