Cost-Effectiveness of the Management of Rh-Negative Pregnant Women

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Abstract

Objective: The purpose of this study was to determine the most cost-effective option to prevent alloimmunization against the Rh factor.

Methods: A virtual population of Rh-negative pregnant women in Quebec was built to simulate the cost-effectiveness of preventing alloimmunization. The model considered four options: (1) systematic use of anti-D immunoglobulin; (2) fetal Rh(D) genotyping; (3) immunological determination of the father's Rh type; (4) mixed screening: immunological determination of the father's Rh type, followed if positive by fetal Rh(D) genotyping. Two outcomes were considered, in addition to the estimated costs: (1) the number of babies without hemolytic disease, and (2) the number of surviving infants.

Results: In a first pregnancy, two options emerged as the most cost-effective options: systematic prophylaxis and immunological Rh typing of the father, with overlapping confidence intervals between them. In a second pregnancy, the results were similar. In all cases (first or second pregnancy or a combination of the two) fetal genotyping was not found to be a cost-effective option.

Conclusion: Routine prophylaxis and immunological Rh typing of the father are the most cost-effective options for the prevention of Rh alloimmunization. Considering that immunological typing of the father would probably not be carried out by the majority of clinicians, routine prophylaxis remains the preferred option. However, this could change if the cost of Rh(D) fetal genotyping fell below $140 per sample.

Key Words: Simulation, Rhesus, genotyping, hemolytic disease, alloimmunization, cost-effectiveness

Competing Interests: None declared.

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Résumé

Objectif : Cette étude avait pour objectif d'identifier l'option la plus rentable pour la prévention de l'allo-immunisation contre le facteur Rh.

Méthodes : Une population virtuelle québécoise de femmes enceintes séronégatives pour le facteur Rh a été créée pour simuler la rentabilité de la prévention de l'allo-immunisation. Ce modèle a pris en considération quatre options : (1) l'utilisation systématique d'immunoglobuline anti-D; (2) le génotypage Rh(D) fœtal; (3) la détermination immunologique du type Rh du père; (4) le dépistage mixte : détermination immunologique du type Rh du père, suivie (en présence de résultats positifs) du génotypage Rh(D) fœtal. Deux critères d'évaluation ont été pris en considération, en plus des coûts estimés : (1) le nombre d'enfants nés sans maladie hémolytique et (2) le nombre de nouveau-nés survivants.

Résultats : Dans le cas d'une première grossesse, deux options se sont avérées les plus rentables : la prophylaxie systématique et la détermination immunologique du type Rh du père; leurs intervalles de confiance se chevauchaient. Dans le cas d'une deuxième grossesse, les résultats ont été semblables. Dans tous les cas (première ou deuxième grossesse, ou une combinaison des deux), nous avons constaté que le génotypage fœtal ne constituait pas une option rentable.

Conclusion : La mise en œuvre systématique d'une prophylaxie et la détermination immunologique du type Rh du père constituent les options les plus rentables pour la prévention de l'allo-immunisation contre le facteur Rh. Puisqu'il est peu probable que la détermination immunologique du type Rh du père soit mise en œuvre par la majorité des cliniciens, la prophylaxie systématique demeure l'option à privilégier. Cependant, cela pourrait changer si le coût du génotypage Rh(D) fœtal chutait en deçà de 140 $ par prélèvement.

