Reaction to anti-D immunoglobulin – can we manage it?

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Summary: Approximately one in six women are blood group RhD negative and are offered anti-D immunoglobulin prophylaxis to prevent sensitization and decrease the risk of haemolytic disease of the newborn in subsequent pregnancies. It has been thought that anti-D is harmless, but there is a risk of anaphylaxis. We describe a case of a woman with a possible immunological reaction to anti-D in her first pregnancy. A multidisciplinary team managed her second pregnancy, offering her evidence-based advice, where available, so that she could reach an informed decision regarding administration of anti-D or not. Women value individual tailored information rather than a 'one-size-fits-all' approach.

Keywords: anti-D, anaphylaxis, pregnancy

INTRODUCTION

Approximately 17% of pregnant women are RhD negative. Of these, 60% will have an RhD-positive baby in their first pregnancy. If a woman becomes sensitized in her first pregnancy, all subsequent RhD-positive babies will be at risk of developing haemolytic disease of the fetus and newborn (HDN). It is now routine practice in the UK to administer immunoprophylaxis of anti-D immunoglobulin to women who are RhD negative during their pregnancy and postpartum period. Prior to the use of anti-D prophylaxis, HDN was a significant cause of morbidity and mortality. Mortality was estimated at about 1.2 per 1000 births. This figure has been reduced to 0.02 per 1000 births by the use of anti-D immunoglobulin.¹

It has generally been thought that anti-D is harmless and there is very limited literature available regarding its side-effects. Sulakvelidze² described a young woman who developed an urticarial rash following administration of anti-D. A case of serum sickness following repeated administration of anti-D used intravenously has also been described.³ Here we present an unusual case of a reaction to anti-D immunoglobulin and describe how we managed the case by using a multidisciplinary approach, while taking steps to achieve patient empowerment.

CASE REPORT

A 30-year-old parous woman, blood group O RhD negative, was seen in the antenatal clinic for regular routine check-ups in her second pregnancy. She had had mild depression and mild asthma in the past, was otherwise fit and well, but was

known to have had anaphylactic shock following a wasp sting in the past. She had been advised to carry adrenaline for rapid administration in case of an anaphylactic reaction.

Her first pregnancy was unremarkable. She was administered 1500 U of Rhophylac® (CSL Behring AG, Bern, Switzerland) anti-D intramuscularly at 28 weeks as per local guidelines. She reported that she developed a mild rash following this injection, which she ignored. She subsequently had a normal delivery of a baby boy who was found to have blood group A RhD positive and was administered a further 500 U of anti-D. Within an hour of the injection, she had developed a red itchy blotchy rash covering extensive areas of her body. This lasted five weeks and was an inconvenience.

The woman presented to antenatal clinic early in her subsequent pregnancy and, in the light of her significant history, we developed a multidisciplinary management plan. Initially we grouped the baby's blood using free fetal DNA from maternal serum at 16 weeks. A previous attempt at 12 weeks had been unsuccessful. The baby was found to be RhD positive. A skin prick test confirmed that this was unlikely to have been a type 1 hypersensitivity. We corresponded with ZLB Behring, the company that manufactures the anti-D Rhophylac® product. They advised that as Rhophylac® is a protein solution, anaphylactic or hypersensitivity reactions can occasionally occur (Lorenz Amsler, Bern, Switzerland, personal communication). The rate of this is <1 per 100,000 individual doses, even if the 'non-serious' cases are included. They recommended trying another anti-D product.

After considering the risks and benefits of administering anti-D, we recommended that any further doses of anti-D should be administered in hospital after obtaining informed written consent. She should have intravenous access, suitable anaesthetic supervision and antihistamines should be administered prior to the injection. This should take place where

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resuscitation facilities are available. We had many detailed consultations with the woman as to the optimum management of her index pregnancy with regard to her reaction to anti-D. We devised a personalized information leaflet for her to read before having to make any decisions about her management. It outlined the benefits and risks of anti-D and the risks of HDN if anti-D was not administered. We advised that she had a 2% risk of becoming sensitized in the index pregnancy without the use of anti-D. Were sensitization to occur, the likelihood of it causing problems was extremely low. In England and Wales about 500 babies develop HDN every year and 25–30 babies die from it; about 15 children will have major permanent developmental problems and a further 30 will have minor developmental problems.

