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Prediction of miscarriage in women with viable intrauterine pregnancy- a systematic review and diagnostic accuracy meta-analysis

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Abstract: Prediction of miscarriage in women with viable intrauterine pregnancy- a systematic review and diagnostic accuracy meta-analysis

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Both ultrasound and biochemical markers either alone or in combination have been described in the literature for the prediction of miscarriage. We performed this systematic review and meta-analysis to determine the best combination of biochemical, ultrasound and demographic markers to predict miscarriage in women with viable intrauterine pregnancy. The electronic database search included Medline (1946 to June 2017), Embase (1980 to June 2017), CINAHL (1981 to June 2017) and Cochrane library. Key MESH and Boolean terms were used for the search. Data extraction and collection was performed based on the eligibility criteria by two authors independently. Quality assessment of the individual studies was done using QUADAS 2 (Quality Assessment for Diagnostic Accuracy Studies-2: A Revised Tool) and statistical analysis performed using the Cochrane systematic review manager 5.3 and STATA vs.13.0. Due to the diversity of the combinations used for prediction in the included papers it was not possible to perform a meta-analysis on combination markers. Therefore, we proceeded to perform a meta-analysis on ultrasound markers alone to determine the best marker that can help to improve the diagnostic accuracy of predicting miscarriage in women with viable intrauterine pregnancy. The systematic review identified 18 eligible studies for the quantitative meta-analysis with a total of 5584 women. Among the ultrasound scan markers, fetal bradycardia (n=10 studies, n=1762 women) on hierarchical summary receiver operating characteristic showed sensitivity of 68.41%, specificity of 97.84%, positive likelihood ratio of 31.73 (indicating a large effect on increasing the probability of predicting

miscarriage) and negative likelihood ratio of 0.32. In studies for women with threatened miscarriage (n=5 studies, n= 771 women) fetal bradycardia showed further increase in sensitivity (84.18%) for miscarriage prediction. Although there is gestational age dependent variation in the fetal heart rate, a plot of fetal heart rate cut off level versus log diagnostic odds ratio showed that at ≤ 110 beat per minutes the diagnostic power to predict miscarriage is higher. Other markers of intra uterine hematoma, crown rump length and yolk sac had significantly decreased predictive value. Therefore in women with threatened miscarriage and presence of fetal bradycardia on ultrasound scan, there is a role for offering repeat ultrasound scan in a week to ten days interval.

Key Words: miscarriage; ultrasound; marker; meta-analysis; prediction

Introduction

Miscarriage complicates 2-20% of pregnancies after demonstration of fetal cardiac activity on an ultrasound scan (1, 2). The incidence increases further with vaginal bleeding in early pregnancy (1). Pain and bleeding are associated with significant fear and anxiety about losing the pregnancy. In the presence of markers with high diagnostic value for predicting miscarriage, women can be counselled appropriately and follow up scans pre-empted.

Both ultrasound (USS) and biochemical markers either alone or in combination have been described in the literature for the prediction of miscarriage. Combination of ultrasound and demographic variables have also been investigated with good diagnostic accuracy for predicting miscarriage, however this study was done on all women attending early pregnancy unit and not exclusively for women with confirmed viable intrauterine pregnancy (Bottemley et al., 2013). Similarly, other investigators have studied biochemical, ultrasound and demographic markers in different combinations for prediction of miscarriage in cohorts of symptomatic and asymptomatic women with viable intrauterine pregnancies on scan (3, 4). We sought to perform this systematic review and meta-analysis to determine the best combination of biochemical, ultrasound and demographic markers to predict miscarriage in women with viable intrauterine pregnancy. Initially the systematic review was planned to look into studies that used markers in combination for prediction. However, following the initial review it was evident that many combinations of markers have been tested with varying diagnostic accuracy and it was not possible to perform a meta-analysis due to the diversity of the combinations used. Ultrasound seemed to be the common marker in combination with either demographic or biochemical markers. Therefore, we proceeded to perform a meta-analysis on ultrasound markers alone to determine the best marker that can help to improve

the diagnostic accuracy of predicting miscarriage in women with viable intrauterine pregnancy.

