



# Systematic review of first-trimester ultrasound screening for detection of fetal structural anomalies and factors that affect screening performance

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**KEYWORDS:** congenital abnormalities; fetal anomalies; first trimester; prenatal diagnosis; prenatal screening; ultrasound

## ABSTRACT

**Objectives** To determine the sensitivity and specificity of first-trimester ultrasound for the detection of fetal abnormalities and to establish which factors might impact on screening performance.

**Methods** A systematic review and meta-analysis of all relevant publications was performed to assess the diagnostic accuracy of two-dimensional transabdominal and transvaginal ultrasound in the detection of congenital fetal anomalies prior to 14 weeks' gestation. The reference standard was detection of abnormalities at birth or postmortem. Factors that may impact on detection rates were evaluated, including population characteristics, gestational age, healthcare setting, ultrasound modality, use of an anatomical checklist for detection of first-trimester anomalies and type of malformation included in the study. In an effort to reduce the impact of study heterogeneity on the results of the meta-analysis, data from the studies were analyzed within subgroups of major anomalies vs all types of anomaly and low-risk/unselected populations vs high-risk populations.

**Results** An electronic search (until 29 July 2015) identified 2225 relevant citations, from which a total of 30 studies, published between 1991 and 2014, were selected for inclusion. The pooled estimate for the detection of major abnormalities in low-risk or unselected populations (19 studies, 115 731 fetuses) was 46.10% (95% CI, 36.88–55.46%). The detection rate for all abnormalities in low-risk or unselected populations (14 studies, 97 976 fetuses) was 32.35% (95% CI, 22.45–43.12%), whereas in high-risk populations (six studies, 2841 fetuses) it was 61.18% (95% CI, 37.71–82.19%). Of the factors examined for their impact on detection rate, there was a statistically significant relationship ( $P < 0.0001$ ) between

the use of a standardized anatomical protocol during first-trimester anomaly screening and its sensitivity for the detection of fetal anomalies in all subgroups.

**Conclusions** Detection rates of first-trimester fetal anomalies ranged from 32% in low-risk groups to more than 60% in high-risk groups, demonstrating that first-trimester ultrasound has the potential to identify a large proportion of fetuses affected with structural anomalies. The use of a standardized anatomical protocol improves the sensitivity of first-trimester ultrasound screening for all anomalies and major anomalies in populations of varying risk. The development and introduction of international protocols with standard anatomical views should be undertaken in order to optimize first-trimester anomaly detection. Copyright © 2016 ISUOG. Published by John Wiley & Sons Ltd.

## INTRODUCTION

The main objectives of prenatal ultrasound examination at 11 to 13 + 6 weeks' gestation are to confirm fetal viability, establish an accurate gestational age from the measurement of fetal crown–rump length, identify multiple pregnancies and determine their chorionicity and amnionicity, and to screen for major fetal anomalies, both structural abnormalities and aneuploidy<sup>1</sup>. In many settings, screening for chromosomal anomalies is undertaken by measurement of fetal nuchal translucency (NT) in combination with maternal age, other ultrasound markers (e.g. fetal nasal bone, ductus venosus flow, fetal heart rate and assessment of tricuspid valve flow) and measurement of maternal serum free beta-human chorionic gonadotropin and pregnancy-associated plasma protein-A, in the form of a combined test. This screening

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method is associated with high sensitivity and a relatively low false-positive rate<sup>2-4</sup>.

The recent development of cell-free fetal DNA screening using maternal blood is transforming our expectations of first-trimester aneuploidy detection<sup>5</sup>. As this innovative technology becomes increasingly accessible and cost-effective, it will complement (and may ultimately supersede) current combined screening. Thus, the objectives of the first-trimester ultrasound scan will need to evolve once again. The many advantages of first-trimester ultrasound mean it is likely to continue being used in clinical practice, including for measurement of fetal NT, as increased NT is linked to structural congenital anomalies, notably major cardiac defects<sup>6</sup>, and it may also be indicative of chromosomal aberrations that are not detectable by cell-free fetal DNA screening. In addition, first-trimester screening for pregnancy complications, such as early pre-eclampsia and very early preterm birth, are commonly used as a tool for risk stratification of the pregnancy<sup>7</sup>.

Nevertheless, it is our opinion that the resulting shift in aneuploidy screening, in combination with improvements in ultrasound technology, will mean that the role of first-trimester ultrasound will be increasingly for the visualization of fetal anatomy<sup>8-11</sup>. Thus, while fetal anomaly screening has traditionally been performed in the second trimester, many structural abnormalities can be diagnosed reliably between 11 and 14 weeks<sup>12-14</sup>, with obvious advantages. However, the varying sensitivity of the test means that there is little consensus internationally as to whether first-trimester anomaly screening is valuable for use in daily clinical practice. In addition, there is currently limited understanding of which factors impact on the success of first-trimester anomaly detection and how optimal screening should be performed.

Within this context, the aim of our study was to perform a systematic review and meta-analysis of the current literature in order to assess the sensitivity and specificity of first-trimester anomaly detection and, crucially, to determine which factors might affect the performance of this screening test.

## METHODS

### Search strategy

A systematic electronic search was conducted in order to identify all relevant publications assessing the diagnostic accuracy of first-trimester two-dimensional (2D) ultrasound for the detection of congenital fetal anomalies. The search was conducted using MEDLINE, EMBASE, Web of Science and The Cochrane Library, with no restriction on year of publication. Free-text terms and medical subject headings related to prenatal screening, early pregnancy and congenital anomalies were used. The full search strategy is given in Appendix S1. The electronic search was completed on 29 July 2015.

Study selection was performed in multiple stages. Initially, the database of studies collected from the electronic search was screened using article title and

abstract, where available. On this basis, a list of potentially suitable articles for inclusion in the systematic review was formulated. The full text of these articles was then assessed to determine which studies met the inclusion criteria. Reference lists of all eligible studies were screened for additional citations that may not have been identified by the initial electronic search.

### Study selection

All studies reporting on the detection of fetal structural abnormalities by 2D ultrasound before 14 weeks' gestation were included. Prospective and retrospective observational studies and randomized controlled trials were all eligible for inclusion. Literature reviews, abstracts, case reports, editorial letters, personal communications and non-English language publications were excluded. Every attempt was made to identify incidences in which multiple publications from the same group shared population subjects. In such cases, only the most recent study with the largest cohort was included in the review.

Studies reporting on the sensitivity of first-trimester anomaly screening in either singleton or multiple pregnancies in any healthcare setting and pregnancies of all levels of risk were eligible for inclusion. Prospective studies were included based on their intention to perform ultrasound screening prior to 14 weeks, with the understanding that the reality of clinical practice means that all scans would not necessarily be performed within this time period.

This review included studies with data on all types of structural abnormality, including lethal, major, moderate and minor abnormalities, as defined by the Royal College of Obstetricians and Gynaecologists (RCOG)<sup>15</sup>. Only those studies that gave an individual breakdown of the fetal structural anomalies detected within their population cohort were eligible for inclusion. Publications that focused on a specific malformation or specific groups of anatomical malformations (e.g. cardiac malformations only) were excluded. Studies in which the aim was solely to investigate the use of first-trimester ultrasound for the detection of fetal chromosomal abnormalities or soft markers were also excluded.

Studies utilizing various modes of 2D ultrasound, including transvaginal (TV), transabdominal (TA) and a combination of both approaches, were eligible for inclusion. However, studies evaluating fetuses using three-dimensional ultrasound were excluded.

The reference standard for determining the accuracy of first-trimester anomaly screening was the detection of fetal structural abnormalities at birth or later. As such, studies that did not perform a postnatal examination or obtain data regarding neonatal outcome for the purposes of confirming true-positive, false-positive, true-negative and false-negative results were excluded. Regarding postmortem examination of fetuses, we took a pragmatic approach: postmortem examination did not form a requirement for inclusion in the review, as it is often not possible following first-trimester termination of pregnancy.

## 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) guidelines and the Synthesizing Evidence from Diagnostic Accuracy Tests (SEDATe) guidance<sup>16,17</sup>.

For each study, the following data were recorded: name of the first author; year of publication; sample size; and modifiable and non-modifiable factors that may have impacted on detection rates, including population characteristics, gestational age at which ultrasound was performed, type of healthcare setting, index test used (i.e. ultrasound modality – TV, TA or both), whether an anatomical checklist was used for first-trimester anomaly detection, whether a heart examination was specifically performed during screening and what type of malformations were included in the study. With respect to the use of an anatomical checklist for performing the first-trimester anomaly scan, studies were graded as having a basic checklist, a detailed checklist or no checklist; studies that did not declare the use of an anatomical checklist were deemed to have none. A basic checklist was defined as one that requires observation of certain anatomical regions or the presence of specific organs. A detailed checklist was defined as one that directs the sonographer to visualize multiple specific regions of at least one of the organs listed and which may also include planes of insonation or taking measurements, or uses advanced ultrasound markers such as intracranial translucency or retronasal triangle. For example, a checklist that lists ‘head’ would be considered a basic checklist whereas one that lists ‘cranial ossification, interhemispheric falx, butterfly-shaped choroid plexus’ would be considered detailed.

