Immune Anti-D in Pregnancy: Cases reported up to end of 2018

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Definition:

Cases of D-negative women who become sensitised and are found to have developed immune anti-D, which is detected during pregnancy, either at booking or later in the index pregnancy.

Key SHOT messages

- All cases of alloimmune anti-D found for the first time in pregnancy should be reported to SHOT
- Clinical staff involved in the management of D-negative women in pregnancy should have clear policies for acting appropriately upon 28-week serology results
- Robust procedures should be in place in the clinical area and the laboratory to ensure that, where indicated, women are followed up to ensure clearance of fetal cells after larger fetomaternal haemorrhages (FMH)
- D-typing results should be interpreted with care to avoid classifying D-variant as D-positive, a result of 2+ or less should be further investigated and the woman treated as D-negative until the D-type has been confirmed
- Data on cell-free fetal deoxyribonucleic acid (cffDNA) testing will be collected to provide evidence and learning from errors particularly interpretation of results

Introduction

Since 2012 SHOT has been conducting a prospective study of women who produced immune anti-D detected for the first time in the current (index) pregnancy to improve understanding of the causes of continuing anti-D immunisations. The reporters are requested to provide data on booking weight, management of sensitising events during pregnancy and the administration of routine anti-D immunoglobulin (Ig) prophylaxis, in both the index pregnancy and the pregnancy immediately before the index pregnancy (if applicable).

Results

In 2018 a total of 42 cases were reported, 9 cases occurred in women with no previous pregnancies (NPP), 1 case was excluded as the information provided was insufficient. In 33 women with previous pregnancies (PP), 2 cases were excluded as the information provided was insufficient.

The reason for the fall in reported cases is not clear and could be due to under-reporting or a true fall in the rate of new immunisations.

Anti-D immunisation in pregnancy remains under-reported if the following assumptions are made:

- National Institute for Health and Care Excellence (NICE 2008) evidence for routine antenatal anti-D Ig prophylaxis (RAADP) quoted a reduction in sensitisation rate from 0.95% without RAADP to 0.35% when RAADP was used

- Systematic review in 2004 (Jones et al. 2004) showed that the percentage of sensitised women fell from 1.9-2.2% to 0-0.2% with antenatal prophylaxis
- There were 636,401 births recorded in England on Hospital Episode Statistics up to March 2017, of which 17% will be D-negative mothers (108,188), of which 59% will carry D-positive babies - that is 63,831 pregnancies at risk
- If we use failure rate of 0.2%, then we would expect 128 immunisations per year from RAADP failures

