Immune Anti-D in Pregnancy n=42 27

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Definition:

Cases of D-negative pregnant 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.

Abbreviations used in this chapter

APH	Antepartum haemorrhage	**IUD**	Intrauterine death
BMI	Body mass index	**IV**	Intravenous
BSH	British Society for Haematology	**NICE**	National Institute for Health and Care Excellence
cffDNA	Cell-free fetal deoxyribonucleic acid	**NPP**	No previous pregnancies
FMH	Fetomaternal haemorrhage	**PP**	Previous pregnancies
HDFN	Haemolytic disease of the fetus and newborn	**PSE**	Potentially sensitising event
IAT	Indirect antiglobulin test	**PVB**	Per vaginal bleeding
Ig	Immunoglobulin	**RAADP**	Routine antenatal anti-D Ig prophylaxis

Key SHOT messages

- There are ongoing missed opportunities where pregnancy management is not ideal
- Obesity, delivery beyond 40 weeks and high FMH are potential risk factors for D sensitisation
- Cases of D sensitisation are still occurring even when best practice is followed
- Lack of long-term follow-up of patients following significant FMH impacts management of future pregnancies as immune anti-D may not be detected promptly
- In cases where immune anti-D resulted from an error related to anti-D Ig administration, SHOT reports should be submitted for both categories

Recommendations

- Healthcare organisations must ensure that local policies reflect national guidance to allow best practice
- Healthcare organisations must embed a reviewing process of local policies against current versions of national guidance

Action: Healthcare organisations, transfusion service managers, maternity teams

- Hospital transfusion teams should perform a comprehensive investigation with a system-focused approach when pregnancy management is not ideal

Action: Healthcare organisations, hospital transfusion teams, maternity teams

- Training, education resources and competency-assessments relating to anti-D Ig administration and management of D-negative pregnancies must be extended to non-maternity services e.g., non-gynaecology wards and emergency departments

Action: Training leads

- Cases of immune anti-D found for the first time in pregnancy should be reported to SHOT, aiming to provide a complete data set after delivery

Action: Transfusion teams

Introduction

To improve understanding of the causes of continuing anti-D immunisations, SHOT has been reviewing cases where immune anti-D has been detected for the first time in the current (index) pregnancy since 2012. The reporters are requested to provide data on booking weight and BMI, management of sensitising events during pregnancy and the administration of RAADP, both in the index pregnancy and the pregnancy immediately before the index pregnancy (if applicable). In cases where patients had been previously pregnant, details of delivery including anti-D Ig administration should be reported.

Results

In 2023 a total of 42 cases were reported, 7 cases occurred in women with NPP, and 35 in women with PP. Reporting is fairly consistent, however, the available data would suggest that D sensitisation in pregnancy remains under-reported (see the assumptions and calculation provided in the 2018 Annual SHOT Report (Narayan, et al., 2019)).

Cumulatively SHOT now has useful data on 139 women with NPP and 388 women with PP.

