Systematic review

Assessing the predictive value of first trimester ultrasound and biochemical markers in miscarriage: A scoping review☆

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ABSTRACT

Introduction: Vaginal bleeding in the first trimester of pregnancy generates anxiety and uncertainty for expecting parents. The ability to determine pregnancy outcome through a first trimester ultrasound scan remains a challenge in obstetrics. Several first trimester ultrasound markers used individually or in combination, as well as ultrasound markers used in combination with biochemical markers, have been studied to determine their predictive value in pregnancy outcome. This scoping review was performed to determine which markers have already been investigated for this purpose.
Methods: An extensive and systematic database search was performed using four different categories of keywords which were combined using Boolean terms. A total of 14 variables were included on the final data charting forms. Data was synthesised collectively for each variable and then separately for the studies analysing only one marker. For the studies which analysed multiple markers, data was synthesised based on the number of markers per study.
Results: The search yielded 3608 studies, of which 128 were ultimately used for this review. Data extraction, based on predetermined eligibility criteria, was performed by two authors independently. Seventy-seven (62.6%) studies investigated the predictive value of a single ultrasound marker. The remaining 46 (37.4%) studies explored multiple markers, of which at least one was an ultrasound marker.
Conclusion: This review identified several discrepancies among different studies. This highlights the need for better consensus among researchers to allow for the design of a predictive model which enables extrapolation of findings to all pregnant women.
Implications for practice: Through the study of ultrasound and biochemical markers in the first trimester of pregnancy, clinicians may provide a more accurate prediction of pregnancy outcome following threatened miscarriage.

Introduction

One of the most common obstetric complications in the first trimester of pregnancy, requiring an ultrasound (US) examination, is vaginal bleeding (VB).[1] Threatened miscarriage (TM) is defined as VB prior to the 20th week of gestation, with the presence of fetal cardiac activity on US and a closed cervical os on clinical examination.[2] VB associated with TM in the first trimester of pregnancy may lead to a miscarriage later in pregnancy in more than 50% of patients.[1] Moreover, women who do progress with the pregnancy are at higher risk of both maternal and fetal complications later in pregnancy, such as those associated with abnormal placentation,[3] placental abruption, preeclampsia, low birth weight, premature rupture of membranes (PROM) and preterm labour.[1]

Miscarriage is defined as spontaneous pregnancy loss during the first half of pregnancy. The Royal College of Obstetricians and Gynaecologists defined miscarriage as a loss of a pregnancy prior to the 24th week of gestation,[4] while The National Health Service in the United Kingdom defined miscarriage as loss of a pregnancy during the first 23 weeks of gestation.[5] The American College of

List of abbreviations

US	Ultrasound
VB	Vaginal Bleeding
TM	Threatened Miscarriage
PROM	Premature Rupture Of Membranes
BC	Biochemical
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
WOS	Web Of Science
CINAHL	Cumulative Index to Nursing and Allied Health Literature
EBSCO	Elton B. Stephens Company
MeSH	Medical Subject Headings
TVS	Transvaginal Sonography
3D	3 Dimensional
TV	Transvaginal
TA	Transabdominal
IUH	Intrauterine Haematoma
FHR	Fetal Heart Rate
YS	Yolk Sac
CRL	Crown Rump Length
DS	Doppler Study
CB	Chorionic Bump
UF	Uterine Fibroid
GS	Gestational Sac
FV	Fetal Volume
TT	Trophoblast Thickness
TBV	Trophoblast Volume
MGSD	Mean Gestational Sac Diameter
UAD	Uterine Artery Doppler
RI	Resistive Index

Obstetricians and Gynaecologists defined early pregnancy loss as a nonviable intrauterine pregnancy within the first 12^{+6} weeks of gestation.[6]

The precise aetiology of threatened and spontaneous miscarriages is not precisely known, especially when chromosomal abnormalities, diagnosed in approximately 60% of products of miscarriage, are ruled out.[7] It is estimated that about 25% of spontaneous miscarriages may be prevented if risk factors such as smoking and obesity could be mitigated.[8]

Although various management protocols have been developed, including conservative management and hormonal therapy,[9] overall, TM can generate great anxiety in patients.[10] This is especially because of the paucity of tools which can give an accurate aetiological cause and even be used as predictive markers to give an accurate prognosis of whether bleeding in early pregnancy is going to lead to pregnancy loss and other obstetric complications. Although follow-up is offered by repeating the scan, as well as advising the patient to return to the hospital emergency department in case of heavy bleeding, the uncertainty of 'watching and waiting' fuels more anxiety, whatever the outcome.

