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Evaluation of the role of first-trimester obstetric ultrasound: a systematic review

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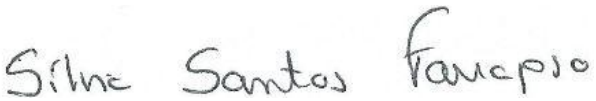
Assinatura: 

To Paulo, Maria and Joaquim

TABLE OF CONTENTS

COMPLETE TITLE

Evaluation of the role of first-trimester obstetric ultrasound: a systematic review

SHORT TITLE

Fetal malformations and first-trimester ultrasound

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WHAT IS ALREADY KNOWN ABOUT THIS TOPIC?

- First-trimester ultrasound is commonly used to detect/diagnose fetal malformations. Lately, an effort is being made to bring anatomical ultrasound from second-trimester to first-trimester.
- Fetal malformations have their timing to be detected, and first-trimester ultrasound alone may not be enough to accomplish that.

WHAT DOES THIS STUDY ADD?

- Last years, technological and human improvements have empowered first-trimester ultrasound, which explains the need to know if its accuracy to detect/diagnose malformations earlier increased or not, and its real usefulness.

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ABSTRACT

Before the late nineties, ultrasound (US) was somewhat useless, mainly due to technological limitations. Only after enhancements in US instrumentation and operator skills, US began to be considered a first-line screening exam to evaluate gestation during first-trimester. Furthermore, currently the last developments are allowing handling during first-trimester tasks characteristically related to the second-trimester US, such as looking for fetal malformations. This time shift raise up a question. Is first-trimester US an accurate mean of detecting fetal malformations, which are characteristically time dependent?

With this systematic review we intend to assess first-trimester US, and to quantify the US improvements in the detection rate of major structural malformations in chromosomally normal fetuses. To accomplish that we have obtained references from the MEDLINE database and analyzed 227.955 fetuses, gathered from 21 studies. Our study suggest that first-trimester US, as a tool for prenatal diagnosis of structural anomalies has potential to evolve since currently, detection rate is around 50%; however we believe that such value may be improved with the standardization of detection protocols, the concomitant use of appropriated markers and better equipment.

Despite all, first-trimester fetal malformation screening still represents a diagnostic challenge in modern obstetrics.

INTRODUCTION

In the last decade, it was estimated that fetal malformations ranged 1%–3% of all births, and constituted the most common cause of infant mortality. Most malformations are of unknown etiology, for which the only risk factor is the pregnancy itself. Hence, in this review and according to the literature, we adopted the term malformation to represent any structural anomaly, including dysmorphologies[1], independently of the etiology. Moreover, according to the European Surveillance of Congenital Anomalies[2] (EUROCAT) a malformation can be minor or major. Major malformations, if not lethal, comprehend all severe handicap that usually require therapeutic termination of pregnancy, and are the focus of this review.

During pregnancy malformations evolve until they reach a critical state of development, which allows the detection by US. The detectability time varies according to the type of malformation, the technical features of the equipment, and the skills of the technician who is in charge of the procedure. Until not long ago, these features favored the anatomical US to be performed between the 18–22th weeks of pregnancy.

However, since 80% of major malformations are present at 12 weeks of pregnancy and considering the evolution of equipment, the improvement of practitioner's skills, and the deeper knowledge about the embryo development[3], abnormality detection is being pulled from the second to first-trimester.

The accuracy and performance of first-trimester scan is being evaluated by several studies. Detection rates ranging between 17% and 90% are referred in the literature[4–6], and several causes have been claimed to explain such variability. The inclusion criteria defined for each study and the type and length of follow-up are pointed as having the major impact on results.

As far as we know, only two papers aimed to review the data from different studies about the detection rate of first-trimester US. Nonetheless, both present some limitations. The one from

Borrell *et al.*[7] only includes 5 studies, and the one from Syngelaki *et al.*[8] approaches the malformations as cardiac and non-cardiac, which is very strict in our point of view.

Hence, this systematic review intends to include all eligible studies presenting major malformations in euploid fetuses, in order to evaluate the sensitivity of first-trimester US.

METHODS

Search strategy and eligibility criteria

Studies were retrieved from a search in MEDLINE database, restricting the search to English references, using the following MeSH terms and keywords: ultrasonography, ultrasonics, ultrasound, pregnancy first trimester, first trimester, sensitivity, specificity, abnormalities, congenital abnormalities, anomalies, malformations, and detection.