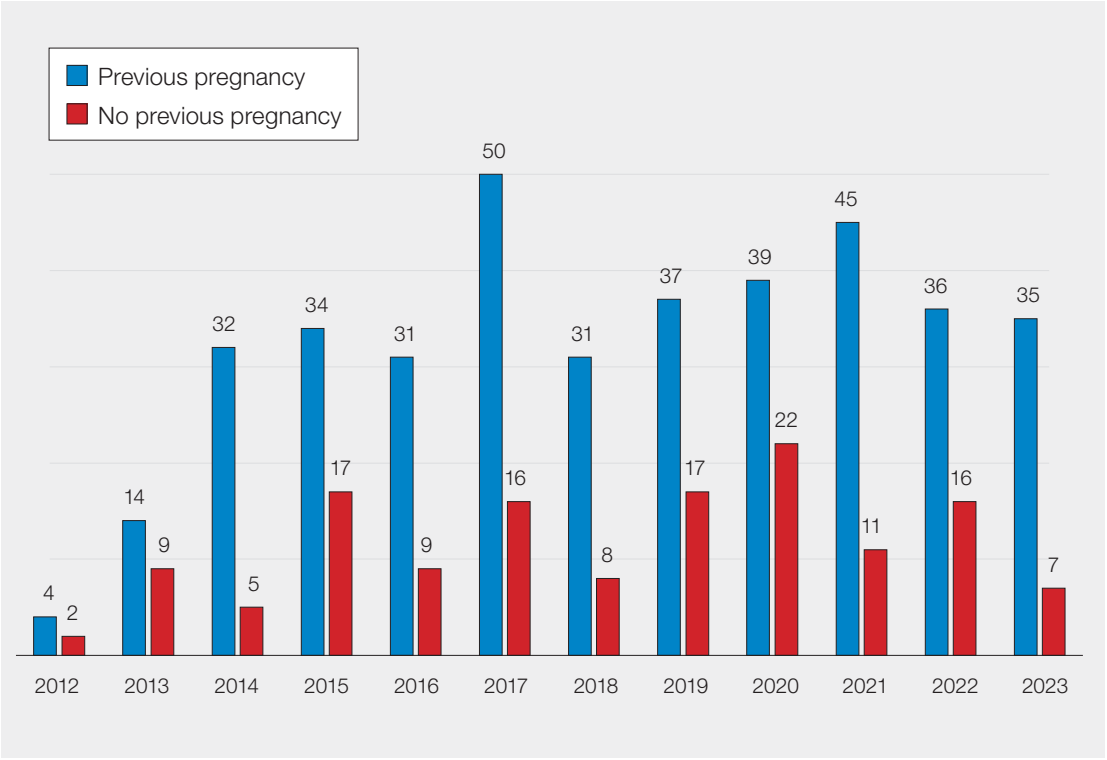

Figure 27.1: Number of reports of anti-D immunisation in pregnancy by year, 2012-2023

No previous pregnancy (NPP) n=7

For a detailed discussion of the NPP cases, and tables containing similar details to those published in previous Annual SHOT Reports, please see the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2023/).

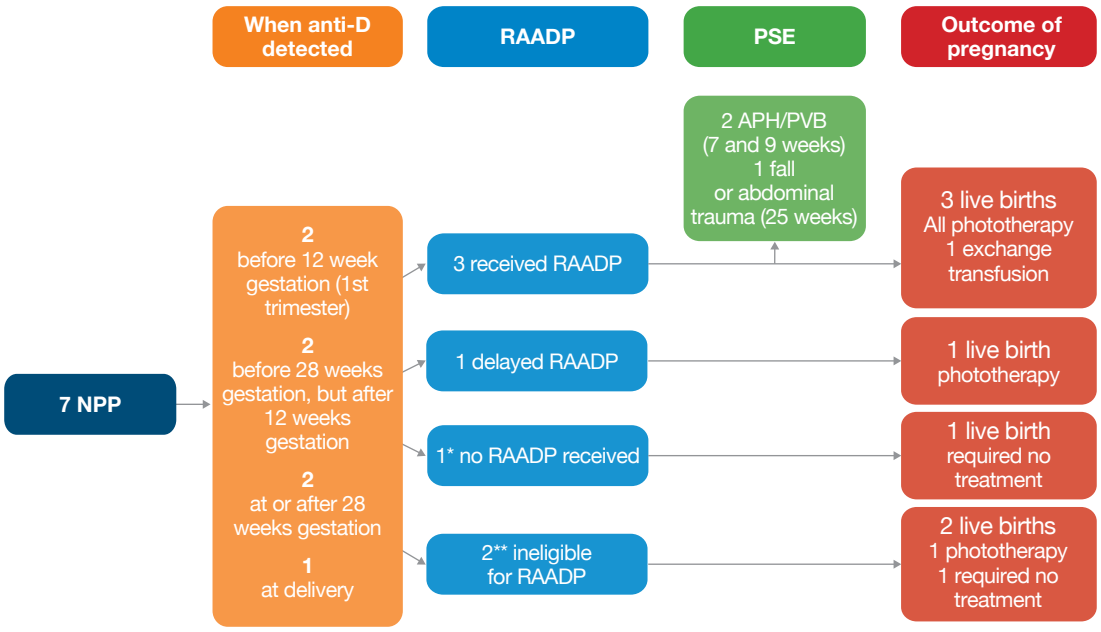

Figure 27.2: Summary of the 2023 NPP data (n=7)

