The use of anti-D immunoglobulins for rhesus prophylaxis: audit on knowledge and practices among obstetricians

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ABSTRACT

Introduction: The development of anti-D antibodies results from foetomaternal sensitisation occurring in rhesus (Rh) negative blood group women who carry an Rh-positive foetus. Despite guidelines on Rh immunoprophylaxis, isoimmunisation continues to occur, suggesting that the guidelines are not being fully applied by obstetricians. This study aims to establish the adequacy of knowledge on Rh immunoprophylaxis among obstetricians and trainees in obstetrics and gynaecology in Singapore, and their usual practice in the care of an Rh-negative mother; and hence to audit their practice in accordance with evidence-based guidelines.

Methods: An anonymous questionnaire survey auditing obstetricians' knowledge of guidelines on anti-D prophylaxis and their usual practice in the clinical setting.

Results: The mean score achieved on the questionnaire was 75.9 percent. Many obstetricians did not know that anti-D immunoglobulins (Ig) should be given within 72 hours of a sensitising event for successful immunoprophylaxis. In clinical practice, all the obstetricians who participated in the questionnaire would offer anti-D Ig prophylaxis to Rh-negative women both antenatally and postnatally. However, only 12.7 percent of them would routinely perform a Kleihauer test in Rh- negative women following delivery.

Conclusion: The knowledge on anti-D prophylaxis among obstetricians can be improved. A continual system of education to raise awareness of evidence-based practices as well as clinical audit has been implemented to address this.

Keywords: anti-D immunoglobulins, anti-D prophylaxis, foetomaternal sensitisation, Kleihauer test, rhesus-negative women

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INTRODUCTION

The population in Singapore is predominantly Asian, with Chinese forming the largest ethnic group. Although rhesus (Rh) negative blood groups are rare in Singapore, with a prevalence of less than 2%, it is still important to understand the appropriate management of Rh-negative women. This will indirectly result in a decrease in the incidence of haemolytic disease of the newborn. The development of anti-D antibodies is generally a result of foetomaternal haemorrhage (FMH) occurring in RhD-negative women who carry an RhD-positive foetus. The most important cause of this isoimmunisation is "silent sensitisation". This refers to the development of maternal antibodies from antenatal sensitisation of the maternal immune system in the absence of an overt sensitising event. Failure to administer antenatal and postnatal immunoprophylaxis would allow these sensitising events to cause foetal haemolysis, usually in a subsequent pregnancy. In severe cases, foetal anaemia results in foetal hydrops from cardiac failure. When untreated, this can result in foetal loss. The management of women who are Rh negative in pregnancy has evolved rapidly over the last decade, in line with recently available evidence. We undertook this audit as we felt that the current level of understanding among clinicians was inadequate. It was anticipated that deficiencies in knowledge may be more apparent in senior clinicians who may be expected to be less familiar with recently published evidence. Trainees pursuing postgraduate qualifications in this specialty would require knowledge of these guidelines to pass membership examinations.

METHODS

Obstetricians from hospitals in Singapore completed a questionnaire survey auditing their knowledge of guidelines on anti-D prophylaxis and their usual practice in the clinical setting. In addition, basic specialty trainees (BSTs) in obstetrics and gynaecology in Singapore participated in the same questionnaire survey. BSTs are doctors who have not passed the postgraduate specialty examinations. Typically, this would encompass the first four years of a doctor's career in the specialty. This audit was conducted based on the Royal College of Obstetrician and Gynaecologists Clinical Green-Top Guidelines,[1] and the National Institute for Health and Clinical Excellence

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review on pregnancy-routine anti-D prophylaxis for RhD-negative women.[2] These documents provide established evidence-based guidelines for the management of pregnancies in Rh-negative women.

A sample of the questionnaire with the correct answers is shown in Appendix 1. There were 18 questions in total. Questions 1–16 audited the obstetricians' knowledge on anti-D prophylaxis following the established guidelines. The last two questions audited the obstetricians' usual practice with regard to anti-D prophylaxis in the clinical setting. Marks were awarded for each correct answer out of a total score of 16 marks. The participants were approached individually and asked to complete the short questionnaire without opportunity for prior preparation.

RESULTS

There were 55 participants in this audit study, of which 34 were specialists, and the remaining 21 participants were BSTs (non-specialists). The overall mean score for this audit was 75.9%, with an overall median score of 75.0%. The mean and median scores for the specialist group were 75.9% (12.15/16) and 81.3% (13/16), respectively, while those for the non-specialist group were 75.9% (12.14/16) and 75.0% (12/16), respectively. The individual scores were divided into three categories: ≥ 80% to denote adequate knowledge; 60%–79% inadequate knowledge; and < 60% poor knowledge. The authors assigned limits for these categories on the basis that appropriate clinical management demanded a high level of understanding. Based on the individual scores, only 49.1% of the participants (27/55) had adequate knowledge of the guidelines on anti-D prophylaxis. The remaining 40.0% (22/55) and 10.9% (6/55) of the participants had inadequate and poor knowledge, respectively.

