Diagnostic performance of intracardiac echogenic foci for Down syndrome: a meta-analysis
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CRD summary
This review assessed the diagnostic performance of intracardiac echogenic foci, and evaluated whether they could be used in prenatal screening for trisomy 21. The authors concluded that the presence of these foci increases the risk of Down syndrome by five to seven times. However, since the quality of the primary studies was not assessed, these conclusions should be viewed with caution.

Authors’ objectives
To assess the diagnostic performance of intracardiac echogenic foci, and to evaluate whether they have a role in prenatal screening for trisomy 21.

Searching
MEDLINE and EMBASE were searched from 1985 to August 2002 using the keywords 'intracardiac (echogenic) focus/foci', 'golfballs', 'trisomy 21' and 'Down syndrome' with explode terms. The bibliographies of retrieved articles were also screened for additional references. Studies written in English, French and German were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
Prospective, retrospective and case-control studies were eligible for inclusion. In order for a study to be eligible for inclusion, it was also necessary that the foetal karyotype was unknown at the time of the diagnostic test, to avoid diagnosis bias.

Specific interventions included in the review
Studies on intracardiac echogenic foci were eligible. Single and multiple intracardiac echogenic foci were included in the review, regardless of cardiac location.

Reference standard test against which the new test was compared
Studies had to confirm the chromosomal status of the foetuses by either karyotype (considered the 'gold' standard) or by postnatal clinical examination.

Participants included in the review
Trials that included any pregnant women were included in the review, although no inclusion criteria relating to the participants were defined. Also included were women that had other sonographic findings (termed 'combined' settings) and studies that included pregnant women without any other sonographic findings (termed 'isolated' settings).

Outcomes assessed in the review
Studies that presented 2x2 tables, or provided sufficient detail for their construction, were eligible for inclusion. The primary outcome measures were the sensitivity and specificity of intracardiac echogenic foci in diagnosing trisomy 21 in the 'combined', 'isolated', or 'all' settings.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors stated that they extracted data on the potential verification bias in each study, although it was unclear on what criteria this was assessed. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
Data extraction
Two reviewers independently extracted the data, with a third reviewer resolving any disagreements. The primary investigators of the studies were contacted if further clarification of the data was required. Data were extracted on the study population, age of pregnancy, inclusion and exclusion criteria, study design, outcome assessment and potential verification bias. The authors constructed 2x2 tables for each included study, with separate tables for the 'combined' and 'isolated' settings where possible.

Methods of synthesis
How were the studies combined?
Pooled estimates of diagnostic accuracy were calculated for women with other ultrasound findings (termed 'combined'; 27,730 foetuses) and no other ultrasound findings (termed 'isolated'; 39,360 foetuses). Furthermore, data from the 'combined' settings were included with data from the 'isolated' settings where no combined data were available, termed 'all' (51,831 foetuses). The pooled sensitivities and specificities were estimated using both fixed-effect (weighted by the inverse of the variance) and random-effects models. A summary receiver operating characteristic curve for 'all' data was also presented. Pooled estimates of the sensitivity and specificity were used to determine a typical positive likelihood ratio (LR) and negative LR for 'combined', 'isolated' and 'all' settings. These likelihoods were then considered as risk ratios and compared between settings.

How were differences between studies investigated?
Heterogeneity was assessed using Fisher's exact test, and the results of both fixed-effect and random-effects models were presented. Sensitivity analyses were also performed by excluding studies where karyotyping (the gold standard) had not been performed in all cases; studies that were conducted in the first trimester; and studies in which the cohort had an overall risk of Down syndrome of less than 1:1,000.

Results of the review
The authors stated that 11 studies were eligible for inclusion in the review. However, owing to a partial overlap between a single-centre and a multicentre study, the results from 12 studies were reported. There were 7 prospective cohort studies (40,053 participants), 3 retrospective cohort studies (12,690 participants) and 2 case-control studies (9,140 participants).

When using a random-effects model, the pooled sensitivity and specificity were 0.29 (95% confidence interval, CI: 0.19, 0.35) and 0.963 (95% CI: 0.937, 0.979), respectively, in the 'combined' settings and 0.22 (95% CI: 0.14, 0.35) and 0.959 (95% CI: 0.910, 0.982) in the 'isolated' settings. The use of a fixed-effect model did not appear to change the results significantly. There was no significant difference in performance between the 'combined' and 'isolated' settings. The sensitivity and specificity for 'all' findings were similar to the 'combined' findings.

Based on the random-effects summary estimates, the positive LRs were 7.0, 5.4 and 6.2 for the 'combined', 'isolated' and 'all' settings, respectively; the negative LRs were 0.77, 0.81 and 0.77, respectively. There was significant heterogeneity between the positive LRs (P<0.01). The sensitivity analyses performed did not affect the summary results significantly. The prevalence of Down syndrome in the populations of the primary studies ranged from 1 in 50 to 1 in 2,698.

Authors' conclusions
The presence of intracardiac echogenic foci increases the risk of Down syndrome by five to seven times. This information should be used in conjunction with a woman's background risk when considering an amniocentesis.

CRD commentary
This review addressed an explicit research question, although the populations studied were very diverse in terms of the background risk for Down syndrome. By including studies in languages other than English the authors attempted to reduce language bias. However, even though bibliographies were screened, only two electronic databases were searched.
and there was no attempt to search for unpublished studies, thus some studies might have been missed and the potential for publication bias remains. The assessment of the quality of the primary studies was very limited and the results were not reported. It is therefore not possible to assess the potential impact of methodological flaws in the primary studies on the results of the review.

Adequate details of the individual studies were reported, but more studies were reported than the authors stated were included in the review. The statistical methods used appear to have been appropriate but, because of the low prevalence of Down syndrome in some of the included studies, the individual study estimates of sensitivity and specificity may not be robust. The authors’ conclusions should therefore be viewed with caution.

**Implications of the review for practice and research**
Practice: The authors stated that information on the presence of intracardiac echogenic foci should be used in conjunction with background risk when considering an amniocentesis.

Research: The authors stated that meta-analyses of moderately large studies may provide guidance on the best use of sonographic markers, whether in 'isolated' or 'combined' settings.

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