High-throughput non-invasive prenatal testing for fetal rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen: a systematic review and economic evaluation

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Declared competing interests of authors: none

Published March 2018
DOI: 10.3310/hta22130

Scientific summary

Non-invasive fetal RhD status testing in RhD-negative women

Health Technology Assessment 2018; Vol. 22: No. 13
DOI: 10.3310/hta22130

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Approximately 17% of women giving birth in England and Wales are rhesus blood group (D antigen) (RhD) negative. Pregnant women who have RhD-negative blood type may carry a RhD-positive fetus. The entry of fetal RhD-positive cells into the maternal circulation can cause a mother who is RhD negative to produce anti-D antibodies against the RhD antigen. This process, called sensitisation, can happen at any time during pregnancy, although it is most common in the third trimester and during childbirth.

In a subsequent pregnancy with a RhD-positive fetus in women who have been sensitised, the woman's anti-D antibodies may respond to the presence of RhD-positive blood in the fetus, which may result in haemolytic disease of the fetus and newborn infant. Prophylaxis with anti-RhD immunoglobulin can substantially reduce the risk of sensitisation in RhD-negative women and the prevalence of haemolytic disease of the fetus and newborn infant.

High-throughput non-invasive prenatal testing (NIPT) for fetal RhD status may enable anti-D immunoglobulin to be withheld from RhD-negative women who are carrying a RhD-negative fetus. These women could avoid unnecessary treatment with routine anti-D immunoglobulin, as well as the potential risk associated with the administration of blood products, although this may also lead to an increased risk of RhD sensitisations. In addition, these women may not need the provision of anti-D immunoglobulin following potentially sensitising events and there may no longer be a need for serological cord testing at birth. However, the clinical effectiveness and cost-effectiveness of high-throughput NIPT for fetal rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen for the NHS is uncertain.

Objectives

This assessment aims to evaluate both the clinical effectiveness and cost-effectiveness of using high-throughput NIPT to identify fetal rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen and any consequent changes in treatment management.

Methods

Assessment of clinical effectiveness

Three systematic reviews were conducted. A range of bibliographic sources, including MEDLINE and EMBASE, were searched from inception to February 2016 for published and unpublished literature.

For diagnostic accuracy outcomes, we included prospective cohort studies reporting absolute numbers, which allowed for the calculation of diagnostic accuracy. For clinical effectiveness outcomes, we included any study in which high-throughput NIPT was used, in which anti-D prophylaxis was given as required and that reported relevant clinical outcomes. For implementation outcomes, we considered all publications reporting issues related to the implementation of, or practical advice relating to, high-throughput NIPT.

For all reviews, the eligible population were pregnant women who were RhD negative and not known to be sensitised to RhD antigen. The index test was high-throughput NIPT free-cell fetal deoxyribonucleic acid tests of maternal plasma used to determine fetal RhD status. The reference standard was serological cord blood testing at birth or any other suitable postnatal blood test of the infant.

Two researchers independently screened the titles and abstracts of all reports identified by the search strategy and full-text papers were subsequently obtained for assessment. Data extraction and quality assessment were undertaken by one researcher and checked by a second. The risk of bias of diagnostic accuracy studies was assessed using a modified Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist.

For diagnostic accuracy outcomes, bivariate models were fitted to calculate summary estimates of false-positive rates (FPRs) and false-negative rates (FNRs) with 95% confidence intervals (CIs).

For clinical effectiveness outcomes, data including sensitisation, NIPT uptake, anti-D prophylaxis uptake, reduction in anti-D use and adverse events were synthesised narratively. For the review of implementation studies, the following data were synthesised narratively: study findings, issues for implementation, practical guidance and recommendations for research. In addition, we performed a simulation study to simulate possible clinical outcomes of high-throughput NIPT in the UK based on results from the diagnostic accuracy review and existing reviews of antenatal anti-D prophylaxis.

Assessment of cost-effectiveness

A range of bibliographic databases were searched to identify relevant cost-effectiveness evidence. Citation searches were also undertaken. Only full economic evaluations were considered for review. Characteristics from the review findings were extracted and critically appraised using a published checklist. Studies were assessed with respect to the way in which NIPT was assumed to have an impact on the care pathway.

