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Accuracy of first-trimester ultrasound in diagnosis of intrauterine pregnancy prior to visualization of the yolk sac: a systematic review and meta-analysis

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KEYWORDS: diagnostic accuracy; intrauterine; pregnancy; QUADAS-2; systematic review; ultrasound

ABSTRACT

Objectives *To evaluate the diagnostic accuracy of ultrasound in predicting the location of an intrauterine pregnancy before visualization of the yolk sac is possible.*

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. 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. gestational sac, double decidual sac sign, intradecidual sign, chorionic rim sign and yolk sac. 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 *Seventeen studies including 2564 women were selected from 19 959 potential papers. Following meta-analysis, the presence of a gestational sac on ultrasound examination was found to predict an intrauterine pregnancy with a sensitivity of 52.8% (95% CI, 38.2–66.9%) and specificity of 97.6% (95% CI, 94.3–99.0%). The corresponding performance of the double decidual sac sign, intradecidual sign, chorionic rim sign and yolk sac were: 81.8% (95% CI, 68.1–90.4%) and 97.3% (95% CI, 76.1–99.8%); 66.1% (95% CI, 58.9–72.8%) and 100% (95% CI, 91.0–100%); 79.9% (95% CI, 73.0–85.7%) and 97.1% (95% CI, 89.9–99.6%); and 42.2% (95% CI, 27.7–57.9%) and 100% (95% CI, 54.1–100%), respectively.*

Conclusion *Visualization of a gestational sac, double decidual sac sign, intradecidual sign or chorionic rim sign increases the probability of an intrauterine pregnancy but is not as accurate for diagnosis as the detection of the yolk sac. However, the findings were limited by the small number and poor quality of the studies included and heterogeneity in the index test and reference standard.* *Copyright © 2014 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

The earliest reliable ultrasonographic sign of an intrauterine pregnancy is visualization of the gestational sac, identified using transvaginal ultrasound from 28 days' gestation[1]. Initially, the structure does not contain any internal echoes and can be difficult to differentiate from a pseudosac, which is seen in up to 15% of ectopic pregnancies[2]. The yolk sac, visible from 35 days' gestation[3], is the first structure to appear within the gestational sac, and indicates an intrauterine pregnancy with a positive predictive value of 100%[4].

Many healthcare professionals wait until the yolk sac can be observed successfully before confirming the presence of a true gestational sac. This may improve the accuracy of ultrasound for the detection of an intrauterine pregnancy, but there is a time interval during which a gestational sac may be visible without a yolk sac. The potential diagnoses that could be made during this interval are an early intrauterine pregnancy of uncertain viability or an ectopic pregnancy. Prompt differentiation between these would be desirable, as it would minimize the level of anxiety for women, prevent unnecessary investigations for those with intrauterine pregnancies and permit earlier, and potentially less invasive, intervention for women with ectopic pregnancies.

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Visualization of several ultrasonographic signs has been proposed for differentiating a true gestational sac from a pseudosac prior to development of the yolk sac, including the intradecidual[5], double decidual sac[6] and chorionic rim[7] signs. The intradecidual sign is defined as a distinct endometrial stripe with an echogenic area embedded eccentrically into the thickened decidua on one side of the uterine cavity[5]. This differs from that of a pseudosac, which appears as fluid surrounded by the echogenic endometrial lining only. The double decidual sac sign appears as an intra-endometrial fluid collection with two surrounding concentric echogenic rings that impress upon the endometrial stripe in a normal early pregnancy[6]. In an ectopic pregnancy, the decidual reaction consists of only a single ring around the fluid collection[3]. The chorionic rim sign consists of a curvilinear echogenic rim, separate from the underlying decidua, bordering an outwardly convex fluid collection[7]. In practice, owing to varying degrees of accuracy reported in individual studies, none of these signs can be relied upon to confirm the location of a pregnancy.

We performed a systematic review of the literature and a meta-analysis to determine the accuracy of commonly described first-trimester ultrasonographic signs in the diagnosis of a viable or non-viable intrauterine pregnancy, before the appearance of a yolk sac, 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 4 October 2012. The registration number is CRD42012003046. 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 text words, Medical Subject and Emree Headings 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 research question. The search was limited to human subjects and the English language. Duplicates were removed during the process of assessing 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 intrauterine pregnancy (viable or non-viable) 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 was no limitation on publication date 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 cases of duplicates, the most recent version was selected. Any disagreements concerning selection were resolved by consensus or arbitration by a third reviewer (N.R.F.).

Data collection process

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 included studies were juxtaposed to identify duplicate publications; in cases of duplicates, both articles were considered as a single study.

Data items

The following data were extracted from the 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 used (ultrasound approach i.e. transabdominal or transvaginal, frequency/resolution of ultrasound machine, operator; ultrasonographic feature under evaluation, i.e. intradecidual sign, double decidual sac sign, chorionic rim sign, gestational sac, yolk sac); outcome investigated; and quality and accuracy of the

results. Accuracy data were used to construct 2 × 2 tables of ultrasonographic findings and pregnancy location.