The objective of this review is to report on first trimester US and biochemical (BC) markers and pregnancy outcome. The review seeks to examine whether first trimester US markers, used alone or in combination, or in combination with BC markers, may predict pregnancy outcome (i.e. miscarriage or ongoing pregnancy). To meet this objective, the following research questions have been formulated:

1. Which first trimester US markers, individually or in combination, have already been examined?
2. Which BC markers have been examined in combination with first trimester US markers?
3. What is the predictive value of the identified markers in pregnancy outcome?

A preliminary search of the area being investigated demonstrated that, owing to a high level of variation among different research publications (owing to diverse combinations of US and BC markers with varying diagnostic accuracy), extracted data are best suited for a scoping review.[11]

All the studies included in this review investigated sonographic and/or blood markers to determine the potential predictors of pregnancy outcome on symptomatic and/or asymptomatic cohorts in the first trimester of pregnancy.

Methodology

The guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) have been followed to draw up the report of this review.[12]

Eligibility criteria

The inclusion criteria for the scoping review were prospective and retrospective cohorts, including case–control studies, which used individual first-trimester US markers, a combination of first-trimester US markers, as well as a combination of first-trimester US and BC markers, to predict pregnancy outcome. This review included cohorts with singleton, intrauterine pregnancies with the presence of fetal cardiac activity, with or without pain and/or VB. The studies that investigated abnormal pregnancy outcome during any trimester of pregnancy, following an US scan performed between 5^{+0} and 15^{+0} weeks' gestation, were included.

Case reports, case series, letters, commentaries, review papers, guidelines and dissertations were excluded from this review. Studies which predicted pregnancy outcome based on second or third trimester US scans were excluded. Recurrent miscarriage cohorts, studies which included patients with trophoblastic disease and known fetal structural and/or chromosomal abnormalities, known uterine malformations or maternal medical conditions, such as diabetes mellitus, thyroid disorders and hypertension, were also excluded, as were studies in which the entire cohort received fertility treatment and/or included only assisted conceptions. Studies were excluded if only normal pregnancy outcome was investigated or if patients opted for an elective abortion following the first trimester US scan and/or pregnancy outcome was not recorded. This is because the main outcome of interest for this review was miscarriage following a first trimester US scan. Studies which predicted pregnancy outcome based solely on artificial intelligence for estimation of measurements, as opposed to human measurements, were excluded. Studies which included non-human subjects or were not available in the English language or where full papers could not be retrieved, were also excluded.

Information sources

The searches were conducted on 20th January 2022, and repeated on 23rd March 2023, in the databases PubMed (including MEDLINE) and Web of Science (WOS). Cochrane and Cumulative

Index to Nursing and Allied Health Literature (CINAHL) databases were accessed through the Elton B. Stephens Company (EBSCO) search engine. For the search to be as comprehensive as possible, the search string did not include any constraints on the studies' publication dates.

Search strategy and data extraction

The Medical Subject Headings (MeSH) terms used for the search were split into four categories, as follows:

- **Category 1** - ultrasound, scan, sonogram, transvaginal, TVS, endovaginal, sonography, sonographic, sonographically, ultrasonography, ultrasonographic, ultrasonographically, volumetric, three-dimensional, volume measurement, 3D, Doppler, colour Doppler.
- **Category 2** - combination markers, scoring system, combination, compound, composite, mixed, log regression model
- **Category 3** - ultrasound marker, gestational sac, amniotic sac, yolk sac, crown-rump length, fetal heart, fetal heart rate, embryonic heart rate, chorio-decidual plate thickness, corpus luteum, trophoblast thickness, uteroplacental thickness, hematoma, chorionic bump, cervical length, coelomic cavity, fibroid, leiomyoma, gestational sac volume, yolk sac volume, embryonic volume, trophoblast volume, amniotic sac volume, subchorionic vessels, subtrophoblastic arteries, intervillous circulation, uterine artery, uteroplacental circulation, pulsatility index, resistive index, nuchal translucency.
- **Category 4 -** threatened miscarriage, miscarriage, abortion, early pregnancy loss, early pregnancy outcome, early pregnancy viability, threatened abortion, early abortion, spontaneous miscarriage, spontaneous abortion.

