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SUMMARY WITH CRITICAL APPRAISAL

Non-invasive fetal RHD genotyping: A Rapid Qualitative Review

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Abbreviations

HDFN	hemolytic disease of the fetus and newborn
NIPT	non-invasive prenatal test
RhD	rhesus blood group, D antigen
RhIG	Rh immunoglobulin

Context and Policy Issues

Non-invasive fetal RhD blood group genotyping, also known as fetal RhD genotyping, is meant to identify Rh compatibility between pregnant persons and their fetus. It offers the potential to avoid unnecessary prenatal treatment or other invasive forms of fetal blood group identification.

Rh blood group incompatibility occurs most often when a pregnant person's blood type is RhD negative (RhD-) (i.e., lacks the Rh protein on their red blood cells) and the fetus' blood type is RhD positive (RhD+). Alloimmunization may occur in Rh incompatible pregnancies when a sufficient amount of the fetus' RhD+ red blood cells cross into the maternal RhD- blood stream during or after childbirth. Alloimmunization is the development of maternal anti-D antibodies as an immune response to the presence of the fetal blood's foreign antigens. Once these antibodies have been produced in an Rh incompatible pregnancy, the person and pregnancy are referred to as alloimmunized. While alloimmunization during pregnancy rarely affects the first pregnancy, in subsequent pregnancies the antibodies can pass through the placenta to the fetus, which risks causing hemolysis and hemolytic disease of the fetus and newborn (HDFN).

When a pregnant person's blood type is RhD-, during their first pregnancy they are given prophylactic injections of anti-D Rh-immunoglobulin (RhIG). These injections help prevent alloimmunization and decrease the subsequent risk of developing HDFN (of varying severity). This prophylaxis is given to all RhD- pregnant persons because current standard of care (i.e., routine blood work during pregnancy) is unable to determine the fetus' RhD status prior to birth. While there are no documented adverse effects of prophylaxis administration in Canada, it is important to note that as a blood product there is always a risk of transmitting infection. Further, as the availability of RhIG is based on the current blood supply (and therefore donations), some healthcare providers have indicated concern regarding its ongoing availability for the RhD- population and advocate thoughtful resource stewardship.

Research Questions

1. What is the meaning and impact of noninvasive fetal RhD blood group genotyping for pregnant people, and their health care providers?
2. What are pregnant peoples', and their health care providers', expectations of noninvasive fetal RhD blood group genotyping, and the results of such tests?
3. How do patients and clinicians make decisions related to noninvasive fetal RhD blood group genotyping, and how do they make decisions based on the results?
4. How does the option, or not, of noninvasive fetal RhD blood group genotyping help to shape pregnant peoples' and their health care providers' experiences and perceptions of pregnancy and its care?

Key Findings

- Pregnant people and health care providers find fetal RhD genotyping beneficial and feel it should be offered to all RhD negative pregnant persons.
- While fetal RhD genotyping is considered beneficial, there is residual concern around the identification of false negatives leading some people to prefer to receive anti-D immunoglobulin despite their test result.
- Pregnant people often experience information overload throughout pregnancy and appreciate when information on fetal RhD genotyping can be taken home in the form of informational pamphlets.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline via OVID, CINAHL via EBSCO, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to qualitative studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 1997 and April 3, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and the full-text of potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Inclusion Criteria

Population	People with any type of serologically confirmed RhD negative pregnancies (i.e. alloimmunized and nonalloimmunized; singleton or multiple pregnancy). Health care providers who use the test or consult people on the use of the test or test results.
Intervention	Noninvasive prenatal RhD genotyping with cell-free fetal DNA in maternal blood (laboratory-developed tests or commercial test kits)
Context	Any
Outcomes	Issues emerging from the literature that relate to the research questions, including but not limited to perspectives on and experiences with (unnecessary) RhIG treatment and monitoring, and the potential to avoid the same; perspectives on risk of alloimmunization; awareness of Rh (in)compatibility; trust in test results; experiences with testing and test results; experiences with negative test results (i.e. RhD positive) and resultant standard monitoring; experiences with positive test results (i.e. RhD negative) and intensive monitoring; perspectives on and experiences with RhIG treatment, including in a "treat all" strategy; relationship between understanding of RhIG as a blood product, and related perspectives and experiences. Where possible, differences were explored between people of different backgrounds (e.g., Caucasians, black-Africans, etc.), as prevalence of RhD negative status varies by ethnicity, and by different geographies (i.e., urban, rural, remote), as perspectives may vary depending on proximity to care for treatment and monitoring.
Study Designs	Primary qualitative studies, mixed-methods (only qualitative portion), qualitative evidence syntheses

RhD = rhesus blood group, D antigen; RhIG = Rh immunoglobulin

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or they were duplicate publications.

