First trimester ultrasound for the detection of fetal heart anomalies: A systematic review and meta-analysis

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Contribution

What are the novel findings of this work?

In this systematic review (63 studies 328,214 fetuses), first trimester examination of the heart identified over half the fetuses affected by major cardiac pathology. There was an association between detection rates and structured anatomical assessment including outflow tract views and colour Doppler

What are the clinical implications of this work?

When undertaking detailed examination of the fetal heart in the first trimester a structured anatomical assessment protocol should be considered, which includes visualisation of the outflow tracts and colour Doppler.

ABSTRACT

Objectives: To determine the diagnostic accuracy of ultrasound at 11-14 weeks gestational age in the detection of fetal cardiac abnormalities, and to evaluate factors that impact detection rates.

Methods: A systematic review of studies evaluating the diagnostic accuracy of ultrasound in the detection of fetal cardiac anomalies at 11-14 weeks gestational age was undertaken by two independent reviewers. Prospective and retrospective studies evaluating pregnancies at all levels of prior risk and in any healthcare setting were eligible for inclusion. The reference standard used was the detection of a major cardiac abnormality on postnatal or post-mortem examination. Data were extracted from included studies to populate 2 x 2 tables. Meta-analysis was performed using a random-effects model in order to determine the overall performance of first trimester ultrasound in the detection of major cardiac abnormalities overall and in addition, for individual types of cardiac abnormalities. Data were analysed separately for high-risk populations vs. non-high risk populations. Pre-planned secondary analyses were conducted in order to assess factors which may impact screening performance including: the imaging protocol used for cardiac assessment (including use of Colour Doppler), mode of ultrasound, publication year of study, and the index of sonographer suspicion at the time of scan. A risk of bias and quality assessment was undertaken for all included studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2).

Results: An electronic search of four databases (Medline, Embase, Web of Science Core Collection and Cochrane Library) was conducted from January 1998 until July 2020 and identified 4108 citations. This led to 223 full text reviews from which a total of 63 studies were selected for inclusion. Data from a total of 328,214 screened fetuses were included. In non-high risk populations (45 studies, 306,872 fetuses), 1,445 major cardiac anomalies were identified (prevalence 0.41 (95% C.I. 0.39 – 0.43)). Of these, 767 were correctly detected by first trimester examination of the heart and 678 were not detected. Pooled sensitivity was 55.80% (95% CI 45.87– 65.50%,), specificity 99.98% (95% CI 99.97 – 99.99%) and positive predictive value 94.85% (95% CI 91.63– 97.32%). The cases diagnosed in the first trimester represent

63.67% (95% CI 54.35 – 72.49%) of all antenatally diagnosed major cardiac abnormalities. In high risk populations (18 studies, 21,342 fetuses) 480 major cardiac anomalies were identified (prevalence 1.36 (95% C.I. 1.20 – 1.52)). Of these, 338 were correctly detected in the first trimester, and 142 were not detected. The sensitivity was 67.74% (95% CI 55.25 – 79.06%), specificity 99.75% (95% CI 99.47 – 99.92%) and positive predictive value 94.22% (95% CI 90.22 – 97.22%). The cases diagnosed in the first trimester represent 79.86% (95% CI 69.89 – 88.25%) of all antenatally diagnosed major cardiac abnormalities in high risk populations. The imaging protocol used for examination was found to have an important impact on screening performance in all populations ($p<0.0001$), with significantly higher detection rates in those studies using outflow tract views and colour-flow Doppler imaging (both $p<0.0001$). Results showed that individual cardiac anomalies are not equally amenable to first trimester detection.

Conclusions: First trimester examination of the heart allows identification of over half of fetuses who are highly likely to be affected by major cardiac pathology. Future first-trimester screening programmes should follow structured anatomical assessment protocols, and introduction of outflow tract views and colour Doppler would be expected to improve detection rates.

Introduction

Congenital cardiac abnormalities are the most prevalent structural malformation, affecting 8 per 1000 fetuses. While the majority of these are minor, 3 per 1000 fetuses will suffer from severe forms of cardiac pathology[1,2]. The associated mortality remains high, with recent data linking congenital cardiac abnormalities to over 50% of all infant deaths in England[2]. Importantly, the morbidity and mortality of these neonates may be favourably impacted by a prenatal diagnosis[3-7].

The detection of cardiac abnormalities represents a distinct challenge for prenatal screening, and most occur in patients deemed to be of low a-priori risk[8,9]. The gold standard in many countries consists of a second trimester evaluation of cardiac anatomy. However, there is widespread variation in how screening is performed, and detection rates vary due to factors including anatomical views and sonographer training[9-12]. Specialist prenatal echocardiography can diagnose at least 80% of all congenital cardiac abnormalities, but during routine second trimester screening a large proportion are still missed[11].

Reports of successful fetal echocardiography in the first trimester were initially described over thirty years ago[13-16]. Since then, considerable improvements in technology have fuelled increasing interest in early anomaly detection [17-20]. As in the second trimester, practice between centres in routine first trimester screening varies: assessment without cardiac examination beyond demonstrating a heartbeat; routine visualization of a four-chamber view; detailed examinations involving outflow tract visualization including Doppler; or early risk stratification of patients using, for example, nuchal translucency, tricuspid regurgitation or ductus venosus measurements. Thus, there is little international consensus as to how first trimester cardiac anatomy assessment should be performed routinely[21-23].

Apart from the value of detecting a cardiac abnormality in itself, the finding is independently associated with fetal aneuploidy, genetic conditions and additional extra-cardiac malformations[24,25]. Thus, first trimester detection of cardiac abnormalities is complimentary to

the over-arching objective of diagnosing chromosomal abnormalities earlier and will often constitute an indication for invasive prenatal testing, rather than screening using cell-free DNA.

The aim of this study was to determine the diagnostic accuracy of two-dimensional ultrasound at 11-14 weeks gestational age in the detection of fetal cardiac abnormalities; and to evaluate factors that impact detection rates.

Methods

The study protocol was developed and registered with the PROSPERO Database (ID CRD42018112434) prior to undertaking the search strategy, the selection of studies and data extraction. The review of all articles included within this meta-analysis, and the reporting of all results, were based on the Meta-Analysis of Observational Studies in Epidemiology (MOOSE), the Synthesizing Evidence from Diagnostic Accuracy Tests (SEDATE) guidance, and the Preferred Reporting Items for a Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies (PRISMA – DTA)[26-29]. We also consulted the Cochrane Collaboration Systematic Reviews of Diagnostic Test Accuracy handbook[30].

Search Strategy

A systematic electronic search was designed with the help of a specialist librarian (NR) in order to identify all relevant studies evaluating the diagnostic accuracy of two-dimensional ultrasound in the detection of fetal cardiac anomalies at 11-14 weeks gestational age (Appendix 1). The search was initially developed using free-text terms and subject headings related to prenatal screening, early pregnancy and congenital abnormalities as previously described[19]. In order to increase sensitivity, we incorporated free-text terms and subject headings for specific congenital anomalies. The search was conducted on Medline(OvidSP), Embase(OvidSP), Science Citation Index and Conference Proceedings Citation Index-Science(Web of Science Core Collection) and Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (Cochrane Library, Wiley) from January 1st, 1998 until July 17th, 2020. Non-English language papers, single case reports, commentary and animal studies were excluded within Endnote X9 after full de-duplication of references (NR).

Study selection was performed in stages by two independent reviewers (JNK and EB). Titles of citations obtained from the systematic electronic search and abstracts were reviewed to identify potentially relevant studies. Full texts were subsequently evaluated to determine their eligibility for inclusion. The reference lists of all eligible studies were screened for additional citations not identified by the initial electronic search. Agreement regarding inclusion and

exclusion of studies was achieved by consensus and, if this was not reached, by consultation with a third reviewer (ATP).

Study Selection

All studies reporting on the detection of fetal cardiac abnormalities using two-dimensional ultrasound in the first trimester of pregnancy were included, including transvaginal (TV), transabdominal (TA) or a combination of both approaches. We included prospective and retrospective observational studies and randomized controlled trials. Studies evaluating pregnancies with all levels of prior risk were eligible for inclusion, including women with singleton and multiple pregnancies in any healthcare setting. Every attempt was made to identify publications from the same research groups that shared screened subjects, and in such cases we included only the study judged to be the most relevant (in relation to the study aims); or with the largest cohort. Literature reviews, conference abstracts, case reports with fewer than five subjects, editorials, letters, personal communications and non-English language publications were excluded.

The review included studies which evaluate first trimester ultrasound in the detection of (1) cardiac abnormalities specifically; (2) all types of structural fetal abnormalities, as long as cardiac abnormalities were included in the reported cohort, and only when individual breakdown of each cardiac abnormality was reported. Studies that exclusively investigated the use of first-trimester ultrasound for the detection of fetal chromosomal abnormalities; and those that evaluated markers (such as raised nuchal translucency, tricuspid regurgitation and abnormal ductus venosus flow) were excluded.

Based on our previous work[19], the reported gestational age is often not clearly defined in first trimester screening studies, and could be interpreted as 11^{+0} to 13^{+6}, 11^{+0} to 14^{+0}, or 11^{+0} to 14^{+6} weeks of gestational age. In order to ensure a systematic approach, an a-priori decision was made to include all examinations completed within the fourteenth week of gestational age up to 14^{+6} weeks. Prospective studies were included based on their intention to perform such screening prior to 14^{+6} weeks, with the understanding that in real-life clinical practice a small proportion of scans may have been performed outside the intended gestational age window.

The reference standard for determining the accuracy of first-trimester cardiac assessment was the detection of a cardiac abnormality postnatally or on post-mortem examination. Studies that did not state an aim of obtaining postnatal or post-mortem outcomes for the purposes of confirming screening results were excluded. A pragmatic approach was taken: studies that aimed to, but did not always achieve, complete follow up of their patient cohort were still eligible for inclusion in the study. Similarly, postmortem examination was not a requirement for inclusion of individual cases, as this is not always achievable following termination of pregnancy.

Data Extraction

All data included within this review was collected from tables or text on two independent occasions from each study in order to reduce the risk of error in data collection.

For each study, we extracted: name of first study author, year of publication, sample size, gestational age window at time of screening, population characteristics, study type, patient recruitment details, healthcare setting, index test used (i.e. ultrasound modality – TV, TA or both), the length of time allocated to ultrasound assessment, the number of sonographers participating in the study and their level of experience, the type of cardiac malformations included in the study, and information regarding postnatal follow-up. Details regarding the ultrasound protocol used by each study for the purposes of first trimester cardiac assessment were recorded, including evaluation of cardiac situs, cardiac axis, the four-chamber view, inflow and outflow tracts as well as the routine use of colour flow and pulsed Doppler studies.

Data were extracted to populate 2 x 2 tables and to calculate true positive, false positive, true negative and false negative rates in order to determine the diagnostic accuracy for the detection of major cardiac abnormalities overall; the process was repeated for individual types of cardiac abnormalities, to determine which might be most amenable to first trimester detection.

Owing to anticipated heterogeneity amongst studies included, considerable efforts were made to ensure that the results from the studies were comparable. Thus, we recorded (and analysed) data separately for high risk populations. High risk populations were grouped according to the

author's definitions, and included populations with a previously affected pregnancy, personal or family history of major cardiac anomaly, pre-gestational diabetes, raised fetal nuchal translucency, fetal extra-cardiac abnormalities, and multiple pregnancy. Non-high risk populations were defined as studies described as low risk, unselected or mixed risk populations.

Manual counting of each cardiac abnormality was undertaken and recorded separately from the number of affected fetuses. This was to enable the calculation of screening characteristics of individual conditions. For example if one fetus was affected by an AVSD and coarctation of the aorta, we would be able to distinguish between a scenario where both abnormalities were identified on first trimester scan ('two true positive abnormalities diagnosed; one affected fetus correctly identified in the first trimester') and one where only the AVSD was identified in the first trimester with the coartation of the aorta only seen postnatally ('one true positive diagnosis, one false negative diagnosis in one fetus affected by cardiac anomaly correctly identified in the first trimester'). The exception to this procedure was in the case of known cardiac syndromes, for example Tetralogy of Fallot, which was considered as one major cardiac anomaly. In addition, a number of studies described the diagnosis of a 'complex cardiac defect', often not further defined, and this was considered as 'one major cardiac abnormality' for the purposes of this review.

The commonly used definition of a major cardiac abnormality, as a malformation assumed to be lethal, require surgery or interventional cardiac catheterization during the first year of postnatal life, was followed. We excluded from this group of major anomalies those that were not considered structural, but that may need treatment, such as pericardial effusion, hydrops and fetal heart block.