Keywords within each category were combined using the Boolean term 'OR'. Categories two and three were also combined using the Boolean term 'OR' and then combined with categories one and four using the Boolean term 'AND.'

The literature search strategy was drafted by the main author of the study and executed by two authors independently. The final search results were exported into a spreadsheet using different sheets for each database. A new sheet was then created to combine the results from each database, excluding duplicates. Following an abstract review, the studies were then sorted as 'Potentially Relevant' or 'Not Relevant', by each of the authors of the studies, based on the eligibility criteria of this scoping review. Any differences in the sorting process among the authors during data extraction were resolved unanimously by the authors.

Data charting process and data items

To provide a summary of the results obtained and to enable better flow in evidence synthesis, the dataset was organised into three forms. These were collaboratively drafted by the two reviewers, based on the objectives of this review. Although the variables to be extracted from the 'Relevant' studies were selected jointly by the reviewers, data were charted independently, and the outcomes were compared. A total of 14 variables were included on the final data charting forms. The first data charting form included all the studies which analysed only one US marker. The second data charting form was for studies which analysed more than one US marker, while the third form included the studies which analysed US and BC markers. The data on all three charting forms were primarily sorted by US marker/s or the US and BC markers which were analysed. Within each group of studies for each marker, they were then sorted by date, starting from the oldest article through to

the most recent one. Summarised versions of these charts are shown in Tables S1–S3. The data were synthesised using the PRISMA-ScR descriptive synthesis process. Data were synthesised collectively for each variable and then separately for the studies analysing the same US marker for those studies which only analysed one marker. For the studies which analysed multiple markers, data was synthesised based on the number of markers per study.

Results

The studies from all the databases, including duplicates, amounted to 3608. After removing the 1013 duplicates, the abstract of the remaining 2431 studies was reviewed and sorted as 'Potentially Relevant' or 'Not Relevant' based on the eligibility criteria of this scoping review. In accordance with PRISMA-ScR guidelines, the data collected has been summarised in a flow chart as shown in Fig. S1, detailing the selection process for the chosen studies for the review.

Of the 128 studies included in this review, 82[13–94] (64.1%) studies investigated the predictive value of a single US marker. Hereinafter, these studies are referred to as 'single marker studies.' The remaining 46[95–140] (35.9%) studies explored multiple markers, of which at least one was an US marker. These studies are hereinafter referred to as 'multiple marker studies.'

General characteristics of included sources of evidence

Study design type
All the studies included in this review were cohort studies. Of the 128 included studies, 96 (75%) were prospective, 24 (18.7%) were retrospective and 8 (6.3%) were either unclear or unspecified as to how they were carried out.

Sample population
There was great variation in the number of participants included in each study. The total number of participants in the prospective studies reviewed amounted to 38,702, while those in the retrospective studies amounted to 69,806. These figures were divided by the number of respective studies to calculate the average number of participants in both study types. For prospective studies, the average number of participants was 403, while the average number of participants for the retrospective studies was 2908.

Scanning method
There were varying methods of scanning across the studies included in this review; however, as the transvaginal (TV) probe became available in the 20th century, it became apparent that most studies conducted after the 1980s used only the TV method for first trimester pregnancy. The studies in which only TV scanning was used amounted to 76 (59.4%), while there were only 14 (10.9%) studies which used only the transabdominal (TA) method. Of all 128 studies, 4 (3.1%) made use of both methods for each patient, while 8 (6.3%) used either of the techniques on each patient. Five (3.9%) studies used either both or one technique, while the remaining 21 (16.4%) did not specify which method was used.

Number of ultrasound practitioners
Of the 128 included studies, 71 (55.5%) did not specify the number of practitioners, while 30 (23.4%) included only one practitioner. Eighteen (14.1%) studies did not specify the number of practitioners but mentioned that there was more than one. Six (4.7%) studies specified that two practitioners were involved, while three (2.3%) studies involved three.

Gestational age

Although all the studies in this review included only first trimester US markers, 20 (15.6%) of the 128 studies exceeded the twelfth week of pregnancy by a maximum of three weeks. This was especially common for the intrauterine haematoma (IUH) as well as fetal heart rate (FHR) markers. Unlike other first trimester markers, the measurement protocol of these two markers is not dependent on the trimester of pregnancy and are therefore still measured in the same way beyond the twelfth week of pregnancy. Consequently, these studies were retained for this review.

