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Review Article

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

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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

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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

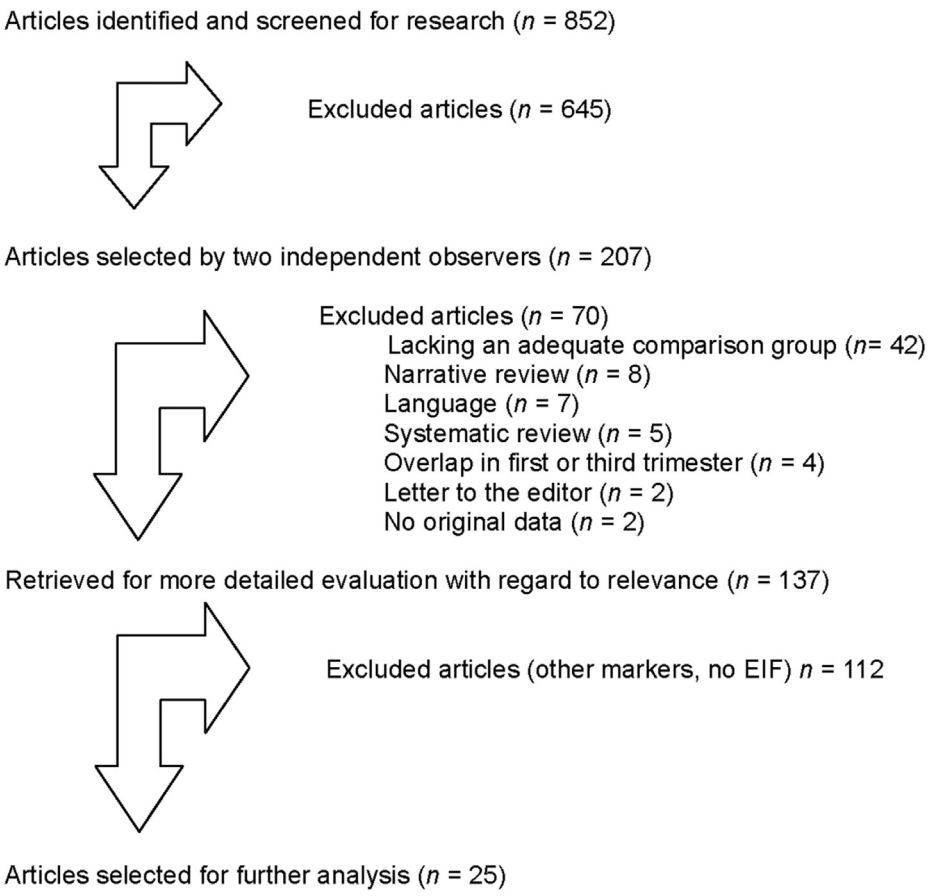

Figure 1. Flowchart of the study selection process; summary of the process for systematic review of second-semester echogenic intracardiac foci (EIF) findings.

Table 1
Characteristics of included studies.

Reference	Type of population	Weeks of gestation	Interobserver concordance	Quality
Bromley et al [15]	High risk	13–21	No	Medium
Bromley et al [26]	High risk	14–20	No	High
Huggon et al [16]	High risk	Ne	No	Medium
Sohl et al [10]	High risk	14–25	No	Medium
Manning et al [17]	High risk	16–24	No	Medium
Winter et al [18]	High risk	14–24	No	Medium
Bromley et al [19]	High risk	15–20	No	Medium
Lamont et al [28]	Ne	18–24	No	Low
Anderson and Jyoti [29]	Ne	16–24	No	Medium
Nyberg et al [24]	High risk	14–20	No	High
Wax et al [5]	High risk	14–24	No	Medium
Smith-Bindman et al [3]	High risk	15–20	No	Medium
Bromley et al [7]	High risk	15–20	No	Medium
Prefumo et al [20]	Unselected population	20[a]	No	Low
Schluter and Pritchard [30]	Ne	15–22	No	Medium
Coco et al [35]	Ne	16–23	Yes	Medium
Bottalico et al [21]	High risk	15–22	No	Low
Weisz et al [32]	Ne	15–22	No	Low
Vergani et al [25]	High risk	15–22	No	High
Zhong et al [22]	High risk	15–22	No	High
Shanks et al [33]	Ne	Ne	No	Low
Towner et al [31]	Ne	15–32	No	Medium
Huang et al [36]	Ne	18–22	No	Medium
Sooklim and Manotaya [23]	High risk	16–20	Yes	High
Aagaard-Tillery et al [34]	Unselected population	15–23	No	Low

ne = no evidence.
[a] Average.