APH=antepartum haemorrhage; NPP=no previous pregnancy; PSE=potentially sensitising event; PVB=per vaginal bleeding; RAADP=routine antenatal anti-D Ig prophylaxis

**RAADP appointment was not arranged. Anti-D detected at 38 weeks gestation*

***Immune anti-D detected before 28 weeks gestation (at 11 weeks and 9 weeks gestation)*

Illustrative cases

Case 27.1: Incorrect management of pregnancy results in development of clinically significant antibodies

A woman delivered at 38^{+6} weeks gestation and suffered post-partum major haemorrhage. Anti-D and anti-C were detected in this sample for the first time. This could have led to a delay in issuing crossmatched units while further testing was performed, but fortunately there was no delay in providing appropriate blood. During pregnancy, the woman had not received RAADP and was not offered cffDNA testing to enable correct management of pregnancy and prevent development of clinically significant antibodies.

The initial anti-D Ig error in this case has been described in Chapter 9: Adverse Events Related to Anti-D Immunoglobulin (Ig) in the major morbidity section.

The presence of maternal alloantibodies not only affects blood supply at delivery but also future transfusions and subsequent pregnancies. The requirement for antigen-negative red cells and IAT crossmatch can cause delays with potential adverse consequences for the patient including unavailability of suitable red cells. In emergency situations, the benefit versus risk of haemolytic transfusion reaction needs to be assessed by the clinical team on a case-by-case basis. In Case 27.1, emergency O D-negative red cells should be suitable for transfusion as the phenotype selected for these units are C- and E- (rr). It is important to note that emergency group O red cells may not always be suitable for patients with alloimmunisation to other antigens from different blood group systems.

Case 27.2: High anti-D level contributed to premature induction of labour

A woman attended the early pregnancy assessment unit with pain and bleeding at 9^{+5} weeks gestation. Pregnancy booking had been completed and the blood group was available. Anti-D Ig was not administered as per organisational guidelines. Immune anti-D was detected at 28 weeks. At 34^{+5} weeks the anti-D quantification was 170.6IU/mL. Labour was induced at 34^{+5} weeks. After delivery the baby required double volume exchange transfusion and phototherapy due to HDFN and recovered.

In this pregnancy, the management following PSE was not ideal and was likely the cause of the D sensitisation. According to the current BSH guideline, PSE in pregnancies occurring at <12 weeks gestation where uterine bleeding is associated with abdominal pain require administration of a minimum 250IU anti-D Ig (Qureshi, et al., 2014). Healthcare organisations must ensure that local policies reflect national guidance for best practice. In this case the presence of immune anti-D resulted in premature induction of labour, and consequently the baby required phototherapy as well as double volume exchange transfusion as part of the treatment for HDFN.

Learning points

- The presence of alloantibodies has an impact in blood provision for mother and baby with potential to cause delays due to blood unavailability and serological crossmatch requirement
- Local policies must reflect national guidelines for best practice to avoid maternal alloimmunisation

Previous pregnancies (PP) n=35

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

For a detailed discussion of the PP cases, and tables containing similar details to those published in previous Annual SHOT Reports, please see the supplementary information on the SHOT website (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2023/).