Materials and Methods

A protocol of this review was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42016046470).

Study eligibility criteria

The inclusion criteria for the systematic review were prospective cohort studies, which used combination markers or individual USS markers to predict miscarriage in women from six weeks up to 15+6 weeks gestational age with or without bleeding and viable intrauterine pregnancy. A gestational age of 15+6 weeks was chosen as the early pregnancy assessment units in United Kingdom widely treats women up to this gestational age. Case control studies, retrospective studies, case reports, case series, letters, and reviews were excluded as well as studies which included multiple pregnancies and intrauterine pregnancy of unknown viability. Other exclusion criteria were studies that involved treatment for miscarriage, those with Doppler USS criteria and studies in languages other than English where translated versions of the manuscript were not available. The main outcome of interest was prediction of miscarriage.

Information sources and search strategy

The electronic database search included Medline (1946 to June 2017), Embase (1980 to June 2017), CINAHL (1981 to June 2017) and Cochrane library. The following MESH terms were used to create three subset of citations (1) miscarriage (abortion, early pregnancy loss, early pregnancy outcome) (2) combination markers (scoring system, combination, compound,

composite, mixed, log regression model) (3) USS markers (gestational sac, amniotic sac, yolk sac, crown rump length, fetal heart, fetal heart rate, embryonic heart rate, chorio-decidual plate thickness, corpus luteum, endometrial thickness, trophoblastic thickness, uteroplacental thickness, sub chorionic hematoma, fetal growth delay, fetal motion, chorionic bump). The second and third subsets were combined using the Boolean term 'OR' and the combination of those two subsets were combined with the first subset using the Boolean term 'AND' to obtain a subset of citations relevant to our research question. Two authors (RNP and NP) performed independent literature searches and the reference lists of all recent reviews and primary articles were examined to identify any articles not captured by the search. Any disagreements in selecting the papers and data extraction were resolved by consensus.

Data extraction and quality assessment

Using predetermined forms, data were extracted independently by 2 authors (RNP and NP). Data were collected on study design and conduct, country of study, sample size, gestational age, marker used and miscarriage prediction. From each study, outcome data were extracted in 2×2 tables. Study quality assessment was performed using QUADAS-2 (Quality Assessment for Diagnostic Accuracy Studies-2: A Revised Tool) for evaluating the diagnostic accuracy of studies (5). The tool consists of four key domains covering patient selection, index test(s), reference standard and the flow and timing. Each domain was assessed in terms of risk of bias, and the first 3 domains were also assessed for concerns regarding applicability. Signalling questions were included in the tool to help judge the risk of bias. The index test(s) for the included studies were combination of various markers or ultrasound markers alone and the

reference standard was miscarriage confirmed clinically or by ultrasound scan or by histopathological examination during follow up.

Statistical analysis

Data from the studies using combination markers were summarised in a tabulated manner with the sensitivity and specificity data for each combination of markers. For ultrasound markers, statistical analysis was performed using the Cochrane systematic review software (Review Manager 5.3) and the meta-analysis of the eligible studies performed using the diagnostic test accuracy review stream (Cochrane Collaboration 2011). Data from each primary study were summarized in a 2 x 2 table of test results and forest plots constructed showing within-study estimates and confidence intervals (CI) for sensitivity and specificity of each ultrasound marker. Further subgroup analysis was performed based on the presence or absence of vaginal bleeding. Sensitivity analyses were performed based on the year of the study due to technological advances in the ultrasound machines (studies before the year 2000 and studies after the year 2000) and mode of scanning (Trans abdominal [TA] or Trans vaginal [TVS]) since these could potentially bias the results. For USS markers with data from four or more studies, modelling was performed using hierarchical summary receiver operating characteristic model (HSROC) graphs plotted (6, 7) (Stata vs. 13.0, Texas, USA). The graphs demonstrated summary receiver operating characteristic curves and the prediction region, the summary point and the confidence region. The between study heterogeneity was accounted for in the HSROC model. The sensitivity, specificity, positive and negative likelihood ratio for each ultrasound marker were tabulated. For the FHR, the log diagnostic odds ratio was plotted against the cut off levels given in the studies to determine the best cut off level to predict miscarriage.

