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Noninvasive fetal RhD genotyping using maternal plasma

English summary

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SUMMARY

Noninvasive fetal RhD genotyping using maternal plasma

Assessment context

Hemolytic disease of the fetus and newborn (HDFN) is caused by maternal alloimmunization, which occurs when antibodies from the mother are directed against antigens (rhesus D; RhD) present on the surface of fetal red blood cells and cause their destruction. The consequences of HDFN range from jaundice and mild fetal anemia to fetal or neonatal death.

Currently, to prevent the maternal alloimmunization that occurs as a result of maternal-fetal RhD incompatibility, routine prenatal prophylaxis is offered to RhD-negative women around the 28th week of pregnancy, during potentially sensitizing events during pregnancy, and within the 72 hours following the birth of an RhD-positive newborn. It is known that the administration of these prophylaxis, which is derived from human plasma, is associated with a risk, albeit very low, of pathogen transmission and allergic reactions. Pregnant women known to be alloimmunized are rigorously managed by way of high-risk pregnancy (HRP) monitoring.

However, according to the scientific literature, nearly 40% of RhD-negative pregnant women carry an RhD-negative fetus and are therefore not at risk for alloimmunization. Since the vast majority of these women are non-alloimmunized, prophylaxis is administered unnecessarily, whereas in previously alloimmunized women, HRP monitoring should not be done because of the unborn child’s RhD-negative status. By permitting the determination of the fetus’s RhD status early in pregnancy, maternal plasma-based fetal RhD genotyping would make it possible to avoid these interventions in these women.

Proposed test

Héma-Québec would like to offer all pregnant women in Québec who are known to be RhD-negative a molecular test for determining the unborn child’s RhD status from fetal DNA circulating in the mother's blood. Fetal RhD genotyping consists in extracting fetal DNA from maternal plasma and detecting the *RHD* gene sequences on several exons using a real-time quantitative nucleic acid amplification test (NAAT). A commercial kit, which has yet to be decided on, or an "in-house" test would be used. Currently, no commercial kit for noninvasive prenatal testing for fetal RhD genotype has been approved by Health Canada for clinical use.

Methodology

A rapid review of the scientific literature was conducted to document the various aspects related to the performance, clinical utility, ethics and cost-effectiveness of fetal RhD genotyping tests. The current management of RhD-negative women and the various

ethical and organizational issues pertaining to the possible implementation of prenatal genotyping were considered and summarized following consultations with various stakeholders. In addition, economic analyses were performed using the available data.

Clinical validity

A search of the scientific literature on the clinical validity of fetal RhD genotyping yielded 1 health technology assessment (HTA) report, 2 systematic reviews with meta-analysis, and 13 primary studies published after the HTA report. The currently available scientific data support high clinical performance in the "Caucasian" population. Uncertainty remains as to the transposability of this performance to the Québec context. The rate of false-negative results reported in the studies is low, and the diagnostic accuracy is higher after the 11th week of pregnancy.

Clinical utility

Compliance with fetal RhD screening is very high in the countries where it has been implemented. Based on the available data, anti-D Ig administration as prenatal prophylaxis could be avoided in 25% to 39% of non-alloimmunized RhD-negative pregnant women. No evidence was found regarding the proportion of alloimmunized RhD-negative pregnant women for whom testing could obviate the need for HRP monitoring. Little or no data is available on the impact of false-negative results on the risk of alloimmunization. An increase in adverse events associated with anti-D Ig has been observed in recent years. However, the number of events is very low, considering the amount of anti-D Ig administered in Québec annually.

Issues and stakeholder perspective

The published clinical data indicate that the test is effective, but the uncertainties in the choice of method are highly likely to influence the test’s clinical performance and its cost-effectiveness. In addition, several organizational issues were raised during the consultations with women and with experts in perinatal medicine, genetics, hematology, transfusion safety and molecular biology, such as the implementation of genotyping in clinical practice, sample transport and storage, the transmission of results, and training for the various stakeholders. The experts point out that, currently, midwives who provide care to RhD-negative pregnant women would not be able to order this test. In addition, ethical concerns were raised regarding the administration of a blood product to women who do not require it, given the existence of a noninvasive genotyping test, despite the fact that the risks inherent in genotyping are poorly documented. The stakeholders consulted consider it essential that women be able to make an informed choice between the two treatment options, this in accordance with their values and beliefs.