Further keywords were tried when defining the query. However, since they did not enhance the sensitivity of the search, they were not considered in the final query. The last search was performed on November 28, 2012.

The references of each eligible study were screened for possible missing articles. None of the publications had overlapping populations.

Studies were eligible if they provided data on the detection rate of major malformations in euploid fetuses, screened by first-trimester US. Table 1 presents the inclusion and exclusion criteria defined to decide about the eligibility of each paper in our pool.

Table 1

The criteria were applied in two phases: first, studies were screened by title and abstract for relevance. Secondly, full papers of studies, which appeared potentially relevant, were assessed for inclusion.

Data extraction

For each study we recorded the name of the author, country of origin, sample size, type of population, study design, length of study, gestational age and type of follow-up. The

prevalence of major malformations in fetuses with normal karyotype was calculated for each study, too. We also recorded the detection rate of major malformations detected by first-trimester US. In some studies this value was not available, so we had to extract the necessary information to obtain the detection rate.

Quality assessment of included studies was carried out using the QUADAS[9] tool and the criteria for assessment of risk of bias defined by Pedrosa *et al.*[10], both adapted as appropriate (Table 2).

Table 2

This review was elaborated according to the PRISMA[11] statement in order to ensure a transparent, complete and unbiased reporting of valuable data.

RESULTS

Eligible studies

Of the 175 items retrieved with the electronic search, 127 were excluded when assessing the titles and abstracts. The remaining 38 papers were retrieved for screening in full text. Fifteen (15) new studies were identified through scanning of bibliographic references of included papers, performing a total of 63 (48 + 15) entries to review. As depicted in Figure 1, we further excluded 43 studies that examined major malformations out of the scope of the first-trimester US and studies that did not have enough information to calculate general US sensitivity. This was the case of papers voted to a specific major malformation, such as congenital heart disease (CHD) or central nervous system (CNS) malformation, or papers that addressed specific technical issues about US examination. Hence the final data included information from 20 papers (63 - 43).

Figure 1

Study characteristics

Descriptive characteristics of each eligible study are presented in Table 3. The studies have been performed in Europe, Brazil, China and Middle East, contributing with a total of

Table 3

227.955 fetuses, and 3255 major malformations. Fifteen (15) were prospective cohorts, one of which cross-sectional, 2 were retrospective cohorts, 2 were reviews and 2 randomized controlled trials (RCT), which perform a total of 21 studies. In practice 20 papers were included in our review, however, the one from Syngelaki *et al.*[8] presents simultaneously a prospective study and a review, both in accordance with our inclusion criteria.

Among all the studies, 10 aimed at evaluating the detection rate of major malformations in euploid fetuses [7–8, 12–19]. The studies from Hildebrand *et al.*[17], Chen *et al.*[20], Ebrashy *et al.*[21], Saltvedt *et al.*[22], Souka *et al.*[23] and Öztekin *et al.*[24] intended to compare the accuracy of first-trimester versus second-trimester US in diagnosing major abnormalities in fetuses. Two studies were focused on evaluation of aneuploidy markers as a means to enhance first-trimester US detection rate[6, 25], and 3 studies aimed for a specific aspect of first-trimester US[26–28]. Nonetheless, all of the studies had available data in order to calculate the sensitivity of US, during first-trimester time-range.

In all studies, the population was described as being low-risk, except in the paper by Chen *et al.*[27], in which only women above 35 years were selected. However, as stated in the same paper, it seems that the maternal age may account for an increased number of malformations due to chromosomal abnormalities, but the same cannot be said about euploid fetuses.

Risk of bias

Figure 2 presents the results obtained when assessing the risk of bias, according to our modified criteria. Generally, the included studies were adequate in what concerned the selection of participants, the definition of the population, the conditions in which the screening tests were performed and the results obtained.

Figure 2

Concerning the definition of the population, none of the studies was unclear. However, a total of 8 studies, from our pool of 21 papers, were quoted as inadequate. One (1) of them defined in its protocol a population aged more than 35 years, 2 were concerned in looking for

increased NT from an unselected population, and 1 was focused on CHD, also from an unselected population. The other main cause for an inadequate mark was the time range considered to perform the US. Six (6) studies did not respect the 11–14 weeks time range defined in our bias criteria and stated by the Fetal Medicine Foundation[29] (FMF) as the most valuable time-range to gather first-trimester US information. Particularly, the paper by Syngelaki *et al.*[8] extended its evaluation until the 16th week of gestation. However, only 3 fetuses were scanned at such pregnancy time.