Defining screen positives

A screen positive result following cardiac anatomical assessment in the first trimester might reflect one of three possible situations based on the index of suspicion:

(1) the diagnosis of a specific cardiac anomaly in the first trimester;

(2) the suspicion of a specific cardiac anomaly in the first trimester; or

(3) a finding of an anatomical abnormality of undetermined significance (AUS) after assessment of the four chamber-view or outflow tracts (e.g. ventricular and/or outflow tract disproportions, unclear spatial relationship of vessels, etc.).

All three situations represent 'a screen positive' test result and for the primary analysis detection rates were calculated regardless of the index of suspicion.

As the different screen positives situations may lead to different counselling, management and follow-up strategies, all cardiac anomalies were recorded as diagnosed, suspected or labelled as "AUS", and true positive/false positive rates were also calculated separately.

We also recognised that a specific diagnostic "label" in the first trimester may be modified later in pregnancy. Initial anomalies may evolve (e.g. severe aortic stenosis progressing to hypoplastic left heart), or diagnoses may be re-classified (e.g. a ventricular septal defect subsequently found to actually be part of a tetralogy of Fallot). In this situation, the fetus was correctly identified as having a major cardiac anomaly, but the initial diagnosis was revised. These cases could not be fairly considered as either a true positive or a false positive and therefore they were documented separately as "a change of first trimester diagnosis".

Estimation of false positive rates and specificity

False positive rates (and therefore specificity) of first trimester ultrasound screening are difficult to determine because many fetuses with severe or lethal anomalies undergo early termination of pregnancy, without post-mortem confirmation[19]. In order to estimate specificity, we assumed that reported true positive results were accurate when these led to pregnancy termination, even if post-mortem confirmation was not available. This is consistent with previous studies in this area, although this practice risks under-ascertainment of false positives. In order to address this, we undertook a subanalysis of individual fetuses that were assumed screen-positive and underwent subsequent physical confirmation on either post-mortem or post-natal examination.

Quality Assessment of Studies

Risk of bias and quality assessment based on the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was undertaken for all included studies. This evaluates four key areas: patient selection, index test, reference standard and flow of patients throughout the study. Each study in the review was graded as having either a low, high or unclear risk of bias for each domain and for lack of applicability based on a series of signaling questions developed specifically for this review (Appendix S2).

Statistical Analysis

Meta-analysis for all data extracted from eligible studies was performed in two steps.

Summary statistics with 95% Confidence Intervals (CI) were derived for each study for sensitivity, specificity, positive and negative predictive values of first-trimester anomaly screening both for detection of major cardiac defects by anomaly; and by affected fetus. Individual study statistics within each population sub-group were combined in order to obtain a pooled summary estimate, using a random-effects model. A Haldane-Anscombe correction was used, where a value 0.5 was added to cells in any 2 by 2 when required, in order to avoid a division by zero error. Heterogeneity between studies was estimated using the I^2 statistic. Meta-analysis was then used to derive summary statistics for the detection of major cardiac anomalies following first trimester screening.

In the meta-analysis for the primary outcome, all women screened, in all population groups, and taking into account all types of screen positive results (diagnosis, suspicion and AUS) were included. This allowed us to determine the overall performance of first trimester ultrasound in the detection of major cardiac abnormalities. For the purposes of this primary analysis, a major cardiac anomaly detected in the first trimester that subsequently changed to a different major cardiac anomaly was considered a true positive.

Pre-planned secondary analyses were then conducted to assess which factors might impact screening performance, in the following pre-planned subgroups:

1. The imaging protocol used for cardiac assessment, such as four-chamber assessment only, addition of colour flow Doppler, and examination of outflow tracts.
2. Mode of ultrasound (TA versus TV versus a combination).

3. Publication year of the study.
4. The index of reported diagnostic certainty, with cardiac abnormalities diagnosed, suspected or labelled as AUS.
5. The type of individual cardiac anomaly. Here, an a-priori decision was made to only perform meta-analysis when at least ten cases of a specific anomaly were present in the pooled sample.
6. The impact of the gestational age week at time of first trimester screening on test sensitivity was planned, but not undertaken due to insufficient data.

All statistical analysis was performed using StatsDirect statistical software version 3.3.0. (StatsDirect Ltd, Altrincham, Cheshire, UK).

Results

The electronic search yielded 4108 citations after removal of duplicates, leading to 223 full text reviews from which a total of 63 studies were included, screening 328,214 fetuses (Figure 1); 45 were non-high risk populations (n= 306,872 fetuses, Table 1) and 18 studies assessed high-risk women (n = 21,342 fetuses, Table 2).

The included studies were published between 1998 and 2020. Studies were performed in a variety of healthcare settings, although the majority (n=45) took place, at least in part, in either a university hospital or tertiary-care affiliated centre. Five studies included multi-centre data collection. The methodological quality assessment of included studies are summarized in Figures 2 and 3. Details of the imaging protocols undertaken by each study are summarized in supplemental tables S1 and S2.

Primary outcome: Screening performance for cardiac abnormalities

Non-high risk pregnancies

A total of 306,872 fetuses were screened and 1,445 major cardiac anomalies were identified, giving a prevalence of major cardiac anomalies of 0.41% (Fixed effects model calculation, 95% CI 0.39 – 0.43%). Of these, 767 were correctly detected during first trimester ultrasound, while the remaining 678 were not detected; and a further 43 were false positive. Based on the pooled analysis, the sensitivity was 55.80% (95% CI 45.87– 65.50%, Figure 4), specificity 99.98% (95% CI 99.97 – 99.99%) and positive predictive value 94.85% (95% CI 91.63– 97.32%, Table 3). The cases diagnosed in the first trimester represent 63.67% (95% CI 54.35 – 72.49%) of all antenatally diagnosed major cardiac abnormalities (Table 3 and Figure 4).

In the calculation per fetus (26 studies, 99,621 screened fetuses), 340 of 585 fetuses with a major cardiac defect were detected during the first trimester (pooled sensitivity 63.78% (95% CI 51.21 – 75.45%), pooled specificity 99.98% (99.97 – 99.99%)).

Of the 699 major cardiac anomalies that were diagnosed (n=683) or suspected (n=16), and assumed to be true-positive, 155 (22.17%) had a post-mortem or postnatal examination confirming this result (Table S3).

High risk populations

A total of 21,342 fetuses were screened and 480 major cardiac anomalies were identified, giving a prevalence of major cardiac anomalies of 1.36 (Fixed effects model calculation, 95% CI 1.20 – 1.52%). Of these, 338 were detected during first trimester ultrasound, while the remaining 142 were not detected; and a further 20 were false positive. Based on the pooled analysis, the sensitivity was 67.74% (95% CI 55.25 – 79.06, Figure 5), specificity 99.75% (95% CI 99.47 – 99.92%) and positive predictive value of 94.22% (95% CI 90.22 – 97.22%, Table 3). The cases diagnosed in the first trimester represent 79.86% (95% CI 69.89 – 88.25%) of all antenatally diagnosed major cardiac abnormalities (Table 3).

In the calculation per fetus (14 studies, 6854 fetuses), 180 fetuses with a major cardiac defect were detected during the first trimester (pooled sensitivity 70.00% (95% CI 55.65 - 82.59%), pooled specificity 99.61% (95% CI 99.16 – 99.89%).

Of the 335 major cardiac anomalies that were diagnosed or suspected and assumed to be true-positive, 73 (21.79%) had a post-mortem or postnatal examination confirming this result (Table S4).

Secondary analysis: Factors Affecting Screening Performance

Imaging protocol used

We identified five imaging protocols (Tables S1 and S2):

(1) studies that did not report use of a systematic protocol;

(2) studies assessing a four-chamber view, without colour-flow Doppler;

(3) studies assessing a four-chamber view, with colour-flow Doppler;

(4) studies assessing the four chamber view and at least one view of the outflow tracts, without colour-flow Doppler; and

(5) studies assessing the four chamber view and at least one view of the outflow tracts, with colour-flow Doppler.

Comparison of these sub-groups demonstrated significant differences in pairwise comparisons and in linear trend (both p<0.0001), showing that there was an increase in sensitivity with increasing level of detail in the anatomical protocol used (Table 4 and 5).

We assessed imaging factors that could affect detection rates in routine screening (i.e. in the non-high risk group). Both adding at least one outflow tract view to a four-chamber assessment; and adding colour-flow Doppler assessment were independently associated with significantly higher rates of detection (both p<0.0001, Table 6). This analysis was not undertaken in high-risk fetuses as targeted ultrasound meant almost all had an extended imaging protocol including outflow tracts.

TA versus TV ultrasound

Again, this was assessed in the non-high risk group. The vast majority of studies favoured an approach which combined the use of TA and TV ultrasound (n=36; 294,185 fetuses), while a minority of studies used solely TA (n=9; 17,444 fetuses) or TV (n = 2; 648 fetuses) ultrasound alone. A chi-squared test (2 by k) comparing detection rates achieved with the three possible modalities showed no statistical differences (p = 0.4662, Table 7).

Publication year of the study.

Analysis by year of study publication (≤ 2004, 2005-2009, 2010-2014, ≥ 2015) in the non-high risk population group demonstrated improved screening sensitivity with increasing year of publication (p=0.0006), but no such trend was seen in the high risk group.

Screening characteristics in relation to the diagnostic certainty

Screening characteristics in relation to the diagnostic certainty are shown in table 8. In the non-high risk group there were 767 detected anomalies. Of these, 683 were given a diagnosis, 16 were suspected, and 68 were considered AUS. Of the cases given a label (diagnosed or suspected), 10 had a change in diagnosis. Detailed information is provided in Tables S5, S6, S7 and S8.

In the high-risk group, of the 338 detected anomalies, 320 were given a diagnosis, 15 were suspected, and 3 were considered AUS. Of the cases given a label (diagnosed or suspected), 19 had a change in diagnosis. Detailed information is provided in Tables S9, S10, S11 and S12.

Results for individual cardiac anomalies

Screening characteristics for individual cardiac anomalies were assessed in both high and low risk groups, following the a-priori decision to analyse only those where at least 10 cases were available. In the non-high risk group, these could be grouped into those where detection rates exceeded 60%, those where sensitivity ranged between 25% and 60%, and those with detection rates below 25% (Table 9 and Table S13). In the high-risk group, the twelve individual cardiac anomalies where more than ten cases were available are reported in Table S14. Differences in detection rates between non-high risk and high-risk women are reported in Table S15. In both non-high risk and high risk populations, VSDs were associated with a higher false positive rate and change of diagnosis rate compared with other anomalies in the study. (Tables S13 and S14)

Discussion

In this meta-analysis including 328,214 screened fetuses we show, firstly, that the majority of cardiac anomalies can be identified at the 11-14 week scan; secondly, that imaging protocols have an important impact on screening performance, with significantly increased detection rates seen in those studies using outflow tract views and colour-flow Doppler imaging; and thirdly that the type of cardiac anomaly under evaluation has a strong impact on detection rates.

In non-high risk populations (i.e. studies that included populations that were unselected, or a-priori low or mixed risk), first trimester assessment identified just over half (56%) of major cardiac abnormalities, two-thirds (64%) of all cardiac anomalies diagnosed antenatally. In high risk populations the detection rates were higher: over two-thirds (68%) were detected, representing approximately 80% of antenatally detected abnormalities. The positive predictive value of an abnormal first trimester cardiac assessment was approximately 95% in both groups.

The finding of higher detection rates for cardiac abnormalities in high-risk, compared to lower-risk populations is in keeping with previous studies for first-trimester fetal anomaly detection[18,19] and is likely due to targeted screening: increased awareness when the a-priori risk is high will result in more detailed examination to provide early reassurance or confer a high-risk status.

Clinical impact for screening

After a first trimester cardiac evaluation, possible outcomes are (1) the diagnosis of a major cardiac anomaly (2) the suspicion of a major cardiac anomaly (3) an anatomical variant of undetermined significance, (4) an inconclusive result secondary to inadequate imaging for evaluation, or (5) early reassurance in the context of normal findings. Many studies have concentrated on treating the scan as a diagnostic test. In our analysis we evaluated the diagnostic accuracy as a screening test, with women in categories 1-3 above being screen positive, category 5 as screen-negative, and category (4) as “no-call”. We believe that greater clarity in future reporting will better inform future screening strategies.