Table 2
Meta-analysis of diagnostic studies for ultrasound detection of echogenic intracardiac foci in the second trimester of pregnancy for detection of Down syndrome.

Variable	Value (95% CI)
Sensibility (IC95%)	0.218 (0.196–0.241)
Specificity (IC95%)	0.959 (0.958–0.959)
Positive likelihood ratio (IC95%)	5.08 (4.04–6.41)
Negative likelihood ratio (IC95%)	0.81 (0.75–0.87)
Presence of heterogeneity	Sn/Sp/LR+/LR−
Threshold effect	Yes

95% CI = confidence interval; LR+ = positive likelihood ratio; LR− = negative likelihood ratio; Sn = sensitivity; Sp = specificity.

Table 3
Analysis of subgroups according to different study variables (prior risk for Down syndrome, methodological quality of study, and last week of pregnancy in which ultrasound scan was performed)

		Absence
		Sn/Sp/LR+/LR−
Production risk	High risk	0.212/0.947/4.98/0.81
	Low risk	0.230/0.962/5.25/0.81
Quality	Low	0.186/0.965/5.17/0.85
	Medium/High	0.228/0.952/4.99/0.80
Last week of ultrasound	<24 wk	0.212/0.958/5.27/0.80
	≥24 wk	0.257/0.963/4.71/0.83

LR+ = positive likelihood ratio; LR− = negative likelihood ratio; Sn = sensitivity; Sp = specificity.

concluded that their presence should be interpreted as a possible risk factor for congenital heart defects. However, other authors found that fetal EIF was not associated with heart disease, structural heart defects, or extracardiac anomalies [6,8,9,16,38,42].

The racial distribution of this marker is also controversial. Shipp et al [43] found significant differences in the prevalence of EIF among ethnic groups; their study found that 30.4% of Asian women had a chromosomally normal fetus with an EIF (although there were only 46 Asian fetuses in the study group). Thus, this study suggests that EIF in the Asian population may be less useful in genetic sonogram as in other races as it would be more common in Asian women (30.4%) than in the DS population (18%) [43]. The ethnic variation of this marker has been confirmed in large studies in recent years [44,45]. The study of Rebarber et al [44] focuses only on Japanese patients and has a larger sample (148 vs. 49), finding 14.8% of patients with EIF, without registering any case of DS [44]. Tran et al [45] noted that not only the Asian population (6.9%), but also African-American (6.7%) and Middle East patients (8.1%), were significantly more likely to have an EIF compared with Caucasians (3.3%). Taking ethnicity into account, Caucasian fetuses and Asian-American mothers with EIF still have an increased risk of DS [45]. Shanks et al [33] found an EIF prevalence of 6.9% in Asian patients compared with 3.4% in non-Asians; however, there are not enough cases to calculate the risk of DS in the Asian population with EIF [33]. In the studies included in our meta-analysis, no analysis by ethnicity is possible because these articles do not assess this population characteristic with respect to DS and EIF. Therefore, further studies on this aspect would be advisable.

There is also controversy about the association of EIF findings with chromosomal abnormalities [5,7,8].

In spite of the number of articles about EIFs, only three systematic reviews have been published to date on the diagnostic performance of this ultrasound finding [40,46,47]. We would like to emphasize three issues about our work. First, our work has more articles analyzed than the other published meta-analyses. Second, we have evaluated the quality of included studies according to