An initial attempt was made to collect data with respect to the level of experience and training of sonographers in each study. However, the majority of studies reported no such data and those that did provide data were not amenable to comparison, therefore this was abandoned.

Finally, a search of all studies was undertaken to determine which modifiable and non-modifiable factors were specifically cited by study authors as having a significant impact on the accuracy and efficiency of first-trimester anomaly screening.

When assessing the sensitivity of first-trimester anomaly screening, it is possible to define this as the number of abnormalities detected or as the number of fetuses with one or more anomaly. Both outcomes are important; the first determines the accuracy of first-trimester ultrasound in detecting individual anomalies of varying severity, while the second provides an understanding of how many fetuses are affected by first-trimester anomaly screening. Therefore, the number of abnormalities present in each study population and the proportion detected at first-trimester screening were documented. In addition, the number of fetuses in each study cohort affected with one or more structural malformation(s) was noted, along

with the number of those that were identified in the first trimester.

Owing to the heterogeneity of the studies included in this review, considerable efforts were made to ensure that the results of the studies were comparable. Our review was therefore required to develop strict definitions for what constitutes ‘one detected structural abnormality’. First, it was decided that all bilateral defects, such as bilateral renal agenesis, would be counted as two individual structural anomalies. This was done so that our review would be able to distinguish between a fetus with exclusive unilateral renal agenesis diagnosed in the first trimester (‘one correctly diagnosed anomaly’) and a fetus diagnosed with unilateral renal agenesis with a missed bilateral defect (‘one correctly identified anomaly, one missed anomaly diagnosis’). This is particularly important because it provides the most accurate data for analysis of the sensitivity of first-trimester screening. Second, fetuses that were diagnosed with a syndrome (e.g. Dandy–Walker syndrome) were considered to have one abnormality. The diagnosis of a syndrome is often made based on the findings of multiple malformations on ultrasound. However, in the majority of studies, there was no specification as to how many constituent anomalies were detected in order to make the diagnosis of a specific syndrome, and moreover whether these anomalies were all detected in the first trimester. As such, the only way to unify the analysis of all the studies was to treat the ultrasound diagnosis of one syndrome as one anomaly. Third, in several studies, a single fetus would be said to have multiple anomalies within one organ system (e.g. ‘multiple skeletal abnormalities’). In this case, the fetus was considered to have one structural (‘a skeletal’) abnormality. Finally, single umbilical artery was considered a structural variant of normal anatomy and therefore excluded from data collection, as were soft markers for fetal aneuploidy, including increased NT and absent nasal bone. Of note, cystic hygromas were excluded from the analysis. The diagnosis of a cystic hygroma is often defined as the presence of a bilateral, cystic structure within the occipitocervical region, distinguished by the presence of septations within the cystic fluid. However, evidence suggests that cystic hygromas should not be considered as a distinct entity from increased NT and do not confer any ‘risk status’ independent of that related to increased NT<sup>18</sup>. As such, within our review, cystic hygromas were considered soft markers for aneuploidy, much like increased NT, and were therefore excluded from our analysis of structural anomalies.

Data regarding the number of false-positive diagnoses made during the first-trimester screening process were also collected. In many studies, women were offered the option of anomaly screening in the second and/or third trimester of pregnancy in addition to the first-trimester anomaly scan. In these cases, the number of antenatal diagnoses made outside the first trimester was recorded. All data were collected and extracted from tables or text on two independent occasions for each study in order to reduce the risk of error in data collection.

## Quality assessment of studies

Assessment of the quality of the studies included within this review was performed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2)<sup>19</sup>. This is a tool designed to evaluate the risk of bias within each study and assess its applicability to the systematic review. It provides a framework for evaluating studies within four key domains: patient selection, index test, reference standard and flow of patients through the study, along with the timing of the index test. Each domain is assessed with respect to bias and the first three domains with respect to applicability. A judgment of low, high or unclear risk of bias and lack of applicability was made for each study based on a series of signaling questions developed specific to our review (Appendix S2).

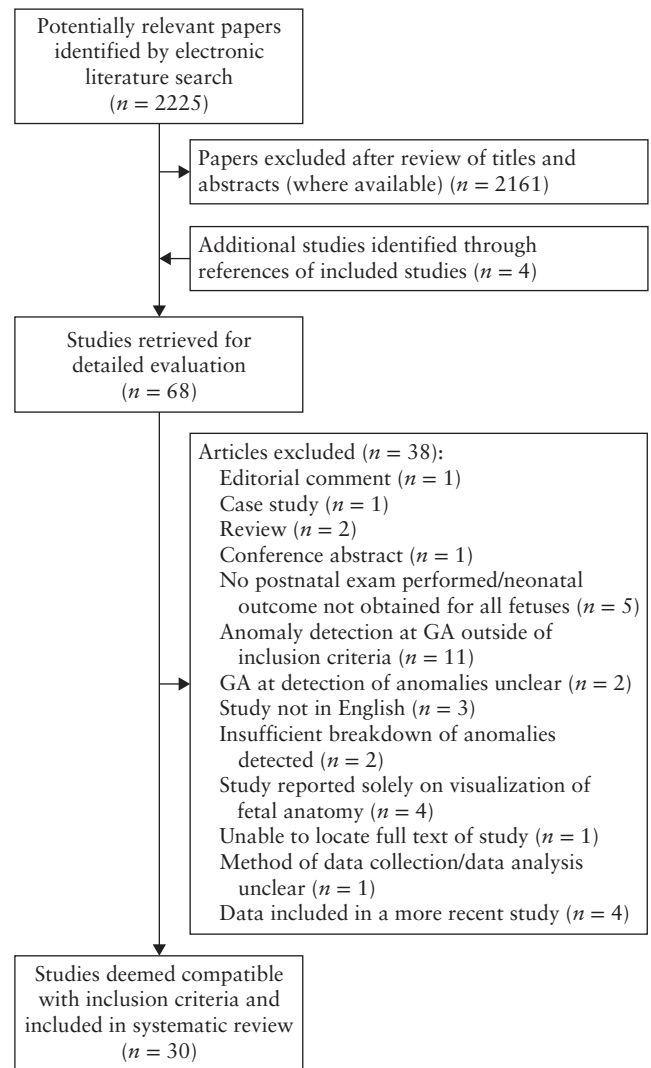
## Statistical analysis

In an effort to reduce the effect of study heterogeneity on the results of the meta-analysis, data from the studies were analyzed within subgroups that reflected the type of abnormality included and the type of population assessed in each study. Extracted data were assessed within one of three subgroups: (1) studies reporting on major anomalies in a low-risk or unselected population; (2) studies reporting on all types of anomaly in a low-risk or unselected population; and (3) studies reporting on all types of anomaly in high-risk populations.

When studies published adequate data on two distinct cohorts, the relevant data from each study were included within more than one subgroup. For studies performed in unselected populations, in which anomaly type was defined using RCOG criteria, anomalies labeled as lethal or severe were considered 'major anomalies' and therefore analyzed as part of Subgroup 1, whereas anomalies labeled as 'lethal, severe, moderate or minor' were included as part of Subgroup 2. In studies not based on the RCOG criteria, the definition provided by the study itself was used to determine what constituted a major anomaly.

Meta-analysis of data extracted from eligible studies was performed in two steps. First, summary statistics with 95% CIs were derived for each study with respect to both the sensitivity of first-trimester anomaly screening for detecting fetal anomalies and for detecting fetuses affected by one or more abnormality. Second, individual study statistics within each subgroup were combined in order to obtain a pooled summary estimate. In those studies providing adequate data for the construction of 2 × 2 tables, pooled summary estimates of sensitivity and specificity were calculated. The pooled summary statistics were estimated using random-effects models<sup>17</sup>. Heterogeneity between studies was estimated using the  $I^2$  statistic. Further analysis was undertaken within each subgroup in order to determine whether factors such as year of study publication, mode of ultrasound and use of an anatomical protocol affected outcomes.

All statistical analysis was performed using StatsDirect statistical software 2013 (StatsDirect Ltd, Altrincham, Cheshire, UK).