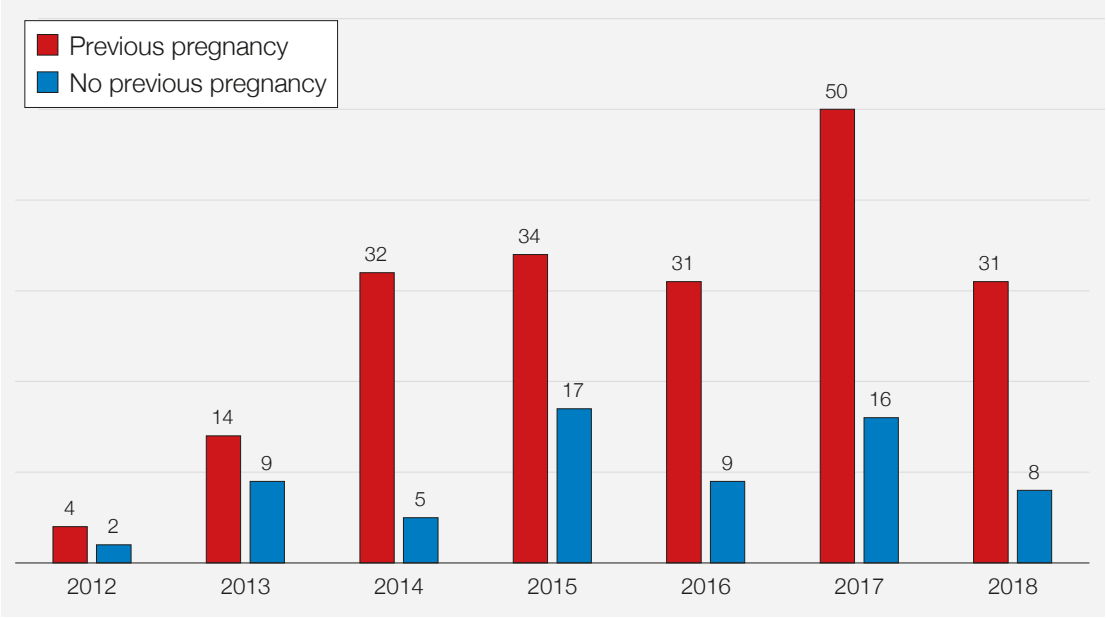
Plus

- There were 272 reports to SHOT of omission or late administration of anti-D Ig in 2018, some of which may result in immunisation

For the first time, questions on the use of cffDNA were asked but as the test has not been implemented in many centres yet, the data are too sparse to draw meaningful conclusions this year. However, going forward this data should provide important information on areas where errors can occur for example due to wrong blood in tube, laboratory testing and resulting, transcription of results and interpretation of results.

Cumulatively SHOT now has useful data on 66 women with NPP and 196 women with PP.

Figure 11.1: Number of reports of anti-D immunisation in pregnancy by year, 2012-2018



No previous pregnancy (NPP) n=8

There were 8 new cases in 2018 (one case excluded), cumulative to date 66 cases.

Further information, and tables containing similar details to those published in previous Annual SHOT Reports, can be found in the supplementary information on the SHOT website www.shotuk.org.

Summary of 2018 NPP data

Half of the women were found to be immunised at delivery, and all of these cases were delivered beyond 40 weeks. One case had been grouped as D-positive and so received no RAADP. She was subsequently shown to be D-variant. The other 3 cases received apparently 'ideal' care, with timely RAADP and no identifiable sensitising episodes. However, in these, as in other cases where no potentially sensitising event (PSE) is reported, there can never be certainty that the woman has not experienced an unreported early termination or miscarriage. It is of note that 3 cases where immune anti-D was only detected at delivery were obese and delivered beyond term.

Pregnancy outcomes in NPP case

In 2018 outcome was reported in 7/8 cases (one case provided no outcome information). All 7 pregnancies resulted in live births of which 4 pregnancies where alloimmune anti-D was detected only at delivery had a gestation of >40 weeks (41^{+4}, 42, 42, 42^{+6}).

There were 4 babies that had no complications, 2 cases required phototherapy, 1 case required phototherapy and exchange transfusion. In 1 case no information on interventions was submitted apart from an ultrasound for anaemia performed during pregnancy.

Cumulatively, all 66 pregnancies resulted in 67 live births, of which 41 had no complications, 15 babies required phototherapy and 7 cases required exchange transfusion. No details were provided in 3 cases.

Case studies

Case 11.1: D-variant

A primiparous woman in her 30s, with a booking weight of 95kg (BMI 35), typed as D-positive. She had a live birth at 42 weeks gestation. Alloimmune anti-D was detected on the delivery sample. Samples were referred to the Blood Service for investigation, and the woman typed as partial D category DIV. The baby required no interventions for haemolytic disease of the fetus and newborn (HDFN).

The problem of D-variants is discussed in the conclusions at the end of this chapter.

Case 11.2: Delivery at 42+6 weeks

A primiparous woman in her 30s, with a booking weight of 61kg (gestation at booking 8 weeks), received a single dose of RAADP (1500IU) at 28 weeks. She delivered at 42^{+6} weeks. Alloimmune anti-D was detected at delivery (titre 1 in 256), and there were no reported PSE. The baby required no interventions for HDFN.