If we are to screen, how should this be done? Directly relevant is the finding that the use of an anatomical protocol is associated with increased detection rates for fetal cardiac abnormalities. A "dose-response" improvement in detection rates with increasing detail of the anatomical study protocol was seen in all population groups. The strength of this association, clinical plausibility and similar findings from previous studies further support that this is not a chance finding. [19,31,32].

Our data suggest that when undertaking routine screening for fetal cardiac anomalies at 11-14 weeks both outflow tract views and Colour-Flow Doppler should be included, as both have a statistically significant impact on detection rates. Studies using the most extensive cardiac protocols (four chamber view with outflow tract view and colour-flow Doppler) are associated with detection rates in non-high risk populations that are comparable with those from high risk populations (Tables 4 and 5).

Barriers to implementation of such protocols include the high level of sonographer training required; as well as appropriate allocation of time and use of high-resolution ultrasound equipment. It is likely that the combined impact of these factors contributed to the overall increased detection rates seen in studies with more detailed protocols, although it was not possible to examine this given the limitations of data. Another consideration is the safety of Doppler before 14 weeks[21,33], although colour-flow Doppler is thought to be safe between 11 and 14 weeks as long as ALARA principles are followed [23,34,35]. Studies assessing the use of Doppler during first trimester cardiac screening have demonstrated that this assessment is consistently feasible with a Thermal Index (T1) and Mechanical Index (MI) well below the maximum levels recommended for practice, and that a satisfactory assessment is possible to achieve within 3-4 minutes of exposure time, not only for experienced sonographers but also through the learning curve [36-38]. Finding the balance between (demonstrated) benefits of improved diagnostic accuracy and (theoretical) risk needs to be considered when undertaking screening.

There is no consensus on whether TA or TV ultrasound should be used for primary screening [18,39]. Our analysis did not demonstrate a difference in detection rates between use of TA alone, TV alone or a combination. However, very few studies relied on a single modality with the

majority of studies using a combination - most often beginning with TA followed by TV ultrasound when visualization was insufficient. We believe that this flexible approach will be the most likely to continue in practice, and depend on patient preference, clinician expertise, and factors such as obesity[40].

Detection of Individual Cardiac Anomalies

It was possible to categorize cardiac abnormalities based on our ability to detect them in the first trimester (Tables 9, S13 and S14). The variation seen is logical: for some anomalies pathophysiological mechanisms involve gradual changes in utero, for example stenotic valvular pathologies or narrowing of the pulmonary artery and aortic arch, meaning that such abnormalities may only be amenable to diagnosis at later gestations or even postnatally[11,41]. For others, size may be below the resolution of ultrasound, such as VSDs. It is therefore unlikely that first trimester ultrasound will ever be able to detect every fetus affected by these types of abnormalities. We must acknowledge that the focus of first trimester screening should be primarily on the detection of anomalies which might impact prenatal decision-making and care as these are the patients who will benefit most from an early diagnosis. Our review has shown that a comprehensive first trimester evaluation can detect a very high proportion of certain anomalies including complex cardiac defects, single ventricle pathologies, ectopia cordis, heterotaxy, atrio-ventricular septal defects and valvular atresias.

Strengths and limitations

In this systematic review we have assessed the totality of the evidence on diagnostic accuracy of first trimester cardiac screening. It was undertaken using a prospective and registered protocol, and involved detailed extraction of individual data on cardiac anomalies. Pre-planned sub-group analysis based on a-priori risk of population group, index of suspicion at time of scan, anatomical protocols and mode of ultrasound allow an in-depth understanding of first trimester cardiac screening and evidence based recommendations for future work.

Our study had some expected weaknesses. Many of the studies published in this review were performed in centres of excellence and often by a small group of highly experienced experts

(Tables 1 and 2). There may also be an element of reporting bias from authors wishing to demonstrate positive results. As a consequence, pooled first trimester detection rates in this review are comparable (if not higher) to those reported in second trimester cardiac screening initiatives. This means that our findings reflect the highest standards available in our field, which may not be achieved on a larger scale [2,11,42-45]. Useful data in this regard comes from one of the largest multi-centre studies involving 476 sonographers; this may provide a more realistic estimate of what can be achieved from a high quality, first trimester population-based cardiac screening program[46] (Table S5). In addition, considerable heterogeneity between included studies was seen. These were mitigated with subgroup analysis and strict definitions regarding the types of cardiac anomalies included in the analysis. Variation remains between studies in their inclusion and exclusion criteria, sonographer experience, detail-level of postnatal examinations, length of post-natal follow-up and outcome reporting. Variation also exists on the nomenclature as defined by individual study authors: for example, hypoplastic right heart syndrome, tricuspid atresia, pulmonary atresia with intact septum and univentricular heart may all be overlapping diagnoses; however, we believe this is a secondary issue, as the detection of an abnormality in the corresponding plane is more important than the precise anatomical diagnosis given. Despite the limitations above, we believe the pooled data give us the best estimate of the screening performance and relative factors that affect this.

An important challenge we faced was the determination of false positive rates. As with other major anomalies in the first trimester, early surgical termination may preclude post-mortem examination; in this study we found that only approximately 25% of all assumed true positive results had a reported physical secondary confirmation (Tables S3 and S4). The result is a relative uncertainty surrounding the true false positive rate following first trimester cardiac evaluation. We attempted to quantify this uncertainty by assessing each individual first trimester cardiac diagnosis in relation to secondary confirmation. A large proportion of the false positive cases seen were in patients where the diagnostic certainty was low (i.e. in suspicious and AUS cases, see Table 3). Our best estimate is that the FPR is low: in the most relevant group (those not at high risk) there were 674 true positive diagnoses; 9 changes of diagnosis; and 15 reported false positives. Therefore, only 15 out of 698 diagnoses (2.1%) were

false positive. This low rate is reassuring, but we call on researchers to report reference tests (post-mortem, subsequent imaging or postnatal examination) clearly and comprehensively in future screening studies, including a clear description in what proportion of cases this is not available.

Our review provides strong evidence that first trimester examination of the fetal heart allows effective stratification by identifying a cohort of fetuses at high risk of a cardiac anomaly. Based on available data and uncertainty regarding false positive rates, the action after a positive screening scan should be expert fetal cardiac ultrasound follow-up. The development of information and support for parents will also be a key consideration. Future first-trimester screening programmes should follow a standard anatomical assessment protocol; recognise that not all anomalies are amenable to detection and that some evolve through pregnancy based on their natural history. Combined with appropriate training and implementation of referral pathways, this would be expected to have an important positive impact on the earlier detection of fetal cardiac anomalies.

Conflict of interest

ATP is a Senior Advisor of Intelligent Ultrasound. All other authors declare no competing interests.

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Figure legends

Figure 1: Flowchart of search strategy and selection of studies for inclusion in systematic review and meta-analysis. GA, gestational age.

Figure 2: Quality assessment of studies included in systematic review for risk of bias based on QUADAS-2 guidance.

Figure 3: Quality assessment of studies included in systematic review for concerns regarding study applicability based on QUADAS-2 guidance.

Figure 4: Forest plots demonstrating sensitivity of first-trimester ultrasound for the detection of major cardiac abnormalities in low risk, mixed risk and unselected populations. I2 = 91.8% (95% C.I. 90.3-93.0%).

Figure 5: Forest plots demonstrating sensitivity of first-trimester ultrasound for the detection of major cardiac abnormalities in high risk populations. I2 = 85.8% (95% C.I. 79.1-89.6%).

Table 1: Characteristics of studies reporting on detection of major cardiac anomalies by first-trimester ultrasound in non-high risk populations

Study (year)	Fetuses (n)	Prevalence of Major Cardiac Anomalies (n per 100 fetuses)	GA (weeks) or CRL (mm)	Population & Recruitment Characteristics	Healthcare Setting	Aneuploid Fetuses Included? (%)*	Index Test**	Sonographer Experience
Whitlow 1999[47]	6634	0.18 (0.09 – 0.32)	11-14^{+6}	Unselected, consecutive recruitment	University Hospital	Yes (0.7%)	TA/TV (20.1)^	6 clinicians & 4 sonographers. All trained in first trimester US
Michailidis 2001[48]	6650	0.15 (0.07 – 0.28)	38-84	Unselected, consecutive recruitment, prospective study	University Hospital	No	TA/TV (14%)^	NA
McAuliffe 2005[49]	325	0.62 (0.07 – 2.21)	11-13^{+6}	Unselected, singleton pregnancies only, prospective study	University Hospital, Tertiary Care	No	TA/TV (24.6%)^	NA
Cedergren 2006[50]	2708	0.11 (0.02 – 0.32)	11-14	Unselected, consecutive recruitment	University Hospital	Yes (0.3%)	TA	Midwife sonographers with at least ten years experience
Souka 2006[51]	1148	2.54 (1.92 – 3.29)	11-14	Unselected	Unclear	Yes	TA/TV^	NA
Srisupundit 2006[52]	597	0.34 (0.04 – 1.20)	11-14	Unselected women attending NT scan, singleton pregnancies only, prospective study	University Hospital	Yes	TA	NA
Vimpelli 2006[53]	584	1.03 (0.38 – 2.22)	11-13^{+6}	Unselected	Unclear	Yes	TV	NA
Dane 2007[54]	1290	0.31 (0.08 – 0.79)	11-14	Unselected	Research Hospital	Yes	TA/TV^	2 operators with 6 and 2 years experience respectively
Lombardi 2007[55]	623	0.48 (0.10 – 1.40)	12^{+3}-13^{+6}	Unselected women attending routine NT scan; singleton pregnancies only	Unclear	Yes	TA	NA
Chen 2008[56] (control group)	3693	0.48 (0.10 – 0.77)	10-14^{+6}	Unselected, singleton pregnancies only, consecutively randomized (RCT)	One university & one regional hospital	Yes	TA/TV^	8 experienced operators
Chen 2008[56] (study group)	3949	0.43 (0.25 – 0.69)	12-14^{+6}	Unselected, singleton pregnancies only, consecutively randomized (RCT)	One university & one regional hospital	Yes	TA/TV^	8 experienced operators
Li 2008[57]	2232	0.22 (0.07 – 0.52)	11-14	Unselected, consecutive recruitment	Unclear	Yes	TA/TV^ (2.0%)	NA

Bennasar 2009[58]	64	17.19 (8.90 – 28.68)	11-14^{+6}	Mixed cohort (majority unselected combined with high risk women), singleton pregnancies only, prospective study	University Hospital	Yes	TV	'Non-expert' operators trained in first trimester US and fetal echocardiography
Oztekin 2009[59]	1085	0.28 (0.06 – 0.81)	11-14	Unselected	Research Hospital	Yes	TA/TV^	Single sonographer
Abu Rustum 2010[60]	1370	0.80 (0.40 – 1.43)	11-13^{+6}	Unselected, retrospective study	Unclear	Yes	TA/TV^	Single sonographer with FMF certification
Sinkovskaya 2010[61]	100	8.00 (3.52 – 15.16)	11-14^{+6}	Consecutive recruitment; singleton pregnancies only; prospective study	Unclear	Yes	TA/TV^ (19%)	NA
Hartge 2011[62]	3521	2.87 (2.34 – 3.47)	11-13^{+6}	Mixed high risk and low risk population, singleton pregnancies only, retrospective study	Tertiary referral centre;	Yes	TA/TV^ (35.8%)	NA
Jakobsen 2011[63]	9324	0.46 (00.33 – 0.06)	11-14	Unselected, retrospective study	University Hospital	Yes	TA/TV^	NA
Krapp 2011[64]	690	2.75 (1.67 – 4.27)	45-84	Mixed high and low risk population, retrospective study	Unclear	Yes	TA/TV^ (5.2%)	NA
Syngelaki 2011[17]	44,859	0.26 (0.21 – 0.31)	11-13	Unselected, singleton pregnancies only (presumed euploid), retrospective study,	University Hospital, Tertiary referral centre	No	TA/TV^ (1%)	NA
Volpe 2011[65]	4445	0.58 (0.38 – 0.86)	45-84	Unselected, prospective cohort	Single centre, University Hospital	Yes	TA/TV^ (7.3%)	Sonographers with extensive experience, FMF certified.
Becker 2012[66]	6544	0.23 (0.13 – 0.38)	11-13^{+6}	Women with normal NT only (≤ 95th centile), prospective, consecutive recruitment	University Hospital	Yes (0.6%)[$]	TA/TV^ (23.4%)	Single examiner with 10 years experience
Eleftheriades 2012[67]	3774	0.90 (0.62 – 1.26)	11-13^{+6}	Unselected fetuses undergoing routine prospective ultrasound	Private Fetal Medicine Unit	Yes	TA	Obstetrician with extensive experience & FMF certificate. In case of abnormality, further examination by fetal cardiologist.
Grande 2012[68]	13,723	0.27 (0.19 – 0.37)	11-14	Mixed (majority low risk scans, 13% for raised NT), singleton pregnancies only, retrospective study	Tertiary Care Centre	No	TA/TV	19 Obstetricians
Novotna 2012[69]	9150	0.20 (0.12 – 0.31)	11-14	Unselected, prospective study	Single centre	Yes	TA/TV	23 operators with minimun 2 years experience.