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

## RESULTS

### Study selection and description of included studies

The initial electronic search yielded 2225 citations, from which a total of 30 relevant studies<sup>14,20–48</sup> were selected for inclusion in the systematic review (Figure 1). The studies evaluated were published between 1991 and 2014. The gestational age at which first-trimester ultrasound screening was performed ranged from 9 to 15 + 6 weeks, with the vast majority performed before 14 weeks. Studies were performed in a variety of healthcare settings, with the majority (20 studies) taking place, at least in part, in either a university hospital, tertiary-care center or research facility<sup>14,21,23,25–28,30,33–38,40,41,43–45,47</sup>. Three studies involved multicenter data collection<sup>21,28,36</sup>. Several studies included adequate data on several distinct cohorts, allowing for data from these studies to be analyzed in subgroups (Appendix S3).

In total, 26 studies<sup>14,20–24,26–29,31–46</sup> evaluated unselected and low-risk populations (Table 1), of which 19

**Table 1** Characteristics of studies reporting on detection of fetal structural anomalies by first-trimester ultrasound in low-risk and unselected populations

Study	Fetuses (n)	GA (weeks)	Population	Healthcare setting	Aneuploid fetuses included*	Index test†	Anatomy checklist used	Cardiac exam included	Subgroup for analysis
Achiron (1991) <sup>42</sup>	800	9 to 13	Mixed indications: vaginal bleeding, dating and early anomaly screening	Unclear	Yes	TV/TA	Basic	Yes	2
Hernádi (1997) <sup>31</sup>	3991	11 to 14	Unselected	Unclear	Yes (0.2%)	TV	Basic	No	1
Bilardo (1998) <sup>43</sup> (low-risk group)	1543	10 to 14	Consecutive, singleton pregnancies, normal NT (< 3.0 mm)	University hospital	No	TA/TV	None	Unclear	2
Whitlow (1999) <sup>26</sup>	6443	11 to 14 + 6	Unselected, consecutive recruitment	University hospital	Yes (0.7%)	TA/TV (20.1%)	Detailed	Yes	1
Carvalho (2002) <sup>40</sup>	2853	11 to 14	Unselected	University hospital, tertiary care	Yes (0.9%)	TA/TV§	Basic	No¶	2
Drysdale (2002) <sup>39</sup>	917	12 to 14	Unselected	District general hospital	Yes	TA/TV	None	No	1
Taipale (2003) <sup>29</sup>	20 751	11 to 15 + 6	Unselected, consecutive recruitment	Local hospital	Yes (0.3%)	TV/TA (< 1%)	Detailed	Yes**	1
McAuliffe (2005) <sup>41</sup>	325	11 to 13 + 6	Unselected	University hospital, tertiary care	No	TA/TV§ (24.6%)	Detailed	Yes	2
Cedergren (2006) <sup>33</sup>	2708	11 to 14	Unselected, consecutive recruitment	University hospital	Yes (0.3%)	TA	None	Unclear	1
Souka (2006) <sup>24</sup>	1148	11 to 14	Unselected	Unclear	Yes	TA/TV	Detailed	Yes	1
Saltvedt (2006) <sup>28</sup>	18 053	11 + 5 to 13 + 5	Unselected	Multicenter (n = 8)	No	TA/TV§	Detailed	Yes¶	1
Dane (2007) <sup>23</sup>	1290	11 to 14	Unselected	Research hospital	Yes	TA/TV	Basic	No	1
Li (2008) <sup>22</sup>	2232	11 to 14	Unselected, consecutive recruitment	Unclear	Yes	TA/TV§ (2.0%)	None	Unclear	1
Chen (2008) <sup>21</sup> (control group)	3693	10 to 14 + 6	Unselected, consecutively randomized	Multicenter (one university and one regional hospital)	Yes	TA/TV§	None	No	1,2
Chen (2008) <sup>21</sup> (study group)	3949	12 to 14 + 6	Unselected, consecutively randomized	Multicenter (one university and one regional hospital)	Yes	TA/TV§	Detailed	Yes	1,2
Oztekin (2009) <sup>38</sup>	1085	11 to 14	Unselected	Research hospital	Yes	TA/TV§	Detailed	Yes	1
Hildebrand (2010) <sup>35</sup>	6692	11 to 15	Unselected, consecutive recruitment	University hospital	Yes (0.2%)	TA	None	No	1,2
Abu-Rustum (2010) <sup>32</sup>	1370	11 to 13 + 6	Unselected, retrospective	Private practice	Yes (4.4%)	TA/TV§	Detailed	Yes	1,2
Syngelaki (2011) <sup>14</sup>	44859	11 to 13 + 6	Unselected, retrospective	University hospital, tertiary care	No	TA/TV (1%)	Detailed	Yes	2
Jakobsen (2011) <sup>44</sup>	9324	11 to 15	Unselected, retrospective	University hospital	Yes	TA/TV§	None	No	1,2
Vavilala (2011) <sup>34</sup>	7916	11 to 13 + 6	Unselected	Tertiary care	Yes	TA/TV§	Detailed	Yes	1
Grande (2012) <sup>37</sup>	13 723	11 to 14	Unselected retrospective	Tertiary care	No	TA/TV	Detailed	Yes††	1,2
Pilalis (2012) <sup>20</sup>	3902	11 to 14	Unselected, retrospective	Private maternity hospital	Yes	TA/TV	Detailed	No	1
Becker (2012) <sup>45</sup>	6544	11 to 13 + 6	Normal NT ( $\leq$ 95 <sup>th</sup> centile)	University hospital	Yes (0.6%)‡	TA/TV§ (23.4%)	Detailed	Yes‡‡	1
Iliescu (2013) <sup>36</sup>	5472	12 to 13 + 6	Unselected	Multicenter (n = 2)	Yes (0.4%)	TA/TV (7.8%)	Detailed	Yes	2
Wang (2013) <sup>27</sup>	2822	11 to 14	Not stated	University hospital	Yes	TA	Detailed	Yes	2
Natu (2014) <sup>46</sup> (low-risk group)	551	11 to 14	Low risk: age < 30 years, no FH, no comorbidity	Unclear	Yes	Unclear	Detailed	Yes††	2

Only first author given for each study. Subgroup 1 includes studies that assessed all major fetal anomalies in low-risk or unselected populations and Subgroup 2 includes studies that assessed all types of fetal anomaly in low-risk or unselected populations. \*In studies in which aneuploid fetuses were included, percentage of study population confirmed as aneuploid by karyotyping is indicated in parentheses. †In studies in which both transabdominal (TA) and transvaginal (TV) ultrasound were used, number in parentheses refers to percentage of study population that received this screening test. ‡Only known euploid fetuses included in analysis, as insufficient data provided on entire cohort in study. §TV performed only in situations in which visualization with TA was suboptimal. ¶Fetal echocardiography performed selectively in fetuses with increased nuchal translucency (NT). \*\*Performed at first-trimester scan but cardiac malformations excluded from analysis. ††Fetal echocardiography offered in cases in which cardiac anomaly suspected based on first-trimester scan. ‡‡Fetal echocardiography performed routinely. FH, family history; GA, gestational age.

study cohorts (115 731 fetuses) focused on the detection of major anomalies and 14 study cohorts (97 976 fetuses) assessed all types of anomaly. Six studies<sup>25,30,43,46–48</sup> (2841 fetuses) focused on the detection of all types of anomaly in high-risk populations (Table 2).

*Subgroup 1: sensitivity of first-trimester ultrasound screening for detection of major anomalies in a low-risk/unselected population*

Nineteen study cohorts (115 731 fetuses) evaluated a low-risk or unselected population for the presence of major fetal structural anomalies (Table 3). The number of anomalies present was provided for all study cohorts, with a total of 1165 major anomalies (mean number of anomalies per 100 fetuses, 1.01 (95% CI, 0.95–1.07)). Of these, 529 were detected during the first trimester, giving a pooled sensitivity of 46.10% (95% CI, 36.88–55.46%) for first-trimester ultrasound in the detection of major fetal abnormalities (Figure 2a). Heterogeneity, as estimated by  $I^2$ , was 90.1% (95% CI, 86.5–92.4%).

In 15 of these study cohorts (77 664 fetuses), an ultrasound examination was performed on an additional occasion after the first trimester. In these studies, the abnormalities detected in the first trimester represented 53.47% (95% CI, 43.42–63.37%) of all antenatally diagnosed ultrasound abnormalities.

In 12 of these study cohorts (61 930 fetuses), data on the number of fetuses affected with one or more structural abnormality were provided; 573 were affected with major structural anomalies, giving a pooled prevalence of affected fetuses within the study cohorts of 0.93% (95% CI, 0.85–1.00%) (Table 3). Of these, 264 fetuses with anomalies were detected during the first trimester. The pooled sensitivity of first-trimester ultrasound in the detection of fetuses affected by one or more major anomaly was 45.25% (95% CI, 38.44–52.14%) (Figure 2b). It was possible to create complete 2 × 2 tables for the three studies providing false-positive rates for the detection of affected fetuses<sup>26,29,39</sup>, giving a pooled sensitivity of 41.98% (95% CI, 23.83–61.33%) and pooled specificity of 99.96% (95% CI, 99.90–100%).