Economics

The results of the literature search regarding the cost-effectiveness of targeted prophylaxis guided by fetal RhD genotyping are not transposable to clinical practice in Québec. INESSS therefore developed its own models. Since the requester has not yet

decided on a kit, the modeling is based on clinical performance data from the scientific literature. The results of INESSS's modeling, which are accompanied by uncertainties, indicate that fetal RhD genotyping would be a potentially cost-effective approach for RhD-negative pregnant women who are alloimmunized, while it would unlikely be cost-effective for those who are not alloimmunized. It should be noted that these results are transposable only if the kit that is chosen achieves the clinical performance reported in the literature. The possible inclusion of this test in the *Répertoire québécois et système de mesure des procédures de biologie médicale* for this alloimmunized patient population could lead to annual cost reductions of approximately $45,000 for the next 3 years, while additional costs of approximately $500,000 for the same period are expected for the non-alloimmunized population.

Positions and orientations of organizations of interest

The Society of Obstetricians and Gynaecologists of Canada (SOGC), among other organizations that have spoken on this matter, recommends implementing such testing in order to optimize the management of RhD-negative pregnant women.

Deliberation concerning noninvasive fetal RhD genotyping using maternal plasma

The members of the Comité scientifique permanent des analyses de biologie médicale (CSABM) and the Comité d'excellence clinique (CEC) en services de santé recognized the clinical value of noninvasive fetal RhD genotyping using maternal plasma for RhD-negative women in Québec. However, they noticed that it would be too early to include it in the *Répertoire québécois et système de mesure des procédures de biologie médicale* because of various uncertainties regarding the method and its implementation.

<u>Reasons for the unanimous position</u>

- The members expressed their concerns about the lack of clinical performance data on the kits specifically proposed by the requester, particularly with respect to the rate of false-negative results and its impact on the management of the mother, fetus and newborn. They also mentioned the impact of these uncertainties on the conclusions of the economic aspect.
- In light of the data from the available scientific literature, the members considered the test's clinical performance to be high in the population of European (or "Caucasian") origin. The rate of false-negative results is low in this population, and the accuracy is high, especially after the 11th week of pregnancy.
- The members recognized that fetal RhD genotyping could potentially avoid the administration of anti-D Ig as prenatal prophylaxis in a significant proportion of non-alloimmunized RhD-negative women. It would also reduce the number of HRPs to be monitored in an equal proportion of RhD-negative alloimmunized women.
- The members expressed their concerns about the requester's proposed 4- to 6-week turnaround time and its impact on the management of the mother and her