Critical Appraisal of Individual Studies

One reviewer assessed the quality of the included publications. The ten items from the CASP Qualitative Tool[1] were used as prompts for reflection, and the appraisal was guided by three primary questions intended to assess if and how a study demonstrated that it collected rich data, conducted a rigorous analysis, and incorporated reflexive practices leading to robust results that were useful for the objectives of this review: Is it credible? Is it trustworthy? Are the results transferable?[2] Results of the critical appraisal were not used to exclude studies from this review, rather they were used to understand the methodological and conceptual limitations of the included publications in specific relation to this review. Particularly, the critical appraisal contributed to the analysis by identifying the limits of transferability of the results of included publications.

Data Analysis

A "best fit" framework approach[3] was used to analyze data relating to the perspectives and experiences of both pregnant people and health care providers engaging with fetal RhD blood group genotyping. The thematic categories identified in Health Quality Ontario's (HQO) recent systematic review and qualitative meta-synthesis investigating the perspectives of pregnant people and clinicians on non-invasive prenatal testing (NIPT)[4] were chosen a priori to serve as the foundational framework for this review. As fetal RhD genotyping is a form of NIPT, HQO's report on NIPT provided an appropriate foundation from which to build an understanding of the varied ways in which pregnant people and health care providers might engage with fetal RhD genotyping. Situated within an overarching theme of access, the categories identified therein include those related to both a desired for increased access to NIPT as well as the preferences for and perils of this widened access.[4] Where necessary, these categories have been supplemented or amended to include those that emerged throughout this analysis.

One reviewer conducted the analysis. The included primary study was read and re-read to identify key findings and concepts that mapped onto the framework, which was modified as new concepts emerged. During the reading and re-reading of the study, memos were made, noting details and observations about the study's methodology, findings, and interpretations, and connections to other concepts in the framework. Re-reading and memoing continued until themes were appropriately described and supported by data from the included publication. During the analysis, issues with transferability and the results of the critical appraisal were reflected on to aid with interpretation.

A note on terminology: We recognize that many people who give birth may not identify as women and that gender identities are individual; thus, we use gender neutral pronouns and terms where possible. When reporting results from published literature, gender-neutral language is not used, to be consistent with the terms used in the source material.

Summary of Evidence

Quantity of Research Available

A total of 1,103 citations were identified in the literature search. Following screening of titles and abstracts, 1,088 citations were excluded and 15 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 16 publications were excluded for various reasons. Eight were excluded because they reported an irrelevant intervention (i.e., NIPT screening for rare chromosomal abnormalities). Another four did not meet population, study design or language inclusion criteria. The final four were excluded as they were clinical guidelines or background information on cell-free DNA testing and prenatal screening. One publication met the inclusion criteria and was included in this report.[5] Appendix 1 presents the PRISMA[6] flowchart of the study selection process.

Summary of Study Characteristics

Details regarding the characteristics of the included study are reported in Appendix 2. Characteristics of the study's participant population are included in Appendix 3.

Study Design (and Data Collection)

The included study reported a mixed method design and thematic analysis for the qualitative portion of the study.[5] Only the qualitative portion of the study was included in this review. Nine interviews and two focus groups were used to complete data collection for the qualitative portion of the study.[5]

Country of Origin

The single included study was conducted in the United Kingdom.[5]

Participant Population

The participant population of the study included six women and 13 health professionals (i.e. obstetric registrars and midwives).[5]

Interventions (and Comparators)

Each of the six pregnant women were RhD negative and had undergone fetal RhD genotyping. Where testing indicated that the women were carrying an RhD positive fetus, all three approved the use of anti-D immunoglobulin prophylaxis. One of the three women carrying an RhD negative fetus also received anti-D immunoglobulin prophylaxis.[5]

Summary of Critical Appraisal

The included study is of low quality. Details of the critical appraisal, capturing key points on credibility, trustworthiness, and transferability, can be found in Appendix 4.