*Subgroup 2: sensitivity of first-trimester ultrasound screening for detection of all types of anomaly in a low-risk/unselected population*

Fourteen study cohorts (97 976 fetuses) evaluated a low-risk or unselected population for the presence of all types of fetal structural anomaly (Table 4). The number of anomalies present was provided for 13 of these study cohorts, with a total of 1521 anomalies (84 253 fetuses) (mean number of anomalies per 100 fetuses, 1.81 (95% CI, 1.72–1.90)). Of these, 526 were detected during the first trimester, giving a pooled sensitivity of 32.35% (95% CI, 22.45–43.12%) for first-trimester ultrasound in the detection of fetal abnormalities (Figure 3a). Heterogeneity, as estimated by  $I^2$ , was 93.5% (95% CI, 91.1–95.0%).

Table 2 Characteristics of studies reporting on detection of all types of fetal structural abnormality by first-trimester ultrasound in high-risk pregnancies

Study	Fetuses (n)	GA (weeks)	Population	Healthcare setting	Aneuploid fetuses included	Index test	Anatomy checklist	Cardiac exam included	Type of anomaly reported
Pandya (1995) <sup>47</sup>	565	10–14	Euploid fetuses with increased NT ( $\geq 3.0$ mm)	University hospital, tertiary care	No	TA	None	No	NS
Bilardo (1998) <sup>43</sup> (high-risk group)	47	10–14	Euploid fetuses with increased NT ( $\geq 3.0$ mm)	University hospital	No	TA/TV	None	Unclear	NS
den Hollander (2002) <sup>30</sup>	101	11–14	Women with previously affected infant (92%), fetuses with parental consanguinity	Tertiary care	Yes	TA/TV	Detailed	Yes	NS
Chen (2004) <sup>25</sup>	1609	12–14	Women aged $\geq 35$ years	University hospital	Yes	TA/TV	Detailed	Yes	NS
Bronshtein (2008) <sup>48</sup>	23	11–14	Fetuses with increased NT ( $\geq 3.5$ mm)	Unclear	Yes	TV	Used, but not provided	Yes*	All
Natu (2014) <sup>46</sup> (high-risk group)	496	11–14	Mixed indications including age $> 30$ years, previous affected child, family Hx of anomalies, multiple pregnancy, Hx of smoking/EtOH, maternal RF	Unclear	Yes	Unclear	Detailed	Yes†	All

Only first author given for each study. \*Fetal echocardiography performed routinely. †Fetal echocardiography offered in cases in which cardiac anomaly suspected based on first-trimester scan. EtOH, alcohol use in pregnancy; GA, gestational age; Hx, history; NS, not specified; NT, nuchal translucency; RF, risk factor; TA, transabdominal ultrasound; TV, transvaginal ultrasound.

**Table 3** Summary of results from studies assessing sensitivity of first-trimester ultrasound for detection of major fetal structural abnormalities in low-risk and unselected pregnancies (Subgroup 1)

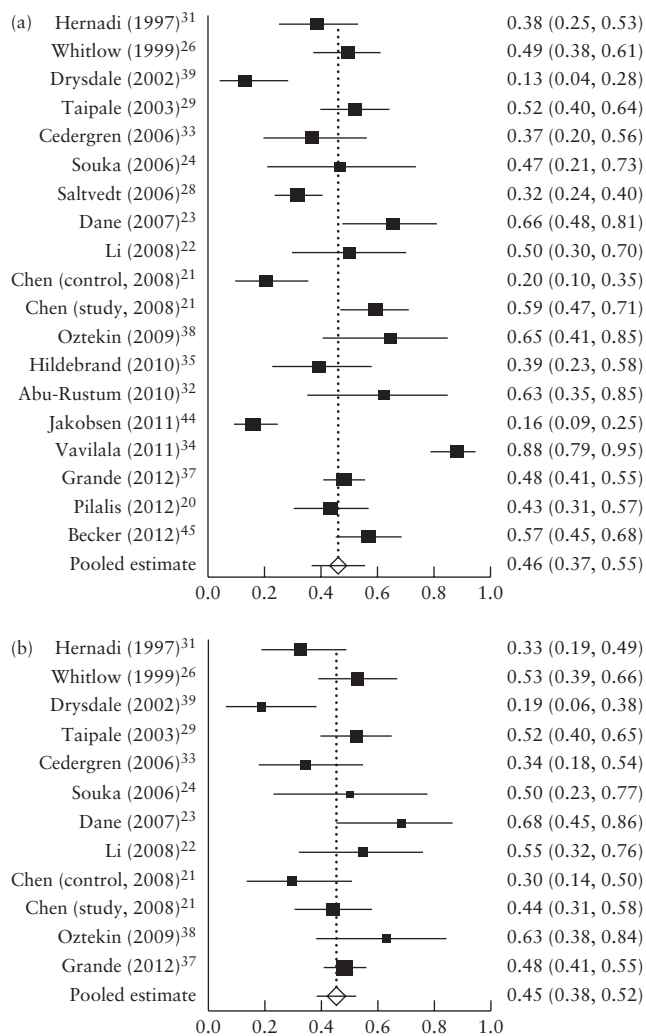
Study	Anomalies present (n per 100 fetuses)	Prevalence of affected fetuses (%) <sup>*</sup>	Anomalies detected (TP) (n)	Total anomalies present		Sensitivity for detection of anomalies (%)	Sensitivity for detection of affected fetus (%) <sup>*</sup>	Antenatal diagnoses in first trimester (%) <sup>†</sup>
				(TP + FN) (n)	FP (n)			
Hernádi (1997) <sup>31</sup>	1.30 (0.97–1.71)	1.08 (0.78–1.45)	20	52	NA	38.46 (25.30–52.98)	32.56 (19.08–48.54)	48.78 (32.88–64.87)
Whitlow (1999) <sup>26</sup>	1.20 (0.94–1.49)	0.85 (0.64–1.11)	38	77	3	49.35 (37.76–61.00)	52.73 (38.80–66.35)	57.58 (44.79–69.66)
Drysdale (2002) <sup>39</sup>	4.14 (2.95–5.64)	2.94 (1.95–4.26)	5	38	1	13.16 (4.41–28.09)	18.52 (6.30–38.08)	11.76 (3.30–27.45)
Taipale (2003) <sup>29</sup>	0.34 (0.27–0.43)	0.32 (0.25–0.41)	37	71	2	52.11 (39.92–64.12)	52.24 (39.67–64.60)	NA
Cedergren (2006) <sup>33</sup>	1.11 (0.75–1.58)	1.07 (0.72–1.53)	11	30	NA	36.67 (19.93–56.14)	34.48 (17.94–54.33)	NA
Souka (2006) <sup>24</sup>	1.30 (0.73–2.15)	1.22 (0.67–2.04)	7	15	3	46.67 (21.27–73.41)	50.00 (23.04–76.96)	50.00 (23.04–76.96)
Saltvedt (2006) <sup>28</sup>	0.74 (0.62–0.87)	NA	42	133	2	31.58 (23.80–40.20)	NA	34.43 (26.06–43.57)
Dane (2007) <sup>23</sup>	2.71 (1.90–3.75)	1.71 (1.07–2.57)	23	35	NA	65.71 (47.79–80.87)	68.18 (45.13–86.14)	71.88 (53.25–86.25)
Li (2008) <sup>22</sup>	1.16 (0.76–1.70)	0.99 (0.62–1.49)	13	26	NA	50.00 (29.93–70.07)	54.55 (32.21–75.61)	65.00 (40.78–84.61)
Chen (2008) <sup>21</sup> (control group)	1.19 (0.87–1.60)	0.73 (0.48–1.06)	9	44	NA	20.45 (9.80–35.30)	29.63 (13.75–50.18)	20.45 (9.80–35.3)
Chen (2008) <sup>21</sup> (study group)	1.75 (1.36–2.21)	1.44 (1.10–1.87)	41	69	NA	59.42 (46.92–71.09)	43.86 (30.74–57.64)	61.19 (48.50–72.86)
Oztekin (2009) <sup>38</sup>	1.81 (1.11–2.78)	1.75 (1.06–2.72)	13	20	NA	65.00 (40.78–84.61)	63.16 (38.36–83.71)	72.22 (46.52–90.31)
Hildebrand (2010) <sup>35</sup>	0.49 (0.34–0.69)	NA	13	33	NA	39.39 (22.91–57.86)	NA	NA
Abu-Rustum (2010) <sup>32</sup>	1.17 (0.67–1.89)	NA	10	16	1	62.50 (35.43–84.80)	NA	66.67 (38.38–88.18)
Jakobsen (2011) <sup>44</sup>	1.07 (0.87–1.30)	NA	16	100	NA	16.00 (9.43–24.68)	NA	33.33 (20.40–48.41)
Vavilala (2011) <sup>34</sup>	0.99 (0.78–1.23)	NA	69	78	NA	88.46 (79.22–94.59)	NA	NA
Grande (2012) <sup>37</sup>	1.39 (1.20–1.60)	1.39 (1.20–1.60)	92	191	NA	48.17 (40.90–55.50)	48.17 (40.90–55.50)	51.11 (43.57–58.62)
Pilalis (2012) <sup>20</sup>	1.54 (1.18–1.97)	NA	26	60	NA	43.33 (30.59–56.76)	NA	44.07 (31.16–57.60)
Becker (2012) <sup>45</sup>	1.18 (0.93–1.47)	NA	44	77	NA	57.14 (45.35–68.37)	NA	64.71 (52.17–75.92)
Pooled result	1.01 (0.95–1.07)	0.93 (0.85–1.00)	529	1165	12	46.10 (36.88–55.46)	45.25 (38.44–52.14)	53.47 (43.42–63.37)