Results

Study Selection

The electronic database search identified 4094 articles and a further 46 articles were found from other sources and review of reference lists of individual manuscripts. The study selection process is detailed in the PRISMA flow chart (Fig. 1) (8). A total of 27 studies were included in the qualitative data synthesis. Nine studies were further excluded from the quantitative meta-analysis because there was only one study available for each investigated item (3, 4, 9-15). The USS markers or combination of markers studied by a single study were mean sac diameter/CRL (15), difference between the observed an expected CRL for the gestational age (16), trophoblast thickness (11), amniotic sac volume and gestational sac (GS) volume – amniotic sac volume (14), rapid heart rate (12), discriminant analysis using GS, CRL and FHR (13), Gestational age (GA) + FHR and GA + YS diameter (3), FHR outside 95% CI (9) and log model including mean GS size and YS size (4) . Overall, 18 studies were eligible for the quantitative meta-analysis and included 5584 women.

Study characteristics

All included studies were prospective cohorts (N=28) that investigated combination markers or USS markers for the prediction of miscarriage in women with or without vaginal bleeding and viable intrauterine pregnancy. Of these, 10 studies were on women with vaginal bleeding and viable intrauterine pregnancy; eight studies were on asymptomatic women with confirmed fetal viability and 10 studies were on a mixed population of women with and without vaginal bleeding. The characteristics of the included are summarized in table 1.

Risk of bias assessment

The risk of bias was assessed in 4 main domains using the 'QUADAS-2: A Revised Tool' for patient selection, index test, reference standard and flow and timing (Fig. 2). Under the patient selection domain if the study included women with uterine malformation, fetal and chromosomal abnormalities and any medical conditions that can contribute to miscarriage, then it was considered at high risk for bias. If the study did not specify about their exclusion criteria, it was considered unclear risk for bias. For the index tests, many studies had not specified a cut off level to differentiate between ongoing pregnancies and miscarriage, and those that did, had not specified it prior to starting the study. This was an area of bias for the included studies. Similarly, if the same sonographer did not perform the USS, then there was a potential for inter observer bias. The reference standard for this review was occurrence of miscarriage, which can best be diagnosed using USS or clinical history and histopathological examination of the products of conception. In some studies it was not clearly stated whether the reference standard was interpreted without the knowledge of the index test. However, this is unlikely to affect applicability of the studies since miscarriage is an objective diagnosis and is not prone to subjective interpretation. In the flow and timing domain, although it was difficult to predict a specific time interval from the index test to reference standard (occurrence of miscarriage), we used the sampling question to determine whether the patients were followed up until at least 22 weeks. The World Health Organisation (17) has defined miscarriage as premature loss of a fetus up to 22 weeks of pregnancy or below 500 grams of weight. Some studies used telephone interviews or review of case notes to determine the outcome, which can contribute to bias.

Quantitative data summary and synthesis of results

Combination markers

There were four studies that have qualified for the review and used a combination of markers for prediction of outcome of viable intra uterine pregnancy and presented their results using sensitivity and specificity. Table 2 summarises those studies with the sensitivity and specificity values in predicting the outcome. However, it was not possible to do a meta-analysis due to the diversity in the combinations of markers used. Interestingly, it was observed that in combinations that used certain specific markers such as FHR, were noted to have higher diagnostic accuracy. This urged us to look into individual ultrasound markers that have got high diagnostic accuracy in predicting the outcome of viable intra uterine pregnancy and also in a sub population of threatened miscarriage.

Ultrasound markers

Data were summarized for the USS markers of FHR (bradycardia), CRL, mean gestational sac diameter (MGSD) minus CRL, YS and intra uterine haematoma (IUH). Test results were tabulated in a 2 x 2 table and forest plots constructed for the sensitivity and specificity of the USS marker with their confidence intervals. Further subgroup analysis was done for women with threatened miscarriage and sensitivity analyses were also performed for the year of the publication (pre year 2000 and after 2000) and mode of scanning (TAS vs TVS).