Publication year

Of all the 128 studies reviewed, the oldest study, sought through references, dated back to 1973, while the most recent one was published in 2023. There were 7 (5.5%) studies published between 1980 and 1989, 23 (18%) between 1990 and 1999, 26 (20.3%) between 2000 and 2009, 55 (42.9%) between 2010 and 2019 and 17 (13.3%) between 2020 and 23rd March 2023.

Symptoms of threatened miscarriage. All the studies included in this review investigated sonographic and blood markers to determine the potential predictors of miscarriage on symptomatic and/or asymptomatic cohorts. Of 128 studies, 23 (18.0%) studies included a sample population which consisted entirely of TM patients, while 29 (22.6%) studies stated that only part of the cohort had symptoms of TM. Thirteen (10.2%) studies investigated pregnancy outcome on a cohort without TM symptoms, while the remaining 63 (49.2%) studies did not specify whether participants presented with any symptoms.

Predictive value. Of the 82 studies which investigated only one marker, 64 (78.0%) concluded that the marker was useful to predict pregnancy outcome (i.e. miscarriage or ongoing pregnancy), 16 (19.6%) studies concluded that the marker was of no predictive value, while 2 (2.4%) studies concluded that it was unclear whether the marker had any predictive value in pregnancy outcome. Table 1 provides a summary of the predictive value per marker according to the studies investigated. Due to the various marker combinations which were analysed in studies which included more than one marker, it was not possible to reach a conclusion on the predictive value of each marker in isolation.

Follow up duration for outcome

Although the two main outcomes were 'miscarriage' and 'ongoing pregnancy', some authors continued to follow up participants also during the second or third trimesters of pregnancy. They were able to describe other outcomes, such as IUGR, PROM and APH potentially adding more weight to the predictive value of the marker/s being analysed. The follow up duration for outcome variable was classified into: 'first trimester', 'second trimester', 'term', 'no follow up duration for outcome specified' or 'unclear'. Different studies had varying follow up durations, with 30 (23.4%) studies following up participants until the first trimester of pregnancy; 29 (22.7%) studies up till the second trimester; 46 (35.9%) studies till term; 22 (17.2%) studies not specifying a follow up duration for outcome and one (0.8%) study remaining unclear.

Synthesis of single marker studies

Although 22 US markers were included in the search string, a total of 12 markers were ultimately analysed in the 82 single marker studies included in this review (Table S1), based on the eligibility criteria. In order of prevalence, these included the IUH (20, 24.4%), yolk sac (YS) (18, 21.9%), FHR (16, 19.5%), crown-rump length (CRL) (8, 9.8%), Doppler studies (DSs) (9, 11.0%), chorionic bump (CB) (5, 6.1%), uterine fibroid (UF) (2, 2.4%), gestational sac (GS) (1, 1.2%), fetal volume (FV) (1, 1.2%), trophoblast thickness (TT) (1, 1.2%), trophoblast volume (TBV) (1, 1.2%) and IUH volume-GS ratio (1, 1.2%) as shown in Table 2.

Synthesis of multiple marker studies

Of the 46 multiple marker studies included in this review, 32 (69.6%) studies included only US markers (Table S2), while 14 studies (30.4%) included both US and BC markers (Table S3). Table 3 demonstrates the frequency of US and BC markers in the multiple marker studies, with FHR being the most common marker across all the studies and CB, UF, AS, CC, CL, CDPT and UT not occurring in any of the multiple marker studies.

Table 1
Summary of the predictive value of each US marker according to the studies found.

Individual Marker Studies	Useful Predictor	No Predictive Value	Unclear
Intrauterine Haematoma (IUH)	15	5	0
Yolk Sac (YS)	13	3	2
Fetal Heart Rate (FHR)	13	3	0
Crown-Rump Length (CRL)	8	0	0
Chorionic Bump (CB)	3	2	0
Doppler - uterine artery	3	0	0
Doppler - spiral artery	2	0	0
Doppler- ductus venosus	2	0	0
Trophoblast Thickness (TT)	1	0	0
Trophoblast Volume (TBV)	1	0	0
Gestational Sac (GS)	1	0	0
Uterine Fibroids (UF)	1	1	0
Fetal Volume (FV)	1	0	0
Intrauterine Haematoma Volume - Gestation Sac Ratio (IUH volume-GS ratio)	1	0	0
Doppler - corpus luteum	0	2	0
Total	**65**	**16**	**2**

Table 2
The frequency of ultrasound markers in individual marker studies.