Only first author given for each study. Values in parentheses are 95% CI. Specificity of first-trimester ultrasound for detection of major anomaly was not calculated owing to low numbers of studies that provided data on false-positive (FP) diagnoses. \*Studies that did not provide data on number of affected fetuses within cohort were not included in pooled estimates of prevalence of affected fetuses and sensitivity for detection of affected fetuses. †Studies that performed only one fetal ultrasound examination during pregnancy were not included in pooled estimate of antenatal diagnoses in first trimester. FN, false negative; NA, not available; TP, true positive.

In 12 of these study cohorts (77 561 fetuses), antenatal ultrasound was performed on an additional occasion after the first trimester. In these studies, the abnormalities detected in the first trimester represented 41.10% (95% CI, 32.13–50.38%) of all antenatally diagnosed ultrasound abnormalities.

In nine of these study cohorts (77 186 fetuses), data on the number of fetuses affected with one or more structural abnormality were provided; 1256 were affected with structural anomalies, giving a pooled prevalence of affected fetuses within the study cohorts of 1.63%

(95% CI, 1.54–1.72%) (Table 4). Of these, 435 fetuses were detected during the first trimester. The pooled sensitivity of first-trimester ultrasound in the detection of fetuses affected by one or more anomaly was 35.56% (95% CI, 26.27–45.44%) (Figure 3b). It was possible to create complete 2 × 2 tables for the three studies providing false-positive rates for the detection of affected fetuses<sup>14,27,41</sup>, giving a pooled sensitivity of 44.44% (95% CI, 32.76–56.44%) and a pooled specificity of 99.86% (95% CI, 99.82–99.89%).



**Figure 2** Forest plots of sensitivity of first-trimester ultrasound in detecting major fetal structural anomalies (a) and fetuses affected with major structural anomalies (b) in low-risk and unselected pregnancies. Only first author given for each study.

### Subgroup 3: sensitivity of first-trimester ultrasound screening for detection of all types of anomaly in a high-risk population

Six studies (2841 fetuses) evaluated a high-risk population for the presence of all types of anomaly (Table 5). The number of anomalies present was provided for all study cohorts, with a total of 186 anomalies (mean number of anomalies present per 100 fetuses, 6.55 (95% CI, 5.66–7.52)), confirming the high-risk status of this population. Of these, 116 were detected during the first trimester, giving a pooled sensitivity of 61.18% (95% CI, 37.71–82.19%) for first-trimester ultrasound in the detection of all types of fetal anomaly (Figure 4a). Heterogeneity, as estimated by  $I^2$ , was 90.5% (95% CI, 82.1–94.0%).

Antenatal ultrasound was performed on an additional occasion after the first trimester in all study cohorts. The abnormalities detected in the first trimester represented 66.29% (95% CI, 43.47–85.69%) of all antenatally diagnosed ultrasound anomalies.

In five of these study cohorts (2345 fetuses), data on the number of fetuses affected with one or more structural abnormality were provided; 88 were affected with structural anomalies, giving a pooled prevalence of affected fetuses within the study cohorts of 3.75% (95% CI, 3.02–4.60%) (Table 5). Of these, 48 cases were detected during the first trimester. The pooled sensitivity of first-trimester ultrasound in the detection of fetuses affected by one or more anomaly was 62.42% (95% CI, 33.40–87.24%) (Figure 4b). Completed  $2 \times 2$  tables for the three studies providing false-positive rates were created, giving a pooled sensitivity of 79.85% (95% CI, 43.87–99.29%) and a pooled specificity of 97.78% (95% CI, 90.96–100%).

### Factors affecting detection rate in first-trimester ultrasound screening

The use of a standardized anatomical protocol during first-trimester anomaly screening was found to be significantly associated with the sensitivity of this assessment in the detection of fetal anomalies in all subgroups (Subgroup 1:  $\chi^2$ , 60.95 ( $P < 0.0001$ ); Subgroup 2:  $\chi^2$ , 112.46 ( $P < 0.0001$ ); Subgroup 3:  $\chi^2$ , 24.71 ( $P < 0.0001$ )).

In Subgroups 1 and 2, there was a statistically significant linear trend between the use of an increasingly detailed protocol and a higher sensitivity for the detection of fetal anomalies ( $\chi^2$   $P < 0.0001$ ). Simple linear regression analysis did not show a statistically significant relationship between the year of study publication and sensitivity of first-trimester screening for fetal anomalies in Subgroups 1, 2 or 3 ( $R^2 = 0.066, 0.030$  and  $0.44$ , respectively).

The impact of mode of ultrasound used for screening on detection rate was explored. The vast majority of studies used a combination of TA and TV ultrasound, often beginning with the former and complementing the assessment with the latter when organ visualization was suboptimal. In all three subgroups, there was an insufficient number of studies using TA or TV ultrasound exclusively to make useful comparisons between detection rates using the three ultrasound methods (TA, TV or a combination of both).

Finally, with respect to the collection of qualitative data, studies included in this systematic review cited numerous factors as having an impact on first-trimester detection rates of fetal anomalies. Non-modifiable factors cited included: small size of fetal anatomy at this gestational age<sup>20–26</sup>, progressive pathophysiology of certain fetal anomalies and the fact that some anomalies are not yet present in the first trimester<sup>14,21,22,24–30</sup>, increased maternal body mass index<sup>24,31</sup> and presence of uterine fibroids<sup>27,31</sup>. A number of modifiable factors were considered to impact on first-trimester detection rates of fetal anomalies, including: gestational age at time of scan<sup>24</sup>, mode of ultrasound<sup>20,24,28,32,33</sup>, time allocated for screening<sup>14,20,24,25,29,31</sup>, use of an anatomical protocol with standard sonographic

**Table 4** Summary of results from studies assessing sensitivity of first-trimester ultrasound for detection of all types of fetal structural abnormality in low-risk and unselected pregnancies (Subgroup 2)