The criterion of credibility assessed whether and how researchers were true to their participants' voices. Credibility could be demonstrated through clear descriptions of data collection methodology, supporting descriptive analyses with raw data, and reflexively engaging with the processes leading to their findings. The included study was identified as being of low credibility[5] due to a thin analysis that was poorly supported by raw data.

The criterion of trustworthiness involves the concepts of dependability and confirmability. It assessed whether there was analytical consistency in the findings and whether the authors demonstrated reflexive engagement with assumptions. The included study was identified as being of low trustworthiness.[5] While the researchers provide a table of abstracted quotes and refer to them throughout their analysis, the ways in which quotes link with analysis is considered to be self-evident. There is little engagement with the context within which the quotes exist and how the researchers came to understand the quotse as indicating a particular analytic finding. While it is possible this is the result of restricted word counts or that the qualitative portion of this study may not have been meant to stand alone from the larger questionnaire it was being used to develop, it does limit the study's overall trustworthiness.

The criterion of transferability assessed whether and how the study was relevant to the current review. The assessment was made by exploring reporting of characteristics of individual study participants, situations and analyses. The included study[5] was identified as transferable within the context of this review as it was conducted in a similar jurisdiction to Canada and included an appropriate participant population.

Summary of Findings

Desire for Increased Access to NIPT

This study indicates that all the participants included believed fetal RhD genotyping was beneficial and should be offered to all RhD negative women.

Better Accuracy

Both women and health care professionals indicated that test accuracy was an important factor when deciding whether to engage with fetal RhD genotyping and how to trust the results of testing.[5] By and large, concern with test accuracy seemed situated around the possibility of false negatives as this could put a fetus at risk of developing HDFN. No concerns with false positives were indicated in the study. This is likely due to the National Health Authority's implementation of routine antenatal anti-D prophylaxis (RAADP) which would be recommended for any RhD negative pregnant person carrying an RhD positive fetus.

Two of the six women included in the study noted that even if testing had indicated they were carrying an RhD negative fetus they would still be interested in receiving anti-D prophylaxis "to be on the safe side."(p. 690)[5] Interestingly, this is not reflected in the included table which indicates that of the three women who received a test result predicting an RhD negative fetus, only one still received anti-D immunoglobulin. Nonetheless, as part of this desire to stay on the "safe side" was couched in RhD genotpying's relative novelty (at the time of the study in 2013),[5] perhaps this would be less relevant today as it has become routine in several jurisdictions.

Physical Risk

Neither health professionals nor women indicated being concerned with any physical risks that may be associated with genotyping. As a blood product, anti-D immunoglobulin is often noted as a potential health risk, but neither health professionals nor women expressed concern and considered the benefits of anti-D to outweigh any associated risks.

Earlier Availability of Results

Even if testing was postponed until a bit later in pregnancy, women indicated that test accuracy was valued over earlier availability of results.[5] This does not mean women would not want testing earlier, they simply wanted it when it was most likely to be accurate.

Preferences for and Perils of Widened Access

Logistical Aspects of Access

Health professionals were concerned about the timing of testing due to the added strain of explaining the test. Professionals were also concerned about offering additional appointments due to limited staffing levels and the extra time that was required.[5]

Informational aspects of access

Women indicated feeling a bit overwhelmed by the amounts of information being given to them throughout pregnancy.[5] As such, even printed information was left unread, although having it available was considered important and helped women feel more comfortable with testing. Health care professionals understood they would be the largest informational source for women and expressed interested in receiving further training on genotyping.

Limitations

The greatest limitation of this review is the dearth of available literature exploring expectations, experiences and perspectives of pregnant people and health care professionals toward fetal RhD genotyping. With only one included study of low quality, it is difficult to imagine all points of interest have been covered in this review. While this does not lessen the validity of the findings indicated above, the contextual depth a qualitative review is meant to offer to the technology in question is largely absent.