Marker	Frequency
Intrauterine Haematoma (IUH)	19
Yolk Sac (YS)	18
Fetal Heart Rate (FHR)	16
Doppler Studies (DS)[a]	9
Crown-Rump Length (CRL)	8
Chorionic Bump (CB)	5
Uterine Fibroids (UF)	2
Gestational Sac (GS)	1
Fetal Volume (FV)	1
Trophoblast Thickness (TT)	1
Placental/Trophoblast Volume (TBV)	1
Intrauterine Haematoma Volume - Gestation Sac Ratio (IUH volume-GS ratio)	1
Corpus Luteum (CPL)	0
Amniotic Sac (AS)	0
Coelomic Cavity (CC)	0
Cervical Length (CL)	0
Chorio-Decidual Plate Thickness (CDPT)	0
Uteroplacental Thickness (UT)	0
Amniotic Sac Volume (ASV)	0
Gestational Sac Volume (GSV)	0
Yolk Sac Volume (YSV)	0
Nuchal Translucency (NT)	0
Nasal Bone (NB)	0
Total number of individual marker studies	**82**

[a] Including uterine arteries (3), spiral arteries (2), corpus luteum (2) and ductus venosus (1).

Table 3
Frequency of ultrasound and biochemical markers in multiple marker studies.

Marker	Frequency
Ultrasound Markers	
Fetal Heart Rate (FHR)	28
Gestational Sac (GS)	27
Crown-Rump Length (CRL)	26
Yolk Sac (YS)	25
Doppler Studies (DS)[a]	16
Intrauterine Haematoma (IUH)	7
Gestational Sac Volume (GSV)	6
Yolk Sac Volume (YSV)	4
Fetal Volume (FV)	3
Placental/Trophoblast Volume (TBV)	2
Corpus Luteum (CPL)	2
Trophoblast Thickness (TT)	1
Nuchal Translucency (NT)	1
Nasal Bone (NB)	1
Amniotic Sac Volume (ASV)	1
Chorio-Decidual Plate Thickness (CDPT)	0
Uteroplacental Thickness (UT)	0
Amniotic Sac (AS)	0
Chorionic Bump (CB)	0
Uterine Fibroid (UF)	0
Coelomic Cavity (CC)	0
Cervical Length (CL)	0
Biochemical Markers	
Progesterone (P)	9
Beta-hCG (β-hCG)	5
Cancer Antigen 125 (CA-125)	4
Estradiol (E2)	3
Inhibin A (INHA)	2
17 hydroxyprogesterone (17-OHP)	1
Activin A (Act A)	1
Homocysteine (HCY)	1
Lactate Dehydrogenase (LDH)	1
Total Leucocyte Count (TLC)	1
Pregnancy-Associated Plasma Protein A (PAPP-A)	1

[a] Including tricuspid valve (1), ductus venosus (1), decidual artery (1), uterine artery (6), subtrophoblastic arteries (1), spiral artery (1), corpus lutem (2), utero-placental circulation (3).

Multiple marker studies analysing only ultrasound markers

Of the 32 multiple marker studies which included only US markers, five studies analysed two markers, six studies analysed three markers, twelve studies analysed four markers, six studies analysed five markers, two studies analysed six markers and one study analysed seven markers.

Multiple marker studies analysing ultrasound and biochemical markers

Of the 14 multiple marker studies which included both US and BC markers, four studies analysed two markers, four studies analysed four markers, three studies analysed five markers, two studies analysed six markers and one study analysed ten markers, as depicted in Table 4.

Table 4
Frequency of ultrasound and biochemical markers in multiple marker studies.

Total number of markers	Type of Marker	Frequency
2	1 US, 1 BC	4
4	1 US, 3 BC	2
	2 US, 2 BC	1
	3 US, 1 BC	1
5	1 US, 4 BC	1
	4 US, 1 BC	2
6	4 US, 2 BC	2
10	4 US, 6 BC	1