Risk of bias in individual studies

One reviewer (A.R.) completed the quality assessment using the quality assessment of diagnostic accuracy studies (QUADAS)-2 methodology checklist[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 patients through the study and timing of the index test and reference standard.

Summary measures

All data were inserted 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 from 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 difference in precision between them, and the overall sensitivity and specificity for the test when all studies are pooled together. When all 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 pre-test 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 papers. Following review of the titles and abstracts, 294 full-text papers were selected for further examination and subsequently 277 of these studies were excluded (Figure 1). Seventeen studies[5–7,12–25], including 2564 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 gestational sac for predicting intrauterine pregnancy

Twelve cohort studies[12,13,15–24], including 1920 women in early pregnancy, evaluated the diagnostic accuracy of visualization of a gestational sac on ultrasound examination to predict the likelihood of an intrauterine pregnancy. Figure 2 shows the sensitivities and specificities of the presence of a gestational sac for predicting an intrauterine pregnancy in the individual studies. The precision estimates for each of the studies and the estimated summary sensitivity and specificity for differentiating between an intrauterine and an extrauterine pregnancy are shown in Figure 3 and Table 1. Following meta-analysis of these 12 studies, we found that the presence of a gestational sac predicts an intrauterine pregnancy with a pooled sensitivity of 52.8% (95% CI, 38.2–66.9%), specificity of 97.6% (95% CI, 94.3–99.0%), positive likelihood ratio of 22.2 (95% CI, 9.8–50.6) and negative likelihood ratio of 0.48 (95% CI, 0.36–0.66). Of the studies included in this meta-analysis, the median prevalence of an

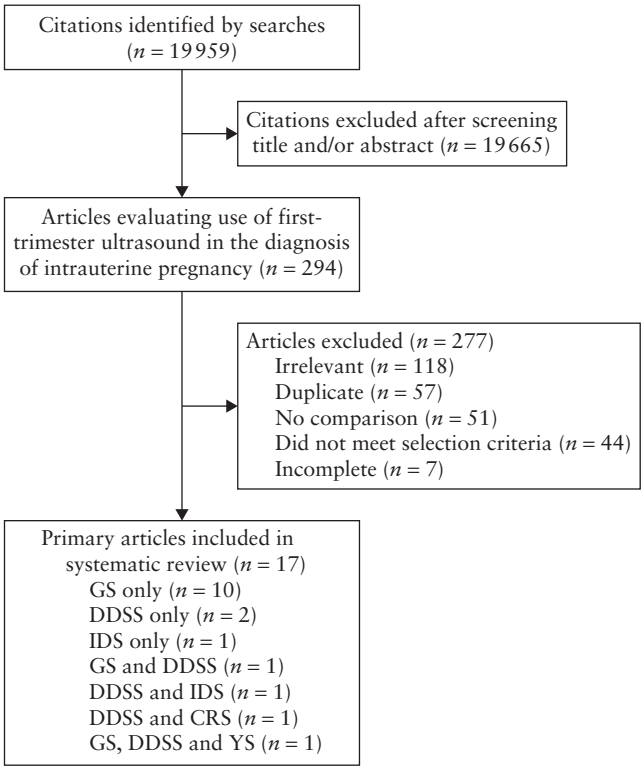

Figure 1 Flowchart summarizing study selection of papers on first-trimester ultrasound signs in the diagnosis of intrauterine pregnancy prior to development of the yolk sac. CRS, chorionic rim sign; DDSS, double decidual sac sign; GS, gestational sac; IDS, intradecidual sign; YS, yolk sac.

