Noninvasive fetal RhCE genotyping from maternal blood

CRD summary
The review evaluated fetal RhCE genotyping using maternal blood and found overall accuracy was 96.3% for RhC/c and 98.2% for RhE/e; free fetal DNA in maternal plasma provided the best source. The conclusion that more research was needed before non-invasive testing could replace current methods was appropriate given the paucity of data and weaknesses of the review.

Authors' objectives
To estimate the accuracy of foetal RhCE (Rhesus Blood Group, CcEe Antigens) genotyping using peripheral maternal blood and to compare the results of genotyping when foetal cells and free foetal DNA (FfDNA) were used.

Searching
PubMed, CINAHL, The Cochrane Library, ACP Journal Club and OCLC were searched to 2007; some search terms were reported. Conference abstracts and the bibliographies of retrieved articles were searched for additional studies.

Study selection
Studies that described foetal RhC/c or foetal RhE/e determination using maternal blood, plasma or serum and confirmation of fetus/newborn RhC/c or RhE/e status were eligible for inclusion. Studies were included regardless of the alloimmunisation status of pregnant participants. Abstracts and studies not published in English were excluded. Included studies used a number of different genotyping protocols and reported data for samples taken during the first, second and third trimesters.

The authors stated neither how studies were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed the validity of included studies. They stated that articles were reviewed against the standards for reporting studies of diagnostic accuracy (STARD) guidelines, but no further details were provided.

Data extraction
Testing protocols and the rate of correct identification (total correct tests/total tests) were extracted for each study/data set using standardized data collection forms developed a priori.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Summary estimates of diagnostic accuracy, with 95% confidence intervals (CIs), were calculated using a random-effects model weighted by sample size. Separate estimates were calculated for RhC/c and RhE/e determination. Subgroup diagnostic accuracies were calculated for each trimester (from studies which reported gestational age at testing) and for source of fetal DNA (fetal cells or FfDNA).

Results of the review
Six studies were included in the review. They reported a total 20 protocols for fetal RhC/c (seven protocols) and fetal RhE/e (13 protocols) determination. For RhC/c, there was a total of 176 samples from 125 women; for RhE/e there was a total of 193 samples from 123 women.

The combined accuracy for RhC/c determination was 96.3% (95% CI 80 to 100). Combined accuracy for RhE/e was 98.2% (95% CI 91.4 to 100). FfDNA obtained from maternal plasma and amplified was consistently the best source of fetal DNA (100% accuracy for both RhC/c and RhE/e determination). Accuracy varied with gestational age when fetal
cells were used. No significant differences were noted when FfDNA was used.

**Authors' conclusions**

Further studies were needed before prenatal determination of fetal RhC/c or RhE/e genotypes from maternal blood could safely replace methods used at the time of the review.

**CRD commentary**

The review stated a clear research objective and the inclusion criteria reported were appropriately broad. The search strategy examined a number of sources for relevant studies, but the restriction to published English-language studies left open the possibility of language and publication biases. The review process was poorly reported and it was unclear whether measures were taken to minimise error and/or bias in the review process. The authors stated that they assessed included studies against the STARD reporting guidelines for diagnostic accuracy studies, but reported only that study authors did not always follow these guidelines; the potential impact of the quality of included studies upon the results of the review was, therefore, unclear. The included studies were small in size and used a wide range of different protocols, so generation of pooled accuracy estimates using a simple random-effects model was of questionable value. The authors' conclusion that more research was needed was appropriate given the paucity of data and the weaknesses of the review.

**Implications of the review for practice and research**

**Practice:** The authors did not specify any recommendations for practice.

**Research:** The authors stated that a large-scale study of fetal Rh genotyping from maternal blood was needed.

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