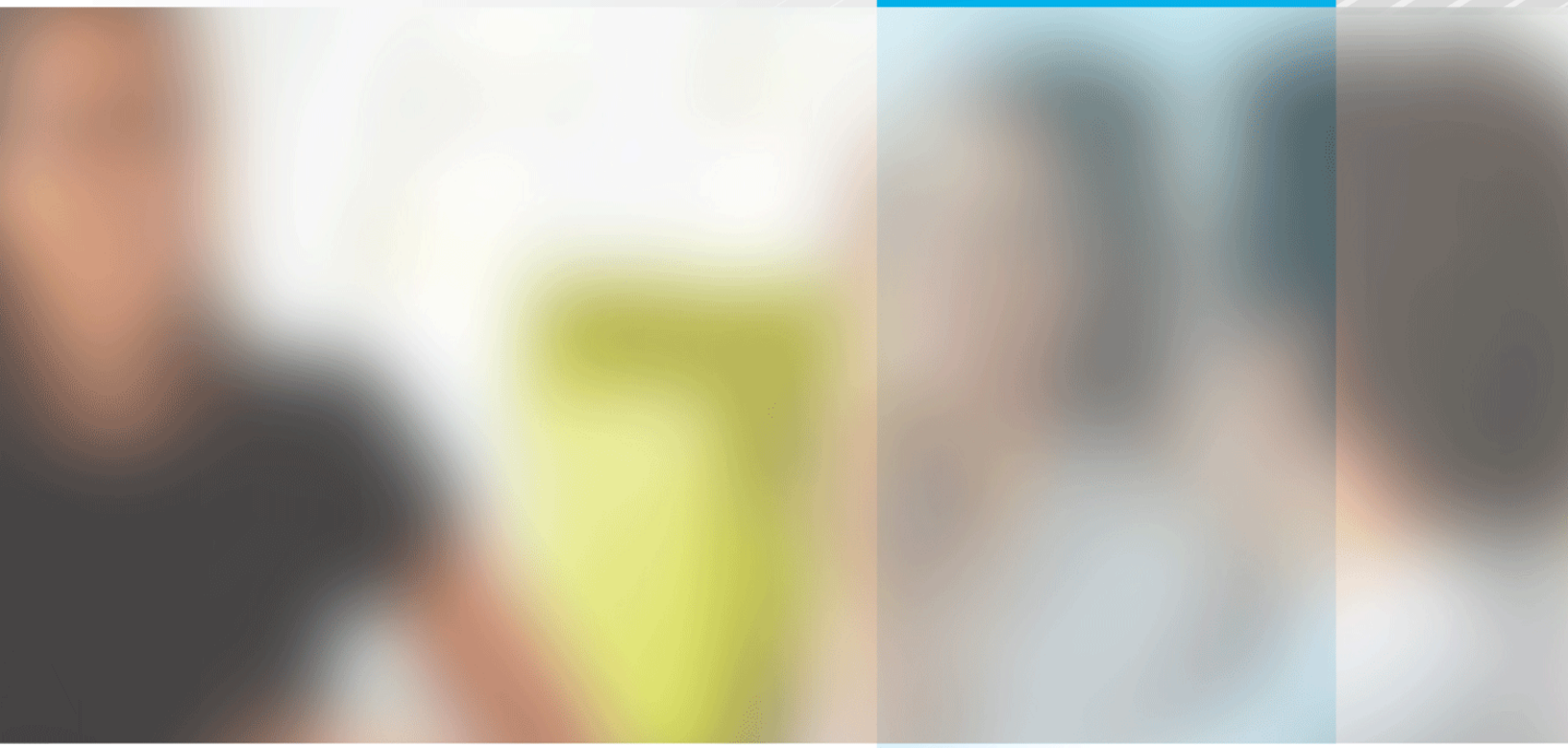
fetus, particularly in the case of sensitizing events that would occur before the genotyping result is known.

- The members raised concerns about the logistics and costs of transporting samples in rural areas.
- The members also pointed out that administering a biological product to women who do not need it raises certain ethical concerns, given the existence of a genotyping test.
- In line with the findings of the consultations with women and experts, the members stressed the importance of coordinating the blood sampling required for the test and the transmission of the results with the current prenatal visit schedule.
- They also stressed the importance of coordinating all the stakeholders to facilitate the implementation of the test. To this end, midwives should be able to order the test and have access to the results.
- According to the members, it is essential that appropriate training be provided to all the stakeholders, including health professionals and pregnant women, on the various aspects of genotype testing.
- Genotype testing appears to be a safe and less invasive option than routine anti-D Ig prophylaxis and would optimize the management of these women. However, as the consultations with RhD-negative women revealed, the members reiterated the importance of allowing women to make an informed choice between the two treatment options, this in accordance with their values and beliefs.

INESSS's recommendation

In light of the available data, INESSS recommends that fetal RhD genotyping using maternal plasma not be included in the *Répertoire*. However, this test could be offered to the target population in the event:

- that the method chosen (commercial kit or "in-house" test) be specified and that its performance and limitations are determined prospectively through a validation study carried out in real-world care settings. During this validation period, the risk of false-negative results should be mitigated by maintaining confirmatory RhD testing of cord blood in the postpartum period, and access to anti-D Ig should be maintained to ensure the safety of women and their fetus;
- that, based on this new data, the offer of service is recognized as being effective and safe and that the costs it entails are acceptable relative to the clinical benefits obtained.



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