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gestational sac						
Ankum (1993)[12]	49	1	70	88	0.41 (0.32, 0.51)	0.99 (0.94, 1.00)
Bateman (1990)[13]	68	1	24	33	0.74 (0.64, 0.83)	0.97 (0.85, 1.00)
Dart (1997)[21]	20	0	124	19	0.14 (0.09, 0.21)	1.00 (0.82, 1.00)
Dart (1998)[20]	29	0	167	32	0.15 (0.10, 0.21)	1.00 (0.89, 1.00)
Enk (1990)[15]	34	2	26	45	0.57 (0.43, 0.69)	0.96 (0.85, 0.99)
Kadar (1981)[16]	50	2	28	17	0.64 (0.52, 0.75)	0.89 (0.67, 0.99)
Nyberg (1987)[22]	57	6	19	68	0.75 (0.64, 0.84)	0.92 (0.83, 0.97)
Nyberg (1988)[23]	45	6	43	42	0.51 (0.40, 0.62)	0.88 (0.75, 0.95)
Nyberg (1988)[24]	35	1	23	25	0.60 (0.47, 0.73)	0.96 (0.80, 1.00)
Romero (1985)[17]	139	2	140	102	0.50 (0.44, 0.56)	0.98 (0.93, 1.00)
Tongsong (1993)[18]	52	0	44	105	0.54 (0.44, 0.64)	1.00 (0.97, 1.00)
Weckstein (1985)[19]	11	0	0	26	1.00 (0.72, 1.00)	1.00 (0.87, 1.00)
Double decidual sac sign						
Bradley (1982)[6]	34	0	10	6	0.77 (0.62, 0.89)	1.00 (0.54, 1.00)
Nyberg (1983)[25]	59	1	4	64	0.94 (0.85, 0.98)	0.98 (0.92, 1.00)
Nyberg (1987)[22]	54	0	3	6	0.95 (0.85, 0.99)	1.00 (0.54, 1.00)
Nyberg (1988)[23]	36	2	9	4	0.80 (0.65, 0.90)	0.67 (0.22, 0.96)
Parvey (1996)[7]	108	0	61	69	0.64 (0.56, 0.71)	1.00 (0.95, 1.00)
Yeh (1986)[5]	23	2	13	3	0.64 (0.46, 0.79)	0.60 (0.15, 0.95)
Intradecidual sign						
Chiang (2004)[14]	92	0	61	34	0.60 (0.52, 0.68)	1.00 (0.90, 1.00)
Yeh (1986)[5]	33	0	3	5	0.92 (0.78, 0.98)	1.00 (0.48, 1.00)
Chorionic rim sign						
Parvey (1996)[7]	135	2	34	67	0.80 (0.73, 0.86)	0.97 (0.90, 1.00)
Yolk sac						
Nyberg (1988)[23]	19	0	26	6	0.42 (0.28, 0.58)	1.00 (0.54, 1.00)

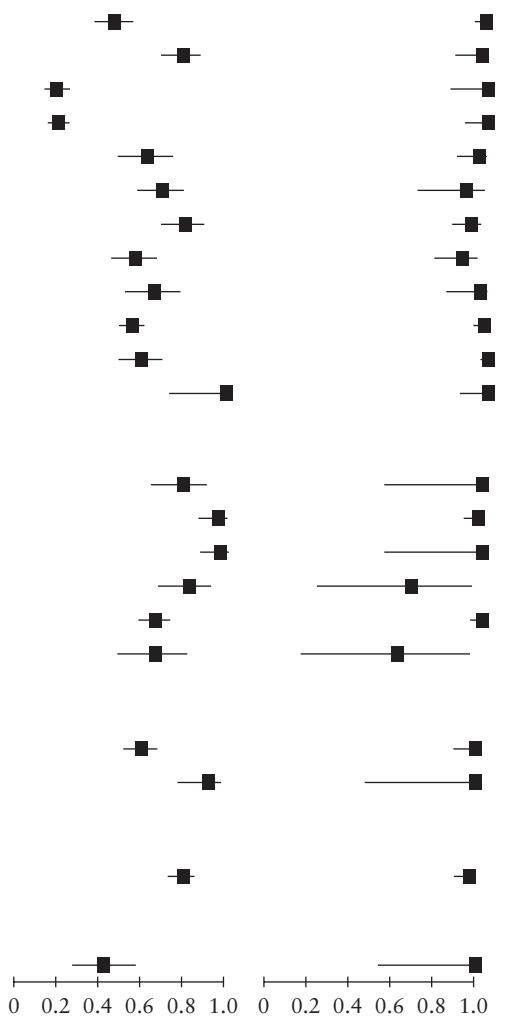

Figure 2 Forest plots of performance of first-trimester ultrasound signs for predicting intrauterine pregnancy. Only the first author of each study is given. FN, false negative; FP, false positive; TN, true negative; TP, true positive.

intrauterine pregnancy was 67.6% (range, 29.7–88.3%), however if the gestational sac was present the probability of an intrauterine pregnancy was as high as 98% (range, 96–99%) compared with 50% (range, 48–52%) if the gestational sac was absent.

Diagnostic accuracy of double decidual sac sign for predicting intrauterine pregnancy

Six cohort studies[5–7,22,23,25], including 571 women in early pregnancy, evaluated the diagnostic accuracy of the double decidual sac sign for predicting the likelihood of an intrauterine pregnancy. Figure 2 shows the sensitivities and specificities of the individual studies. The precision estimates for each of the studies and the estimated summary sensitivity and specificity for differentiating between an intrauterine and an extrauterine pregnancy are shown in Figure 3 and Table 1. Following meta-analysis of these six studies, we found that the presence of the double decidual sac sign predicts an intrauterine pregnancy with a pooled sensitivity of 81.8% (95% CI, 68.1–90.4%), specificity of 97.3% (95% CI, 76.1–99.8%), positive likelihood ratio of 30.3 (95% CI, 2.8–330.9) and negative likelihood ratio of 0.19 (95% CI, 0.10–0.35). Of the studies included in this meta-analysis, the median prevalence of an intrauterine pregnancy was 89.4% (range, 49.2–90.5%), however if the double decidual sac sign was present the probability of an intrauterine pregnancy was as high as 99.6% (range, 96.7–99.7%) compared with 61.1% (range, 15.3–64.0%) if the double decidual sac sign was absent.