Case 11.3: A small antepartum haemorrhage (APH) at 8-9 weeks, thought to be clinically insignificant

A primiparous woman in her 20s, with a booking weight of 58.3kg, had a cffDNA test at 17^{+5} weeks which was inconclusive. She received a single dose of RAADP (1500IU) at 28 weeks. A sample taken at this time was subsequently shown to contain alloimmune anti-D 12.8IU/mL, rising to a level of 66IU/mL at 34^{+2} weeks gestation. The baby was delivered at 35 weeks gestation and required exchange transfusion and phototherapy.

RAADP was given before the result from her 28-week sample, which showed the presence of alloimmune anti-D, was available. The only identifiable PSE was a very small APH at 8-9 weeks gestation for which the woman visited her general practitioner (GP) and no action was taken.

Previous pregnancies (PP) n=31

The index pregnancy in these cases refers to the current pregnancy – the pregnancy in which alloimmune anti-D was first detected.

There were 31 new cases in 2018, cumulative to date 196 cases.

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When was alloimmune anti-D detected in the index (current) pregnancy?

Where alloimmune anti-D was detected at booking in the index (current) pregnancy, only the events in the preceding pregnancy are relevant to the sensitisation (assuming no other exposure to the D antigen occurred e.g. transfusion, an unlikely event in healthy fertile women). Where anti-D is detected later in the index pregnancy, the relative contribution of events in the previous and index pregnancy is less certain.

There were 6 women who had alloimmune anti-D detected for the first time at delivery of the index pregnancy, 1 had a gestation of >40 weeks (40^{+2}).

The cumulative data show that of 30 pregnancies where alloimmune anti-D was first detected at delivery in the index pregnancy, 10 cases (33.3%) were delivered after 40 weeks gestation.

Summary of 2018 PP data

There were 12 women found to be immunised at first trimester booking indicating that sensitisation had probably occurred in the preceding pregnancy. In 19 cases, alloimmune anti-D was detected later in the index pregnancy so that the relative contribution of previous pregnancies is less clear. In 1 case alloimmune anti-D was detected in a sample taken from a non-pregnant woman.

Although the data has gaps, cases continue to be reported where despite apparently 'ideal' care in the preceding or index pregnancy, sensitisation to anti-D occurs and alloimmune anti-D develops. It is a possibility that in some of these cases there may have been a preceding 'undeclared' PSE e.g. termination of pregnancy (TOP) (medical or surgical), or cases where although anti-D Ig has been issued it was not given or not given effectively.

Nine out of 27 of the previous pregnancies (that went to term) lasted longer than 40 weeks. Cumulatively (data collected from 2015 onwards) 30 out of 128 previous pregnancies (23.4%) lasted longer than 40 weeks. NHS maternity statistics 2014-2015 indicate 17.5% pregnancies extended beyond 40 weeks. (NHS Digital 2015).

Body weight has been used in place of body mass index (BMI) as a marker for obesity as weight is more regularly reported than BMI. Using parameters for an average female in the UK, 80kg would equate to obesity in most women. We do however acknowledge the limitations in this interpretation. Of the 12 PP cases where booking weight in the previous pregnancy was known, 2 were obese. Cumulatively, of the 98 women where booking weight in the previous pregnancy was provided, 28/98 (28.6%) were obese, significantly higher than the 19% incidence of obesity in pregnant women reported by Public Health England in 2018.