A de novo decision-analytic model using a decision tree cohort approach was developed to estimate, based on best available data, the costs and health outcomes. Four scenarios were designed to evaluate different impacts of NIPT on the existing postpartum care pathway. These evaluated how NIPT could impact on the use of cord serology, fetal–maternal haemorrhage (FMH) tests and anti-D immunoglobulin following delivery. First and subsequent pregnancies, together with the long-term consequences of sensitisations, in terms of costs and utilities, are evaluated within the model, with a yearly cycle and a lifetime horizon. The main outcomes of interest within the model were the total lifetime costs and total lifetime quality-adjusted life-years (QALYs) for each of the alternative pathways. The decision model was populated using the results from the systematic clinical review on the diagnostic accuracy of high-throughput NIPT. Various assumptions were based on the previous independent economic evaluation developed for NICE technology appraisal (TA) 156 on routine antenatal anti-D prophylaxis (RAADP). Primary model results are the total expected costs and expected QALYs for each alternative strategy. Population net health benefits are used to summarise the cost-effectiveness results in addition to the cost-effectiveness ratio. Uncertainty regarding the appropriate source of data, the appropriate assumptions or model structure and other scenarios are explored using one-way and two-way sensitivity analyses (SAs).

Results

Diagnostic accuracy

Eight studies were included in the diagnostic review of high-throughput NIPT, which were conducted in five European countries. There were three high-quality studies in which NIPT was performed by the NHS Blood and Transplant International Blood Group Reference Laboratory (Bristol, UK). The reference standard in all studies was cord blood serology at birth. The majority of included studies were judged as having a low risk of bias, but two studies were judged as having a high risk of bias.

Meta-analyses included women mostly at or post 11 weeks' gestation and showed very high diagnostic accuracy of high-throughput NIPT. In the primary analyses, in which women with inconclusive test results were treated as having tested positive, the pooled FNR (i.e. women at risk of sensitisation) was 0.34% (95% CI 0.15% to 0.76%) and the pooled FPR (i.e. women receiving anti-D unnecessarily) was 3.86% (95% CI 2.54% to 5.82%). SAs did not materially alter the overall result.

The diagnostic accuracy performance of high-throughput NIPT varied by gestational age. The data suggest that high-throughput NIPT was less accurate before around 11 weeks' gestation (i.e. in first trimester), but diagnostic accuracy was consistent at any time after 11 weeks' gestation. We were unable to conduct a subgroup analysis based on ethnicity because of a lack of relevant data from included studies.

Clinical effectiveness

Seven studies were included in the clinical effectiveness review. All studies were judged as having a high risk of bias. One large cohort study reported that implementation of NIPT for targeted antenatal anti-D prophylaxis was associated with a significant risk reduction in sensitisation (adjusted odds ratio 0.41, 95% CI 0.22 to 0.87) compared with historical controls.

Three non-comparative studies reported on the reduction in administration of anti-D. All suggested that anti-D administration was largely avoided in women with a RhD-negative fetus.

The compliance rate with antenatal anti-D prophylaxis ranged from 86% to 96.1% (four studies) and compliance rates with postpartum anti-D ranged from 92% to 99.7% (three studies) in women who undertook NIPT and received a positive result. High-throughput NIPT uptake rates ranged from 70% to > 95% (seven studies). None of the included studies reported data on adverse events associated with NIPT.

The results from the simulation study suggested that use of NIPT to determine antenatal anti-D use would substantially reduce the number of women receiving anti-D unnecessarily, from 38.9% to 5.7%, consistent with evidence identified by the review. The use of NIPT would cause an extra three sensitisations per 100,000 women if cord blood testing is continued (at least in women with a negative NIPT result) as the basis for administering postpartum anti-D. If cord blood testing is withdrawn (except for women who did not receive NIPT or who had an inconclusive test result) and NIPT is used to decide on postpartum anti-D administration, then there would be an extra 13 sensitisations per 100,000 women. These additional sensitisations are few compared with the underlying rate of sensitisation with antenatal anti-D (280 per 100,000 women). These results suggest that cord blood testing could potentially be withdrawn and NIPT results (if available and conclusive) may be used to prescribe postpartum anti-D. This conclusion will depend partly on whether or not the 10 extra sensitisations per 100,000 RhD-negative women caused by withdrawing cord blood testing can be considered an ethically acceptable increase.

Evidence on implementation

Twelve studies were included in the review of implementation. Most of the included studies were large cohort studies reporting implementation data alongside diagnostic accuracy data, although one study was a survey based in the UK (London). All the cohort studies suggested that high-throughput RhD genotyping of fetuses in all RhD-negative women was feasible. Key issues of implementation included ensuring anti-D prophylaxis compliance, the effective management of transporting samples and greater knowledge of NIPT among physicians, midwives and pregnant women.