Regarding the results, the majority of the studies only presented the sensitivity of the test or had available data to calculate it (which explains the number of inadequate studies). Only a few studies presented other measures of accuracy such as specificity (2 studies) or likelihood ratios (2 studies), which is in accordance with the studies that involve US sensitivity. The majority of them present detection rate data, but only a few exhibit other measures of accuracy.

With regard to the follow-up and verification, in most of the cases the number of patients that abandoned the study was not explicit, but there was enough information to calculate such value (12 papers). In 3 of them, there was not enough data.

Summary of results

Table 4 summarizes the results obtained from each series. It presents the number of fetuses for each study, the total of major malformations in the sample, the prevalence of major malformations, the number of malformations detected by the first-trimester US screening, and the sensitivity of the study.

Table 4

The lowest and highest calculated prevalences are 0.5% and 2.8%, as found in the studies of Hildebrand *et al.*[17] and Becker *et al.*[26], respectively. The mean value of overall studies is 1.5% (95% CI 1.2 – 1.7). Except for the lowest prevalence, all values are in the estimated range, presented by different reports, and stated above in the introduction.

In respect to the performance accuracy of the screen test under evaluation, sensitivity varies from 12.5% in the study of Hafner *et al.*[25] and 83.7% in the study of Becker *et al.*[26]. Both values are out of the interval of the overall average sensitivity, 49.2% (95% CI 41.1 – 57.3), and away from the overall pooled sensitivity, 40.0% (it was not possible to calculate the 95% confidence interval due to the lack of values in all studies).

DISCUSSION

The findings of this systematic review on chromosomally normal fetuses revealed that first-trimester US alone, as a tool to detect major structural malformations, has a moderate sensitivity. When considering pooled and averaged sensitivity the detection rate is about 40.0%, and 49.2% (95% CI 41.1 – 57.3), respectively. These values slightly increase, when the two review studies are removed from the analysis group: 42.0% and 50.7%, respectively. The more significant change in the pooled average is due to the sample size of the study presented by Syngelaki *et al.*[8], which involved 67.779 fetuses.

Despite the moderate detection rate, we have obtained better values than the ones presented by Borrell *et al.*[7] and Syngelaki *et al.*[8], in their studies. For instance, some aspects may be pointed out to explain such differences. First, the number of studies included in each review, 8 and 15, respectively, against our 21 studies. Moreover, in our case, from each included paper, we only have used information related to major malformations, excluding values related to minor malformations or aneuploidy. The other reviews used combined euploid, non-euploid, major and minor malformations in their results, which decrease sensitivity. Particularly, minor malformations considered in both cases, are prevalent but are hardly detected when considering first-trimester US. These outcomes strengthened our decision of evaluating first-trimester US independently of the class of malformation, since each group of malformations drifts the sensitivity of US.

Nonetheless, looking at our study that targeted US detection rate, independently of the major structural malformation, several aspects can be raised to explain why a promising detection tool revealed itself limited.

Only half of the elected studies had as main goal the evaluation of first-trimester US as a tool to detect major structural abnormalities. The other half considered the detection rate by US as a secondary aspect, or did not considered such point of view at all. Moreover, the malformations aimed by each study were not the same, and it is known that US sensitivity is intrinsically connected to the malformation under evaluation. For example, Becker *et al.*[26] targeted cardiac defects, while Carvalho *et al.*[13] looked for malformations at skull, brain, abdominal wall, with no interest in CHD. The later obtained a better US sensitivity. Also, the classification of malformations changed among studies. In some studies no classification was set down as in Weiner *et al.*[18] and Hafner *et al.*[25], while in other studies, specific arrangements were defined according to the purpose of the study[12–13, 23]. Besides, the detection rates presented by each study were not consistent. As reported above, the highest detection rate was achieved in the paper presented by Becker *et al.*[26], while the lowest sensitivity was 12.5%, in the study of Hafner *et al.*[25]. Furthermore, each paper had its own protocol to evaluate first-trimester US, with its own inclusion criteria and its own scanning technique. The paper presented by Chen *et al.*[27] was devoted to women over 35 years of age, while the paper from Hernádi *et al.*[28] intended to evaluate the transvaginal approach as a mean of enhancing the screening of fetal anatomy.

External factors to the study design may also be pointed out as causes for the variance in the results, for instance, the skills of the technicians performing the US, the fetal size, the maternal habitus, etc.

