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Is the management of Rh-Rh incompatibility with noninvasive fetal Rh genotyping for targeted prophylaxis cost-effective in the Turkish population?

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Background/aim: The aim of this study was to assess unnecessary immunization rates and compare the cost-effectiveness of targeted prophylaxis with fetal Rh genotyping with that of traditional management of Rh-Rh incompatibility in a virtual economic model.

Materials and methods: This retrospective data analysis was conducted at two tertiary centers between 2011 and 2015. The data of 1135 pregnant women were analyzed. The main outcome measure was to determine the unnecessary immunization rate among the whole Rh-Rh incompatibility group. The second outcome measure was to compare the cost-effectiveness of universal immunization with that of targeted prophylaxis with fetal Rh genotyping in a virtual economic model.

Results: Average cost per patient was found as $259.20 with universal prophylaxis and the total cost was $177,344, whereas if targeted prophylaxis had been applied to these patients the total cost would have been $263,392 and cost per patient would have been $385. Universal prophylaxis was more cost-effective than targeted prophylaxis in terms of both total cost and cost per patient ($P < 0.0001$).

Conclusion: Unless the cost of noninvasive fetal Rh genotyping is reduced, a universal approach of anti-D immune globulin prophylaxis is more cost-effective than noninvasive determination of fetal Rh genotyping with targeted prophylaxis.

Key words: Anti-D prophylaxis, cell-free DNA, cost-effectiveness, noninvasive, Rh genotyping

1. Introduction

Rh-Rh alloimmunization is a potential result of fetomaternal hemorrhage, which occurs during childbirth or during pregnancy in Rh-negative women who have an Rh-positive fetus. If a sufficient volume of fetal RhD-positive blood enters the maternal circulation, the mother will be sensitized and hemolytic disease of the fetus or newborn may occur. The severity of the disease is variable and it may result in fetal hydrops, fetal anemia, developmental problems, and even intrauterine death (1).

Since the 1960s, routine antenatal prophylaxis with anti-RhD immunoglobulin in the third trimester to prevent rhesus sensitization for all RhD-negative pregnant women, regardless of the rhesus status of the baby, has been standard in many countries as recommended by most clinical guidelines (1,2). Anti-RhD immunoglobulin is given antenatally in the third trimester and repeated postpartum prophylaxis within 72 h of delivery is offered only to RhD-negative women who have given birth to an RhD-positive baby (3). Routine antenatal anti-D prophylaxis (RAADP) at the beginning of the third trimester has been introduced in several countries, reducing the incidence of RhD immunization to 0.2%–0.3%. Unfortunately, there are also rare side effects of this application and there are limited stocks of anti-D immunoglobulin as well as other blood products.

After the identification of cell-free fetal DNA in the blood of pregnant women, several institutes have provided a fetal RhD genotyping service for RhD-negative women with a measureable concentration of anti-RhD antibody (3,4). Cell-free fetal DNA constitutes 3%–6% of the cell-free DNA in maternal serum (5). Cell-free fetal DNA from maternal blood is tested for the presence or absence of the RhD gene, and results are used to direct management of the pregnancy. Several studies have confirmed the safety and high diagnostic accuracy of this approach (6–10). Fetal RhD genotyping was found to be sufficiently accurate to be used from 11 weeks' gestation (3).

In the NICE guidelines issued in 2008, a single dose of anti-D immunoglobulin at 28 weeks was reported to be suitable in terms of cost-effectiveness. However, RAADP has often been administered to all RhD-negative pregnant

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women, even though 40% will carry a compatible RhD-negative fetus and so are not at risk for RhD immunization (2,3). RAADP treatment in such women unnecessarily exposes them to a human plasma product and is wasteful of the limited supply of anti-D immunoglobulin, which should be given only when strictly indicated. This allows administration of RAADP selectively to RhD-negative women with an RhD-positive fetus and avoids giving it to women who are not at risk (11).

The aim of this study is to estimate the incidence of RhD-negative pregnant women who have given birth to an RhD-negative baby with RAADP in the third trimester, to assess unnecessary immunization rates, and to compare the cost-effectiveness of fetal Rh genotyping with targeted prophylaxis with that of traditional management of Rh-Rh incompatibility in a mathematical model.

