Systematic review and meta-analysis of the test accuracy of ductus venosus Doppler to predict compromise of fetal/neonatal wellbeing in high risk pregnancies with placental insufficiency

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CRD summary
This review concluded that abnormal ductus venosus Doppler was moderately predictive of compromised foetal or neonatal well-being and of perinatal mortality, in high-risk pregnancies with placental insufficiency. Between-study heterogeneity and some weaknesses in the review methods and reporting mean that these conclusions should be interpreted cautiously.

Authors' objectives
To assess the accuracy of ductus venosus Doppler for the prediction of compromise of foetal or neonatal well-being.

Searching
MEDLINE, EMBASE, the Cochrane Library, and Medion were searched for articles from their inception to May 2009. Search terms were described, and methodological filters were included for the identification of test accuracy studies. The bibliographies of included studies and review articles were screened for additional studies. No language restrictions were applied.

Study selection
Studies that used ductus venosus Doppler to predict any compromise of foetal or neonatal well-being in the second or third trimester of pregnancy, with any level of risk and in any health care setting, were eligible for inclusion. The outcome measures were those reported by the study authors, and included studies were required to report sufficient data to determine the numbers of true-positive, false-negative, false-positive and true-negative results. Studies with fewer than 10 participants were excluded.

Two reviewers independently assessed studies for inclusion and disagreements were resolved by consensus or arbitration of a third reviewer.

The included studies were of Doppler performed within two weeks of delivery, with gestational age ranging from 20 to 41 weeks; 11 studies were of pre-term (less than 37 weeks) births only. All studies were performed in high-risk populations, defined by suspected placental insufficiency. Most of the studies reported exclusively on singleton pregnancies and excluded foetuses with chromosomal or structural anomalies. The reference standard for foetal compromise varied across studies and all included multiple assessments and outcomes.

Assessment of study quality
The included studies were assessed for methodological and reporting quality by at least one reviewer. Methodological quality was defined as the confidence that the study design, conduct, and analysis minimised bias in addressing the research question. The criteria were a prospective design with consecutive or random recruitment, full verification of the test result with an outcome measure (for over 90% of patients), adequate description of the population (level of obstetric risk given in the methods) and index test, and the use of an appropriate outcome measure. The results of a quality assessment using Quality Assessment of Diagnostic Accuracy Studies (QUADAS) criteria were reported.

Data extraction
The data were extracted for the numbers of true-positive, false-negative, false-positive, and true-negative results. These data were used to calculate the sensitivity and specificity, and positive and negative likelihood ratios, with 95% confidence intervals. Where two-by-two tables contained cells with zero, 0.5 was added to every cell to enable calculations.

The authors did not state how many reviewers extracted the data.
Methods of synthesis
A bivariate meta-regression model was used to calculate the pooled estimates of sensitivity and specificity, with their 95% confidence intervals, and to fit the summary receiver operating characteristic (ROC) curves. Pooled estimates or positive and negative likelihood ratios were presented. The results were pooled for groups of studies with similar populations and the same outcome measure for compromise of well-being. To maximise data in the meta-analysis, a composite outcome measure of adverse perinatal outcome was used.

Heterogeneity was assessed visually using ROC space and forest plots and statistically using the $\chi^2$ test. Subgroup analyses for the method of performing ductus venosus Doppler, whether babies with chromosomal anomalies or multiple pregnancies were excluded from the results, and the quality of the study, were performed where there were at least three studies in a group. The possibility of publication and related bias was explored using funnel plots of the log diagnostic odds ratio versus the inverse of variance.

Results of the review
Eighteen studies, reporting on 2,267 pregnancies, with 75 data sets, were included in the review. There were 16 cohort studies and two cross-sectional studies. Eight studies reported prospective patient recruitment, one of which was consecutive, four were retrospective, and six were unclear. Quality assessment showed that 11 studies provided an adequate description of the performance of the index test and one that of the outcome measure. Blinding of outcome assessors was poorly reported. Verification bias was minimal as more than 90% of participants progressed to the reference standard.

An abnormal ductus venosus waveform on the Doppler ultrasound predicted adverse perinatal outcome with a pooled positive likelihood ratio of 3.15 (95% CI 2.19 to 4.54) and negative likelihood ratio of 0.49 (95% CI 0.40 to 0.59; 14 studies). The pooled estimate of sensitivity was 0.61 (95% CI 0.50 to 0.70) and of specificity was 0.81 (95% CI 0.70 to 0.88). There was significant statistical heterogeneity. Subgroup analyses for the exclusion of congenital abnormalities, the exclusion of multiple pregnancies, and the Doppler ultrasound method, produced similar results.

Doppler ultrasound was most accurate for the prediction of perinatal mortality, with a positive likelihood ratio 4.21 (95% CI 1.98 to 8.96) and a negative likelihood ratio of 0.43 (95% CI 0.30 to 0.61; five studies). The results were reported for the prediction of acidaemia, Apgar score of less than seven at five minutes, and for all subgroup analyses. The subgroup analysis for study quality could not be performed as there were too few high-quality studies.

Funnel plots showed asymmetry, but were symmetric when subgrouped by outcome, suggesting that the asymmetry was due to heterogeneity in the combined reference standard rather than publication bias.

Authors’ conclusions
Abnormal ductus venosus Doppler showed moderate predictive accuracy for compromise of foetal or neonatal well-being and for perinatal mortality, in high-risk pregnancies with placental insufficiency.

CRD commentary
The review provided a clearly stated aim and defined appropriate inclusion criteria. A number of sources were searched for relevant studies, without language restrictions, and the potential for publication bias was assessed and considered to be unlikely. The study selection process included measures to minimise error and bias, but it was unclear whether similar methods were applied to data extraction and quality assessment. Some aspects of methodological quality were assessed and the findings were included in the interpretation of the results. Appropriate meta-analytic methods were applied and the authors acknowledged the limitations of their study, particularly the residual heterogeneity after subgroup analyses.

The authors conclusions reflected the data presented, but should be interpreted cautiously, given the limitations of the data and some weaknesses in the review methods and reporting.
Implications of the review for practice and research

**Practice:** The authors stated that their review suggested that ductus venosus Doppler was a useful test in the management of a pregnancy at high risk of foetal or neonatal compromise.

**Research:** The authors stated that further prospective research should address the limitations identified in this review; including suitable populations, the use of appropriate well-defined outcome measures, and the use of tests in combination and how they interact in the individual patient. They stated that a randomised controlled trial (Trial of Umbilical and Fetal Flow in Europe, TRUFFLE) was recruiting to determine the use of ductus venosus Doppler in the timing of delivery of pre-term growth-restricted infants and to determine the most appropriate threshold to ensure that delivery is timed to minimise not only mortality, but also neurological morbidity. The need for such a threshold should be considered in future systematic reviews of the test accuracy.

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