Regardless of the detection rate obtained, we cannot look at this study only as a number. The review presented herein intended to evaluate the sensitivity of first-trimester US for the

detection of major malformations without further considerations. Nonetheless, three aspects should always be taken into account when approaching first-trimester US: (1) the human factor; (2) the technological improvements in the detection of malformations; and (3) the malformations itself.

As far as malformations are concerned, several authors have experienced in their studies[30–33], that the part of the body system under evaluation can significantly impact on the US detection rate. For instance, sensitivity can go from less than 20%, in some cases of limb malformation, to more than 70% in some cases of CNS malformations. Considering the groups of malformations outlined by EUROCAT[2], we present a summary of the major abnormalities that can be found using an US, and current US sensitivity.

As stated before, CNS is associated with some of the malformations with the highest detection rates, and comprises about 40% of all fetal malformations[34]. Particularly, acrania and anencephaly have detection rates above 90%[37], with an abnormal shape of the head noticeable from the 8th week of pregnancy.

In the opposite, hydrocephalus is rarely diagnosed in first-trimester, since dilation of ventriculus occur at a more advanced gestational stage. The same is true for agenesis of corpus callosum and microcephaly[6].

The detection of spina bifida in first-trimester US is controversial. While some studies present detection rates of 60% or more as in the study of Syngelaki *et al.*[8], other studies state that spina bifida is very difficult to detect before the 14th week of pregnancy, since nor the "lemon" or "banana" sign are present.

Along with CNS malformations, CHD are those with the highest prevalence, and an incidence of 0.5-1/100 live born infants[35], but one of the lower detection rates, when using US alone.

The heart can be visualized since the 7th week, and the four-chamber view is the conventional approach, with the following results for the most common cardiac abnormalities: 20% for

hypoplastic left heart, 10% for coarctation of the aorta, 5% for tetralogy of Fallot and ventricular septal defect and 0% for transposition of the great arteries. In order to increase detection rate, echocardiography, Doppler and soft/biochemical markers are being considered as a natural part of the fetal cardiac evaluation[7].

Abdominal wall abnormalities encompass a group of malformations, each with its own rate of detection. Omphalocele and gastroschisis can be detected more than 65% of the times[16], as other large defects. In turn, diaphragmatic hernias, unless they are of considerable size and produce a mediastinal shift, are hardly perceived with a first-trimester US. As for cardiac malformations, the use of soft markers, such as nuchal translucency (NT) and ductus venosus (DV), may be helpful in such cases.

According to Grande *et al.*[6] detection rate of major urogenital tract malformations is approximately 25%. At the upper end of the spectrum are obstructive uropathies, in the form of megacystis. In the opposite extreme is renal agenesis.

Fetal megacystis at 10–14 weeks of gestation, is defined by a longitudinal bladder diameter of 7 mm or more, and found in about 1 in 1500 pregnancies[38]. Usually it portends a poor fetal outcome. If the longitudinal diameter of the fetal bladder is moderate (7 to 15 mm) there is a risk of about 25% of chromosomal defects. In chromosomally normal fetuses there is spontaneous resolution of the megacystis without any obvious adverse consequence on the development of the urinary system in about 90% of cases. In contrast, in megacystis with bladder diameter >15mm the risk of chromosomal defects is about 10%, but in fetuses with normal karyotype the condition is invariably associated with progressive obstructive uropathy.

Renal agenesis, during first-trimester evaluation, is not characterized by oligohydramnios, and moreover kidneys are easily confused with adrenal glands, which are enlarged in this stage of

pregnancy. Then, renal agenesis is suspected when hypoechogenic masses are detected in the renal bed, which occurs less then 20% of the times.

As before, when urinary malformations are suspected, it is common to have abnormal NT and DV. Moreover, the rate of detection is slightly increased if the TV route is used, when assessing the urinary tract.

While minor skeletal abnormalities are more frequent than major ones, they are hardly detected in first-trimester US evaluation. Amongst the major skeletal malformations osteochondrodysplasia is the one that presents the highest detection rates in several studies[6–7].

Limbs are traditionally assessed during pregnancy as markers of fetal growth, nutrition and gestational age, and because of that, better detection rates would be expected. But it is not the case. According to the study of Rice *et al.*[33], the most reported abnormalities are club hand, followed by absence of long bones, missing limb, club foot and shortening of long bones. Also important, is that most of the cases that involve limb malformations had other abnormalities associated. The most common include abdominal wall defects, single umbilical artery and hydrops. *Paladini et al.*[39] described a 41% association with concomitant non-chromosomal syndromic conditions and limb abnormalities.