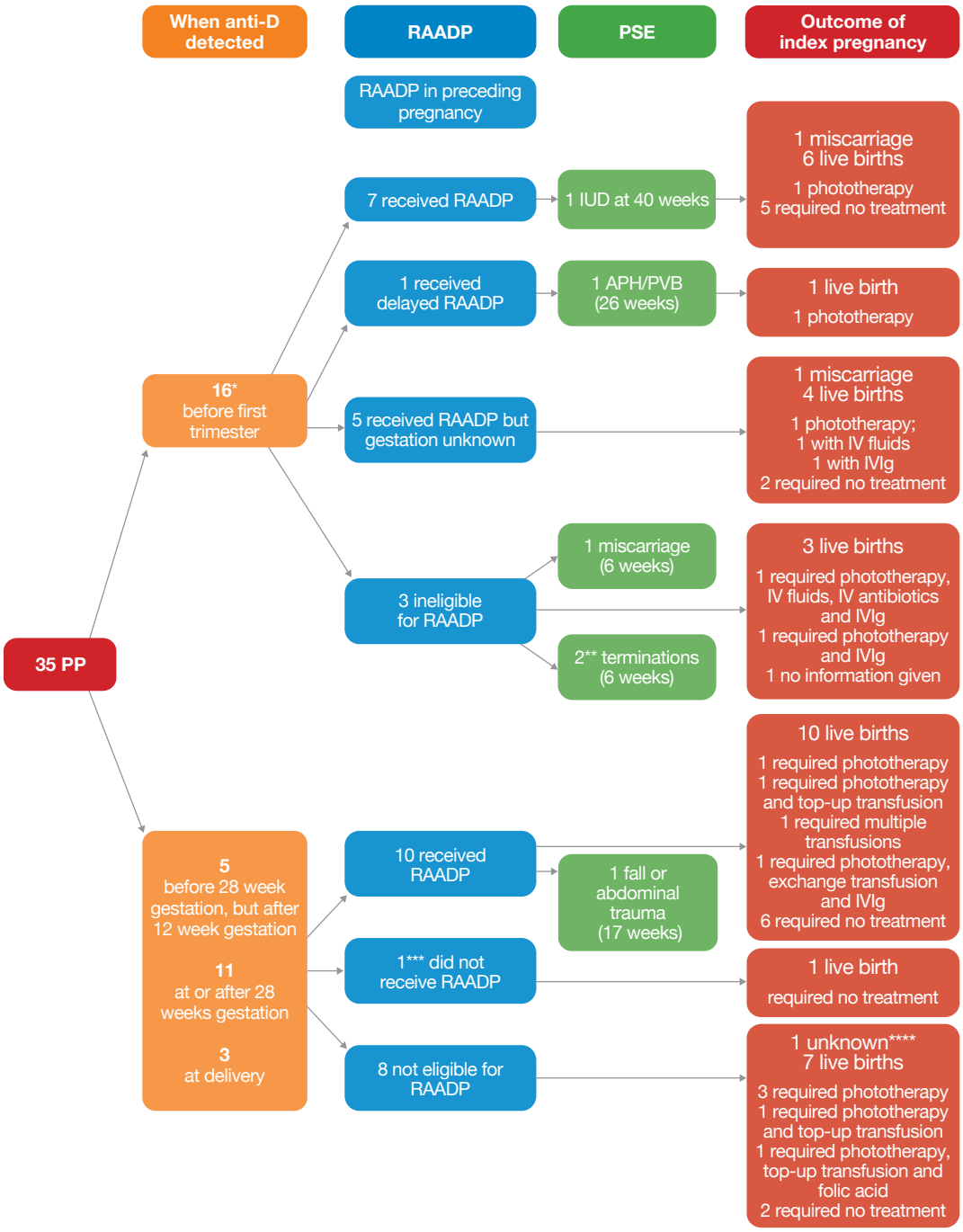

Figure 27.3: Summary of the 2023 PP data (n=35)

APH=antepartum haemorrhage; IUD=intrauterine death; IV=intravenous; IVIg=intravenous immunoglobulin; PP=previous pregnancy; PSE=potentially sensitising event; PVB=per vaginal bleeding; RAADP=routine antenatal anti-D Ig prophylaxis

**In 1 case, the anti-D was detected at delivery in previous pregnancy but regarded as prophylactic. Detected at booking in the index pregnancy*

***No information provided of the gestation when pregnancy was terminated*

****D-variant, patient regarded as D-positive throughout pregnancy*

*****Patient moved to India*

Illustrative cases

Case 27.3: Two-dose RAADP regime and no group and screen sample at delivery

Immune anti-D was detected for the first time at booking (11^{+2} weeks) during the 4^{th} pregnancy. No red cell antibodies were detected in the previous pregnancy up to 1 month prior to delivery (no group and screen sample taken at delivery). The Kleihauer test performed after delivery at 36 weeks

gestation estimated <2mL fetal bleed and 500IU anti-D Ig was given within 72 hours. The RAADP regime followed in the preceding pregnancy was two 500IU doses.