Pilalis 2012[70]	3902	0.28 (0.14 – 0.50)	11-14	Unselected, retrospective study	Private maternity hospital	Yes	TA/TV^	FMF certified; 2 years special training in ultrasound.
Iliescu 2013[71]	5472	0.62 (0.43 – 0.87)	12-13^{+6}	Unselected, prospective study	University Hospital	Yes (0.4%)	TA/TV^ (7.8%)	Obstetricians specializing in prenatal diagnosis with at least 5 years accreditations and specific training for early fetal cardiac assessment.
Wang 2013[72]	2822	0.35 (0.17 – 0.65)	11-14	Not stated	University Hospital	Yes	TA	5 Experienced obstetric sonographers
Orlandi 2014[73]	4820	0.44 (0.27 – 0.67)	11-14	Unselected, singleton pregnancies only, prospective study	Centre for prenatal diagnosis	Yes	TA/TV^ (5%)	3 Experienced sonographers with FMF certificates for NT, NB, TR, DV.
Chitra 2015[74]	4421	0.07 (0.01 – 0.20)	11-14	Unselected, consecutive recruitment, retrospective study	Tertiary referral centre;	Yes	TA/TV^	4 operators with NT certification
Colosi 2015[75]	5924	0.05 (0.01 – 0.15)	11-13^{+6}	Unselected, singleton pregnancies only, prospective study	Fetal Medicine Unit	Yes (4.7%)	TA/TV (1.9%)^	4 operators with FMF Certification
Wiechec 2015[76]	1084	3.41 (2.41 – 4.67)	11-13^{+6}	Unselected, prospective study	University Hospital Clinic	Yes (6.6%)	TA/TV (5.25%)^	NA
Takita 2016[77]	2028	0.74 (0.41 – 1.22)	11-13^{+6}	Unselected, singleton pregnancies only, prospective study	University Hospital	Yes (0.6%)	TA	NA
Tudorache 2016[78]	3240	0.99 (0.68 – 1.39)	11^{+2}-13^{+4}	Unselected, prospective, consecutive recruitment	University Hospital, Tertiary referral centre	Yes	TA	NA
De Robertis 2017[79]	5343	0.62 (0.43 – 0.87)	45-84	Unselected, singleton pregnancies only, consecutive recruitment, prospective study. Excluded all pregnancies which underwent TOP for cardiac anomaly in the first trimester.	Tertiary Care	Yes	TA/TV (7%)	Expert sonographers, FMF certified
Vellamkondu 2017[80]	440	0.91 (0.25 – 2.31)	11-14	Unselected, singleton pregnancies only, prospective study	University Hospital, Tertiary care	Yes (0.5%)	TA/TV	NA
Fernandez 2018[81]	663	0.75 (0.25 – 1.75)	11-13^{+6}	Low risk singleton pregnancies only, prospective study	Fetal Medicine Unit	Yes	TV/TA	2 sonographers with >10 years experience
Kenkhuis 2018[82]	5534	0.23 (0.13 – 0.40)	11-13^{+6}	Unselected women offered Combined Test for Aneuploidy screening (n=5237) and women at a priori high	2 Referral centres; 6 community	Yes	TA/TV^	Sonographers given specific first trimester US training

				risk of fetal anomalies (297)	ultrasound practices			
Sainz 2018[83]	504	2.98 (1.68 – 4.87)	11-14^{+6}	Mixed low risk (n = 433) and high-risk population (n = 71), singleton pregnancies only, prospective study	University Hospital	Yes	TA	2 sonographers: one with >5 years obstetric US experience, one with SESEGO Level 3 training but <1 year experience.
Vayna 2018[84]	6114	0.51 (0.34 – 0.72)	11-14	Unselected, retrospective study	University Hospital	Yes	TA/TV^	NA
Zheng 2018[85]	1592	1.88 (1.27 – 2.68)	45 - 84	Unselected women presenting for NT scan, consecutive recruitment	University Hospital	Yes	TA/TV^	2 Sonographers with FMF certification
Chen 2019[86]	10,294	1.18 (0.98 – 1.40)	11-13^{+6}	Low risk cohort, prospective study,	Single centre	Yes	NA	Sonographers with DEGUM II Certificate
Duta 2019[87]	7693	0.44 (0.31 – 0.62)	11-14	Unselected, retrospective study of prospectively, consecutively collected data	Fetal Medicine Unit, Single centre	No	TA/TV^	8 sonographers certified for 11-14 week scan
Ebrashy 2019[88]	3400	2.94 (2.40 – 3.57)	11-13^{+6}	Unselected, prospective study	Fetal Medicine Unit, University Hospital	Yes	TA/TV^ (31.3%)	Fetal medicine specialists with FMF Certification
Erenel 2019[89]	707	1.70 (0.88 – 2.95)	11-14	Prospective, Unselected	Perinatology clinic affiliated with University and Research Hospital	Yes	TA/TV^ (4.6%)	5 clinicians with experience in first trimester ultrasound
Syngelaki 2019[46]	101,793	0.35 (0.31 – 0.39)	11-13^{+6}	Unselected, singleton pregnancies only (presumed euploid), retrospective study of prospectively collected data,	2 University Hospitals (One Tertiary care, one regional)	No	TA/TV^ (3%)	476 Sonographers with FMF Certification

Only first author given for each study. Total number of fetuses included in this subgroup n = 306,872. Pooled prevalence of major cardiac anomalies (n per 100 fetuses) in this subgroup was 0.68 (95% C.I. 0.54 – 0.84) *In studies where aneuploid fetuses were included, percentage of the study population confirmed as aneuploid by karyotyping has been indicated in parentheses. **In studies where both transabdominal (TA) and transvaginal (TV) ultrasound were used, the number in parentheses refers to the percentage of the study population who received screening with both screening tests. ^Studies where TV ultrasound was performed only in situations when visualization with TA was suboptimal. $^{\$}$Only known euploid fetuses included in this meta-analysis as insufficient data provided on entire study cohort. NB – Nasal bone examination. NT – Nuchal translucency examination. DEGUM –German Society of Ultrasound in Medicine and Biology. DV – Ductus Venosus examination. FMF – Fetal Medicine Foundation. SESEGO – Spanish Society of Gynecology and Obstetrics (SEGO) ultrasonography certification. TR – Tricuspid regurgitation examination. US – Ultrasound.

Table 2: Characteristics of studies reporting on detection of major cardiac anomalies by first-trimester ultrasound in high risk populations

Study Year	Fetuses (n)	Prevalence of Major Cardiac Anomalies (n per 100 fetuses)	GA (weeks) or CRL (mm)	Population & Recruitment Characteristics	Healthcare Setting	Aneuploid Fetuses Included? (%)*	Index Test**	Sonographer Experience
Carvalho 1998[16]	15	26.67 (7.79 – 55.10)	11-13^{+6}	Women with history of cardiac anomaly and/or raised NT	Tertiary Care	Yes	TA	NA
Zosmer 1999[90]	112	8.93 (4.37 – 15.81)	11-13^{+6}	Fetuses with NT ≥ 99% centile or ≥ 3.5mm, with normal CVS result	Tertiary Care	No	TA/TV (5%)	Expert in fetal echocardiography
Comas Gabriel 2002[91]	200	16.50 (11.64 – 22.38)	11-14	Women with increased a priori risk for cardiac anomalies	Multi-centre (3), FM Referral Centres	Yes	TV/TA	3 experienced operators
Den Hollander 2002[92]	101	2.97 (0.62 – 8.44)	11-14	Women with previous infant affected with CHD (92%) and/or parental consanguinity	Tertiary Care	Yes	TA/TV^	NA
Haak 2002[93]	45	35.56 (21.87 – 51.22)	11-14	Fetuses with NT>95%, singleton pregnancies only, consecutive recruitment, prospective study	Tertiary Care	Yes	TV	Single experienced examiner
Huggon 2002[94]	478	16.11 (12.93 – 19.72)	40 - 84	Women with increased NT (≥ 4mm) and/or abnormal DV Flow; Women with first degree relative with CHD; Suspicion of CHD or extra-cardiac anomaly at 10-14 weeks scan	Tertiary Referral Centre	Yes	TA/TV^ (<1%)	2 experienced sonographers (one fetal cardiologist; one gynaecologist with specific experience in fetal echocardiography)
Weiner 2002[95]	392	1.79 (0.72 – 3.64)	11-14	High risk patients undergoing fetal echocardiography (predominantly for maternal diabetes and previous pregnancy affected by CHD)	Unclear	Yes	TV/TA^	NA
Chen 2004[96]	1609	0.87 (0.47 – 1.45)	11-14	High risk women aged 35 or older	University Hospital	Yes	TA/TV^	2 operators with >10 years experience each
Bronshtein 2008[97]	23	34.78 (16.38 – 57.27)	11-14	Fetuses with increased NT (≥ 3.5mm)	Unclear	Yes	TV	NA
Weiner 2008[98]	200	11.00 (7.02 – 16.18)	11-13^{+6}	Fetuses with NT ≥ 3mm or cystic hygroma	Unclear	Yes	TV	Specialists in MFM trained in fetal echocardiography
Persico 2011[99]	886	6.32 (4.81 – 8.13)	11-13^{+6}	Patients with US exam prior to CVS (majority for increased risk after Combined Screening), prospective	Tertiary Care	Yes	TA	Obstetricians with extensive experience in T2 anomaly scanning and T1 US; Images

				study				reviewed by fetal cardiologist.
Volpe 2012[100]	870	6.55 (5.00 – 8.41)	11-13^{+6}	Women at high risk for CHD. Fetuses who underwent ECHO at both 11-14 and 18-22 weeks. Retrospective study	FM Referral Centre	Yes	TA/TV^ (9%)	NA
Votino 2012[101]	15	13.33 (1.66 – 40.46)	11^{+2}-13^{+4}	High risk women: Maternal CHD, Maternal risk factors, maternal diabetes, NT>95%, Abnormal TR, DV. Singleton pregnancies only, prospective study	Single Centre; University Hospital; Fetal medicine unit.	Yes	TA	Single trained operator
Miller 2013[102]	341	2.40 (0.97 – 4.86)	45-84	Women with pre-gestational diabetes, prospective, observational study	University Hospital	Yes	TA/TV	Sonographers certified by FMF or NT Quality Review Program
Zidere 2013[103]	1200	6.08 (4.80 – 7.59)	11-14	Fetuses undergoing detailed fetal echocardiography for various indications: raised NT, family history, extracardiac malformation, co-twin affected by anomaly	Tertiary Care	Yes	TA/TV^	Single specialist fetal cardiologist
D'Antonio 2016[104]	2128	0.56 (0.29 – 0.98	11-13^{+6}	Consecutive twin pregnancies, retrospective cohort analysis,	Tertiary Care	Yes	TA/TV^	NA
Zalel 2017[105]	43	62.79 (46.73 – 77.02)	11-13^{+6}	Fetuses with NT>99% centile (>3.4mm), prospective study	Tertiary care affiliated centre	Yes	TV	Single experienced examiner
Syngelaki 2020[106]	12,732	26.67 (7.79 – 55.10)	11-14	Twin pregnancies (MCDA and DCDA), retrospective cohort analysis	Multi-centre (3)	No	TA/TV^ (3%)	Sonographers certified by the Fetal Medicine Foundation

Only first author given for each study. Total number of fetuses included in this subgroup n = 21,375. Pooled prevalence of major cardiac anomalies (n per 100 fetuses) in this subgroup was 9.42 (95% C.I. 6.04 – 13.47) **In studies where both transabdominal (TA) and transvaginal (TV) ultrasound were used, the number in parentheses refers to the percentage of the study population who received screening with both screening tests. ^Studies where second listed ultrasound modality was performed only in situations when visualization with the first modality was suboptimal. CHD – Congenital Heart Disease. CVS – Chorionic Villus Sampling. DV – Ductus Venosus examination. DCDA – Dichorionic Diamniotic Twin pregnancy. FMF – Fetal Medicine Foundation. MCDA – Monochorionic Diamniotic Twin pregnancy. NB – Nasal bone examination. NT – Nuchal translucency examination.TR – Tricuspid regurgitation examination. US – Ultrasound.