In view of the paucity of literature on reactions to anti-D or on the effect of possible anaphylaxis on a pregnant woman or her fetus, our advice was limited. Regarding the mode of delivery, a previous study⁴ showed there was no increased risk of foeto-maternal transfusion following vaginal delivery compared with caesarean. We advised vaginal delivery. The proposed management for this pregnancy and postnatal period, as well as future pregnancies, was explained. References and further reading materials were listed for the woman.

Following long discussions, she decided she did not want anti-D to be administered in her second pregnancy. A Kleihauer test to detect foeto-maternal transfusion would be performed postnatally and, if necessary, she would receive anti-D at that time with the provisions mentioned above. She made this decision to avoid the risk to her fetus of a potential anaphylactic reaction during pregnancy. She planned to have the postnatal anti-D to help prevent sensitization putting further pregnancies at risk. She later declined this. We measured anti-D at three months postnatal to help assess the risk to any further pregnancies and she remained negative. This does not preclude antibody formation below the level of detection that would only be identified during a subsequent RhD exposure such as a further pregnancy.

She has decided she would like another child. Our plan for the next pregnancy would be to withhold anti-D prophylaxis and to review the decision again at delivery depending on her subsequent plans regarding further pregnancies at that point.

DISCUSSION

It has been assumed that anti-D is harmless. As mentioned above, there is very little literature about reactions to anti-D. In particular, there are no guidelines regarding management of future pregnancies when a woman has reacted to anti-D, as happened in our case. We used free fetal DNA in this case to determine the baby's blood group while avoiding other diagnostic procedures such as amniocentesis that have an inherent risk of sensitization. At 12 weeks gestation, we tried to obtain a sample to enable us to determine the fetal blood group before any potential sensitizing events. The use of free fetal DNA may help simplify the management of reactions to anti-D in the future, but the technique would have to first be refined to a level adequate to provide reliable and accurate results as early as the first trimester.

This case has raised our awareness that the use of anti-D is not without risk. ZBL Behring quotes a risk of reacting to anti-D to be <1:100,000 cases. In the UK, there are 800,000 births per year and in 17% of these the woman will be RhD negative. This gives an estimated incidence rate of one to two reactions per year. In the USA, the estimated risk would be seven to eight per year.

The incidence of such reactions can be estimated, but their impact cannot: there is paucity of literature concerning the incidence of anaphylactic and other immunological reactions in pregnancy, the risks to the fetus or how pregnancy modifies maternal outcome in the context of anaphylaxis. Moreover, in an obstetric emergencies simulation course, maternity teams achieved the lowest score for completion of medical tasks for the anaphylaxis scenario.⁵

This case necessitated a significant investment of a variety of resources and involvement of a multidisciplinary team. Regarding the balance of risks and benefits, the advice given was essentially limited by the availability of good quality evidence. However, it has been shown⁶ that patients value individually tailored information based on the best available evidence, even if such evidence is limited, rather than a 'one-size-fits-all' approach. It is possible that this approach may not only increase patient satisfaction but also reduce litigation. By adapting how information is given to women, we may boost their sense of empowerment, which is our main lesson from this case study.

CONTRIBUTION TO AUTHORSHIP

O'BK authored the manuscript; DS conceived the idea and co-authored the manuscript; BJ co-authored and edited the manuscript (expertise in transfusion reactions); GM co-authored the manuscript (immunological perspective); AS co-authored the manuscript (haematological perspective); KB conceived the idea, co-authored and edited the manuscript.

ETHICS AND CONSENT

The woman has given explicit written consent to the publication of this case.

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