Fetal bradycardia

There were ten studies that investigated fetal bradycardia in predicting miscarriage (18-27) and included asymptomatic women and those with vaginal bleeding (N=1762) (Fig. 3a). HSROC showed a sensitivity of 68.41% (95% CI 43.62- 85.84%), specificity of 97.84% (95% CI 94.50-99.17%), positive likelihood ratio of 31.73 (95% CI 12.78- 78.75) and negative likelihood ratio of 0.32 (95% CI 0.16-0.65) (Fig. 3b). The positive likelihood ratio indicates a large effect

of fetal bradycardia on increasing the probability of predicting miscarriage, although the CI is wide.

Further subgroup analysis was performed for women with vaginal bleeding (five studies; N=771) (18, 19, 21, 23, 24) (Fig. 4a). The HSROC analysis showed a significant increase in the sensitivity of FHR to predict miscarriage from 68.41% to 84.18% (95% CI 42.02% - 97.50%), specificity of 95.68% (95% CI 87.76% - 98.56%), positive likelihood ratio of 19.51 (95% CI 5.44-69.84) and negative likelihood ratio of 0.16 (95% CI 0.03- 0.91)) (Fig. 4b).

A sensitivity analysis based on the year of the study (before and after the year 2000 AD) showed a significant increase in the sensitivity for the studies performed after year 2000 (sensitivity of 90.70% (95% CI 65.75- 98.02%), specificity of 95.20% (95% CI 87.08-98.31%), positive likelihood ratio of 18.91 (95% CI 6.25- 57.21) and a negative likelihood ratio of 0.09 (95% CI 0.02-0.43)). Most of the studies for FHR were done with TVS.

Seven studies (18-20, 22, 23, 26, 27) specified a cut of value of FHR for the prediction of miscarriage. The log diagnostic odds ratio plotted against the cut off level of FHR given for each of the seven studies showed that a cut-off of ≤110 beats per minute (bpm) predicts miscarriage best and beyond 110 bpm the diagnostic power of the test diminishes (Fig. 5). Only two (22, 26) of these seven studies investigated FHR based on the gestational age and a meta-regression model showed a FHR of ﹥134 bpm at seven weeks and 158 bpm at eight weeks gestation was predictive of an on-going pregnancy (i.e. did not miscarry).

CRL

Five studies with 1136 women investigated the use of CRL for the prediction of miscarriage (20, 21, 23, 28, 29) (Fig. 6a). HSROC showed a sensitivity of 59.81% (95% CI 48.78-69.93%),

specificity of 55.68% (95% CI 39.95-70.35%), positive likelihood ratio of 1.34 (95% CI 0.91-2.00) and negative likelihood ratio of 0.72 (95% CI 0.49-1.06) (Fig. 6b).

A subgroup analysis was performed on women with vaginal bleeding (three studies; N= 595) (21, 23, 29) and asymptomatic women (two studies; N= 541) (20, 28). No significant difference in the sensitivity and specificity was noted between the two groups.

Sensitivity analysis based on the year of the study (studies after the year 2000 AD) did not show any significant difference in the results. All the eligible studies on CRL were done as TV scans and hence we were not able to do a sensitivity analysis comparing studies with both TA scan and TV scan.

IUH

Three studies on 564 women with vaginal bleeding used IUH to predict miscarriage (21, 30, 31) (Fig. 7) in women with confirmed fetal viability. These had a sensitivity range of 17% - 92% and specificity range of 17%-83%.

Difference between the mean gestational sac diameter and crown rump length (MGSD-CRL)

Two studies (N=349 women) evaluated the MGSD minus CRL difference (MGSD-CRL) in the prediction of miscarriage in women with confirmed fetal viability. These had a sensitivity range of 39% -96% and a specificity range of 73% - 88% (20, 21).

YS

Three studies (N= 605 women) investigated YS (abnormal shape, size, echogenicity or absent YS) for the prediction of miscarriage (32-34). All the studies that investigated YS in miscarriage

prediction were on asymptomatic women. The studies demonstrated a wide variation in sensitivity ranging from 17%- 69% and specificity ranging from 79%- 99%.