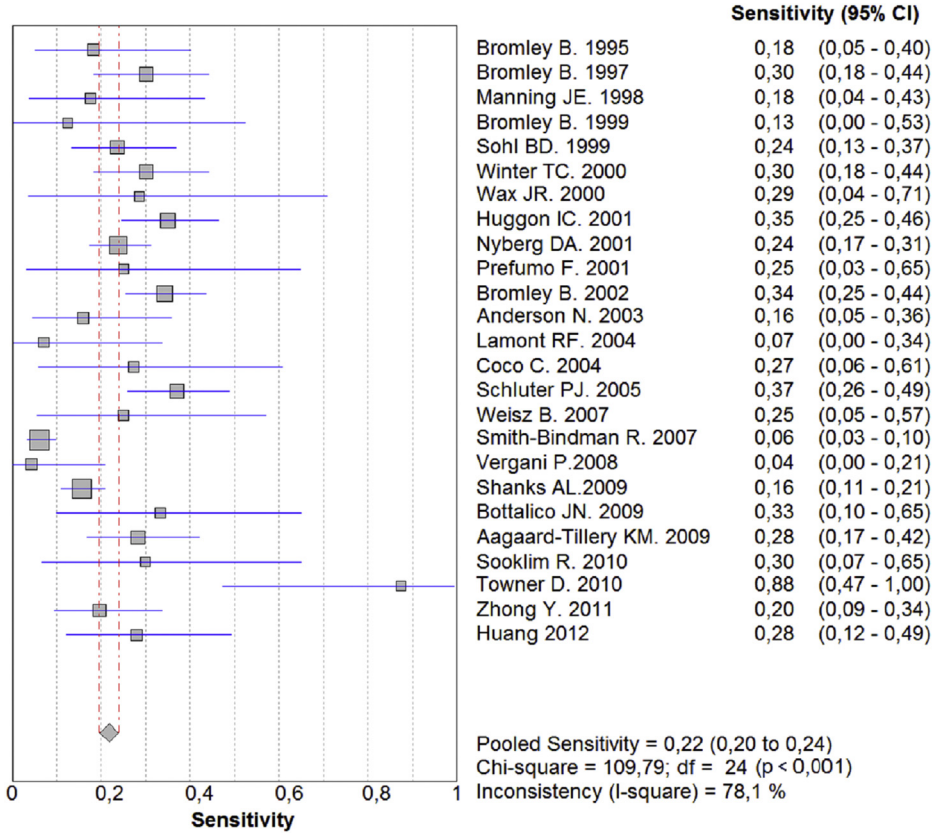

Figure 2. Forest plot of sensitivity for echogenic intracardiac foci for detection of Down syndrome. CI = confidence interval.

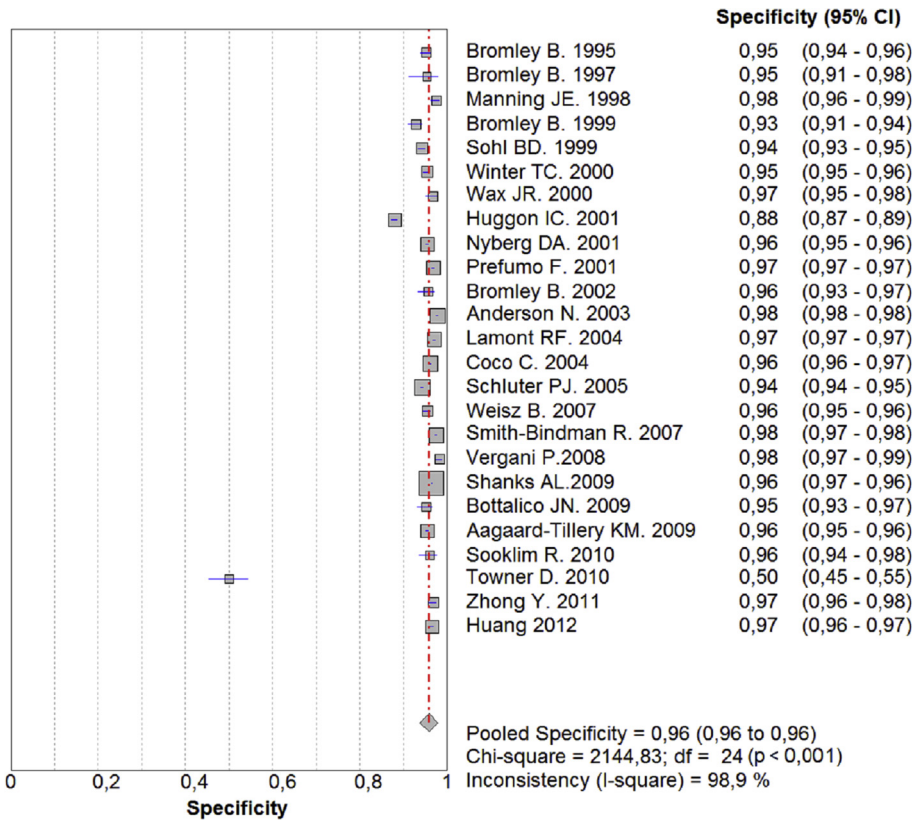

Figure 3. Forest plot of specificity for echogenic intracardiac foci for detection of Down syndrome. CI = confidence interval.

