Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 16–22

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Review Article

Meta-analysis of validity of echogenic intracardiac foci for calculating the risk of Down syndrome in the second trimester of pregnancy

Ana María Rubio Lorente [a,*], María Moreno-Cid [a], María José Rodríguez [a], Gema Bueno [a], José María Tenías [b], Carmen Román [b], Ángel Arias [b], Ana Pascual [a]

[a] Obstetrics and Gynaecology Department, Hospital La Mancha Centro, Alcázar de San Juan, Ciudad Real, Spain
[b] Research Support Unit, Hospital La Mancha Centro, Alcázar de San Juan, Ciudad Real, Spain

ARTICLE INFO

Article history:
Accepted 3 November 2016

Keywords:
Down
echogenic focus
intracardiac
meta-analysis
screening

ABSTRACT

Echogenic intracardiac foci are a second trimester marker associated with aneuploidy in high-risk populations. The objective of this study is to assess the validity of echogenic intracardiac foci for Down syndrome detection in the second trimester ultrasound scan. A systematic search in major bibliographic databases was carried out (MEDLINE, EMBASE, CINAHL). Twenty-five studies about echogenic intracardiac foci were selected for statistical synthesis in this systematic review. Those 25 considered to be relevant were then subjected to critical reading, following the Critical Appraisal Skills Programme criteria, by at least three independent observers. Then, the published articles were subjected to a meta-analysis. A global sensitivity of 21.8% and a 4.1% false positive rate were obtained. The positive likelihood ratio was 5.08 (95% confidence interval, 4.04–6.41). The subgroups analysis did not reveal statistically significant differences. In conclusion, echogenic intracardiac foci as an isolated marker could be a tool to identify—rather than exclude—the high-risk group of Down syndrome, although it should be noted that it shows low sensitivity.

Introduction

Down syndrome (DS) is the third leading congenital defect in terms of frequency [7.23/10,000 live births; 95% confidence interval (CI), 5.56–9.13 in 2010] [1]. DS causes important morbidity and associated psychosocial burdens and therefore carries high economic costs [1,2]. Detection of this genetic alteration is the most frequent indication of invasive prenatal diagnosis [3]. Furthermore, the need for early diagnosis in these cases has revolutionized screening performance during pregnancy.

We can detect ultrasound soft markers in the second trimester ultrasound scan. However, the challenge lies in the lack of common guidelines concerning these findings because of several factors: the lack of diagnostic validity studies; their presence in 11–17% of normal fetuses [4]; and their presence or absence can modify the baseline risk of DS (obtained by a first trimester screening or by risk according to age, if the first one has not been performed) applying likelihood ratios (LRs).

Since the four-chamber view became part of the basic ultrasound examination, new sonographic findings began to appear, such as the echogenic intracardiac focus (EIF). In 1987 Schechter first described EIF in the left ventricle, which he attributed to a thickening of the chordae [5,6].

EIFs are small structures typically found within the ventricles in the region of the papillary muscle or chordal moving in synchrony with the mitral or tricuspid valve, which do not bind to the ventricular wall and have comparable echogenicity to fetal bone [5,7,8]. The reduction of the current gain to ensure that it does not fade prior to echogenicity of the ribs is an important test to minimize false positive results because the papillary muscles are often visible as echogenic points [9]. The etiology is unclear, but is probably a normal variant of the development of the papillary muscle [7].

EIFs are observed more frequently (90%) in the left ventricle, are often unique, and are between 1 mm and 4 mm. They occasionally appear in the right ventricle or bilaterally. Their intra-atrial location or diffuse echogenic cardiac foci are rare [5,8].

This marker was observed in 0.5–20% of fetuses, with an overall frequency of 5.6% [5,6,8,10]. However, the incidence varies according to the indication of the performing ultrasound. In high-risk patients, studies suggest a possible association of EIF with fetal

* Corresponding author. Plaza Mayor Bloque 7, 2-2, Alcázar de San Juan, 13600 Ciudad Real, Spain.
E-mail address: arubiolorente@gmail.com (A.M.R. Lorente).

http://dx.doi.org/10.1016/j.tjog.2016.11.002

aneuploidy. Other studies showed that EIF could be a benign finding in low-risk populations [5,7,8].

Detecting a minor marker causes anxiety in the patient, even at clinically significant levels compared with the control group [9]. So their partners need proper advice. In addition, some patients will need to undergo invasive tests that, unfortunately, are not free of risks (0.6% risk of abortion) [9].

There are few systematic reviews on the diagnostic performance of the presence of echogenic cardiac foci for detection of DS. We have also incorporated recent changes in the methodology of systematic reviews of diagnostic studies (based on PRISMA declaration) [11,12]. Therefore, the objective of our work is to conduct a systematic review and meta-analysis of published studies on the diagnostic performance of the presence of EIF for the detection of DS in the second trimester of pregnancy in order to minimize the variability in interpretation of this marker in clinical practice.