Discussion

To the best of our knowledge, this is the first systematic review of various combination markers and USS markers for predicting miscarriage in women with diagnosed viable intrauterine pregnancy. Among individual ultrasound markers studied, FHR (bradycardia) had the highest sensitivity and specificity (sensitivity of 68.41% and specificity of 97.84%) for prediction of miscarriage. Further subgroup analysis showed that for FHR, the sensitivity is even higher for women with threatened miscarriage (sensitivity of 84.18 and specificity of 95.68%). There were seven studies that described a cut-off level for FHR (18-20, 22, 23, 26, 27) and a combined logistic diagnostic odds ratio showed a FHR cut off value of 110 bpm to be useful in predicting miscarriage. Although the FHR changes during normal early pregnancy, the studies in this review had a gestational age range of 6-14 weeks and on the basis of these studies, the cut off of 110 bpm was determined. These results will need to be interpreted with caution in view of the small number of studies and a wider gestational age range. The results have been demonstrated that studies which have used FHR in its combination model have highest sensitivity and specificity in predicting miscarriage.

Other ultrasound markers such as IUH, CRL, and MGSD-CRL have been studied but noted to have lower predictive values. An IUH can affect pregnancy outcome by its pressure effect on the gestational sac or irritation of the uterus and this effect depends on its size/volume and location in relation to the placenta (35). In the literature, the impact of IUH on the occurrence of miscarriage is variable with some studies supporting an increased miscarriage rate (35)

and others against an association with miscarriage (36). Our results demonstrate that the presence of an IUH is not a useful tool in miscarriage prediction. It was not possible to do subgroup analysis based on the size of haematoma because of lack of information in the published studies.

The results of this meta-analysis showed that CRL has lower predictive value than FHR for miscarriage (CRL sensitivity of 59.81% and specificity of 55.68%; FHR sensitivity of 68.41% and specificity of 97.84%). This could be due to the fact that embryos that measure small at the initial scan are due to incorrect dates or are pregnancies that are likely to have fetal growth restriction later on (37).

Abnormal YS size and appearance have been reported to be useful markers for miscarriage prediction before the demonstration of fetal viability (38), however in presence of established viable intra uterine pregnancy, its usefulness is limited. Probably for this reason there was obvious lack of reporting about yolk sac measurements in the included studies.

We recognize some of the limitations of this meta-analysis. We were unable to do a meta-analysis on combination markers (biochemical, ultrasound and demographic factors), which would have been extremely valuable. However, there was wide variation in the combination markers used by the studies to do a meta-analysis. Another limitation was that the included studies used both TA and TV scan to measure ultrasound markers, which could contribute to measurement bias. Although at the protocol stage of the review the plan was to perform a sensitivity analysis based on the scanning approach, this was not possible because there were not enough studies in the two groups.

Although it is generally known that fetal bradycardia is an ominous sign in early pregnancy, follow-up scans based on fetal bradycardia are often not offered. Studies in literature have shown variable results regarding predictive ability of FHR, however, this review highlights that FHR is the best ultrasound marker to aid in miscarriage prediction and fetal bradycardia had a positive likelihood ratio of 31.73 (indicating a large effect on increasing the probability of predicting miscarriage). A plot of FHR cut off level versus log diagnostic odds ratio showed that at ≤ 110 beat per minutes the diagnostic power to predict miscarriage is higher. The rate of prediction increases further in women with threatened miscarriage.

This is the first systematic review investigating the evidence of ultrasound markers in predicting miscarriage in women with viable intrauterine pregnancy. In the UK, current practice is of reassuring women with threatened miscarriage with no further follow up. Based on the results of this review it is evident that in women with threatened miscarriage and presence of fetal bradycardia on USS, there is a role of offering repeat USS in a week to ten days interval.

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Conflict of Interest

No conflict of interest.

Author's role

Rekha N Pillai: Contributed to the concept, study design, database search, data extraction and quality analysis, statistical analysis, writing the manuscript and final approval of the manuscript

Justin C Konje: Contributed to the concept, reviewing of the manuscript and final approval of the manuscript

Mathew Richardson: Contributed to the analysis and interpretation of the results, reviewing of the manuscript and final approval of the manuscript

Douglas G Tincello: Contributed to the concept, reviewing of the manuscript and final approval of the manuscript

Neelam Potdar: Conceived the idea, study design, database search, data extraction and quality analysis, statistical analysis, writing the manuscript and final approval of the manuscript

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Figures

Figure 1 Flow chart for identification and selection of studies in the systematic review and meta-analysis (Moher *et al*., 2009)

Figure 2 Summary of quality assessment of the included studies for meta-analysis using the QUADAS-2: A Revised Tool.