Case studies

Case 11.4: Lack of follow up for clearance of fetal cells

A woman in her 30s received a single dose of RAADP (1500IU) at 28 weeks in the preceding pregnancy. She had an elective caesarian section at 38 weeks gestation. The Kleihauer test showed a FMH of >4mL and flow cytometry confirmed a 16mL FMH. The woman was given a total of 2500IU anti-D Ig but there was no evidence that she was followed up to confirm clearance of the fetal cells. Alloimmune anti-D was detected at 28 weeks gestation in the next pregnancy. In this case a further error in management occurred as the anti-D detected at 28 weeks in the index pregnancy was interpreted as passive, due to RAADP, which was given after the blood sample had been taken. The pregnancy was not followed up serologically and the baby was delivered as an emergency at 34 weeks and required an exchange transfusion.

This case emphasises the importance of following up cases where anti-D is detected to establish whether it is passive or immune (BSH White et al. 2016) so that the pregnancy can be managed appropriately and also following up large (>4mL) FMH to ensure clearance of fetal cells.

Case 11.5: Management followed current guidelines

A woman in her 30s received a single dose of RAADP (1500IU) at 28 weeks in the preceding pregnancy. She had no PSE, and had an emergency caesarian section at 41 weeks gestation. The Kleihauer test showed a FMH of 2.7mL. The woman received 500IU anti-D Ig postpartum. Alloimmune anti-D was detected at 10 weeks (booking appointment) in the next pregnancy. The baby required no interventions for HDFN.

British Society for Haematology (BSH) guidance (BSH Austin et al. 2009) recommends that where a Kleihauer shows a FMH >2mL, the sample is sent for flow cytometry to confirm the size of the bleed.

Case 11.6: Apparently ideal care in the preceding pregnancy but possible risk in the way FMH is reported

A woman in her 40s (alloimmune anti-D at booking in the index pregnancy) had apparently ideal care in the preceding pregnancy (in vitro fertilisation pregnancy). She was not obese, received RAADP (1500IU anti-D Ig into the deltoid at 28 weeks gestation), and had no PSE. The baby was delivered by emergency caesarian section at 31 weeks. FMH was measured by flow cytometry and reported as <12mL. She received the 'standard' dose of anti-D Ig used at this hospital (1500IU) but was not followed up for clearance of fetal cells.

The reporter stated that the postpartum sample analysed by flow cytometry was reported to show a FMH <12mL, which would be covered by their standard anti-D Ig dose of 1500IU. However, if FMH is >4mL guidelines advise that follow up samples are required to check for clearance of fetal cells. It was important to clarify if follow up for clearance of fetal cells was performed as there appeared no other cause of immunisation. The laboratory replied that <12mL is the standard report for flow cytometry as their standard dose of anti-D Ig will be sufficient. They stated that they never rely on a clinician to send repeat samples in case of a bleed between 4-12mL and never leave it to a report. If the bleed is >4mL the laboratory staff ring and chase samples for follow up. In this case the bleed size was 0.3mL. SHOT has concerns that clinical staff may become deskilled if all management decisions in such cases are made by the laboratory, and this may cause errors if the clinical staff then transfer to another hospital where the laboratory do not 'actively manage' such cases, as the clinical staff would be unaware that bleeds >4 mL require follow up to check that fetal cells are cleared.

Case 11.7: Misinterpretation of antibody screen at 28 weeks

A woman in her 40s attended the early pregnancy unit at 10 weeks gestation with vaginal bleeding. A transvaginal ultrasound scan confirmed a viable intrauterine pregnancy. Anti-D Ig was not given. At the 28-week appointment the antibody screen was weakly positive but was incorrectly assumed to be due to RAADP. The woman attended triage following trauma to her abdomen at 31 weeks gestation, 1500IU anti-D Ig was given and the Kleihauer showed <4mL fetal cells. At delivery, anti-D quantitation showed an increased level of 9.7IU/mL and the baby required phototherapy.

Further case studies can be found in the supplementary information on the SHOT website www.shotuk.org.

Conclusions

Clear procedures should be in place for interpretation of 28-week serology results in relation to timing of routine antenatal anti-D Ig prophylaxis. Detection of anti-D in the 28-week sample was interpreted as due to RAADP in some cases, even though the blood sample had been taken before RAADP was given. These pregnancies were, therefore, not monitored appropriately and the fetus was at risk of HDFN.