Another limiting factor was the absence of analysis across differing populations, for example as defined by socio-economic status, geographic location, or ethnicity as factors that may be expected to influence or shape patients' experiences. Such differences may be important to explore as people typically classified as within vulnerable or marginalized populations may require specific considerations not addressed or identified in the included publication or this analysis. This is particularly true considering the diversity of gene variants contributing to an RhD negative phenotype and the role ethnicity plays in the display of these variants. How health care professionals and the pregnant people they are guiding through fetal RhD genotyping understand potential gene variants could affect the form of counselling provided or acceptance of testing results which could influence overall experience with genotyping.

Conclusions and Implications for Decision or Policy Making

This review used a "best fit" framework approach to analyze the results of the single included study. It describes some key features of the ways in which pregnant people and health care professionals engage with fetal RhD genotyping.

It appears that pregnant people, in general, believe that fetal RhD genotyping is beneficial and should be offered to all RhD negative women. Understanding and trusting that genotyping could accurately identify the fetus' RhD status was important for both pregnant people and their health care professionals. Even when testing predicts an RhD negative phenotype in the fetus, some pregnant people may still prefer to receive anti-D immunoglobulin prophylaxis to alleviate their concerns of false negatives. When deciding whether to implement genotyping into routine prenatal care, it would be important to consider how these situations might be approached.

That being said, in order to support informed decision making it is also important that providers are knowledgeable about what fetal RhD genotyping may offer, the risks of receiving a false negative (or false positive) and whether some gene variants may run a greater risk of returning a false negative or positive. Knowing how to appropriately counsel and inform pregnant people on these points across diverse ethnicities may require further research into the sensitivities of genotyping tests across populations. In part, it is possible that these concerns could be alleviated with appropriate information sharing strategies.

Pregnant people indicated that the amount of information they were required to take in over the course of pregnancy could be overwhelming and difficult to fully absorb. Providing written information on genotyping was identified as one way to improve comprehension. Similarly, it would be important to explore potential ways of balancing the increased timing burden placed on providers who will need to explain yet another test, in addition to pregnant persons' scheduling concerns. Taking both into account could help to support a more informed decision making process.

Surprisingly, no literature was identified for this review that examined potential emotional or social aspects of engaging with fetal RhD genotyping for pregnant persons. As HQO's report on NIPT identified the possibility for an increased sense of social pressure to undergo testing due to its availability and ease of access (i.e., "a simple blood test"),[4] it could be helpful to pursue this line of questioning with fetal RhD genotyping as well. While it is less likely that there would be similar social pressures as in other forms of NIPT (e.g., for Down Syndrome) as there is less likelihood the fetus would be considered for abortion, understanding how pregnant people respond to and approach fetal RhD genotyping emotionally could further support informed decision making.