Diagnostic accuracy of intradecidual sign for predicting intrauterine pregnancy

Two cohort studies[5,14], including 228 women in early pregnancy, evaluated the diagnostic accuracy of the intradecidual sign for predicting the likelihood of an intrauterine pregnancy. Figure 2 shows the sensitivities

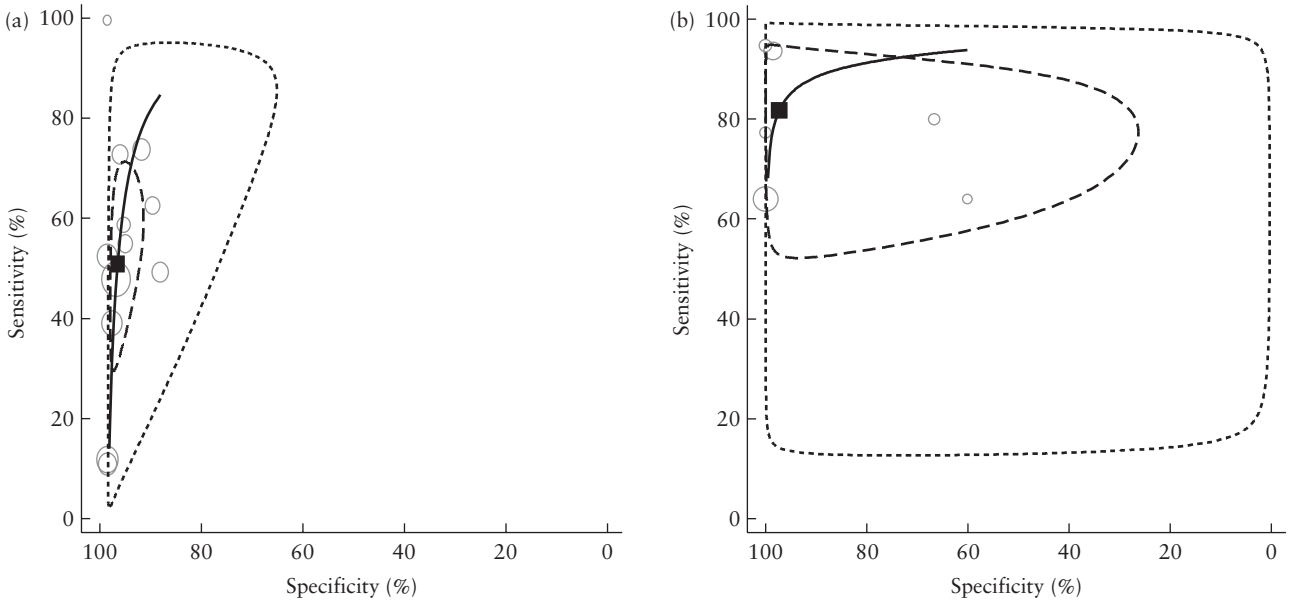

Figure 3 Summary receiver–operating characteristics (ROC) plot of the ability of a gestational sac (a) and the double decidual sac sign (b) to predict intrauterine pregnancy. ○, Study estimate; ——, hierarchal summary ROC curve; ·····, 95% prediction region; ■, summary point; – – –, 95% confidence region.

Table 1 Summary estimates for each ultrasonographic sign for predicting intrauterine pregnancy in women with pain and/or bleeding in early pregnancy

						Pre- and post-test probability (range) (%)		
Studies	n *[N]*	*Sensitivity (95% CI) (%)*	*Specificity (95% CI) (%)*	*LR+ (95% CI)*	*LR– (95% CI)*	*Pretest*	*Post-test if test positive*	*Post-test if test negative*
GS	12 (1920)	52.8 (38.2–66.9)	97.6 (94.3–99.0)	22.2 (9.8–50.6)	0.48 (0.36–0.66)	67.6 (29.7–88.3)	98.0 (96.0–99.0)	50.0 (48.0–52.0)
DDSS	6 (571)	81.8 (68.1–90.4)	97.3 (76.1–99.8)	30.3 (2.8–330.9)	0.19 (0.10–0.35)	89.4 (49.2–90.5)	99.6 (96.7–99.7)	61.1 (15.3–64.0)
IDS*	2 (228)	66.1 (58.9–72.8)	100 (91.0–100)	20.85 (3.08–141.1)	0.22 (0.06–0.88)	85	99.2	56
CRS*	1 (238)	79.9 (73.0–85.7)	97.1 (89.9–99.6)	27.6 (7.02–108.2)	0.21 (0.15–0.28)	71	98.5	66.3
YS*	1 (51)	42.2 (27.7–57.9)	100 (54.1–100)	∞	0.58 (0.45–0.74)	88.2	100	18.7

*Probability ranges not applicable for ultrasonographic signs with fewer than four studies. CRS, chorionic rim sign; DDSS, double decidual sac sign; GS, gestational sac; IDS, intradecidual sign; LR+, positive likelihood ratio; LR–, negative likelihood ratio; *n* [N], number of studies [number of women]; YS, yolk sac.