Study	Anomalies present (n per 100 fetuses)	Prevalence of affected fetuses (%) <sup>*</sup>	Anomalies detected (TP) (n)	Total anomalies present		Sensitivity for detection of anomalies (%)	Sensitivity for detection of affected fetuses (%) <sup>*</sup>	Antenatal diagnoses in first trimester (%) <sup>†</sup>
				(TP + FN) (n)	FP (n)			
Achiron (1991) <sup>42</sup>	2.12 (1.24–3.38)	1.50 (0.78–2.61)	8	17	NA	47.06 (22.98–72.19)	50.00 (21.09–78.91)	53.33 (26.59–78.73)
Bilardo (1998) <sup>43</sup> (low-risk group)	1.56 (1.00–2.31)	1.23 (0.74–1.92)	6	24	NA	25.00 (9.77–46.71)	31.58 (12.58–56.55)	37.50 (15.20–64.57)
Carvalho (2002) <sup>40</sup>	4.98 (4.21–5.84)	NA	30	142	NA	21.13 (14.73–28.77)	NA	29.13 (20.59–38.90)
McAuliffe (2005) <sup>41</sup>	1.85 (0.68–3.97)	1.85 (0.68–3.97)	1	6	1	16.67 (0.42–64.12)	16.67 (0.42–64.12)	20.00 (0.51–71.64)
Chen (2008) <sup>21</sup> (control group)	2.11 (1.67–2.63)	1.41 (1.05–1.84)	9	78	NA	11.54 (5.41–20.78)	15.38 (6.88–28.08)	16.36 (7.77–28.80)
Chen (2008) <sup>21</sup> (study group)	2.30 (1.86–2.82)	1.44 (1.10–1.87)	44	91	NA	48.35 (37.74–59.07)	43.86 (30.74–57.64)	61.97 (49.67–73.24)
Abu-Rustum (2010) <sup>32</sup>	2.41 (1.66–3.37)	NA	12	33	1	36.36 (20.40–54.87)	NA	37.50 (21.10–56.31)
Hildebrand (2010) <sup>35</sup>	1.79 (1.49–2.14)	NA	14	120	NA	11.67 (6.53–18.80)	NA	NA
Syngelaki (2011) <sup>14</sup>	1.18 (1.09–1.29)	1.09 (0.99–1.19)	222	531	62	41.81 (37.57–46.13)	43.65 (39.19–48.18)	42.86 (38.55–47.25)
Jakobsen (2011) <sup>44</sup> (all groups)	1.92 (1.65–2.22)	NA	23	179	NA	12.85 (8.32–18.65)	NA	21.90 (14.42–31.03)
Grande (2012) <sup>37</sup> (all groups)	NA	3.18 (2.89–3.48)	NA	NA	NA	NA	22.48 (18.64–26.69)	NA
Iliescu (2013) <sup>36</sup>	4.77 (4.22–5.37)	2.98 (2.54–3.46)	132	261	187	50.57 (44.34–56.80)	39.88 (32.30–47.83)	53.44 (47.01–59.79)
Wang (2013) <sup>27</sup>	1.24 (0.87–1.72)	0.82 (0.52–1.22)	23	35	3	65.71 (47.79–80.87)	56.52 (34.49–76.81)	69.70 (51.29–84.41)
Natu (2014) <sup>46</sup> (low-risk group)	0.73 (0.20–1.85)	NA	2	4	0	50.00 (6.76–93.24)	NA	50.00 (6.76–93.24)
Pooled result	1.81 (1.72–1.90)	1.63 (1.54–1.72)	526	1521	254	32.35 (22.45–43.12)	35.56 (26.27–45.44)	41.10 (32.13–50.38)

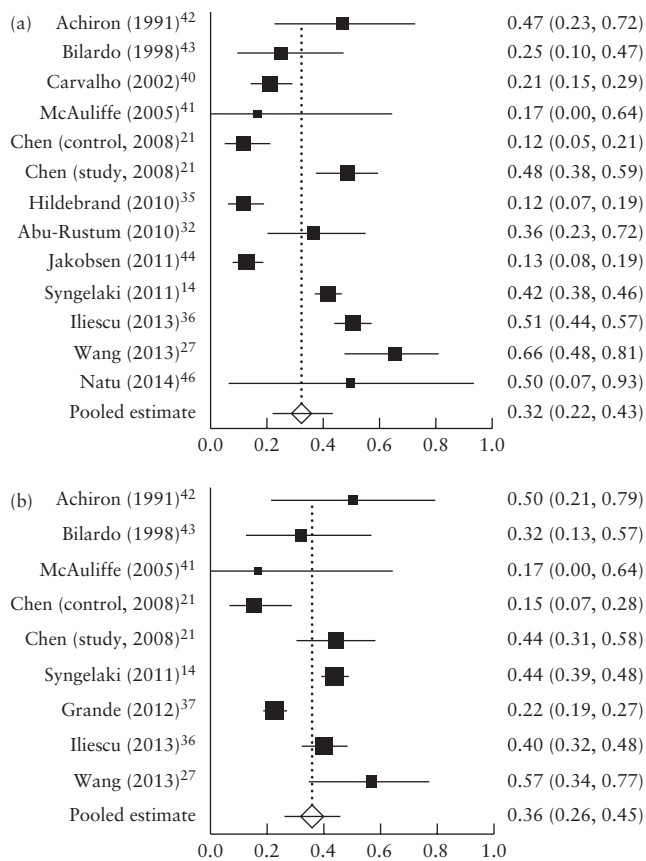
Only first author given for each study. Values in parentheses are 95% CI. Specificity of first-trimester ultrasound for detection of all types of anomaly was not calculated owing to low numbers of studies that provided data on false-positive (FP) diagnoses. \*Studies that did not provide data on number of affected fetuses within cohort were not included in pooled estimates of prevalence of affected fetuses and sensitivity for detection of affected fetuses. †Studies that performed only one fetal ultrasound examination during pregnancy were not included in pooled estimate of antenatal diagnoses in first trimester. FN, false negative; NA, not available; TP, true positive.

views<sup>14,20,27,33–35</sup>, sonographer experience and training<sup>14,20,23–25,27–29,31,33–40</sup>, system in place for regular audit<sup>29,33,34</sup>, knowledge of fetal embryology including normal developmental milestones in the first trimester<sup>21,25,26,30</sup> and knowledge of easily recognizable markers for the diagnosis of anomalies, such as spina bifida and facial clefts<sup>14</sup>.

#### Methodological quality assessment of studies

Results of the QUADAS-2 assessment are summarized in Figure 5. With respect to bias in patient selection, 18 of the 30 included studies were scored as having low risk of bias. Two studies were deemed to be at high risk of bias owing to inappropriate exclusions from their patient cohorts. In total, 10 studies were considered to be at unclear risk with respect to bias in patient selection. Of these, four gave no information pertaining to patient exclusions and nine studies failed to provide adequate

information regarding methods used to enrol patients. With respect to the index test, no study declared whether the sonographers were blinded to the patient history prior to performing the anomaly scan, therefore all studies were labeled as unclear in this regard. Five studies excluded cardiac examinations from the first-trimester anomaly scan and were therefore considered at high risk of bias. Four additional studies provided no specification as to the type of anomaly included in their assessment, and as such were labeled as high risk. All 30 studies were found to be at low risk of bias relating to the reference standard; this was, after all, a criterion for inclusion in the study. In terms of flow and timing, 15 of the 30 studies were labeled as high risk of bias because they included no data pertaining to false-positive diagnoses. One further study was labeled as high risk because the reference standard was performed in less than 90% of the patients enrolled in the study. With respect to applicability, there were no concerns raised regarding the 30 studies included in this review.



**Figure 3** Forest plots of sensitivity of first-trimester ultrasound in detecting all types of fetal structural anomaly (a) and fetuses affected with any type of structural anomaly (b) in low-risk and unselected pregnancies. Only first author given for each study.

## DISCUSSION

In this study, we show that first-trimester ultrasound can identify about half of all major fetal anomalies diagnosed antenatally (Table 6); in unselected and low-risk pregnancies, about 40% of all antenatally diagnosed anomalies were identified at this stage in pregnancy. The detection rate for major fetal anomalies was higher (46%), with 45% of fetuses affected with one or more major malformation being identified. In high-risk populations, the sensitivity for fetal anomaly detection was even higher (61%), with first-trimester screening detecting 66% of all antenatally diagnosed ultrasound anomalies. This higher rate of detection in high-risk populations is probably due to targeted screening<sup>13</sup>; sonologists are aware of the increased risk and women at high risk may be scanned by more experienced examiners. Nevertheless, at least theoretically, the detection rate of an anomaly should not be influenced by its prevalence in the population cohort.

This suggests that first-trimester ultrasound has the potential to identify a high percentage of fetuses affected with structural anomalies in all risk groups. If there is the technology and skill available to achieve sensitivity of over 60% in high-risk populations, there is no reason that, under optimal conditions, these detection rates could not be achieved for all patients. This idea of ‘if you look

you will find’ is further supported by an important result from our analysis of all three subgroups: a significant association ( $P < 0.001$ ) was found between the sensitivity of first-trimester ultrasound and the use of an anatomical protocol for screening, and a trend was seen suggesting that the more detailed the protocol, the greater the detection rate. We therefore suggest that international protocols with standard anatomical views should be used in practice, in order to optimize rates of first-trimester anomaly detection.

Most studies used a combination of TV and TA ultrasound, meaning that a statistically useful comparison between sensitivities for the three ultrasound approaches to screening (TA, TV and a combination of both) could not be performed. Findings from studies evaluating fetal organ detection suggest that optimal visualization rates are obtained with a combination of TA and TV ultrasound<sup>8</sup>. For TA, raised body mass index, the presence of uterine fibroids or retroversion of the uterus will decrease image quality. In contrast, TV ultrasound provides much higher resolution, but has the disadvantage of limited probe maneuverability<sup>41</sup>; however, some women are less accepting of TV ultrasound<sup>32,51</sup>. We believe that adopting a flexible, patient-tailored approach, which may require the use of TA and TV modalities, should be encouraged, as this will be the only way of determining the true potential of first-trimester ultrasound screening for fetal anomalies.