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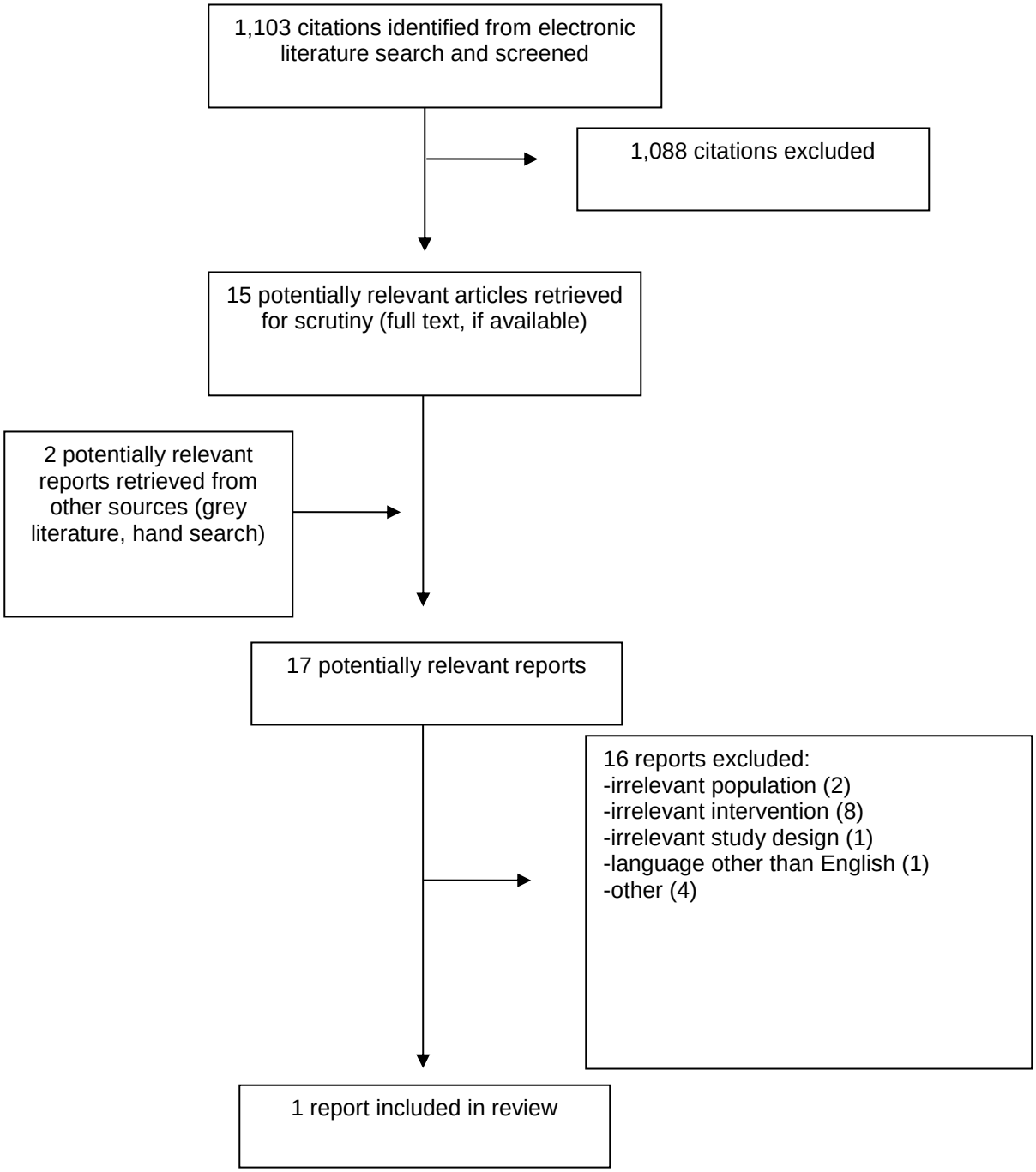
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Study

Table 2: Characteristics of Included Study

First Author, Publication Year, Country	Study Design; Data analysis	Study Objectives	Sample Size	Inclusion Criteria; Sampling strategy	Data Collection
Oxenford, 2013, UK[5]	Mixed Methods; Quantitative: Descriptive Qualitative : Thematic analysis	To investigate women's preferences and information needs for routine implementation of fetal Rhesus D typing using cell-free fetal DNA	6 women 13 health professionals	NR; purposive sampling	Interviews and focus groups

NR = not reported

Appendix 3: Characteristics of Study Participants

Table 3: Characteristics of Study Participants

First Author, Publication Year, Country	Sample Size	Sex (% male)	Age range in years	Fetus RhD status (% positive)
Oxenford, 2013, UK[5]	6 pregnant women 2 obstetric registrars 11 midwives	0	NR	50

NR = not reported; UK = United Kingdom

Appendix 4: Critical Appraisal of Included Study

Table 4: Critical Appraisal of Included Study

First Author, Publication Year, Country	Is this study credible?	Is this study trustworthy? (dependable, confirmable)	Is this study transferable?
Oxenford, 2013, UK[5]	No. Primary concern is situated around the lack of analytical depth as findings are poorly reported and thin. Also, qualitative methods (mixed-methods study) are poorly reported and inclusion criteria not identified.	No. As this trustworthiness is largely contingent on credibility, trustworthiness is limited. Of particular concern, the link between how findings are supported by the data (reported in a table of quotes) is unclear and not well described. Some quotes that are referenced do not appear in the table of quotes. The issue is not with the data's dependability, but with the dependability of the analysis.	Yes. The research question, patient population and health care providers are all relevant to this review.

UK = United Kingdom