Nevertheless, as stated by Economides *et al.*[36] almost all major fetal abnormalities can potentially be diagnosed in early pregnancy, if the appropriate procedures are chosen and employed. Currently, this could be achieved by recruiting more trained personnel as suggested Bellotti *et al.*[40], using transabdominal US combined with transvaginal US, 3D-US, echocardiography, Doppler, and US markers such as NT[41–42], ductus venosus blood flow[43–44], intracranial translucency[30–31] or nasal bones[45].

To conclude, we should remind that the major limitations of this review are due to the diversity of papers included in it, each one with its intrinsic characteristics. As stated before the studies included followed their own classifications, some US were not performed exactly

during the time range 11–13^{+6} weeks (although, more than 95% were), some studies did not intended directly to evaluate the performance of first-trimester US as a detection tool, and most importantly, results were and still are entirely human dependent.

On the other hand, we think that the values presented in our review are valid, in the sense that they were obtained following a precise and reproducible method, allied to strict criteria, that took into account the limitations and bias that the included studies could introduce. Furthermore, all the obtained information was summarized so as to simplify the extraction of prevalences and sensitivities.

Moreover, this paper emphasize that even if first-trimester US alone is far from 100% accurate in the diagnosis of fetal malformations it is an approach that must always be taken into account.

In the future, as more sophisticated equipment will be available, broader knowledge about fetal development and more sophisticated and credible US markers will be accessible, we hope that the number of abnormalities detected earlier will increase and the 11^{th} to 14^{th} week scan will become the first comprehensive anatomic fetal survey.

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Table 1 Criteria of eligibility of studies to include in the systematic review

	Inclusion criteria	
1.	Study design	Prospective and retrospective studies or random controlled trial, in which screening with 2D US was applied for the detection of major malformations.
2.	Study aim	To evaluate the sensitivity of first trimester US in detecting congenital major malformations.
3.	Screening test	TV and/or TA US.
4.	Trimester of screening	First trimester pregnancy (11 to 13^{+6} weeks).
5.	Condition screened Rationale	Presence of major malformations, defined in one of the EUROCAT subgroups[2]. Most papers classify the malformations considering the main body systems, or simply present each malformation as an isolated identity. The EUROCAT defines subgroups that allow a straight correspondence with the body system approach of the studies, and for each subgroup, defines explicitly the type of malformation. Moreover major malformations are ICD coded.
6.	Population screened Rationale	Unselected population or low risk population. Singleton pregnancies or information about the number of fetuses under evaluation. First-trimester US is intended to be a mass-screening test. If high-risk population sample is considered, overestimated values are expected.

7.	Reference standard	2D US, TV or TA, performed by a physician or a technician, between 11 and 13^{+6} weeks of pregnancy, looking for major malformations.
	Rationale	There is no reference standard on how to perform first-trimester US. At a minimum, there are guidelines, country dependent that are followed by some centres.
	Exclusion criteria	
		Malformations due to aneuploidies. Study focused in a specific major malformation. Study using other techniques beside 2D US, such as ecocardiography or 3D ultrasound to confirm the malformation. Study using soft or biochemical markers.
	Rationale	Several studies have proven that the use of markers improve the detection rate of US Language other than English

2D= two-dimensional; 3D= tri-dimensional; ICD= international classification of diseases; US= ultrasound; TA= transabdominal; TV= transvaginal.

Table 2 Criteria for assessment of risk of bias

1.	Selection of participants	
	Adequate	▪ Cohort study in which all eligible women are included consecutively or randomly. ▪ Random controlled trial in which all eligible women are included consecutively or randomly.
	Inadequate	▪ The study does not meet at least one of the afore-mentioned criteria.
	Unclear	▪ The study is unclear in respect to this issue or part of it.
2.	Description of population	
	Adequate	▪ The following information must be present: unselected population and gestational age between $11–13^{+6}$ weeks (equivalent to 11–14 weeks).
	Inadequate	▪ The study does not meet at least one of the afore-mentioned criteria.
	Unclear	▪ The study is unclear in respect to this issue or part of it.