Table 3: Diagnostic accuracy of first trimester ultrasound in the detection of major cardiac anomalies

Population Group:	Fetuses Screened (n)	Studies Included (n)	Total Number of Major Cardiac Anomalies (n)	Major Cardiac Anomalies Correctly Identified (TP - n)	Sensitivity (95% C.I.)	Specificity (95% C.I.)	Positive Predictive Value	Proportion of all antenatally detected major cardiac anomalies^ (95% C.I.)
Non-High Risk	306,872	45	1445	767	55.80 (45.87– 65.50)	99.98 (99.97 – 99.99)	94.85 (91.63– 97.32)	63.67 (54.35 – 72.49)
High Risk	21,342	18	480	338	67.74 (55.25 – 79.06)	99.75 (99.47 – 99.92)	94.22 (90.22 – 97.22)	79.86 (69.89 – 88.25)

Table summarizing the sensitivity, specificity and PPV of first trimester ultrasound for the identification of major cardiac anomalies. The values in this table reflect the global detection rate calculated and refers to any screen positive result following cardiac anatomical assessment in the first trimester reflecting in one of three possible outcomes for the patient based on the index of suspicion of the sonographer: (1) Diagnosis of a specific major cardiac anomaly in the first trimester, (2) Suspicion of a specific major cardiac anomaly in the first trimester, or (3) Finding of an abnormality of unknown significance in either the four chamber or outflow tract view. See text for additional details.

^This refers to the proportion of antenatally detectable major cardiac anomalies which were identified in the first trimester and therefore excludes any anomalies which were detected postnatally.

Table 4: Screening characteristics of first trimester ultrasound in the detection of major cardiac anomalies based on diagnostic certainty

Level of Diagnostic Certainty	(1) Major Cardiac Anomalies Diagnosed in the First Trimester	(2) Major Cardiac Anomalies Suspected in the First Trimester	(3) Abnormalities of Unknown Significance (AUS) in 4CV and/or OT view	(4) Studies exclusively screening for abnormality of the view (4CV and/or OT)^
Non-High Risk Population:				
Number of Studies (n)	42	9	1	3
Number of Fetuses (n)	299,075	34,125	5534	7997
Screen-positive (n)*	698	36	1	75
True Positive (TP, n)	674	15	0	68
Change of Diagnosis (Δ Dx, n)	9	1	-	-
False Positive (FP, n)	15	20	1	7
Pooled Sensitivity, % (95% C.I).**	51.20 (40.92 – 61.43)	44.60 (15.08 – 76.41)	0.00 (0.00 – 36.94)	83.10 (74.30 – 90.35)
Pooled Specificity, % (95% C.I)	99.99 (99.99- 100.00)	99.96 (99.88 – 100.00)	99.98 (99.90 – 100.00)	99.90 (99.81 – 99.96)
Pooled Positive Predictive Value, % (95% C.I).	96.58 (93.95 – 98.48)	67.81 (27.84 – 96.37)	0.00 (0.00 – 97.50)	91.27 (71.81 – 99.84)
High Risk Population:				
Number of Studies (n)	18	6	4	-
Number of Fetuses (n)	21,342	3547	1205	-
Screen-positive (n)*	326	27	5	-
True Positive (TP, n)	304	12	3	-

Change of Diagnosis (Δ Dx, n)	16	3	-	-
False Positive (FP, n)	6	12	2	
Pooled Sensitivity, % (95% C.I).	65.27 (52.31 – 77.17)	24.43 (13.21 – 37.79)	13.37 (0.01 – 37.37)	-
Pooled Specificity, % (95% C.I).	99.93 (99.84 – 99.98)	99.28 (98.17 – 99.88)	99.73 (99.07 – 100.00)	-
Pooled Positive Predictive Value, % (95% C.I)	97.65 (95.76 – 98.99)	60.73 (40.41- 79.29)	55.79 (12.91 – 93.81)	-

This table provides a breakdown of screen positive results obtained after first trimester ultrasound screening based on the index of suspicion of the sonographer performing the scan who would have provided parents with either (1) Diagnosis of a specific major cardiac anomaly in the first trimester, (2) Suspicion of a specific major cardiac anomaly in the first trimester, or (3) Finding of an abnormality of unknown significance in either the four chamber (4CV) or outflow tract view (OT).

^Studies in column (4) screened exclusively for abnormalities of the four chamber or outflow tract views (eg. ventricular and/or outflow tract disproportions, abnormalities in spatial relationship of vessels, etc.) with the objective of providing a formal and specific diagnosis at a later gestation in pregnancy (Ref: Abu Rustum 2010[60], Wiechec 2015[76], De Robertis 2017[79]). As such, these three studies were excluded from analysis (1), (2) and (3).

*Number of anomalies identified in the first trimester refers to all screen positive anomalies which were either diagnosed, suspected or labelled as an abnormality of unknown significance including both true positive (TP), false positive (FP) diagnoses and cases where the initial first trimester diagnosis was subsequently changed.

**For the calculation of sensitivity for diagnosis of major cardiac anomalies, a false negative was considered any anomaly which was not diagnosed, suspected or labelled as AUS in the first trimester in each study respectively. Similarly, for the calculation of sensitivity for suspected major cardiac anomalies in the first trimester, a false negative case was considered as any anomalies which was not diagnosed, suspected or labelled as AUS in the first trimester in each study respectively.

Table 5: Impact of first trimester imaging protocol on the detection of major cardiac anomalies in low risk, unselected and mixed screening populations

Anatomical Protocol Used:	No Formal Protocol*	4-CV (No CF Doppler)	4-CV with CF Doppler	4-CV with any view of outflow tracts (No CF Doppler)	4-CV with any view of outflow tracts and CF Doppler
Number of Studies (n)	8	9	1	7	19
Number of Fetuses (n)	35,121	85,287	5534	8033	171,860
Pooled Sensitivity, % (95% C.I)	**13.51** (7.05 – 21.67)	**32.96** (18.18 – 49.71)	**38.46** (13.86 – 68.42)	**57.54** (31.41 – 81.58)	**80.04** (67.94 – 89.84)

This table demonstrates results from a sub-group analysis performed based on the type of anatomical protocol used for first trimester cardiac screening by each study. Studies were categorized into one of five possible sub-groups based on protocol. A chi-squared test (2 by k) comparing all 5 protocols showed statistical significance difference ($P<0.0001$) with a chi-square test for linear trend suggesting a statistically significant ($P<0.0001$) increase in screening sensitivity with increasing level of detail in the anatomical protocol used. *No formal protocol indicates either studies without a dedicated ultrasound checklist or a protocol without a dedicated cardiac assessment.

Table 6: Impact of first trimester imaging protocol on the detection of major cardiac anomalies in high risk populations

Anatomical Protocol Used:	No Formal Protocol*	4-CV (No CF Doppler)	4-CV + CF Doppler	4-CV + any view of outflow tracts (No CF Doppler)	4-CV + any view of outflow tracts + CF Doppler
Number of Studies (n)	1	1	-	7	8
Number of Fetuses (n)	2128	293	-	1851	4338
Pooled Sensitivity, % (95% C.I)	**16.67** (2.09 – 48.41)	**0.00** (0.00 – 0.41)	-	**78.13** (53.25 – 95.22)	**76.84** (69.78 – 83.23)

This table demonstrates results from a sub-group analysis performed based on the type of anatomical protocol used for first trimester cardiac screening by each study. Studies were categorized into one of four possible sub-groups based on protocol. A chi-squared test (2 by k) comparing all 4 protocols showed statistical significance difference ($P<0.0001$) with a chi-square test for linear trend suggesting a statistically significant ($P<0.0001$) increase in screening sensitivity with increasing level of detail in the anatomical protocol used. *No formal protocol indicates either studies without a dedicated ultrasound checklist or a protocol without a dedicated cardiac assessment.

Table 7: Additional value of Colour Flow Doppler and Outflow Tract Views on First Trimester Screening Sensitivity for Major Cardiac Anomalies in low risk, unselected and mixed populations

	Additional Value of Colour-Flow Doppler		Additional Value of Outflow Tract Views	
Anatomical Protocol Used:	Without CF Doppler	With CF Doppler	4CV only (+/- CF Doppler)	4CV and OT view (+/- CF Doppler)
Number of Studies (n)	16	20	10	25
Number of Fetuses (n)	93,320	177,394	90,821	179,893
Pooled Sensitivity, % (95% C.I)	**42.49** (28.41 – 57.24)	**78.38** (66.39 – 88.32)	**33.79** (20.12 – 49.00)	**75.37** (64.31 – 84.95)

Table summarizing results from a sub-group analysis demonstrating the additional value of (1) Colour Flow (CF) Doppler ($p<0.0001$) and (2) the examination of cardiac outflow tracts (OT) ($p<0.0001$) on the detection of major cardiac anomalies in the first trimester.

Table 8: Impact of Mode of Ultrasound on Detection Rates for Major Cardiac Anomalies in low risk, unselected and mixed populations.

Mode of Ultrasound	TA only	Combination of TA and TV used	TV only
Number of Studies (n)	9	36	2
Number of Fetuses (n)	17,444	294,185	648
Pooled Sensitivity, % (95% C.I)	**57.82** (36.72 – 77.53)	**56.13** (45.30 – 66.67)	**57.06** (1.76 – 99.99)

Table summarizing results from a sub-group analysis evaluating the impact of mode of ultrasound used for cardiac assessment. A chi-squared test (2 by k) comparing 3 possible modality choices showed no significant difference between the groups ($p = 0.4662$).

Table 9: First Trimester Detection Rates for Individual Cardiac Anomalies

Detection Rates ≈ > 60%		**Detection Rates ≈ 25 – 60%**		**Detection Rates ≈ < 25%**	
Anomaly	**Sensitivity (%) with 95% C.I.***	**Anomaly**	**Sensitivity (%) with 95% C.I.***	**Anomaly**	**Sensitivity (%) with 95% C.I.***
Ectopia Cordis	93.26 (76.03 – 99.98)	Transposition of the Great Arteries	45.05 (29.29 – 61.35)	Ebstein's Anomaly	25.03 (4.83 – 54.08)
Hypoplastic Right Heart Syndrome	91.65 (77.23 – 99.21)	Tetralogy of Fallot	40.95 (30.16 – 52.20)	Ventricular Septal Defect	23.92 (14.41 – 34.97)
Tricuspid Atresia/Dysplasia	88.63 (76.00 – 96.94)	Aortic Valve Stenosis	38.81 (15.77 – 64.90)	Atrial Septal Defect	21.53 (6.78 – 41.66)
Atrio-Ventricular Septal Defect	77.24 (63.62 – 88.42)	Coarctation of the Aorta	37.23 (23.96 – 51.56)	Pulmonary Valve or Artery Stenosis	19.45 (8.99 – 32.74)
Truncus Arteriosus	76.73 (58.94 – 90.62)			Rhabdomyoma	4.87 (0.19 – 22.09)
Complex Cardiac Defect	76.31 (57.46 – 90.92)				
Hypoplastic Left Heart Syndrome	73.28 (59.86 – 84.82)				
Heterotaxy Syndrome	72.59 (55.75 – 86.63)				
Univentricle	71.21 (52.11 – 87.03)				
Double Outlet Right Ventricle	63.11 (44.90 – 79.59)				
Pulmonary Atresia	59.68 (23.63 – 90.53)				

*Sensitivities provided reflective of data obtained from low risk, mixed risk and unselected populations.