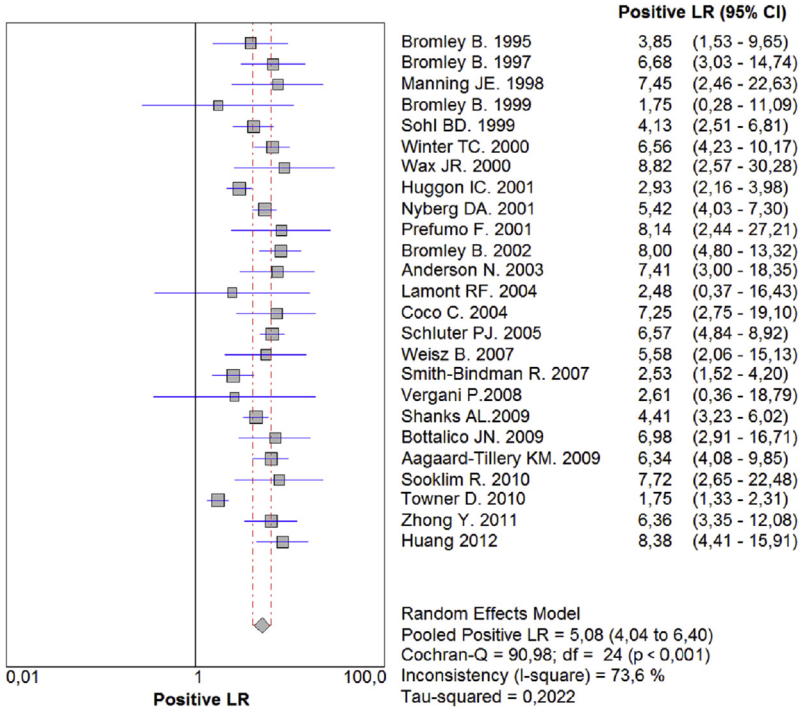

Figure 4. Forest plot of positive likelihood ratio (LR) for echogenic intracardiac foci for detection of Down syndrome.

PRISMA standards for systematic reviews to avoid results bias [12]. Furthermore, this critical reading as well as all data extraction were carried out in duplicate in order to prevent possible errors in calculation and data analysis.

In our meta-analysis (which includes 25 EIF articles without any language restrictions), an overall sensitivity of 21.8% (95% CI, 19.6–24.1%) was obtained with a specificity of 95.9% (95% CI, 95.8–95.9%). This value is higher than that found in the meta-