and specificities of the individual studies. The precision estimates for each of the studies and the estimated summary sensitivity and specificity for differentiating between an intrauterine and an extrauterine pregnancy are shown in Table 1. Following meta-analysis of these two studies, we found that the presence of the intradecidual sign predicts an intrauterine pregnancy with a pooled sensitivity of 66.1% (95% CI, 58.9–72.8%), specificity of 100% (95% CI, 91.0–100%), positive likelihood ratio of 20.85 (95% CI, 3.08–141.1) and negative likelihood ratio of 0.22 (95% CI, 0.06–0.88). The median prevalence of an intrauterine pregnancy was 85%, but if the intradecidual sign was present the probability of an intrauterine pregnancy was as high as 99.2% compared with 56% if the intradecidual sign was absent.

Diagnostic accuracy of chorionic rim sign for predicting intrauterine pregnancy

One cohort study[7], including 238 women in early pregnancy, evaluated the diagnostic accuracy of the chorionic rim sign for predicting the likelihood of an intrauterine pregnancy. The estimated summary sensitivity and specificity for differentiating an intrauterine from an extrauterine pregnancy are shown in Figure 2 and Table 1. This study found that the presence of the chorionic rim sign predicts an intrauterine pregnancy with a sensitivity of 79.9% (95% CI, 73.0–85.7%), specificity of 97.1% (95% CI, 89.9–99.6%), positive likelihood ratio of 27.6 (95% CI, 7.02–108.2) and negative likelihood ratio of 0.21 (95% CI, 0.15–0.28). In the study, the prevalence of an intrauterine pregnancy was 71%, but if

the chorionic rim sign was present the probability of an intrauterine pregnancy was as high as 98.5% compared with 66.3% if the chorionic rim sign was absent.

Diagnostic accuracy of the yolk sac for predicting intrauterine pregnancy

One cohort study[23], including 51 women in early pregnancy, evaluated the diagnostic accuracy of the presence of the yolk sac for predicting the likelihood of an intrauterine pregnancy. The estimated summary sensitivity and specificity for differentiating an intrauterine from an extrauterine pregnancy are shown in Figure 2 and Table 1. This study found that the presence of a yolk sac predicts an intrauterine pregnancy with a sensitivity of 42.2% (95% CI, 27.7–57.9%), specificity of 100% (95% CI, 54.1–100%), positive likelihood ratio was infinite and negative likelihood ratio of 0.58 (95% CI, 0.45–0.74). In this study, the prevalence of an intrauterine pregnancy was 88.2%, but if a yolk sac was present the probability of an intrauterine pregnancy was 100% compared with 18.7% if a yolk sac was absent.

Risk of bias within studies

The risks of bias and applicability concerns of studies based on QUADAS-2 (the assessment of each individual study is presented in Table 2) are summarized in Figure 4. Although some high-quality studies were included in the systematic review[7,14,20], the quality of most of the studies was considered mediocre. Six studies were retrospective in nature[6,14,16,20,21,25], five were small (including fewer than 100 participants)[5,6,16,19,24], and 12 studies were undertaken more than 20 years ago[6,12,13,15–19,22–25]. Many studies did not describe fully the methods of patient selection, most notably with respect to whether a consecutive or random sample of patients was selected, and hence it is unclear whether the selection of patients could have introduced bias[13,15,17,18,22–24].

The inclusion criteria for the different studies were also variable. In some studies the only inclusion criterion appeared to be that of a positive pregnancy test[6,18,23], while most others additionally required symptoms suggestive of an ectopic or failing pregnancy, namely abdominal pain and/or vaginal bleeding[5,7,12,13,15–17,19,20,22,24]. Other studies had more specific inclusion criteria, for example, the study by Chiang *et al.*[14] included patients who were pregnant and whose ultrasonographic findings revealed the presence of either an intrauterine fluid collection associated with an early intrauterine pregnancy of less than 5.5 weeks' gestation (defined as a mean sac diameter of ≤ 8 mm) or an ectopic pregnancy. In contrast, Dart *et al.*[21] included symptomatic pregnant women with indeterminate transvaginal ultrasound scans and either a level of human chorionic gonadotropin (hCG) > 3000 mIU/mL or last menstrual period > 38 days before examination. The results of these studies with more specific inclusion criteria may be less generalizable.