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INTRODUCTION

Despite the availability of prophylactic measures, alloimmunization to the Rh(D) antigen during pregnancy remains the most common cause of hemolytic disease of the newborn (1:1000 newborns).[1] Alloimmunization is the occurrence of an immune response to the presence of an antigen (alloantigen) that an individual lacks, but that is present in other individuals of the same species. In humans, this situation is observed only in special circumstances: pregnancy (immunization of an Rh-negative mother by her Rh-positive fetus), blood transfusion, or transplantation of tissues or organs.[2]

Early determination of the fetal Rh blood type in pregnant Rh-negative women allows better monitoring of the risk of alloimmunization and better prevention of its feared consequences (hemolytic disease of the fetus [HDF] and stillbirth, due to the passage of maternal immunoglobulins through the placenta) by the administration of prophylactic anti-D immunoglobulin (IgG).[3]

Currently accepted recommendations for the prevention of alloimmunization are the routine injection of anti-D IgG at 28 weeks' gestation for all Rh-negative non-sensitized women when fetal Rh type is positive or unknown.[4–8] Such a measure is necessary because there is no practical therapeutic intervention that will slow the process of alloimmunization once it has been initiated.[9–11]

Non-invasive determination of fetal Rh status is now possible through the analysis of cell-free circulating fetal DNA in maternal plasma as early as the 10th week of pregnancy; that is, before the alloimmunization process is triggered. Non-invasive determination of fetal Rh status is expected to reduce the number of women who receive anti-D IgG unnecessarily and undergo surveillance testing according to current recommendations.[4,12]

However, although the diagnostic performance of this new approach is high (clinical sensitivity and specificity approaching 100%), it is not universally available. Its introduction into regular follow-up of pregnancies still requires evidence about its value compared with more traditional approaches. Indeed, two economic studies were performed on non-invasive fetal Rh(D) genotyping. However, those studies should be considered as cost-minimizing studies because they did not estimate clinical outcomes.[13,14] Thus, information on the cost-effectiveness of the various options is still unavailable.

Computer-based simulation modelling is a recognized approach to comparing the putative cost-effectiveness of several clinical interventions for a specific condition.[15–18] It is especially useful to compare the effectiveness of a large number of different interventions in the same cohort of patients, because that would require a very large, costly, and sometimes impossible clinical trial.[19]

METHODS

We built a virtual population of 10 000 Rh-negative pregnant women. This number was considered sufficient to perform statistically meaningful simulations given that 150 cases of Rh(D) incompatibility would be expected. The model assumed that 55% of women will have a second pregnancy,[20] on average 3.15 years after the first.[21] The Rh type of the fetus was established based on the probability of the father being either homozygously or heterozygously Rh positive.[22]

Besides the estimated costs, two clinical outcomes were considered: (1) the number of babies without hemolytic disease, and (2) the number of surviving infants.

Modelling was performed using a previously described agent-based, hybrid-state, and time-driven simulator called SCHNAPS.[23,24] Two decision trees were built (Figure 1). The first decision tree applied to the first pregnancy of an Rh negative woman. The second applied to an eventual second pregnancy in 55% of those women.[20]

The first model reflected the natural evolution of a first pregnancy for an Rh negative pregnant woman and the health of her baby up to 28 days after delivery. The choice of a 28-day follow-up neonatal period was based on the fact that the consequences of alloimmunization and hemolytic disease of the newborn are manifest during this period.[25,26] Weekly cycle units were chosen for the time-driven simulations, which correspond to the usual time interval of events in the pregnancy literature.[27]

A probability of being alloimmunized was assigned to each Rh-negative woman depending on (1) the probability of the fetus being Rh positive, (2) the gestational age, and (3) the use of anti-D prophylaxis at 28 weeks and/or after delivery.[4,28] The probability of the fetus being Rh positive was assigned depending on the father's probable Rh type. Following clinical guidelines, a non-alloimmunized woman had nine prenatal visits, one ultrasound examination, an indirect Coombs test, and administration of prophylactic anti-D IgG at 28 weeks' gestation.[4,11,29,30] If the indirect Coombs test is positive, the woman is followed from 28 weeks as an alloimmunized woman.[4] Alloimmunized women (those with a positive indirect Coombs test at 12 or 28 weeks), are monitored by measuring the level of anti-D antibodies, and have an ultrasound examination every four weeks until 28 weeks, every two weeks from 28 to 37 weeks,