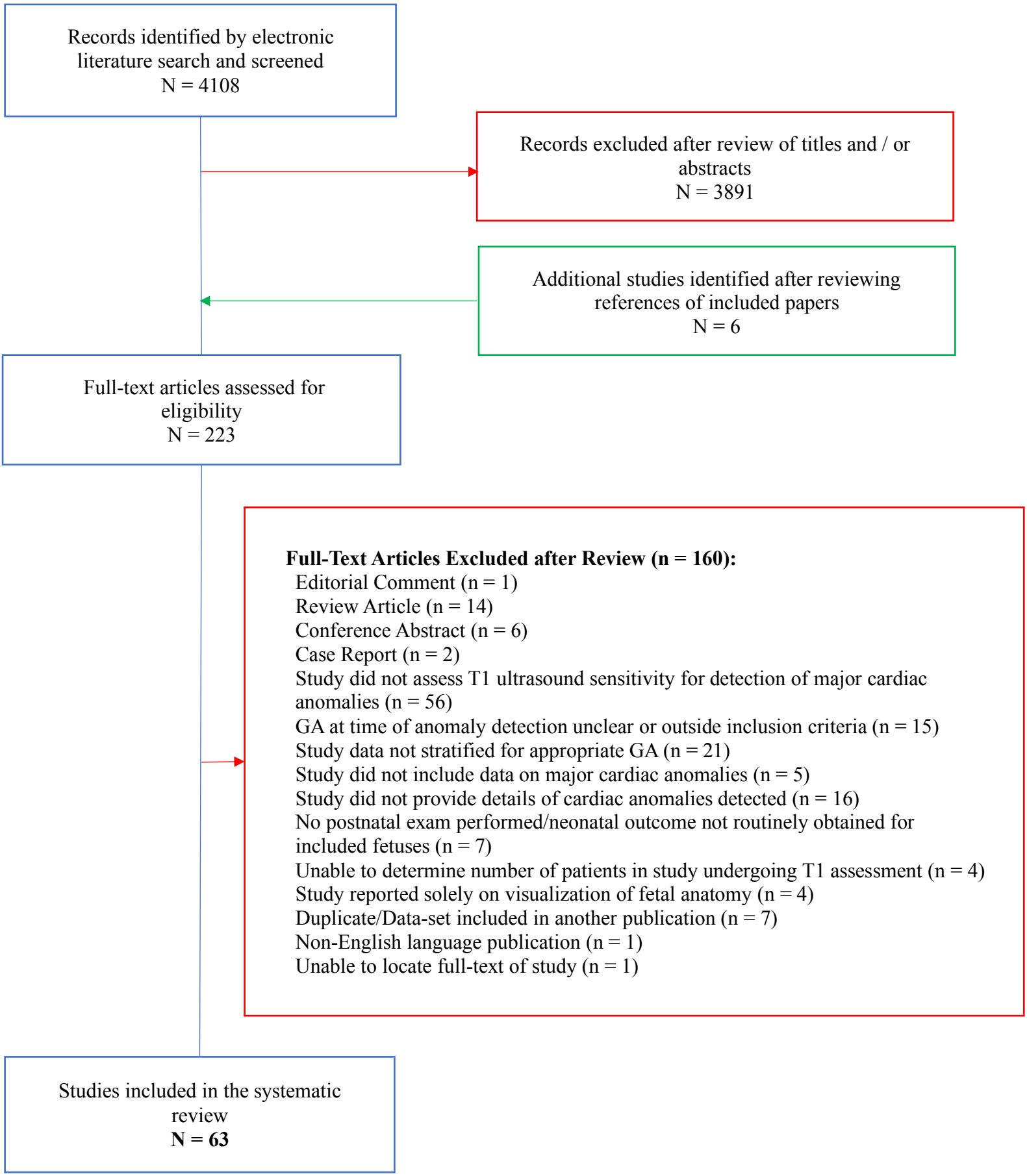

Figure 1: Flowchart of search strategy and selection of studies for inclusion in systematic review and meta-analysis. GA, gestational age.

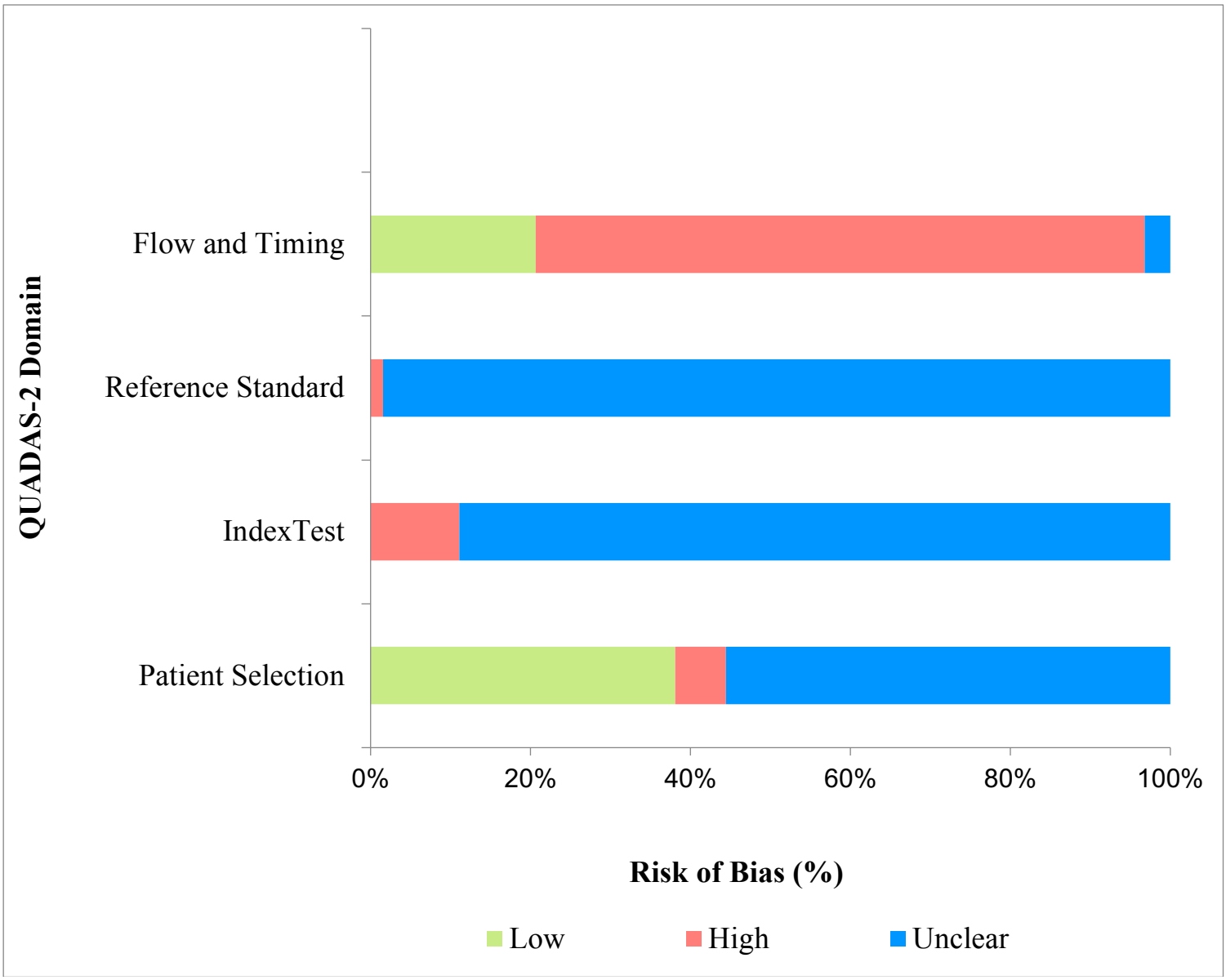

Figure 2: Quality assessment of studies included in systematic review for risk of bias based on QUADAS-2 guidance.

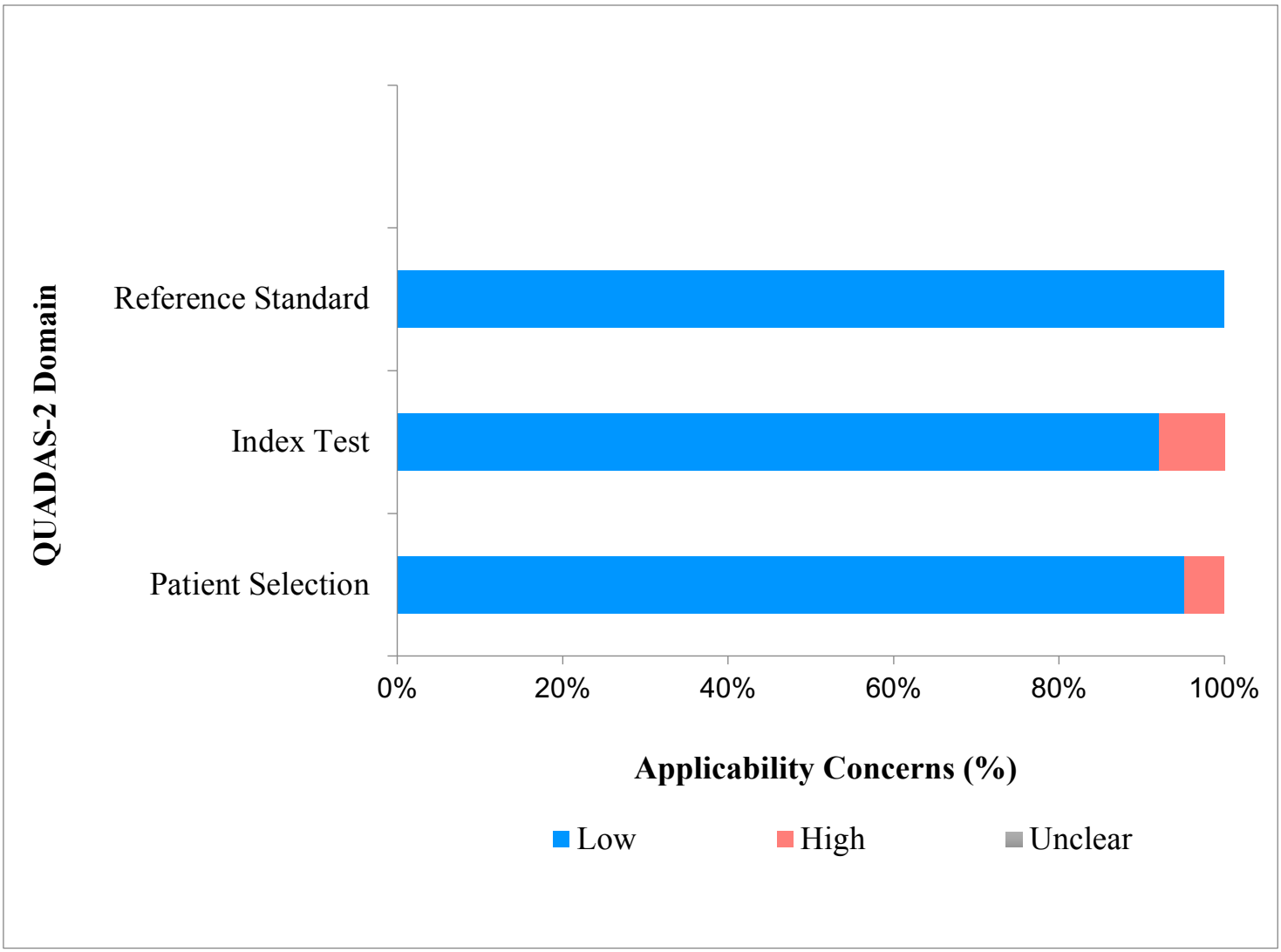

Figure 3: Quality assessment of studies included in systematic review for concerns regarding study applicability based on QUADAS-2 guidance.