3.	Description of screening test	
	Adequate	▪ The following information must be present: first-trimester scan, TA and/or TV US approach, and classification of major malformations.
	Inadequate	▪ The study does not meet at least one of the afore-mentioned criteria.
	Unclear	▪ The study is unclear in respect to this issue or part of it.
4.	Follow-up and verification	
	Adequate	▪ At least 90% of the participants originally subjected to the screening test have a follow-up to confirm the malformation diagnosed (autopsy, later US, after birth observation, enquiry). ▪ Miscarriage, voluntary pregnancy termination and neo-natal death are considered legitimate exclusions, if no malformation was diagnosed or no procedure was accomplished in case of malformation diagnose.
	Inadequate	▪ Less than 90% of the participants originally subjected to the screening test had a follow-up.
	Unclear	▪ The study is unclear in respect to this issue or part of it.

5. Analysis of results		
	Adequate	▪ Measures of accuracy for major malformations are available for the test screen (Sn, Sp, ROC, AUC, LR+ and LR-).
	Inadequate	▪ The Sn of the test screen is not explicitly available

Adapted from QUADAS[9] and Pedrosa *et al*. 2011[10].

AUC= area under curve; LR= likelihood ratio; ROC= receiver operator characteristic; Sn= sensitivity; Sp= specificity; TA= transabdominal; TV= transvaginal; US= ultrasound.

Table 3 Summary of selected studies

Study Reference Country	Study Design	Length of Study*	Type of Population	*n*†	GA‡	Type of US	Follow-up
Abu-Rustum *et al*., 2010[12] Lebanon	Retrospective	7	Unselected	1370	11–13^{+6}	Mostly TA	Pediatric report
Becker *et al*., 2006[26] Germany	Prospective	7	Unselected	3094	11–13^{+6}	Mostly TA	Hospital database + patient enquiry
Borrell *et al*., 2011[7] Spain	Review	6	Unselected	36237	11–13^{+6}	—	—
Carvalho *et al*., 2002[13] Brazil	Prospective	4	Unselected	2853	11–13^{+6}	Mostly TA	Hospital database + patient enquiry
Cedergren *et al*., 2006[14] Sweden	Prospective	2	Unselected	2633	11–13^{+6}	TA	Hospital database

Study Reference Country	Study Design	Length of Study*	Type of Population	*n*†	GA‡	Type of US	Follow-up
Chen *et al*., 2004[27] China	Prospective	3	Women aged >35	1609	12–14	TA + TV	Hospital database + patient enquiry
Chen *et al*., 2008[20] China	RCT	3 ½	Unselected	Control 3974 Case 4282	10–14^{+6} 12–14^{+6}	Mostly TA	Hospital database + patient enquiry
Dane *et al*., 2007[15] Turkey	Prospective	2	Unselected	1290	11–13^{+6}	Mostly TA	Hospital database + patient enquiry
Economides *et al*., 1998[16] UK	Prospective	NS	Unselected	1632	12–13^{+6}	Mostly TA	Hospital database + patient enquiry
Ebrashy *et al*., 2010[21] Egypt	Prospective	5	Unselected	2876	13–14	Mostly TA	NS

Study Reference Country	Study Design	Length of Study*	Type of Population	*n*†	GA‡	Type of US	Follow-up
Grande *et al*., 2012[6] Spain	Retrospective	8	Unselected	13723	11–13+6	TA + TV	Hospital database + patient enquiry
Hafner *et al*., 1997[25] Austria	Prospective	3	NT screening	4233	10–13	Mostly TA	Autopsy report + hospital database
Hernádi *et al*., 1997[28] Hungary	Prospective	3	Unselected	3991	11–14	TV	Autopsy report + pediatric report
Hildebrand *et al*., 2010[17] Sweden	Prospective	4 ½	Unselected	6692	11–14	TA	Autopsy report + hospital database
Öztekin *et al*., 2010[24] Turkey	Prospective	4	Unselected	1085	11–14	Mostly TA	Hospital database + patient enquiry
Saltvedt *et al*., 2006[22] Sweden	RCT	3 ½	Unselected	18053	12–14	Mostly TA	Hospital database + patient enquiry

Study Reference Country	Study Design	Length of Study*	Type of Population	*n*†	GA‡	Type of US	Follow-up
Souka *et al*., 2005[23] Greece	Prospective	1 ½	Unselected	1144	11–14	TA + TV	NS
Syngelaki *et al*., 2011[8] UK	Prospective	3 ½	Unselected	44859	$11–13^{+6}$	Mostly TA	Hospital database + pediatric report
	Review	18	CHD screening	67779	10–16§	—	—
Weiner *et al*., 2007[18] Israel/USA	Prospective	2	NT screening	1723	$10^{+3}–13^{+6}$	Mostly TA	NS
Whitlow *et al*., 1999[19] UK	Prospective cross-sectional	NS	Unselected	6443	11–14	Mostly TA	Hospital database + patient enquiry

Study Reference Country	Study Design	Length of Study*	Type of Population	*n*†	GA‡	Type of US	Follow-up

* Length of study in years.