The degree of blinding in the studies was also unclear. Many studies did not explicitly state whether the ultrasound images were interpreted without knowledge of the final diagnosis. In the prospective studies, it is probable that this was the case owing to the inevitable passage of time that occurred while waiting for the clinical follow-up (reference standard) to occur. It is less clear in the retrospective studies[6,14,16,20,21,25]. Furthermore, three studies did not define clearly the ultrasonographic feature under surveillance[12,16,19] and in those studies that did give a clear definition, there were often considerable differences between the studies. Most studies that investigated the accuracy of a gestational sac defined a gestational sac as being an anechoic intrauterine fluid collection surrounded by an echogenic border[13,17,22–24], but two studies included the presence of internal echoes in the

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*
Ankum (1993)[12]	Low	Unclear	Unclear	Low	Low	Low	Low
Bateman (1990)[13]	Unclear	Low	Low	Low	Unclear	Low	Low
Bradley (1982)[6]	Low	Unclear	Unclear	Low	Low	High	Unclear
Chiang (2004)[14]	Low	Low	Low	Low	Low	Low	Low
Dart (1997)[21]	Unclear	Low	Low	Low	High	Low	Low
Dart (1998)[20]	Low	Low	Low	Low	Low	Low	Low
Enk (1990)[15]	Unclear	Low	Low	Low	Low	Low	Low
Kadar (1981)[16]	Low	Unclear	Unclear	Unclear	Unclear	High	Unclear
Nyberg (1983)[25]	Low	High	Unclear	Low	Low	High	Low
Nyberg (1987)[22]	Unclear	Low	Low	Low	Low	High	Low
Nyberg (1988)[24]	Unclear	Low	Low	Low	Low	High	Low
Nyberg (1988)[23]	Unclear	Low	Low	Low	Low	Low	Low
Parvey (1996)[7]	Low	Low	Low	Low	Low	Low	Low
Romero (1985)[17]	Unclear	Low	Low	Low	Low	High	Unclear
Tongsong (1993)[18]	Unclear	Low	Low	Low	Low	Low	Low
Weckstein (1985)[19]	Low	Unclear	Unclear	Low	Low	High	Low
Yeh (1986)[5]	Low	Low	Unclear	Low	Low	High	Low

Only the first author of each study is given.

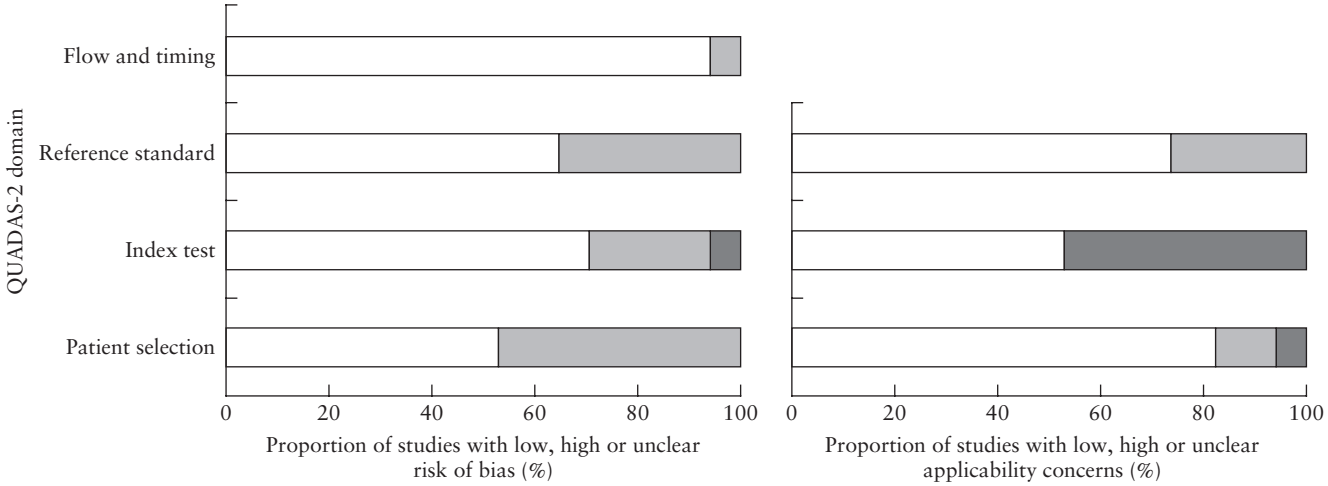

Figure 4 Risk of bias and applicability concerns based on quality assessment of diagnostic accuracy studies (QUADAS)-2 across included studies. □, Low; ▒, unclear; ■, high.

definition[15,18] and two incorporated a size limitation[20,21]. Therefore the conduct and/or interpretation of the index test could have introduced bias. Some of the older studies utilized transabdominal ultrasound[6,16,17,22,23] and the ultrasound approach was not stated in others[19] and hence their results may not be applicable to current practice.

Seven studies[5,6,16–18,20,21] did not clearly define the reference standard and in the majority of studies it was unclear if the results of the reference standard were interpreted without knowledge of the index test. Patient flow was considered to be appropriate in all the studies.

DISCUSSION

Summary of evidence

Our systematic review and meta-analysis summarizes the diagnostic accuracy of commonly used ultrasonographic signs for indicating the location of a pregnancy, and shows that the presence of any of the ultrasonographic features evaluated, namely a gestational sac, double decidual sac sign, intradecidual sign or chorionic rim sign, increases substantially the probability that a pregnancy is of intrauterine location. Therefore, the presence of these signs indicates an intrauterine pregnancy and can be used to guide clinical practice. The exception to this is the use of the presence of a gestational sac, as this test is slightly less specific than the others for predicting an intrauterine pregnancy. The absence of these signs does not exclude the diagnosis of an intrauterine pregnancy, and a negative test result therefore cannot be relied upon to inform clinical practice.