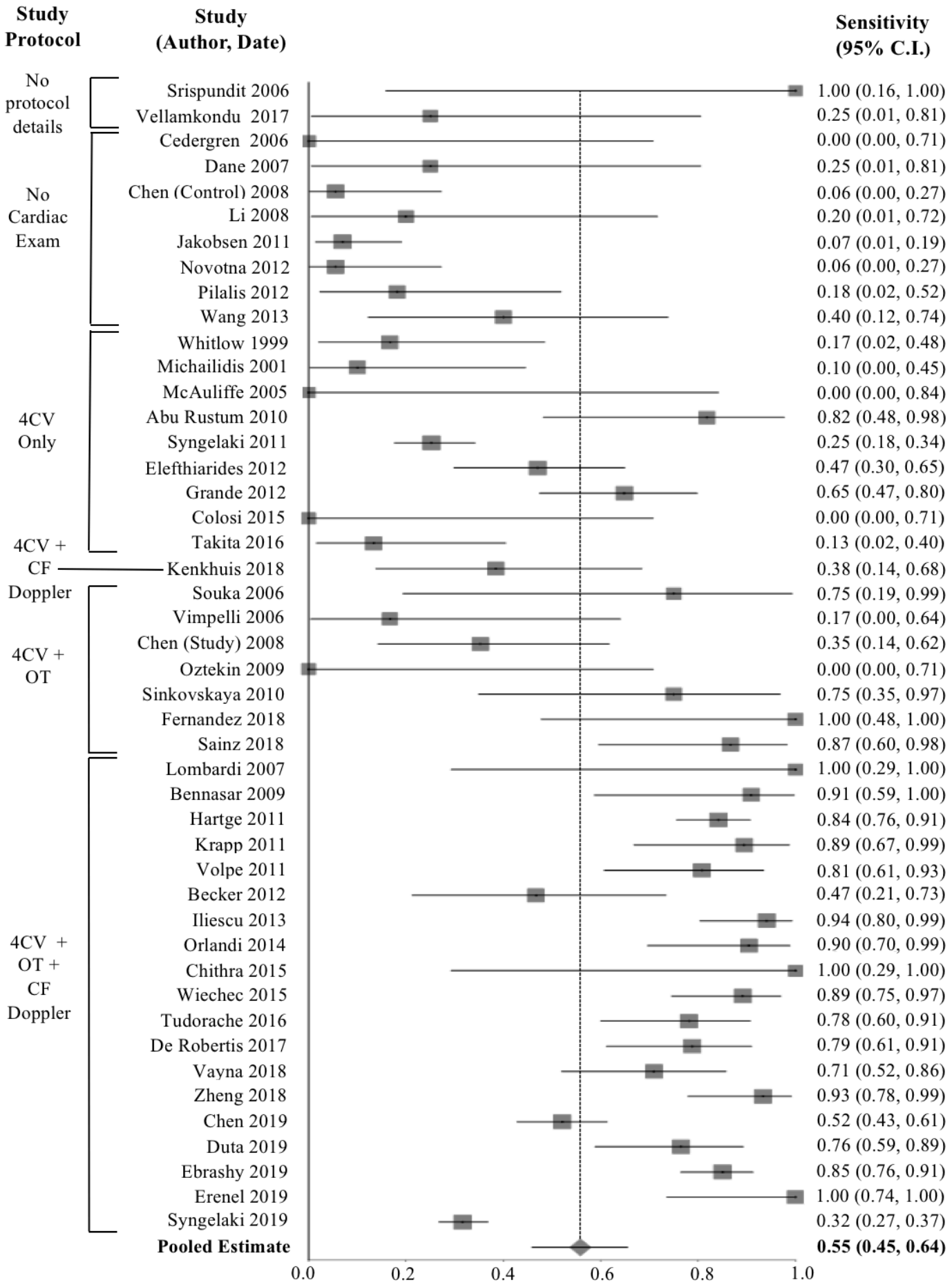

Figure 4: Forest plot demonstrating sensitivity of first-trimester ultrasound for the detection of major cardiac abnormalities in non- high risk populations. I^2 = 91.8% (95% C.I. 90.3-93.0%).

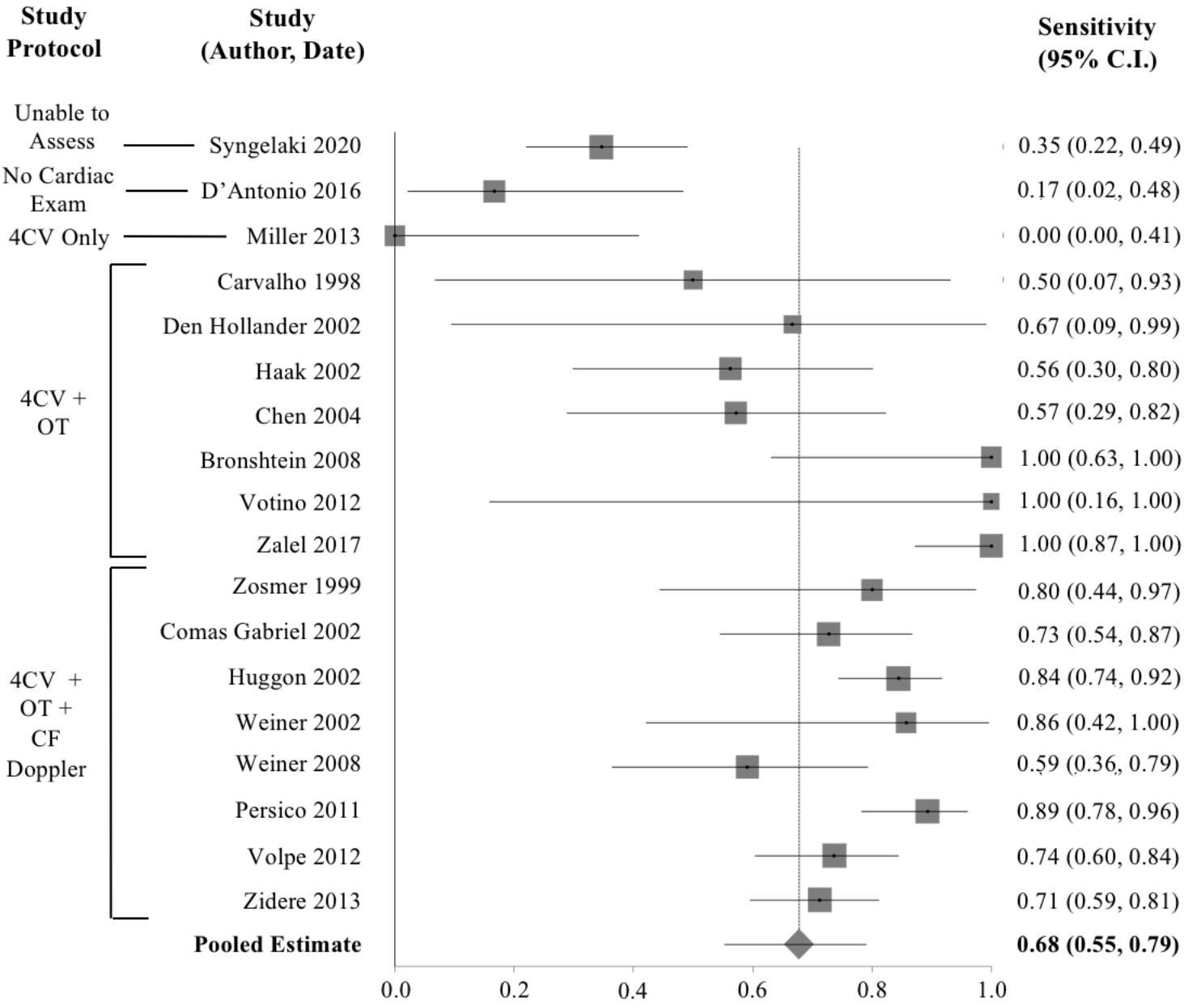

Figure 5: Forest plot demonstrating sensitivity of first-trimester ultrasound for the detection of major cardiac abnormalities in high risk populations. $I^2 = 85.8\%$ (95% C.I. 79.1-89.6%).

Appendix 1 – Search Strategy

The global search strategy involved two independent searches (A and B) combined with an "all" function. The search was conducted using MEDLINE, EMBASE, Web of Science and the Cochrane Library from January 1st, 1998 until July 17th, 2020.

Medline:

Search #	Searches conducted
1	Ultrasonography, Prenatal/
2	Prenatal diagnosis/ and exp ultrasonography/
3	(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*).ti,ab.
4	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*) adj3 (screen* or scan* or structural assessment* or structural survey*)).ti,ab.
5	1 or 2 or 3 or 4
6	Pregnancy Trimester, First/
7	(1st trimester or first trimester).ti,ab.
8	(early pregnan* or early gestation*).ti,ab.
9	((10 week? or 11 week? or 12 week? or 13 week? or 14 week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
10	((10week? or 11week? or 12week? or 13week? or 14week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.

11	(((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
12	6 or 7 or 8 or 9 or 10 or 11
13	exp *Congenital Abnormalities/
14	(congenital* adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
15	((fetal or foetal or fetus or foetus) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
16	(structural adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
17	((non-chromosomal or nonchromosomal or chromosomal) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
18	neural tube defects/ or anencephaly/ or encephalocele/ or exp Spinal Dysraphism/
19	craniofacial abnormalities/ or holoprosencephaly/ or cleft palate/
20	Hernia, Umbilical/
21	Gastroschisis/
22	Bone Diseases, Developmental/ or Leg Length Inequality/ or limb deformities, congenital/ or exp polydactyly/
23	exp "Transposition of Great Vessels"/ or Hypoplastic Left Heart Syndrome/
24	exp heart septal defects/ or "tetralogy of fallot"/
25	hernia, diaphragmatic/ or hernias, diaphragmatic, congenital/
26	(acrania? or anencephaly or exencephaly or holoproscencephaly).ti,ab.

27	(encephalocele or ((brain or cereb*) adj bifid*)).ti,ab.
28	(omphalocele or exomphalos or (umbilical adj2 hernia?)).ti,ab.
29	gastroschisis.ti,ab.
30	megacystis.ti,ab.
31	(skelet* adj2 dysplasia?).ti,ab.
32	((limb? or leg? or arm?) adj2 (short* or reduc* or inequality or unequal*)).ti,ab.
33	polydactyly.ti,ab.
34	(transpos* adj3 (great arteries or great vessel?)).ti,ab.
35	((ventric* or heart) adj2 hypoplas*).ti,ab.
36	"tetralogy of fallot".ti,ab.
37	((atrioventric* or atrio-ventric* or septal) adj2 defect?).ti,ab.
38	double outlet right ventric*.ti,ab.
39	spina bifida.ti,ab.
40	((face or facial or lip* or palate*) adj2 cleft?).ti,ab.
41	(diaphragm* adj2 hernia*).ti,ab.
42	(((kidney or renal) adj2 agenesis) or potter* syndrome).ti,ab.
43	body stalk anomal*.ti,ab.

44	(club foot or club feet or talipes).ti,ab.
45	ventriculomegaly.ti,ab.
46	cystic hygroma?.ti,ab.
47	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	5 and 12 and 47
49	((fetal or foetal or fetus or foetus) adj (anatomy or defect? or malformation? or abnormalit* or anomal*) adj5 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.
50	12 and 49
51	((early pregnan* or early gestation* or 1st trimester or first trimester) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.
52	(((10 week? or 11 week? or 12 week? or 13 week? or 14 week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
53	(((10week? or 11week? or 12week? or 13week? or 14week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and

	(pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
54	(((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week? adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
55	51 or 52 or 53 or 54
56	47 and 55
57	48 or 50 or 56
58	exp animals/ not humans.sh.
59	57 not 58

Embase

# ▲	**Searches**
1	fetus echography/
2	prenatal diagnosis/ and (echography/ or transvaginal echography/)
3	(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*).ti,ab.
4	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*) adj3 (screen* or scan* or structural assessment* or structural survey*)).ti,ab.
5	1 or 2 or 3 or 4
6	first trimester pregnancy/
7	(1st trimester or first trimester).ti,ab.

8	(early pregnan* or early gestation*).ti,ab.
9	((10 week? or 11 week? or 12 week? or 13 week? or 14 week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
10	((10week? or 11week? or 12week? or 13week? or 14week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
11	(((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week?) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
12	6 or 7 or 8 or 9 or 10 or 11
13	exp *congenital malformation/
14	(congenital* adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
15	((fetal or foetal or fetus or foetus) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
16	(structural adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
17	((non-chromosomal or nonchromosomal or chromosomal) adj2 (defect? or malformation? or abnormalit* or anomal*)).ti,ab.
18	neural tube defect/ or anencephalus/ or encephalocele/ or exp spinal dysraphism/ or holoprosencephaly/
19	cleft palate/ or cleft face/ or cleft lip/ or cleft lip palate/
20	umbilical hernia/
21	Gastroschisis/
22	bone dysplasia/ or leg length inequality/ or polydactyly/
23	great vessels transposition/ or hypoplastic left heart syndrome/ or exp heart septum defect/
24	diaphragm hernia/
25	kidney agenesis/
26	(acrania? or anencephaly or exencephaly or holoproscencephaly).ti,ab.