† Number of fetuses.

‡ Gestational age in weeks.

§ Only 3 scans performed at 15th week of gestation.

CHD= congenital heart disease; GA= gestational age; NS= not specified; NT= nuchal translucency; RCT= randomized controlled trial; TA= transabdominal; TV= transvaginal; US= ultrasound.

Table 4 Summary of results for each analyzed series

Study Reference	*n***	Total of Malformations (Prevalence %)	Malformations Detected by First-Trimester US	*Sn*†
Abu-Rustum *et al*., 2010[12]	1370	36 (2.6%)	20	55.6%
Becker *et al*., 2006[26]	3094	86 (2.8%)	72	83.7%
Borrell *et al*, 2011[7]	36237	494 (1.4%)	143	28.9%
Carvalho *et al*., 2002[13]	2823	66 (2.3%)	25	37.9%
Cedergren *et al*., 2006[14]	2633	32 (1.2%)	13	40.6%
Chen *et al*., 2004[27]	1609	16 (1.0%)	7	43.8%
Chen *et al*., 2008[20]	Control			
	4149	64 (1.5%)	21	32.8%
	Case			
	4662	63 (1.4%)	30	47.6%
Dane *et al.*, 2007[15]	1290	24 (1.9%)	17	70.8%
Economides *et al*., 1998[16]	1632	17 (1.0%)	11	64.7%
Ebrashy *et al*., 2010[21]	2876	31 (1.0%)	23	74.2%
Grande *et al*., 2012[6]	13723	194 (1.4%)	95	49.0%
Hafner *et al*., 1997[25]	4233	56 (1.3%)	7	12.5%
Hernádi *et al*., 1997[28]	3991	37 (1.0%)	20	54.1%
Hildebrand *et al*., 2010[17]	6692	34 (0.5%)	14	41.2%
Öztekin *et al*., 2010[24]	1085	21 (1.9%)	14	66.7%
Saltvedt *et al*., 2006[22]	18053	371 (2.1%)	74	19.9%

Souka *et al*., 2005[23]	1148	14 (1.2%)	7	50.0%
Syngelaki *et al*., 2011[8]	44859‡‡	488 (1.1%)	213	43.6%
	67779§§	1087 (1.6%)	443	40.8%
Weiner *et al*., 2007[39]	1723	22 (1.3%)	9	40.9%
Whitlow *et al*., 1999[19]	6443	66 (1.0%)	44	66.7%
Averaged Sensitivity (95% CI)				**49.2% (41.1 – 57.3)**
Pooled Sensitivity				**40.0%**

** Number of fetuses.

†† Study sensitivity.

‡‡ Data from prospective study.

§§ Data from literature review.