Strengths and weaknesses of the study

We conducted a prospective and extensive systematic search of electronic databases using a predefined protocol which was registered with PROSPERO. The high number of included studies in our meta-analyses for the presence of a gestational sac and the double decidual sac sign strengthened the power of these conclusions and enabled us to define the diagnostic accuracy of these signs in confirming an intrauterine pregnancy with relative precision. Our findings for the other ultrasonographic features, i.e. the intradecidual sign, chorionic rim sign and yolk sac, 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. However, the quality of the included studies was relatively poor, as there was a substantial risk of bias and concerns regarding the applicability to current clinical practice. Furthermore, many of the studies reported a different prevalence of pregnancy outcomes compared with more recent studies, which may affect the generalizability of the findings to clinical practice in a variety of settings.

The main limitation of our study is that our conclusions with regard to evaluating the accuracy of visualization of a yolk sac for determining the location of an intrauterine pregnancy have been drawn from one small study. Other studies investigating the significance of a yolk sac in early pregnancy were identified by the search strategy, but these did not meet the prespecified inclusion criteria. These studies were considered to be largely irrelevant, as they were more concerned with the relative size, shape or position of the yolk sac with regard to predicting pregnancy viability than with the actual presence of the yolk sac confirming identification of a true gestational sac and, ultimately, an intrauterine pregnancy, which was the focus of our review. It is surprising that no other studies have been conducted to investigate the performance of visualization of the yolk sac on ultrasound for determining the true nature of an intrauterine fluid collection. It can be speculated that this may be because, embryologically, the yolk sac is derived from migrating hypoblast cells of the inner cell mass and could therefore only occur within a true gestational sac. In the case of a pseudosac, which is merely a fluid-filled space with no gestational tissue, there is no potential to develop a yolk sac. Given this fact and the 100% specificity found in the one included study, further studies to investigate the accuracy of a yolk sac

for predicting an intrauterine pregnancy may have been considered unnecessary.

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 a gestational sac for predicting an intrauterine pregnancy ranged from 14% in the study by Dart *et al.*[21] to 100% in the study by Weckstein *et al.*[19]. This is probably because of the considerable population heterogeneity between the studies. Dart *et al.* included only pregnant women with abdominal pain and/or vaginal bleeding with an indeterminate ultrasound scan, who had either a serum hCG level > 3000 mIU/mL or whose last menstrual period was > 38 days before examination. It was conducted using transvaginal ultrasound, and a gestational sac was defined as an empty anechoic intrauterine fluid collection with a hyperechoic border and mean sac diameter of < 10 mm. In contrast, Weckstein *et al.* included a less specific group of patients, potentially a broader definition of what constitutes a gestational sac and a less accurate ultrasonographic approach. It is therefore no surprise that these studies, with their inherent differences in study design, have yielded considerably different accuracy measures.

A final limitation of this study is that no information regarding pregnancy viability can be inferred from the results. The finding of the double decidual sac sign, for example, suggests an intrauterine pregnancy with a sensitivity of 81.8% and specificity of 97.3%, but whether that pregnancy is viable or not cannot be concluded from our results. However, it was the aim of this systematic review to determine the accuracy of first-trimester ultrasonographic signs in predicting intrauterine pregnancy location, and this has been accomplished. In order to achieve this, of studies that considered three separate outcomes including viable intrauterine, non-viable intrauterine and ectopic pregnancies, all intrauterine pregnancies were combined prior to construction of the 2×2 tables[6,13–18,20,21,23–25]. Of studies that did not differentiate between viable and non-viable intrauterine pregnancies, no such combination was required[5,7,12,19,22].

In conclusion, this review is the first to collate comprehensively evidence of the accuracy of various ultrasonographic features for predicting an intrauterine pregnancy before visualization of the yolk sac. The findings are limited by the relatively small number and poor quality of the included studies and by the heterogeneity seen between the tests and outcome assessment. An appropriately powered study following STARD guidelines[26], using transvaginal ultrasound and an appropriate reference standard, is required to establish standards for the accurate prediction of an intrauterine pregnancy. In the interim, it would be prudent to continue the current practice of waiting until a yolk sac is visualized before confirming that a pregnancy is intrauterine.