27	(encephalocele or ((brain or cereb*) adj bifid*)).ti,ab.
28	(omphalocele or exomphalos or (umbilical adj2 hernia?)).ti,ab.
29	gastroschisis.ti,ab.
30	megacystis.ti,ab.
31	(skelet* adj2 dysplasia?).ti,ab.
32	((limb? or leg? or arm?) adj2 (short* or reduc* or inequality or unequal*)).ti,ab.
33	polydactyly.ti,ab.
34	(transpos* adj3 (great arteries or great vessel?)).ti,ab.
35	((ventric* or heart) adj2 hypoplas*).ti,ab.
36	"tetralogy of fallot".ti,ab.
37	((atrioventric* or atrio-ventric* or septal) adj2 defect?).ti,ab.
38	double outlet right ventric*.ti,ab.
39	spina bifida.ti,ab.
40	((face or facial or lip* or palate*) adj2 cleft?).ti,ab.
41	(diaphragm* adj2 hernia*).ti,ab.
42	(((kidney or renal) adj2 agenesis) or potter* syndrome).ti,ab.
43	body stalk anomal*.ti,ab.
44	(club foot or club feet or talipes).ti,ab.
45	ventriculomegaly.ti,ab.
46	cystic hygroma?.ti,ab.
47	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46
48	5 and 12 and 47
49	((fetal or foetal or fetus or foetus) adj (anatomy or defect? or malformation? or abnormalit* or anomal*) adj5 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.
50	12 and 49

51	((early pregnan* or early gestation* or 1st trimester or first trimester) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)).ti,ab.
52	(((10 week? or 11 week? or 12 week? or 13 week? or 14 week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
53	(((10week? or 11week? or 12week? or 13week? or 14week?) adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
54	(((ten*2 or eleven*2 or twel*3 or thirteen*2 or fourteen*2) adj week? adj3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment?)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)).ti,ab.
55	51 or 52 or 53 or 54
56	47 and 55
57	48 or 50 or 56

Cochrane Library

ID	Search
#1	MeSH descriptor: [Ultrasonography, Prenatal] this term only
#2	ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*:ti,ab,kw (Word variations have been searched)
#3	((fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*) near/3 (screen* or scan* or structural assessment* or structural survey*)):ti,ab,kw (Word variations have been searched)

#4	#1 or #2 or #3
#5	MeSH descriptor: [Pregnancy Trimester, First] explode all trees
#6	1st trimester or "first trimester":ti,ab,kw (Word variations have been searched)
#7	early pregnan* or "early gestation*":ti,ab,kw (Word variations have been searched)
#8	((("10 week*" or "11 week*" or "12 week*" or "13 week*" or "14 week*") and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*))):ti,ab,kw (Word variations have been searched)
#9	(((10week* or 11week* or 12week* or 13week* or 14week*) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*))):ti,ab,kw (Word variations have been searched)
#10	ten week? or "eleven week?" or "twelve week?" or "thirteen week?" or "fourteen week?":ti,ab,kw (Word variations have been searched)
#11	#5 or #6 or #7 or #8 or #9 or #10
#12	MeSH descriptor: [Congenital Abnormalities] explode all trees
#13	((congenital* near/2 (defect* or malformation* or abnormalit* or anomal*))):ti,ab,kw (Word variations have been searched)
#14	(((fetal or foetal or fetus or foetus) near/2 (defect* or malformation* or abnormalit* or anomal*))):ti,ab,kw (Word variations have been searched)
#15	((structural near/2 (defect* or malformation* or abnormalit* or anomal*))):ti,ab,kw (Word variations have been searched)
#16	(((non-chromosomal or nonchromosomal) near/2 (defect* or malformation* or abnormalit* or anomal*))):ti,ab,kw (Word variations have been searched)

#17	(Acrania* or anencephaly or exencephaly or holoproscencephaly OR encephalocele or ((brain or cereb*) NEXT bifid*) OR omphalocele or exomphalos or (umbilical NEAR/2 hernia*) OR gastroschisis OR megacystitis OR (skelet* NEAR/2 dysplasia*) OR ((limb* or leg* or arm*) NEAR/2 (short* or reduc* or inequality or unequal*)) OR polydactyly OR (transpos* NEAR/3 ("great arteries" or "great vessel*")) OR ((ventric* or heart) NEAR/2 hypoplas*) OR "spina bifida" OR ((face or facial or lip* or palate*) NEAR/2 cleft*) OR (diaphragm* NEAR/2 hernia*) OR ((kidney or renal) NEAR/2 agenesis) or "potter* syndrome" OR "tetralogy of fallot " OR ((atrioventric* or atrio-ventric* or septal) near/2 defect*) OR "double outlet right ventric*" OR “Body Stalk Anomal*” OR “Club Foot” OR “Club Feet” OR Talipes OR Ventriculomegaly OR Cystic Hygroma*):ti,ab,kw
#18	#12 or #13 or #14 or #15 or #17
#19	#4 and #11 and #18
#20	(((fetal or foetal or fetus or foetus) next (anatomy or defect* or malformation* or abnormalit* or anomal*) near (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment*))):ti,ab,kw (Word variations have been searched)
#21	#11 and #20
#22	((("early pregnan*" or "early gestation*" or 1st trimester or first trimester) near/3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment*))):ti,ab,kw (Word variations have been searched)

#23	((((("10 week*" or "11 week*" or "12 week*" or "13 week*" or "14 week*") near/3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment*)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*))):ti,ab,kw (Word variations have been searched)
#24	((((("ten week*" or "eleven week*" or "twelve week*" or "thirteen week*" or "fourteen week*") near/3 (ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra* or scan* or screen* or survey* or assessment*)) and (pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*))):ti,ab,kw (Word variations have been searched)
#25	#22 or #23
#26	#18 AND #25
#27	#19 OR #21 OR #26

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# 13	#12 OR #8
# 12	#11 AND #4
# 11	#10 OR #9
# 10	TS=("fetal anatomy" OR "fetal defect*" OR "fetal malformation*" OR "fetal abnormalit*" OR "fetal anomal*" OR "foetal anatomy" OR "foetal defect*" OR "foetal malformation*" OR "foetal abnormalit*" OR "foetal anomal*") AND TS=(scan* OR survey* OR assessment? OR screen*)

# 9	TS=("fetal anatomy" OR "fetal defect*" OR "fetal malformation*" OR "fetal abnormalit*" OR "fetal anomal*" OR "foetal anatomy" OR "foetal defect*" OR "foetal malformation*" OR "foetal abnormalit*" OR "foetal anomal*") AND TS=(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*)
# 8	#7 AND #4 AND #1
# 7	#6 OR #5
# 6	TS=(acrania* or anencephaly or exencephaly or holoproscencephaly) OR TS=(encephalocele or ((brain or cereb*) NEXT bifid*)) OR TS=(omphalocele or exomphalos or (umbilical NEAR/2 hernia*)) OR TS=gastroschisis OR TS=megacystitis OR TS=(skelet* NEAR/2 dysplasia*) OR TS=((limb* or leg* or arm*) NEAR/2 (short* or reduc* or inequality or unequal*)) OR TS=polydactyly OR TS=(transpos* NEAR/3 ("great arteries" or "great vessel*")) OR TS=((ventric* or heart) NEAR/2 hypoplas*) OR TS="spina bifida" OR TS=((face or facial or lip* or palate*) NEAR/2 cleft*) OR TS=(diaphragm* NEAR/2 hernia*) OR TS=(((kidney or renal) NEAR/2 agenesis) or "potter* syndrome") OR TS=("tetralogy of fallot " OR ((atrioventric* or atrio-ventric* or septal) near/2 defect*) OR "double outlet right ventric*") OR TS= (“Body Stalk Anomal*” OR “Club Foot” OR “Club Feet” OR Talipes OR Ventriculomegaly OR Cystic Hygroma*)

# 5	TS=(congenital* NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS=(fetal NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS= (foetal NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS=(fetus NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS=(foetus NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS=(structural NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS=(non-chromosomal NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS=(nonchromosomal NEAR/2 (defect* or malformation* or abnormalit* or anomal*)) OR TS=(chromosomal NEAR/2 (defect* or malformation* or abnormalit* or anomal*))
# 4	#3 OR #2
# 3	TS=("1st trimester" or "first trimester") OR TS=("early pregnan*" or "early gestation*") OR TS=("10 week*" or "11 week*" or "12 week*" or "13 week*" or "14 week*") OR TS=(10week* or 11week* or 12week* or 13week* or 14week*) OR TS=("ten week*" OR "eleven week*" OR "twelve week*" OR "thirteen week*" OR "fourteen week*")
# 2	TS=("1st trimester" or "first trimester") OR TS=("early pregnan*" or "early gestation*")
# 1	TS=((pregnan* or gestation* or fetal or foetal or fetus or foetus or prenat* or pre-nat* or prepart* or pre-part*)) AND TS=(ultrasound* or ultra-sound or ultrasonogra* or ultra-sonogra* or sonogra* or echocardiogra*)

Appendix 2 – QUADAS-2 Assessment Tool

Defining the review question:

1. What is the sensitivity of first trimester ultrasound for the detection of cardiac malformations?

2. What factors might impact detection rates?

- Patient selection: pregnant women with gestational age prior to 14^{+6} weeks, mothers with all levels of risk and with either singleton or multiple pregnancies were included
- Index Test: Transvaginal and/or Transabdominal 2D Ultrasound prior to 14^{+6} weeks gestational age.
- Reference Standard: Postnatal examination of fetus or postmortem of fetus for evidence/confirmation of structural abnormalities.
- Target condition: congenital cardiac abnormalities.

Domain 1: Patient Selection

A. **Risk of Bias:** Could the selection of patients have introduced bias? LOW/HIGH/UNCLEAR

Signaling Questions:

i. Was a consecutive (vs. random sample) of patients enrolled? YES/NO/UNCLEAR

ii. Did the study avoid inappropriate exclusions? YES/NO/UNCLEAR

B. **Applicability:** Are there concerns that the included patients and setting do not match the review question (i.e. severity of the target condition, demographic features, presence of co-morbidity, setting)?	LOW/HIGH/UNCLEAR

Domain 2: Index Test

A. **Risk of Bias:** Could the conduct or interpretation of the index test have introduced bias?	LOW/HIGH/UNCLEAR
<u>Signaling Questions:</u>	
i. Were sonographers blinded to the history (risk profile) of the patients?	YES/NO/UNCLEAR
ii. Were all of the included first trimester scans performed prior to 14^{+6} weeks gestational age?	YES/NO/UNCLEAR
B. **Applicability:** Are there concerns that the index test, its conduct, or interpretation differ from the review question?	LOW/HIGH/UNCLEAR

Domain 3: Reference Standard

A. **Risk of Bias:** Could the reference standard, its conduct, or its interpretation have introduced bias?	LOW/HIGH/UNCLEAR
<u>Signaling Questions:</u>	
i. Was an appropriate reference standard used to correctly classify the target condition?	YES/NO/UNCLEAR

ii. Were the reference standard results interpreted without knowledge of the results of the index test?	YES/NO/UNCLEAR
B. **Applicability:** Are there concerns that the target condition as defined by the reference standard does not match the question?	LOW/HIGH/UNCLEAR

Domain 4: Flow and Timing

A. Risk of Bias: Could the patient flow have introduced bias?	LOW/HIGH/UNCLEAR
<u>Signaling Questions:</u>	
i. Did all patients included in the study undergo examination with the reference standard? (either postnatal examination for live-births or post-mortem for still-births/TOPs in those with diagnosed malformations).	YES/NO/UNCLEAR
ii. Were all patients enrolled in the study included in the analysis?	YES/NO/UNCLEAR
iii. Were all measures of 1st trimester ultrasound detection accuracy (eg. TP, FP, TN, FN) reported?	YES/NO/UNCLEAR

Appendix 3: Members of the Assessing Clinical and Cost Effectiveness of Prenatal first Trimester anomaly Screening (ACCEPTS) study group

Clinical and study design group:
Aris T Papageorghiou (PI, University of Oxford, UK), Zarko Alfirevic (Liverpool Women's NHS Foundation Trust, UK), Trish Chudleigh (Cambridge University Hospitals NHS Foundation Trust, UK), Hilary Goodman (Hampshire Hospital NHS Foundation Trust, UK), Christos Ioannou (Oxford University Hospitals NHS Trust, UK), Heather Longworth (Liverpool Women's NHS Foundation Trust, UK), Jehan N Karim (University of Oxford, UK), Kypros H Nicolaides (Fetal Medicine Research Institute, King's College Hospital, UK), Pranav Pandya (University College London Hospitals NHS Foundation Trust, UK), Gordon Smith (University of Cambridge, UK), Basky Thilaganathan (St George's University Hospitals NHS Foundation Trust, UK) and Jim Thornton (University of Nottingham, UK).

Health economics group: Oliver Rivero-Arias (Lead, University of Oxford, UK), Helen Campbell (University of Oxford, UK), Ed Juszczak (University of Oxford, UK), Louise Linsell (University of Oxford, UK) and Ed Wilson (University of Cambridge, UK).

Qualitative research: Lisa Hinton (University of Cambridge, UK)

Patient Voice: Jane Fisher (Lead, Antenatal Results and Choices, UK), Elizabeth Duff (National Childbirth Trust, UK), Anne Rhodes (Tiny Tickers, UK), Gil Yaz (SHINE UK).