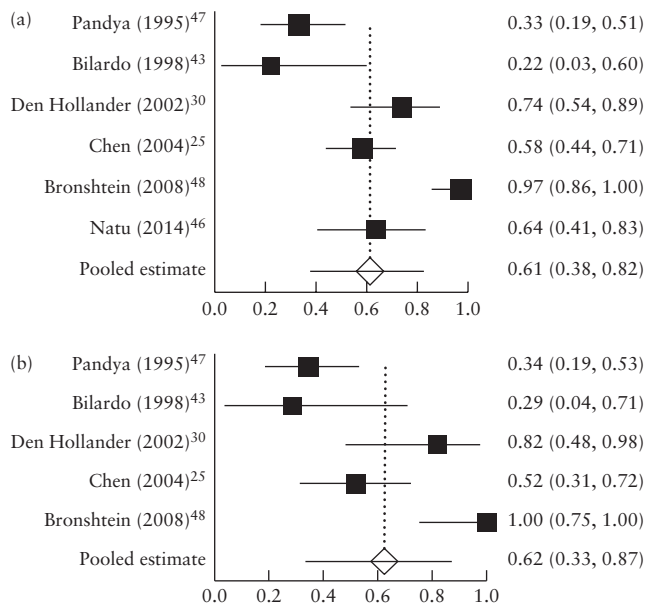
A number of other factors have been suggested to affect first-trimester ultrasound. These provide insight into how the process might be optimized. Several studies demonstrated a significant ‘learning curve’ associated with first-trimester anomaly screening<sup>29,36,52</sup>. Knowledge of fetal embryological development is also important<sup>53</sup>, as is the time allocated for screening. Apart from using an anatomical protocol, Syngelaki *et al.*<sup>14</sup> highlighted the positive impact of having an easily recognizable marker for the diagnosis of anomalies, such as for spina bifida or facial clefts, on overall detection rates.

Non-modifiable factors affecting detection rates included the small size of anomalies and fetal crown-rump length and the presence of anomalies with progressive pathophysiology. Studies assessing the types of anomaly detected<sup>13,14</sup> suggested that there are some conditions that are nearly always detectable in the first trimester, others that are never identifiable and some that have the potential to be diagnosed, dependent on maternal, fetal, sonographer and equipment factors. Undetectable anomalies mostly relate to structures not yet fully developed before 14 weeks, e.g. cerebellar anomalies and echogenic lung cysts, or those diagnosed secondary to changes in amniotic fluid volume, e.g. duodenal atresia, bowel obstruction or renal agenesis. Thus, first-trimester anomaly screening will not replace examinations at later gestational ages completely. What is clear from our assessment is that expectations and future objectives for first-trimester anomaly screening should be tailored to the type of anomaly amenable to detection at this gestational age.

**Table 5** Summary of results from studies assessing sensitivity of first-trimester ultrasound for detection of all types of fetal structural abnormality in high-risk pregnancies (Subgroup 3)

Study	Anomalies present (n per 100 fetuses)	Prevalence of affected fetuses (%)*	Anomalies detected (TP) (n)	Total anomalies present (TP + FN) (n)	FP (n)	Sensitivity for detection of anomalies (%)	Sensitivity for detection of affected fetuses (%)*	Antenatal diagnoses in first trimester (%)†
Pandya (1995) <sup>47</sup>	6.37 (4.50–8.71)	5.66 (3.91–7.90)	12	36	NA	33.33 (18.56–50.97)	34.38 (18.57–53.19)	35.29 (19.75–53.51)
Bilardo (1998) <sup>43</sup> (high-risk group)	19.15 (9.15–33.26)	14.89 (6.2–28.31)	2	9	NA	22.22 (2.81–60.01)	28.57 (3.67–70.96)	33.33 (4.33–77.72)
den Hollander (2002) <sup>30</sup>	26.73 (18.41–36.46)	10.89 (5.56–18.65)	20	27	0	74.07 (53.72–88.89)	81.82 (48.22–97.72)	83.33 (62.62–95.26)
Chen (2004) <sup>25</sup>	3.42 (2.59–4.43)	1.55 (1.01–2.29)	32	55	5	58.18 (44.11–71.35)	52.00 (31.31–72.20)	64.00 (49.19–77.08)
Bronshstein (2008) <sup>48</sup>	94.87 (82.68–99.37)	33.33 (19.09–50.22)	36	37	2	97.30 (85.84–99.93)	100.00 (75.29–100.00)	97.30 (85.84–99.93)
Natu (2014) <sup>46</sup> (high-risk group)	4.44 (2.80–6.64)	NA	14	22	0	63.64 (40.66–82.80)	NA	63.64 (40.66–82.80)
Pooled result	6.55 (5.66–7.52)	3.75 (3.02–4.60)	116	186	7	61.18 (37.71–82.19)	62.42 (33.40–87.24)	66.29 (43.47–85.69)

Only first author given for each study. Values in parentheses are 95% CI. Specificity of first-trimester ultrasound for detection of major anomaly was not calculated owing to low numbers of studies that provided data on false-positive (FP) diagnoses. \*Studies that did not provide data on number of affected fetuses within cohort were not included in pooled estimates of prevalence of affected fetuses and sensitivity for detection of affected fetuses. †Studies that performed only one fetal ultrasound examination during pregnancy were not included in pooled estimate of antenatal diagnoses in first trimester. FN, false negative; NA, not available; TP, true positive.



**Figure 4** Forest plots of sensitivity of first-trimester ultrasound in detecting all types of fetal structural anomaly (a) and fetuses affected by any type of structural anomaly (b) in high-risk pregnancies. Only first author given for each study.

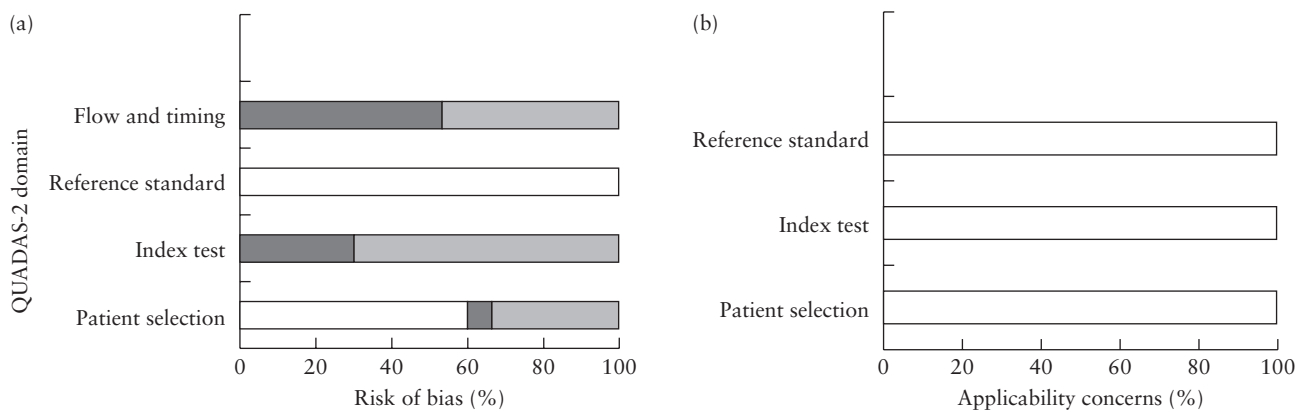
Limitations of this review include the fact that, despite subgroup analysis, there remained considerable heterogeneity between the studies; extensive variation between the studies existed in inclusion and exclusion criteria, the age at postnatal follow-up, use of anatomical protocols and outcome reporting. The types of anomaly examined

were different, even among those aiming to assess solely ‘major anomalies’. We would therefore recommend the use of international definitions in future studies, such as the RCOG, EUROCAT or March of Dimes criteria.

A number of studies excluded cardiac anomalies from their analysis, presumably because these anomalies are often difficult to diagnose in the first trimester and require significant sonographer skill. The latest BINOCAR (British Isles Network of Congenital Anomaly Registers) data<sup>54</sup> suggest that overall antenatal detection rates are low (53.1% (95% CI, 49.1–57.1%)) and this must be seen in the context of them being common anomalies (82.2 (95% CI, 81.30–83.03) per 10 000 fetuses)<sup>55</sup>. It is impossible to develop a proper understanding of the overall impact of first-trimester screening on antenatal care or to compare first- and second-trimester anomaly screening if studies do not include anomalies belonging to all organ systems within their analysis.

Some studies reported only the number of anomalies within their cohort, providing no data with respect to the number of affected fetuses. This limits the ability to understand fully the number of fetuses affected by first-trimester screening initiatives; such information should form a minimum standard to be reported in future studies.