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REFERENCES

1. Timor-Tritsch IE, Farine D, Rosen MG. A close look at early embryonic development with the high-frequency transvaginal transducer. *Am J Obstet Gynecol* 1988; **159**: 676–681.
2. Fleischer AC, Pennell RG, McKee MS, Worrell JA, Keefe B, Herbert CM, Hill GA, Cartwright PS, Kepple DM. Ectopic pregnancy: features at transvaginal sonography. *Radiology* 1990; **174**: 375–378.
3. Lazarus E. What's new in first trimester ultrasound. *Radiol Clin North Am* 2003; **41**: 663–679.
4. Bottomley C, Bourne T. Dating and growth in the first trimester. *Best Pract Res Clin Obstet Gynaecol* 2009; **23**: 439–452.
5. Yeh HC, Goodman JD, Carr L, Rabinowitz JG. Intradecidual sign: a US criterion of early intrauterine pregnancy. *Radiology* 1986; **161**: 463–467.
6. Bradley WG, Fiske CE, Filly RA. The double sac sign of early intrauterine pregnancy: use in exclusion of ectopic pregnancy. *Radiology* 1982; **143**: 223–226.
7. Parvey HR, Dubinsky TJ, Johnston DA, Maklad NF. The chorionic rim and low-impedance intrauterine arterial flow in the diagnosis of early intrauterine pregnancy: evaluation of efficacy. *AJR Am J Roentgenol* 1996; **167**: 1479–1485.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement. *BMJ* 2009; **339**: b2535.
9. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM; QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**: 529–536.
10. Rutter CM, Gatsonis CA. Regression methods for meta-analysis of diagnostic test data. *Acad Radiol* 1995; **2** (Suppl 1): S48–S56; discussion S65–S67, S70–S71 pas.
11. Harbord RM, Deeks JJ, Egger M, Whiting P, Sterne JA. A unification of models for meta-analysis of diagnostic accuracy studies. *Biostatistics* 2007; **8**: 239–251.
12. Ankum WM, Van der Veen F, Hamerlynck JV, Lammes FB. Transvaginal sonography and human chorionic gonadotrophin measurements in suspected ectopic pregnancy: a detailed analysis of a diagnostic approach. *Hum Reprod* 1993; **8**: 1307–1311.
13. Bateman BG, Nunley WC Jr, Kolp LA, Kitchin JD III, Felder R. Vaginal sonography findings and hCG dynamics of early intrauterine and tubal pregnancies. *Obstet Gynecol* 1990; **75**: 421–427.
14. Chiang G, Levine D, Swire M, McNamara A, Mehta T. The intradecidual sign: is it reliable for diagnosis of early intrauterine pregnancy? *AJR Am J Roentgenol* 2004; **183**: 725–731.
15. Enk L, Wikland M, Hammarberg K, Lindblom B. The value of endovaginal sonography and urinary human chorionic gonadotropin tests for differentiation between intrauterine and ectopic pregnancy. *J Clin Ultrasound* 1990; **18**: 73–78.
16. Kadar N, DeVore G, Romero R. Discriminatory hCG zone: its use in the sonographic evaluation for ectopic pregnancy. *Obstet Gynecol* 1981; **58**: 156–161.
17. Romero R, Kadar N, Jeanty P, Copel JA, Chervenak FA, DeCherney A, Hobbins JC. Diagnosis of ectopic pregnancy: value of the discriminatory human chorionic gonadotropin zone. *Obstet Gynecol* 1985; **66**: 357–360.
18. Tongsong T, Pongsatha S. Transvaginal sonographic features in diagnosis of ectopic pregnancy. *Int J Gynaecol Obstet* 1993; **43**: 277–283.
19. Weckstein LN, Boucher AR, Tucker H, Gibson D, Rettenmaier MA. Accurate diagnosis of early ectopic pregnancy. *Obstet Gynecol* 1985; **65**: 393–397.
20. Dart R, Howard K. Subclassification of indeterminate pelvic ultrasonograms: stratifying the risk of ectopic pregnancy. *Acad Emerg Med* 1998; **5**: 313–319.
21. Dart R, Kaplan B, Ortiz L, Cloherty J, Lavoie T. Normal intrauterine pregnancy is 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. *Acad Emerg Med* 1997; **4**: 967–971.
22. Nyberg DA, Filly RA, Laing FC, Mack LA, Zarutskie PW. Ectopic pregnancy. Diagnosis by sonography correlated with quantitative HCG levels. *J Ultrasound Med* 1987; **6**: 145–150.
23. Nyberg DA, Mack LA, Harvey D, Wang KY. Value of the yolk sac in evaluating early pregnancies. *J Ultrasound Med* 1988; **7**: 129–135.
24. Nyberg DA, Mack LA, Laing FC, Jeffrey RB. Early pregnancy complications: endovaginal sonographic findings correlated with human chorionic gonadotropin levels. *Radiology* 1988; **167**: 619–622.
25. Nyberg DA, Laing FC, Filly RA, Uri-Simmons M, Jeffrey RB Jr. Ultrasonographic differentiation of the gestational sac of early intrauterine pregnancy from the pseudogestational sac of ectopic pregnancy. *Radiology* 1983; **146**: 755–759.
26. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, Moher D, Rennie D, de Vet HC, Lijmer JG; Standards for Reporting of Diagnostic Accuracy Group. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003; **138**: W1–12.

SUPPORTING INFORMATION ON THE INTERNET

Table S1 may be found in the online version of this article.