Discussion

Main findings

In order of frequency, the three most investigated individual ultrasound markers which satisfied the criteria of this review were IUH, YS and FHR. Unlike the YS and FHR, an IUH is a complication of pregnancy and therefore, unlike other individual US markers, most participants in the studies included in this category were patients who presented with symptoms of TM. The oldest two studies[47,48] which analysed the predictive value of IUHs in miscarriage and satisfied the eligibility criteria of this review date back to 1989. The literature suggests that YS and FHR were analysed for their predictive value in miscarriage prior to IUHs as evidenced by the fact that the studies included in the YS and FHR categories date further back than the studies included in the IUH category. Thirteen studies in each of the YS and FHR categories included in this review concluded that the YS and FHR are useful predictors of pregnancy outcome, with the oldest studies being conducted by Crooij et al.[13] in the YS category and the study conducted by Robinson & Shaw-Dunn[31] in the FHR category. Through this review, it became apparent that there is a larger concentration of studies in the IUH category which were published since the year 2000, with the two most recent studies[64,65] being published in 2022. Although both these studies concluded that IUHs in the first trimester of pregnancy increase the risk of miscarriage, Gu et al.[64] found that, similar to the findings of previous studies[47,48,50,53,57,61,63] the size of the IUH is an important characteristic determining pregnancy outcome, while Elmas et al.,[65] like Kurjak et al.[49] concluded that there was no correlation between the size of the IUH and miscarriage.

Progesterone was the most common BC marker in multiple marker studies. Nine of the 14 studies which combined US and BC markers to predict miscarriage included progesterone. Altay et al.,[135] Al Mohamady et al.,[139] Maged & Mostafa[140] and Hameed & Hasan[137] all concluded that progesterone is a good positive predictor of pregnancy outcome, while El-Mekkawi et al.[136] concluded that at the seventh week of pregnancy, the mean gestational sac diameter (MGSD), MGSD to CRL ratio and the FHR had higher sensitivity to predicting miscarriage than progesterone and CRL. Shehata et al.[130,134] reported that progesterone is a positive predictor of miscarriage, as opposed to uterine artery Doppler (UAD) indices while Kumari & Wanjari[130] found that although both UAD resistive index (RI) and progesterone were good predictors of miscarriage, uterine artery RI is of higher predictive value than serum progesterone.

Four marker studies were the most common multiple marker studies which included only US markers, with FHR, GSD, YS and CRL being the most popular combination.[106,107,109–113,115–117] Despite the variation in variables across these studies, they all concluded that the analysed markers were all useful in predicting pregnancy outcome.

Strengths and limitations

To ensure a thorough process, the undertaking of this scoping review was a lengthy one and consequently, the findings are up to date as of 23rd March 2023, being the date when the final search was executed on all databases.

Since only articles in the English language were included in this review, one must acknowledge that there may be articles available in other languages which may have contributed to the value of these findings and were not included in this review. One must also

recognise the possibility of selective publication of studies depending on the results obtained by researchers.

Interpretation

This is the first scoping review of its kind to map the gaps across studies which analysed first trimester US markers individually, in combination and in combination with BC markers to predict pregnancy outcome. Due to the heterogeneous nature of the variables and parameters used to predict pregnancy outcome, a precise systematic review of the literature could not be performed.

Through this review it became apparent that there have been several studies which confirmed that US and BC markers are valuable in predicting pregnancy outcome, with some markers exhibiting a stronger relationship than others. This review also highlights the fact that the prediction confidence may be increased when combining multiple US and/or BC markers.

This review revealed that although the objectives of the studies found in the literature were similar, several variations across most variables in both single and multiple marker studies exist across the studies. This clearly indicates that the area of study is still not at a stage where an established model exists which clearly defines the criteria required for US markers or US and BC markers to be used as predictors of pregnancy outcome.

Conclusion

In this scoping review, 128 studies were identified from databases and citation searching which analysed the predictive value of various US and BC markers in miscarriage, published between 1973 and 23rd March 2023. Of these, 82 studies analysed individual US markers, 32 analysed multiple US markers, while 14 analysed US and BC markers. The general characteristics of these studies were discussed collectively, following which a more thorough synthesis of each marker was performed for individual marker studies. Multiple marker studies were discussed according to the number of markers analysed per study.

Without conformity in protocols, a comparison of studies performed across different populations to verify the predictive value of these markers, as is normally done in systematic reviews and meta-analyses, is at high risk of bias and would yield unreliable conclusions. This is neither warranted nor recommended as it adds little to no value to the existing body of knowledge. This advocates the study to establish a list of markers having a strong predictive value, as well as the verification of these markers on a prospective population with the aim of establishing a predictive model and strict protocol that, in the future, may be studied on other populations for wider verification.

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Conflict of interest statement

No conflicts of interest identified.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radi.2024.07.022.

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