Figure 3a Forest plot of study results for FHR in women with viable intrauterine pregnancy FN=false negative; FP=false positive; TN=true negative; TP=true positive.

Figure 3b HSROC curve and Empirical Bayes estimate for FHR for studies with viable intra uterine pregnancy.

Figure 4a Forest plot of study results for FHR in women with threatened miscarriage FN=false negative; FP=false positive; TN=true negative; TP=true positive.

Figure 4b HSROC curve and Empirical Bayes estimate for FHR for studies with threatened miscarriage.

Figure 5 Plot of cut off value for heartrate versus Log Diagnostic Odds of FHR in women with viable intrauterine pregnancy.

Figure 6a Forest plot of study results for CRL in women with viable intrauterine pregnancy FN=false negative; FP=false positive; TN=true negative; TP=true positive.

Figure 6b HSROC curve and Empirical Bayes estimate for CRL for studies with viable intra uterine pregnancy.

Figure 7 Forest plot of study results for IUH in women with viable intrauterine pregnancy FN=false negative; FP=false positive; TN=true negative; TP=true positive.

Tables

Table 1 Characteristics of the included studies in the systematic review

Authors and publication year	Country	Patient characteristic	Index tests (USS markers)	Index test cut off	Miscarriage diagnosis	Follow-up duration
Borlum et al., 1989	Denmark	N= 380, >8 weeks till second trimester, PV* bleed +	IUH TA scan	IUH +	Individual follow up on an ambulatory basis	Until miscarriage or delivery
Laboda et al., 1989	United States of America	N= 65, 5-8 weeks, symptom not specified	FHR Both TA and TV scan	<90 bpm	USS or clinic review	Not clear
Merchiers et al., 1991	Belgium	N= 170, 5-12 weeks, symptom not specified	FHR TA or TV scan not specified	100 bpm	Not specified	Beyond first trimester
Achiron et al., 1991	Israel	N= 603, first trimester, PV bleed +	FHR TV scan	FHR outside the 95%	Telephone, mail and USS	Beyond 13 weeks

				confidence interval		
Jun et al., 1992	Korea	N= 111, 6-9 weeks, both symptomatic and asymptomatic women	Mean Gestational Sac size, CRL, FHR TA scan	Not specified	Medical notes, USS	Until delivery or miscarriage
Tadmor et al., 1994	Israel	N= 603, first trimester, both symptomatic and asymptomatic women	Gestational sac diameter / crown rump length (GSD/CRL) TV scan	Outside 95% CI	Telephone, mail survey and USS	Up to 13 weeks
Falco et al., 1996	Italy	N=270, 5-12 weeks, PV bleed +	MGSD-CRL, CRL, SCH, FHR and menstrual age – sonographic age TV Scan	<14 mm (CRL), ≤ 0.5 SD (MGSD-CRL), <1 SD (FHR), >1 week (menstrual age-sonographic age)	Clinic follow up	Up to 20 weeks
Stampone et al., 1996	Italy	N=117, first trimester, PV bleed +	Size and shape of YS TV scan	+/- 2 SD	Not clear	Not clear
Qasim et al., 1997	United States of America	N= 116, 5.5-9.5 weeks, , both symptomatic and asymptomatic women	FHR TV scan	>2 SD	Not clear	24 week
Stefos et al., 1998	Greece	N= 2164, 6-8 weeks, symptom status not known	FHR TA and TV scan	≤ 85 bpm	USS	12 week
Alcazar and Ruiz-Perez, 2000	Spain	N= 49, 5-12^{+6} weeks, PV bleed+	Retro chorionic hematoma TV Scan	Present or absent	Not clear	End of pregnancy
Bajo et al., 2000	Spain	N= 592, 5-12 weeks, PV bleed -	Trophoblast thickness TV Scan	>3mm	USS	12 weeks