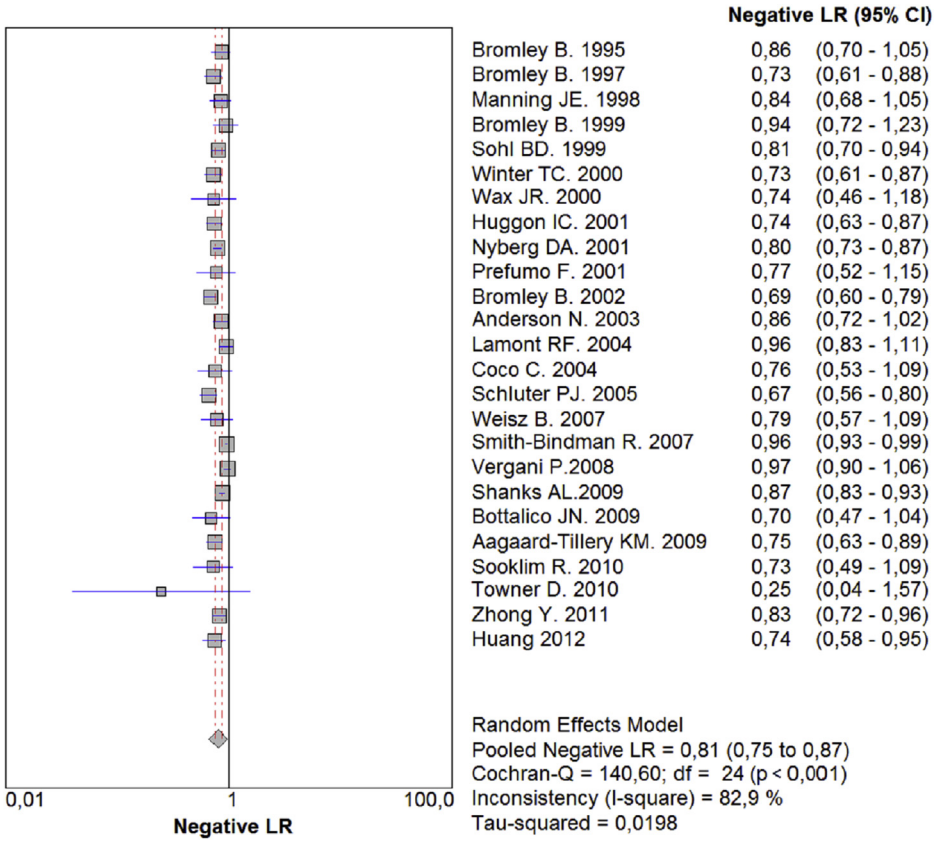

Figure 5. Forest plot of negative likelihood ratio (LR) for echogenic intracardiac foci for detection of Down syndrome.

analysis conducted by Smith-Bindman et al [46] (6 EIF studies restricted to the English language), which showed a sensitivity of 11% (0.06–0.18) and a false positive rate (4%). However sensitivity is similar in two subsequent meta-analysis [40,47]. In 2003 (which included 11 studies in French, English, or German), a detection ratio for EIF of 22% (95% CI, 14–33%) was documented [40], and a subsequent meta-analysis by Agathokleous et al [47] (which includes 14 EIF studies restricted to the English language) reported a sensitivity of 24.4% (95% CI, 20.9–28.2%) [47]; the false positive ratio is similar in all of them (about 4%) [40,47].

Positive LRs of EIF as an isolated finding at different meta-analysis varied between 2.8 [46], 5.4 [40], and 5.82 [47]. The negative LR range from 0.8 (40) to 0.95 [46,47]. Our data are consistent with those observed by Sotiriadis and Makrydimas [40] and Agathokleous et al [47]. If we perform a subgroup analysis in our meta-analysis, the high-risk population (16 studies) shows a sensitivity of 21.2%, which is slightly lower than that found in another meta-analysis [47] that documented a sensitivity of 25.8% (95% CI 19.6–33.1) for high-risk populations (7 studies). The false positive ratio is higher in our meta-analysis (5.3% vs. 3.9% [47]). When studying low-risk populations, the DS sensitivity is very similar to that obtained in our study (23% vs. 25.8% [47]) as well as the false positive ratio (3.8% vs. 3.7% [47]). This could be attributable to the slightly subjective character that the measurement of this marker has.

The EIF sensitivity is higher in studies of medium/high quality, although not a statistically significant level; the false positive ratio is also higher. This may be attributable to a greater selection of the population, as well as ultrasound studies being performed by more trained professionals.

In evaluating the studies according to gestational age, those studying fetuses during later gestational ages are more sensitive and specific. This could be attributed to increased heart sizes and possible enlargement of the focus with gestational age as well as the persistence of EIF display during pregnancy.

In the literature, the persistence of EIF in the ultrasound scans ranges from 25% to 92.3% [8,36]. In 36% of cases, the focus increased in size (but in none of these cases did it exceed 6 mm) and decreased in 12%, whereas 51% remained unchanged [6].

Only two studies (8%) [23,35] assessed interobserver agreement. In order to properly assess the validity of an observer dependent variable, such as ultrasound markers, not only interobserver assessment is very important but also intraobserver variability. This is an important consideration when designing new studies in order to be able to validate the results obtained.

For all of these reasons, EIFs as an isolated marker could be a tool to identify—rather than rule out—the high-risk group of DS; however, it should be noted that it exhibits a low sensitivity.

Conflicts of interest

We declare that we have no conflict of interest.

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