Finally, it should be emphasized that the majority of studies did not report false-positive rates. One of the inevitable consequences of first-trimester screening is the consideration of early termination of pregnancy when major anomalies are identified. There is a self-evident concern regarding termination after first-trimester anomaly screening without a full understanding of a



**Figure 5** Quality assessment of studies included in systematic review for risk of bias (a) and concerns regarding applicability (b), according to QUADAS-2. □, Low; ▨, unclear; ■, high.

**Table 6** Summary of results from meta-analysis on performance of first-trimester ultrasound in detection of fetal anomalies

Sub-group	Type of anomaly assessed/population	Anomalies present (n per 100 fetuses)	Sensitivity for detection of anomaly (%)	Antenatal diagnoses in first trimester (%)
1	Major anomalies in low-risk/unselected population	1.01 (0.95–1.07)	46.10 (36.88–55.46)	53.47 (43.42–63.37)
2	All types of anomaly in low-risk/unselected population	1.81 (1.72–1.90)	32.35 (22.45–43.12)	41.10 (32.13–50.38)
3	All types of anomaly in high-risk population	6.55 (5.66–7.52)	61.18 (37.71–82.19)	66.29 (43.47–85.69)

Values in parentheses are 95% CI.

false-positive diagnosis; however, the rate of false positives is thought to be much lower than it is for second-trimester screening<sup>36,52</sup>. Furthermore, it is not easy to determine what is a false-positive diagnosis, as anomalies evolve; for example, a significant proportion of megacystis (in particular those  $\leq 15$  mm) resolve spontaneously later in pregnancy<sup>56</sup>. In the study by Syngelaki *et al.*<sup>14</sup>, a large proportion of false-positive diagnoses involved either megacystis or bowel-only exomphalos. As such, it is critical not only to understand the rate of false-positive diagnosis in first-trimester screening, but also to know which types of anomaly are most likely to resolve spontaneously.

Based on the recommendations from QUADAS-2<sup>19</sup>, the design of a perfect evaluation of first-trimester anomaly screening would involve blinding of sonographers to patient history, prevention of referral bias in tertiary-center trials, postmortem analysis of every terminated case, standardized neonatal assessment of internal anomalies with neonatal echocardiography in all fetuses and blinding of neonatal assessors to the prenatal sonographic results. Such a rigorous examination of first-trimester anomaly screening is unlikely to be performed on a large scale or, in fact, to be considered ethical. Historical assessment of second-trimester anomaly screening revealed that, at the time, there were concerns that it was not adequately evaluated prior to widespread adoption in prenatal care, particularly with respect to the burden of false-positive diagnoses, optimal timing for screening, cost–benefit analysis and the potential for increasing parental anxiety<sup>57,58</sup>, and there was little consensus or uniformity as to how screening should be performed<sup>59</sup>. However, the implementation of standardized anatomy protocols, a systematic approach

to training of sonographers and an emphasis on quality assessment have allowed the 20-week scan to become a fundamental component of prenatal care, which is now also occurring with first-trimester ultrasound.

In conclusion, this systematic review used subgroup analysis, strict ‘anomaly’ criteria and manual extraction of data to obtain the most accurate sensitivity of first-trimester anomaly screening. Our findings demonstrate that first-trimester ultrasound should be considered a valuable clinical addition to prenatal anomaly screening in low-risk, high-risk and unselected populations. We have demonstrated that the current literature represents only the beginning of what is achievable for first-trimester anomaly screening. It is clear that greater sensitivity could be achieved with the use of a detailed anatomical protocol, increased attention to sonographer training and an appreciation of the learning curve involved in acquiring the appropriate skills.

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## SUPPORTING INFORMATION ON THE INTERNET



Appendices S1–S3 may be found in the online version of this article.



## Revisión sistemática del cribado mediante ecografía en el primer trimestre para la detección de anomalías estructurales en el feto y los factores que afectan el desempeño del cribado

### RESUMEN

**Objetivos** Determinar la sensibilidad y la especificidad de la ecografía del primer trimestre para la detección de anomalías en el feto y determinar qué factores podrían tener un impacto en el rendimiento del cribado.

**Métodos** Se realizó una revisión sistemática y metaanálisis de todas las publicaciones relevantes para evaluar la precisión en el diagnóstico de las ecografías abdominales y vaginales bidimensionales en la detección de anomalías fetales congénitas antes de las 14 semanas de gestación. El estándar de referencia fue la detección de anomalías en el nacimiento o póstumas. Se evaluaron los factores que podrían impactar en las tasas de detección, como las características de la población, la edad gestacional, el sistema sanitario, la modalidad de ecografía, o el uso de una lista de control de rasgos anatómicos, para la detección de anomalías en el primer trimestre y el tipo de malformación incluida en el estudio. En un esfuerzo por reducir el impacto de la heterogeneidad del estudio en los resultados del metaanálisis, los datos de los estudios se analizaron por subgrupos de anomalías principales frente al total de tipos de anomalías, y de poblaciones de bajo riesgo / no seleccionadas frente a poblaciones de alto riesgo.

**Resultados** Una búsqueda electrónica (hasta el 29 de julio de 2015) identificó 2225 citas bibliográficas relevantes, de las cuales se seleccionaron para su inclusión un total de 30 estudios, publicados entre 1991 y 2014. La estimación combinada de la detección de anomalías principales en poblaciones de bajo riesgo o no seleccionadas (19 estudios, 115 731 fetos) fue del 46,10% (IC 95%, 36,88–55,46%). La tasa de detección de todas las anomalías en las poblaciones de bajo riesgo o no seleccionadas (14 estudios, 97 976 fetos) fue del 32,35% (IC 95%: 22,45–43,12%), mientras que en las poblaciones de alto riesgo (6 estudios, 2841 fetos) fue del 61,18% (IC 95%, 37,71–82,19%). Entre los factores examinados por su impacto en la tasa de detección, hubo una relación estadísticamente significativa ( $P < 0,0001$ ) entre el uso de un protocolo anatómico estandarizado durante el cribado de anomalías en el primer trimestre y su sensibilidad para la detección de anomalías fetales en todos los subgrupos.

**Conclusiones** Las tasas de detección de anomalías fetales en el primer trimestre fueron desde el 32% en grupos de bajo riesgo hasta más del 60% en grupos de alto riesgo, lo que demuestra que la ecografía del primer trimestre tiene el potencial de identificar una proporción elevada de fetos afectados de anomalías estructurales. El uso de un protocolo anatómico estandarizado mejora la sensibilidad del cribado mediante ecografía en el primer trimestre para todas las anomalías y anomalías severas en poblaciones de riesgo variable. Con el fin de optimizar la detección de anomalías en el primer trimestre, se deberían desarrollar e introducir protocolos internacionales basados en cortes anatómicos estándar.

### 孕早期超声筛查胎儿结构畸形以及影响筛查能力的因素的系统评价

**目的:** 检测孕早期超声检出胎儿畸形的敏感性和特异性, 证实可能影响筛查能力的因素。

**方法:** 对所有相关文献进行系统评价和 meta 分析, 评估二维经腹和经阴道超声在孕 14 周前检出先天性胎儿畸形的诊断准确性。参考标准为出生时或尸检时检出畸形。对可能影响检出率的因素进行评估, 包括人群特征、孕周、医疗机构、超声方法、采用解剖学检查表检出孕早期畸形以及研究包括的畸形类型。为了减少研究异质性对 meta 分析结果的影响, 对研究数据进行亚组间分析, 将主要畸形与所有畸形类型以及低危/非选择人群与高危人群进行比较。

**结果:** 计算机检索 (时间截至 2015 年 7 月 29 日) 到 2225 条相关文献, 其中共纳入 30 项研究, 其发表时间为 1991-2014 年。低危或非选择人群 (19 项研究, 115 731 例胎儿) 中主要畸形检出率的总估计值为 46.10% (95% CI, 36.88%~55.46%)。低危或非选择人群 (14 项研究, 97 976 例胎儿) 中所有畸形检出率为 32.35% (95% CI, 22.45%~43.12%), 而高危人群 (6 项研究, 2841 例胎儿) 中为 61.18% (95% CI, 37.71%~82.19%)。在检测的影响检出率的因素中, 孕早期畸形筛查采用标准的解剖学检查方法与其检出胎儿畸形的敏感性在所有亚组中均统计学显著相关 ( $P < 0.0001$ )。

**结论:** 孕早期胎儿畸形检出率的范围从低危组的 32%到高危组的 60%以上, 表明孕早期超声检查能够证实大部分结构畸形的胎儿。采用标准的解剖学检查方法能够提高孕早期超声在不同风险的人群中筛查所有畸形和主要畸形的敏感性。应当开发并采用国际化标准的解剖学检查方法, 以提高孕早期畸形检出率。