On whether the participants knew that anti-D Ig should be given within 72 hours for successful immunoprophylaxis, only 83.6% (46/55) had the correct answer. Most participants were aware that intramuscular anti-D Ig is best given into the deltoid muscle (76.4%, 42/55), and is prepared from plasma (87.3%, 48/55).

The only question answered correctly by every participant in the questionnaire was Question 8; all the doctors knew that anti-D Ig should be given to all non-sensitised RhD-negative women having amniocentesis. In addition, almost every participant recognised that anti-D Ig should also be given to all non-sensitised RhD-negative women having termination of pregnancy (98.2%, 54/55), ectopic pregnancy (96.4%, 53/55) and external cephalic version of the foetus (94.5%, 52/55). However, not as many participants knew that anti-D Ig should be given to all non-sensitised RhD negative women having closed abdominal injury (61.8%, 34/55), and that anti-D Ig was not necessary for certain categories of threatened miscarriage (76.4%, 42/55). Only 34.5% (19/55) of the participants were aware that the minimum dose of anti-D Ig given to non-sensitised RhD-negative woman following the delivery of an RhD-positive infant was 500 IU.

21.8% (12/55) of those who completed the questionnaire did not know when routine anti-D prophylaxis should be given, which is at 28 and 34 weeks of pregnancy and after delivery. Most doctors knew the name of the most commonly-used preparation of anti-D Ig in Singapore (90.9%, 50/55). However, only 54.6% of them could identify the cost of a vial of anti-D Ig. In clinical practice, all the obstetricians who participated in the questionnaire would offer anti-D Ig prophylaxis to Rh-negative women antenatally and postnatally. However, only 12.7% (7/55) of them would routinely perform a Kleihauer test in Rh-negative women following delivery. This may stem from the fact that laboratories in Singapore frequently report Kleihauer test results in percentages. This is less useful than reporting results as the equivalent volume of FMH ml. When reported as a percentage, clinicians would have to calculate the volume of FMH using a mathematical formula and decide whether an additional dose of anti-D Ig is necessary. The minimum dose of 500 units of anti-D Ig would be adequate for a FMH of 4 ml.

DISCUSSION

The overall mean score for the audit was 75.9%. Scores for the specialist (75.9%) and non-specialist (75.9%) group were remarkably similar. It had been anticipated that the specialist group which comprised more experienced clinicians would attain better scores. However, the actual scores may be because evidence-based guidelines for the management of Rh-negative women in pregnancy are available relatively recently. These aspects of management would have to be learnt by reading the published literature rather than through clinical experience. Trainees may also have a greater incentive to know these guidelines well, as this would be necessary knowledge for passing professional examinations. It is noted that the overall mean score of 75.9% fell under the category of "inadequate knowledge" (60%–79%). Less than half of the participants (49.1%) had adequate knowledge of the guidelines on anti-D prophylaxis. The remaining participants had inadequate or poor knowledge. The classification of raw scores into adequate, inadequate and poor, though arbitrary, was decided on the basis that a very high level of knowledge would be necessary for sound clinical practice. It was arguable that only a

"perfect" score was appropriate. "Adequate knowledge" did not mean that it was sufficient, as any deficiency in knowledge may result in inappropriate management and poor outcomes.

For successful immunoprophylaxis, anti-D Ig should be given as soon as possible after the sensitising event, but always within 72 hours. Only 83.6% of the participants knew this fact. Although the majority of the participants were aware of this, the authors felt that knowledge of the appropriate window for administration of anti-D was the key to effective immunoprophylaxis. Knowledge of this aspect of immunoprophylaxis must be universal. The popular wrong answer option for Question 4 in this audit was 48 hours. Every obstetrician who participated in the questionnaire knew that anti-D Ig should be given to all non-sensitised RhD-negative women having amniocentesis. This was the only question in the audit that was answered correctly by all participants.

Other sensitising events during pregnancy like external cephalic version of the foetus, closed abdominal injury and threatened miscarriages would also require the administration of anti-D Ig if the patient was RhD negative. This is important as these events, particularly closed abdominal injury of significant force, such as in motor vehicle accidents, may result in more FMH than amniocentesis or delivery. Threatened miscarriages after 12 weeks of gestation (and not regardless of gestations) would warrant immunoprophylaxis. Not as many participants answered Question 7 correctly. This reflected a lack of familiarity with the guidelines, as universal immunoprophylaxis for threatened miscarriages was common practice before these guidelines were published.

It is now apparent that the most important cause of Rh disease is isoimmunisation during pregnancy, where there has been no overt sensitising event. All the obstetricians who completed the questionnaire were aware that routine antenatal anti-D prophylaxis should be given to non-sensitised RhD-negative women. However, not all of them could identify the correct gestations at which it should be given; i.e. at 28 and 34 weeks of pregnancy and after delivery. It is not surprising that most obstetricians did not know the minimum dose of anti-D Ig to be given for postnatal prophylaxis. This is because, in Singapore, the common practice is that every non-sensitised Rh-negative woman would receive a standard dose of 1,500 IU (one vial) of anti-D Ig following the delivery of an RhD-positive infant. The anti-D Ig is only available locally in a preparation of a vial of 1,500 IU. This would explain why most participants in this audit assumed that the minimum dose of anti-D Ig for postnatal prophylaxis was 1,500 IU, instead of 500 IU.