Doubilet et al., 2000	United States of America	N= 2817, <7 weeks, PV bleed +	Rapid heart rate TA or TV scan not specified	134bpm before 6.3 weeks and 154 bpm 6.3 to 7 weeks	USS or delivery of the baby	At least 13 weeks
Reljic, 2001	Slovenia	N= 310, up to 13 weeks, PV bleed +	CRL TV Scan	≤ 18mm	Hospital records and patient interview	Not clear
Chittacharoen and Herabutya, 2004	Thailand	N= 240, 6-12^{+6} weeks, PV bleed last 24 hour +	FHR TV Scan	<120 bpm	Until delivery or outcome	Not clear
Mukri et al., 2008	United Kingdom	N= 292, 5-10 weeks, both symptomatic and asymptomatic women	CRL deficit TV Scan	>2 SD	USS or by contacting women or GP	12-14 weeks
Varelas et al., 2008	Greece	N= 219, 6-12 weeks, PV bleed -	GA+ FHR GA+ Yolk sac diameter (YSD) TV Scan	ROC cut off > 0.948 (GA+FHR) ROC cut off > 0.939 (GA+YSD)	USS	12 weeks
Altay et al., 2009	Turkey	N=99, 10 weeks, PV bleed +	MGSD, FHR, MGSD-FHR TV Scan	No cut off specified	USS	20 weeks
Dede et al., 2010	Turkey	N= 202, 5-14 weeks, PV bleed +	CRL Cervical length FHR TV Scan	<40 mm (cervical length) <130bpm (FHR)	Not clear	Up to 20 weeks
Tan et al., 2011	Turkey	N= 183, 6-8^{+6} weeks, PV bleed -	Irregular YS	Irregular YS present or absent	USS	20 weeks
Phupong and Hanprasertpong, 2011	Thailand	N= 30, 6-14^{+6} weeks, PV bleed +	FHR TV Scan Both TA and TV scan	<2 SD	USS	Not clear
Odeh et al., 2012	Israel	N=90, 6-12 weeks, PV bleed +	Amniotic sac volume (ASV), Gestational sac volume	≤ 1.8 cm^3 (GSV-ASV)	Not mentioned	24 weeks

			(GSV), GSV-ASV			
Abuelghar et al., 2013	Egypt	N= 341, 6-13 weeks, PV bleed -	TV scan Smaller than expected CRL	<2 SD	USS	Not clear
Maged and Mostafa, 2013	Egypt	N=150, 5-12 weeks, PV bleed+	TV scan GSD CRL FHR YSD	21mm (CRL) 110 bpm (FHR)	Not clear	Not clear
Oates et al., 2013	Australia	N= 443, first trimester, , both symptomatic and asymptomatic women	TV Scan Log model using mean gestational sac size and mean yolk sac size.	AUC of 0.55	Obstetrics database	12 weeks
Tan et al., 2014	Turkey	N=305, 6-9 weeks, PV bleed-	TV scan Size, shape and echogenicity of yolk sac	YSD ≥ 5mm	Medical records and telephone interview	Until delivery
El-Mekkawi et al., 2015	Egypt	N=200. 7weeks, PV bleed-	TV Scan MGSD CRL FHR MGSD-CRL	14mm (MGSD) 5.5mm (CRL)	USS and clinical symptoms	20 weeks
			TV Scan			

* Per-vaginal

Table 2 Studies using combination markers for prediction of miscarriage in women with confirmed fetal viability

Study	Prediction model used	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Varelas et al., 2008	GA+FHR	91%	100%		
	GA+YSD	76.8%	91.7%		
Altay et al., 2009	Logistic regression model using maternal age, MGSD, MGSD-CRL, FHR and Progesterone level			50%	98.9%
Maged et al., 2013	FHR+ progesterone	100%	100%		
Oates et al., 2013	Log model using GA by LMP* , presence of PV bleeding, presence of PV clots, GA by USS,	82%	79%		

	consistency with menstrual dates, mean GS size, mean YS size and number of previous caesarean sections	

*Last Menstrual Period