2. Material and methods

This retrospective data analysis was conducted at the İzmir Kâtip Çelebi University and Giresun University Faculties of Medicine, Department of Obstetrics and Gynecology, between 2011 and 2015. After obtaining the approval of the local institutional review boards (2015/), the data of 1135 pregnant women were analyzed.

A total 1135 pregnant women given RAADP were included in this study. Out of those 1135 women, 132 pregnant women were excluded from data analysis due to incomplete records and 319 were excluded from the study because of early or late pregnancy losses, ectopic pregnancy, or positive indirect Coombs test. Thus, the data of a total of 684 pregnant women were analyzed.

Demographic data of pregnant women, number of anti-D prophylaxis administrations, laboratory results, Rh status of newborns, and cost per patient and total cost of traditional management of Rh-Rh incompatibility were recorded. Our main outcome measure was to determine the unnecessary immunization rate and the percentage of Rh-negative newborns with Rh-negative mothers among the whole Rh-Rh incompatibility group. The second outcome measure was to compare the cost-effectiveness of universal immunization and that of targeted prophylaxis with fetal Rh genotyping in a mathematical model.

In this economic model, if fetal Rh genotyping from maternal blood were applied to all of the 684 patients who received universal RAADP, the fetal Rh-negative group would have been excluded from the universal management group and would have been managed without a need for antenatal prophylaxis. The pregnancies having an Rh-positive fetus would have been monitored with conventional methods. Costs of laboratory tests for antenatal prophylaxis, costs of hospitalization and anti-D for antenatal applications, and costs of laboratory tests for fetal Rh genotyping in maternal blood were calculated in total and per patient in US dollars. The cost of conventional prophylaxis was also calculated per patient and in total in US dollars. These two management methods were compared in terms of costs.

2.1. Statistical analysis

Data were analyzed using SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA). Mean, median, standard deviation, and ratio values were used in comparisons of data. The chi-square test was used for analyses of qualitative data. Differences were considered statistically significant at $P \leq 0.05$.

3. Results

A total of 1135 patients with Rh-Rh incompatibility were included in the study from two different tertiary centers; 319 patients were excluded from the study due to early/late pregnancy losses or a positive indirect Coombs test, while 132 patients were excluded due to incomplete records. A total of 1304 anti-D globulin administrations were applied to the 684 patients who were included in the study. Anti-D was given once to 132 patients, twice to 484 patients, and three times to 68 patients. The mean age of patients was 31.8 years and median gravida was three, while parity was two and abortion was one. The incidence of Rh-negative babies born to Rh-negative mothers was 22.2% (152/684) and total pregnancy loss rate was 28.1% (319/1135). Laboratory costs, the cost of visits, hospitalization costs, and RAADP costs were calculated for universal prophylaxis; the average cost per patient was found to be $259.20 and total cost was $177,344. With this type of management, the cost per patient was $153.80 for patients having an Rh-negative baby and the total cost was $23,392. However, the cost per patient was $289.30 for patients having an Rh-positive baby and total cost was $153,952 for pregnant women having an Rh-positive fetus.

If targeted prophylaxis had been applied to these patients with the use of Rh genotyping from maternal blood, with the inclusion of all other costs, total cost would have been $263,392 and cost per patient would have been $385. Cost per patient would have been $160 for patients having an Rh-negative fetus and cost per patient would have been $449.30 for patients having an Rh-positive fetus, with a total cost of $239,027.

Comparisons of universal and targeted management costs are given in the Table. Universal prophylaxis was more cost-effective than traditional prophylaxis in terms of both total and per-patient costs ($P < 0.0001$). However, in subgroup analyses, the Rh-negative subgroups were similar in terms of cost-effectiveness between universal and targeted prophylaxis ($P = 0.88$), but universal prophylaxis was found as more cost-effective than targeted prophylaxis in the Rh-positive subgroup ($P = 0.0016$).

Table. Comparison of cost-effectiveness of noninvasive fetal Rh genotyping for targeted prophylaxis and traditional prophylaxis.

Groups	Total (n = 684)		Rh-negative fetuses (n = 152)		Rh-positive fetuses (n = 532)	
	Traditional management	Targeted management	Traditional management	Targeted management	Traditional management	Targeted management
Cost per pregnancy (USD)	259.20	385	153.80	160	289.30	449.30
Total cost (USD)	177,344	263,392	23,392	24,320	153,952	239,027
P-value	<0.001		0.88		0.0016	

4. Discussion

This retrospective data analysis and virtual economic model showed that noninvasive fetal Rh genotyping and targeted prophylaxis does not seem cost-effective in the Turkish population in today's conditions when compared to universal Rh prophylaxis. However, in subgroup analysis of Rh-negative fetuses, targeted prophylaxis and universal prophylaxis were comparable to each other.