Cost-effectiveness

The de novo health economic model suggested that high-throughput NIPT appears cost saving but also less effective than current practice, irrespective of the postpartum scenario evaluated. However, the magnitude of the potential cost savings appeared sufficient to outweigh the small increase in sensitisations and the associated small QALY loss when using NIPT compared with current practice. Based on a cross-section of 100,000 pregnancies, the probable magnitude of cost savings ranged between £485,000 and £671,000 across the separate postpartum strategies. In the base-case analysis, the strategy in which the NIPT result is used to guide RAADP only (i.e. all women continue to receive cord serology with FMH and postpartum anti-D immunoglobulin) had the highest probability of being cost-effective.

The magnitude of the cost saving appeared highly sensitive to the cost of NIPT itself to the NHS, which comprises the base unit cost per test, the level of any royalty fee and any increase in antenatal care costs

required to accommodate an additional test. A small increase in the cost assumed of (confidential information has been removed) or more per test would alter these conclusions.

Our findings indicate that the timing of the test does not appear influential in determining the cost-effectiveness results, either in terms of diagnostic accuracy or in terms of the extent of management costs for potentially sensitising events that can be avoided. Another important consideration is the rate of high-throughput NIPT inconclusive results. Our findings demonstrate that even with a high-throughput NIPT inconclusive result rate of close to 15%, the introduction of NIPT appears to compare favourably with current practice.

Discussion

Limitations and uncertainties

Few studies reporting clinical effectiveness data of using high-throughput NIPT to detect fetal RhD status in RhD-negative women were identified. Results of the simulation study are sensitive to the parameters used and should be considered speculative.

Owing to the limited evidence, the potential clinical impact of high-throughput NIPT on the care pathway remains unclear. No studies compared NIPT with universal administration of RAADP. No studies were identified reporting comparative data relating to patient-related outcomes, such as quality of life or anxiety. Whether or not the diagnostic performance of high-throughput NIPT differs between different ethnic groups remains unclear.

There remains uncertainty regarding the cost of introducing the high-throughput NIPT, as the unit cost will potentially vary with throughput and may be subject to an additional royalty fee.

Generalisability of the findings

Diagnostic data from three UK (Bristol) studies are mostly generalisable to the UK setting. Differences in high-throughput NIPT devices and in antenatal care within different countries mean that the generalisability of the findings from those non-UK studies to the UK setting is likely to be limited, particularly for the reviews of clinical effectiveness and implementation studies. Owing to a lack of UK-based evidence, the generalisability of studies reporting compliance rates to antenatal anti-D treatment to the UK setting remains uncertain. As most participants in included studies were white Europeans, the generalisability of these findings to a non-white population also remains uncertain.

Conclusions

Implications for service provision

High-throughput NIPT is highly accurate for the detection of fetal rhesus D status in RhD-negative women, if performed after 11 weeks' gestation. Only 1% of women will have an incorrect test result (nearly all false positives) and around 7% will have an inconclusive result.

The use of NIPT can largely remove unnecessary exposure to prophylactic anti-D treatment, without substantially altering the rate of sensitisations. However, there will be a small number of women (about 0.1%) with a false-negative test result who are put at increased risk of sensitisation because they do not receive antenatal anti-D prophylaxis. This risk is unlikely to be substantially increased if postnatal cord blood testing is withdrawn. The test could be administered at any time after the first trimester without adversely affecting accuracy. Achieving high compliance rates may be important for the success of using NIPT, particularly through ensuring high compliance with NIPT and continuing to offer antenatal anti-D to women who refuse, or miss, NIPT.

Cost-effectiveness

Targeted provision of anti-D immunoglobulin prophylaxis through the use of high-throughput NIPT prophylaxis is estimated to be cost saving compared with the current practice of providing prophylactic prenatal anti-D immunoglobulin to all women who are RhD negative. A postpartum strategy that distinguishes between inconclusive results and positive results offers the greatest cost savings. The potential savings appear highly sensitive to the cost of NIPT.

Suggested research priorities

Evidence on the diagnostic accuracy of NIPT in women of non-white ethnicity is needed, for which large prospective cohort studies collecting diagnostic accuracy data will be required. This is of particular concern, as non-white women may be more likely to have inconclusive test results.

Further evidence on the clinical impact of NIPT is needed. If it is implemented, appropriate auditing of NIPT and anti-D administration processes should be considered, recording clinical outcomes, such as sensitisation rates, NIPT and anti-D compliance, and quality of life.

Further clarifications over the potential additional costs for blood drawing, the transportation of samples and antenatal care visits to administer the test and deliver counselling and results are needed.

Further research to comprehensively appreciate the full impact of sensitisations on mothers and children is warranted.

Study registration

This study is registered as PROSPERO CRD42015029497.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

NICE TAR and DAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was commissioned and funded by the HTA programme on behalf of NICE as project number 15/17/02. The protocol was agreed in January 2016. The assessment report began editorial review in June 2016 and was accepted for publication in February 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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