Conversely, women whose 28-week sample contained alloimmune anti-D but were given RAADP (as the serology result was received after RAADP was given) are being reported as anti-D Ig administration errors. In practice, it is recognised that most clinics do not wait for serology results before giving women RAADP, but it is important that robust procedures are in place to recall such women and ensure they are monitored correctly.

It is of note that of 14 cases (4 NPP, 10 PP) where immune anti-D was first detected at or beyond 28 weeks, 7 babies required treatment for HDFN, as some centres have questioned the need to repeat antibody screening at 28 weeks if the booking antibody screen is negative. From SHOT data, had the 28-week antibody screen been omitted, 14 women would only have had anti-D detected at an antibody screen performed at delivery and the fetus/neonate would not have been monitored in utero or following delivery: half of them required phototherapy.

It is always a balancing act when detecting D-variants. From the perspective of a maternal sample ideally the anti-D reagent would either produce a negative result or a sufficiently weak result that it is investigated as a possible D-variant; thus the individual is treated as a D-negative in terms of management of pregnancy and is in receipt of anti-D Ig until the D-type is confirmed. If testing a cord sample, however, you would want to detect any D-variants as positive, particularly if the variant is known to stimulate anti-D production. The strength of reactivity of partial D antigens with those anti-D reagents that react with them may be weaker than that of normal D-positive cells (e.g. DVI), similar to normal D-positive cells (e.g. DIII), or may even appear to have elevated D expression (e.g. DIVa). It is difficult to make recommendations regarding all D-variants since some D-variants react with all anti-D except those produced by an individual with the same D-variant (e.g. DIII).

The current guidelines only cover testing for DVI, this is because it is known that this has the lowest number of D epitopes, and is therefore the most likely to form anti-D if transfused with D-positive blood. With other D-variants it is difficult, if not impossible, to make recommendations regarding detectability with routine anti-D reagents. In general, a straightforward 3+ or 4+ reaction can be reported as D-positive, but a 2+ or less should be investigated further. (R. Haggas, UK NEQAS, personal communication).

Clinical and laboratory staff need to be aware of the importance of following up women who have a FMH of >4 mL to ensure clearance of fetal cells, as although anti-D Ig may be issued the laboratory cannot be sure that it has been administered effectively (or at all!) and the potential for immunisation is high.

Now that the majority of women receive RAADP in the form of one injection of anti-D Ig 1500IU between 28 and 30 weeks gestation, there remains the outstanding question of whether, if the pregnancy extends beyond 40 weeks, an additional dose of prophylactic anti-D Ig required and if so, when should this be given. ‘There is insufficient evidence at this time to make a recommendation for or against administering another dose of anti-D Ig to an unsensitised D-negative woman who remains undelivered at 40 weeks’ (Fung and Eason 2018).

There are several other remaining questions on ideal management to prevent immunisation in D-negative pregnancies, including the increased risk in obesity, the risks of immunisation in complex pregnancies with pathological placental circulation, the possible increased risk of immunisation in twin pregnancy, impact of cell salvage and the risks (if any) in medical termination with no instrumentation. Continued data collection on newly diagnosed cases of alloimmune anti-D may provide answers to these important outstanding questions.

The database now has sufficient cases to enable more detailed analyses. Initially, SHOT experts are planning to interrogate the data for ideal cases (those women who experienced no PSE and who received RAADP and postpartum prophylaxis) and see how many of these women were obese and/or whose gestation extended beyond 40 weeks in the index and/or preceding pregnancy. SHOT also plan to look in more detail at women who experienced PSE which was managed appropriately according to current guidance but who became immunised, with particular emphasis on early pregnancy events.

From 2018, SHOT has been collecting data on cffDNA testing to provide evidence and learning from errors, particularly interpretation of results.

References

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