Materials and methods

Search criteria and study selection

Sources of information: Diagnostic studies were surveyed by running a search in major international bibliographic databases (MEDLINE, EMBASE, and CINAHL), with the final search conducted in October 2012 (updated in June 2013). The references included in the selected articles were also reviewed to search for related citations. In the "Web of Knowledge" website, a list of items that shared the same quotes from the articles included in the study were consulted.

Search strategies: Comprehensive search criteria were used to identify articles that included DS and ultrasound findings. These were combined with the methodological filters developed by Haynes and Wilczynski [11,13] to search for diagnostic studies. The thesauri for MEDLINE (MeSH) and EMBASE (EMTREE) were also used. For the remaining databases, free text searches with truncations were used.

Selection criteria and identification of relevant documents

From the studies thus identified, those diagnostic studies analyzing the screening performance of EIF in the detection of DS were selected. The search was not restricted with regard to date or language of publication. The resulting search lists included the title and/or abstract (for most articles), which were used to carry out an initial identification of the relevant documents.

Two independent researchers participated in this initial stage. An article was considered relevant if at least one of the observers considered it relevant. The agreement between observers was calculated (Kappa index = 0.87). The full text of all articles considered to be relevant was then retrieved.

Data extraction and assessment of methodological quality

Those studies considered relevant were subjected to critical reading by a group of at least three evaluators who used Critical Appraisal Skills Programme criteria and Health Technology Assessment of the Basque Government Service (Osteba) critical reading guidelines for diagnostic studies. For a study to be selected, it had to withstand the removal questions on the evaluation forms. The quality of the studies was rated as low, medium, or high based on the Osteba criteria.

Studies that were considered both relevant and methodologically correct were then examined by at least three independent observers, who extracted the following data from the analyzed ultrasound finding (data of isolated EIF): sensitivity (absolute and relative frequencies), specificity (absolute and relative frequencies), and LRs.

Statistical analysis (meta-analysis)

For EIF, the possible presence of a threshold effect was evaluated with the aid of graphical methods (summary receiver operating characteristics curves), as well as with a statistical method calculating the Spearman correlation coefficient between sensitivity and specificity.

We used the Meta-DiSc program, a software application for meta-analysis of test accuracy data developed by the Clinical Biostatistics Unit, at the Ramón y Cajal Hospital, Madrid (Spain) [14].

Results

From an initial list of 852 articles, two independent observers selected 207 as potentially relevant for the study of ultrasound markers. Of the 207 articles selected, 70 were excluded. Of the 137 remaining articles, 25 analyzing the usefulness of EIF assessment in diagnosing DS were chosen (Figure 1).

The quality of the studies was acceptable (medium or high), according to the criteria outlined in the Osteba Critical Reading guidelines in 19 studies. Interobserver agreements were assessed in only two of these studies (Table 1).

In 16 articles, the studied population consisted of pregnant women at high risk for DS, defined as those who had been referred for a comprehensive ultrasound scan either after a previously positive combined screening result or because of advanced maternal age or other DS risk factors [10,15–27]. In nine studies, the studied population consisted of pregnant women at low risk for DS from the unselected population [28–36]. In one study, the population's risk for DS was not specified [20] (Table 1).

Screening performance indicators are shown in Table 2, with a low sensitivity (21.8%; 95% CI, 19.6–24.1) and a high specificity (95.9%; 95% CI, 95.8–95.9). The global LR+ was 5.08 (95% CI, 4.04–6.41) and the LR− was 0.81 (95% CI, 0.75–0.87; Table 2). No significant differences were found between risks of the populations studied, the quality of the studies, and weeks of gestation (Table 3) (Figures 2–5).

Discussion

In this systematic review, we retrieved, reviewed, and summarized studies about the diagnostic performance of the presence of EIF in the detection of DS in the second trimester of pregnancy.

The results of our systematic review show that the detection rate of DS in the second trimester of pregnancy based on these ultrasound markers (sensitivity) is low (21.8%), although the false positive rate is also low (4.1%). The LRs show that this marker would have more value to confirm (LR+ 5.08) than to rule out a DS. The risk of the population in which the study was done, the quality of the study and gestational age at which the scans are done do not seem to change the accuracy pointers substantially.

The EIF occurs in 0.5–20% of the genetic sonogram [6,19,29,37–39], by about 11% to 18% of fetuses with DS [15,29], and in 4–5% of chromosomally normal fetuses [15,40,41].

In the low-risk population, the incidence of DS ranges from 0.1% to 0.4% [28–30]. The documented chromosomal abnormality rate is 3.3–4.4% in a low-risk population in the presence of EIF [8].

Despite various research endeavors, the relationship of EIF with congenital malformations and chromosomal abnormalities is unclear [5,7,8]. Carriço et al [7] detected 8.1% cardiac defects rate in fetuses with EIF without aneuploidy in fetal echocardiography and