In our study the rate of pregnancy loss was 28.1%. This rate is higher than that expected in the general population and this is due to the fact that our centers were tertiary centers and the study group consisted of referred patients. The incidence of Rh-negative babies born to Rh-negative mothers was 22.2%. This rate was also high as it is reported to be approximately 10%–15% in the Turkish population in the literature (12). The explanation for this is that the babies in our study all had Rh-negative mothers. The entire population consists of both Rh-negative and Rh-positive mothers and so the rate is lower. The presence of the Rh antigen varies between races. A high frequency of Rh-negative genotype exceeding 0.50, as typically described over several decades, is present in the Basque region of France. This rate is 15% in Caucasians, 8% in Africa, and about 1% in East Asia (13). Our higher rate could be related to migration to our region from outside and also to our hospital-based study. This cost-effectiveness study may have more significant results if it is performed in countries that have a higher incidence of the Rh-negative genotype.

In our study the average cost per pregnancy was found to be $259.20 with universal prophylaxis. If we had managed these patients selectively with the detection of fetal Rh genotype prenatally, the cost would have been $449.30 per patient with that approach. Because Rh-negative mothers carrying Rh-negative fetuses would not need immunization, the cost of targeted management would be $385. Fetal Rh genotyping with targeted prophylaxis was not more cost-effective than universal prophylaxis in our model. One study in the United States specifically evaluated the cost-effectiveness of routine antenatal Rh IG prophylaxis in D-negative women versus noninvasive fetal Rh genotyping with targeted prophylaxis. In this economic model, the cost of routine prophylaxis was $351 per pregnancy compared with $682 for noninvasive testing. As approximately 60% of women tested would still require administration of Rh IG, the cost of testing would have to decrease to $119 to have a neutral economic impact (14). A similar analysis was conducted in Quebec in 2013 with similar results, indicating that routine prophylaxis is far more cost-effective than noninvasive fetal Rh genotyping followed by targeted prophylaxis (15). These findings were similar to our results.

It should be kept in mind that anti-D immune globulin products are produced from human plasma, so theoretically they have a risk of transmission of infectious agents. In 1978, one case of hepatitis C transmission was reported in Ireland with the use of contaminated Rh IG products (16). In the United States there is no reported case of transmission by these products (17). All blood products also have a risk of transmission of prion diseases. One possible case of acquisition of Creutzfeldt–Jakob disease in a patient from the United Kingdom who received clotting factor concentrate has been reported (18). In addition to these risks, the second drawback of universal prophylaxis is the limitation of Rh immune globulins stocks due to it being a human product.

The accuracy rates of detection of fetal Rh genotype in maternal blood were reported as 98%–100% in many recent studies (19,20). Cell-free fetal DNA constitutes 3%–6% of the cell-free DNA in maternal serum (5,21). Fetal DNA can be obtained from maternal serum by the fifth week of pregnancy with this method. Fetal RHD genotyping was found to be sufficiently accurate to be used from 11 weeks of gestation (3,19,20). Therefore, if targeted screening becomes cost-effective with time, noninvasive fetal Rh genotyping from maternal blood could be added to screening at 11–13 weeks in obstetrics practice.

A limitation of our study may be the retrospective nature and use of hospital-based data. Furthermore, this study is a virtual economic model. We want to indicate that our results only reflect the cost-effectiveness of

applications in the health system of Turkey; the costs of medications, laboratory tests, hospital visits, or genetic tests may differ from country to country. However, our study has several strengths, such as a large sample size and a relatively homogeneous group of pregnant women.

In conclusion, unless the cost of noninvasive fetal Rh genotyping is reduced over time, a universal approach to anti-D immune globulin prophylaxis seems more cost-effective than noninvasive determination of fetal Rh genotyping followed by targeted prophylaxis. If this expectation is realized, it will enable routine fetal RHD genotyping to avoid unnecessary immunization of RhD-negative women carrying RhD-negative fetuses for ethical and economic reasons.

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