Most doctors knew the name of the most commonly-used anti-D Ig in Singapore. Many obstetricians were ignorant of the cost of a vial of anti-D Ig. This knowledge is important as the patients usually have to bear the full cost. A vial of anti-D Ig in Singapore General Hospital costs S$295.80 (~ USD196.26) per vial. In clinical practice, all the obstetricians who participated in the questionnaire would offer anti-D Ig prophylaxis to Rh-negative women both antenatally and postnatally, as recommended by the guidelines. However, not every Rh-negative woman would agree to this treatment because of the cost. If the guidelines were strictly adhered to, then a non-sensitised Rh-negative woman would require at least three vials of anti-D Ig for each pregnancy (assuming the pregnancy is uncomplicated). This would amount to S$887.40 (~USD588.56) for anti-D Ig prophylaxis alone.

It is interesting to note that only a few obstetricians in this audit would routinely perform a Kleihauer test in Rh-negative women following delivery; the purpose of which is to detect FMH > 12 ml, so that additional anti-D Ig can be given as appropriate. In Singapore General Hospital, the Kleihauer test is performed based on the acid-elucidation test, and is reported in "% of foetal erythrocytes seen". In contrast, the Kleihauer test performed in many other centres is based on flow cytometry, and the result is expressed in "ml of FMH". The guideline states that 500 IU of anti-D Ig will suppress immunisation by 4 ml of RhD-positive red blood cells. One other reason for not performing a Kleihauer test is because higher doses of anti-D Ig are administered in Singapore. There would be fewer clinical scenarios in which 1,500 IU of anti-D Ig would be inadequate. Clinicians should still be aware that a Kleihauer test is indicated in situations in which FMH can be massive, such as in the event of a placental abruption.

It is recommended that the anti-D prophylaxis guidelines be incorporated into the departmental protocols so as to ensure the optimal management of these women. The authors believe this audit is likely to reflect a national practice. We would propose a re-audit, perhaps on a national level, once evidence-based guidelines have been made available to all obstetricians. With regard to the Kleihauer test, we are looking into amending the way results are expressed so as to allow these results to be utilised more effectively. In conclusion, the knowledge on anti-D prophylaxis among obstetricians can be improved. A continual system of education to raise awareness of evidence-based practices as well as clinical audit has been implemented to address this. Appropriate management of these women is a matter of great importance if the potentially disastrous effects of isoimmunisation are to be avoided.

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Appendix 1. Questionnaire: Use of Anti-D Immunoglobulin for Rh Prophylaxis.

Name (optional): _____
Age: _____
Job description (please circle): **MO / MOT / R / C / SC**
Hospital: _____

1. The development of anti-D antibodies generally results from foetomaternal haemorrhages (FMH) occuring in RhD-positive women who carry an RhD-negative foetus. **F**

2. Studies have shown that 99.2%–99.3% of women have a FMH less than 4 ml at delivery. Up to 50% of larger FMHs occur after normal deliveries. **T**

3. Intramuscular anti-D Ig is best given into the deltoid muscle. **T**

4. For successful immunoprophylaxis, anti-D Ig should be given within (please circle):
   (a) 24 hours.
   (b) 48 hours. **C**
   (c) 72 hours.
   (d) 96 hours.

Anti-D Ig should be given to all non-sensitised RhD negative women having:

5. Termination of pregnancy. **T**

6. Ectopic pregnancy. **T**

7. Threatened miscarriage regardless of gestation. **F**

8. Amniocentesis. **T**

9. Closed abdominal injury. **T**

10. External cephalic version of the foetus. **T**

11. What is the minimum dose of anti-D Ig given to non-sensitised RhD-negative woman following the delivery of a RhD-positive infant? _____ IU **500**

12. A patient was given one vial of anti-D Ig equivalent to 300 mcg. How many IU of anti-D Ig did she receive? _____ IU **1,500**

13. Anti-D prophylaxis should be given routinely at these gestations of pregnancy:
   (a) 28 weeks, 32 weeks and after delivery.
   (b) 24 weeks, 32 weeks only.
   (c) 24 weeks, 34 weeks and after delivery. **D**
   (d) 28 weeks, 34 weeks and after delivery.

14. Anti-D Ig is prepared from plasma. **T**

15. What is the name of the most commonly-used anti-D Ig used in Singapore? _____ **Rhogam**

16. How much does a vial of the most commonly-used anti-D Ig costs in Singapore?
   (a) $150.
   (b) $250.
   (c) $300. **C**
   (d) $400.

17. In your daily clinical practice, do you routinely perform the Kleihauer test following delivery in a Rh-negative woman?
   (a) Yes. **As per clinical practice**
   (b) No.

18. In your daily clinical practice, what is your policy for offering anti-D Ig prophylaxis to Rh-negative women?
   (a) Antenatally only.
   (b) Postnatally only.
   (c) Antenatally and postnatally. **As per clinical practice**
   (d) No prophylaxis.

Thank you for your time.