Figure 1 Flowchart of the search strategy and selected studies

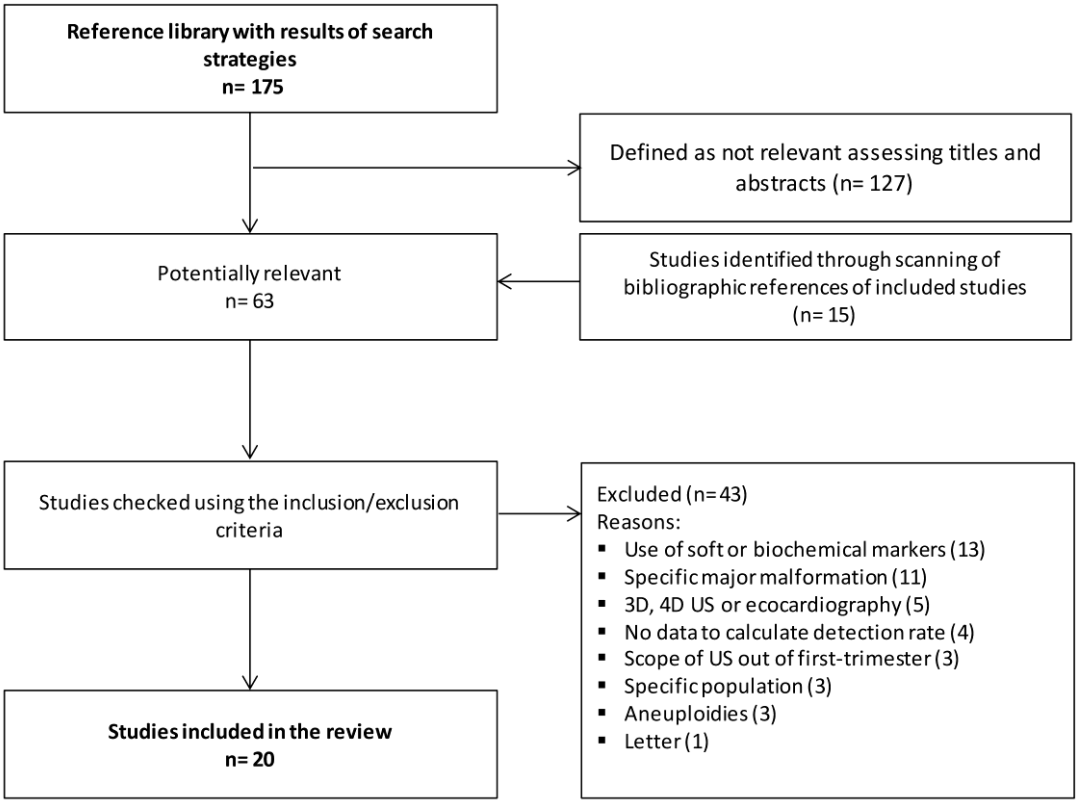
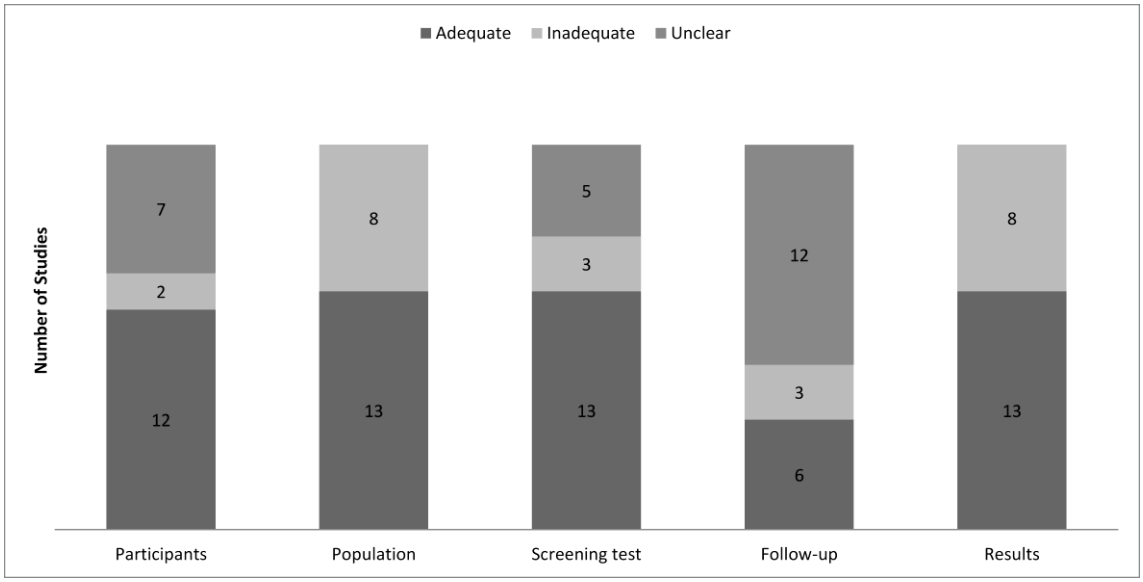


Figure 2 Assessment of the risk of bias



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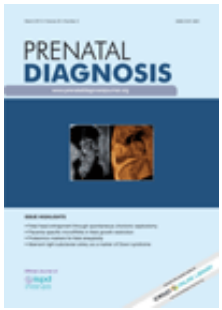
ANNEX I: AUTHOR GUIDELINES

Prenatal Diagnosis



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2 Nolin SL, Glicksman A, Ding X, *et al*. Fragile X analysis of 1112 prenatal samples from 1991 to 2010. Prenat Diagn 2011; 31:925–31.

3 Petrikovsky BM. Fetal Disorders: Diagnosis and Management . New York: Wiley-Liss, 1998.

4 Smith A. Select committee report into social care in the community [WWW document]. URL http://www.dhss.gov.uk/reports/report015285.html [accessed on 7 November 2003].

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