In this case, D sensitisation was not confirmed as to have occurred prior to or after delivery as a group and screen sample was not taken post delivery. From the information provided, the postnatal management appeared to be correct considering the estimated FMH, dose of anti-D Ig administered and the time frame of administration (within 72 hours). In 2023, cases of D sensitisation continue to be reported to SHOT where the management of pregnancy was deemed to be appropriate.

Current guidelines recommend either a two-dose regime (2x500IU) or one-dose regime (1x1500IU) (NICE, 2008). The one-dose regime has been associated with higher compliance as the patient only needs to attend one appointment (MacKenzie, et al., 2011). However, the two-dose regime can provide a higher protection to D sensitisation. A study conducted in Australia showed that a higher proportion of women who had received a two-dose RAADP regime had detectable anti-D Ig levels at delivery compared to those who had received a one-dose regime (White, et al., 2019).

Case 27.4: Immune anti-D detected for the first time in a patient with multiple risk factors for D sensitisation and previous IUD

Immune anti-D was detected for the first time in the index pregnancy at 12^{+1} weeks gestation. The patient had a high BMI >30 in both the previous and index pregnancies. This was the fifth pregnancy, with two previous live births, one miscarriage and one IUD.

The preceding pregnancy resulted in an IUD at 40^{+4} weeks gestation. The FMH volume was 56mL and 5600IU anti-D Ig was administered IV. In the follow-up sample, taken 48 hours after anti-D Ig administration and after delivery of the stillbirth at 40^{+5} weeks, a repeat FMH sample detected a fetal bleed volume of 4mL and further 500IU of anti-D Ig was administered. No follow-up sample was taken after the repeat 500IU dose. It is unclear if the decision to not take further follow-up samples for FMH testing was discussed with the haematology consultant.

In this case, there were multiple risk factors for D sensitisation; delivery beyond 40 weeks gestation, high BMI, and previous high volume FMH. In cases where multiple risk factors are present, it may be beneficial to consider a follow-up after 6 months for assessment of D sensitisation. Current BSH guidelines for FMH considers long term follow-up following significant FMH (Austin, et al., 2009) but it might be of benefit to extend this consideration to other risk factors. In addition, it is recommended that follow-up samples should be taken every 72 hours post anti-D Ig administration until fetal cells are no longer identified in the FMH test (Austin, et al., 2009).

Good practice was noted in this case as the treating team administered anti-D Ig IV appropriately in view of the high volume of fetal bleed and a follow-up sample was taken within the correct time frame considering the route of administration (48 hours when anti-D Ig administered IV).

Learning points

- When fetal cells are detected on follow-up samples, repeat FMH testing should be continued until clearance of fetal cells is confirmed
- The benefit of a long-term D sensitisation follow-up should be considered on a case-by-case basis

Conclusion

The 2023 data demonstrate that issues continue to occur in the management of D-negative pregnant patients. This is not only reflected in this chapter but also in Chapter 9, Adverse Events Related to Anti-D Immunoglobulin (Ig). The cases reported in both categories highlight missed opportunities for correct management relating to anti-D Ig administration following PSE and RAADP.

In 2 cases, the immune anti-D was assumed to be prophylactic where there were no records of anti-D Ig administration in the index pregnancy. In 1 case, the patient did not receive anti-D Ig following a PSE (>20 weeks gestation) nor as part of RAADP.

When considering risk factors for immune anti-D, it is important to evaluate not only the physical factors such as high BMI, large FMH and delivery beyond 40 weeks gestation, but also social and mental health factors that may impact patient's access to receive optimal treatment. These are contributory factors for non-compliance or non-reporting PSE during pregnancy and can result in incomplete, insufficient or absence of management throughout pregnancy.

When reporting these cases to SHOT, it is important to provide the BMI as well as the weight at booking because the BMI can provide a more accurate estimation of the risk obesity poses to D sensitisation.

SHOT appreciate that the information relating to previous pregnancies is not always easily accessible. However, to identify and understand the possible causes for D sensitisation, especially in those cases where the anti-D is detected at booking in the index pregnancy, the report should be completed as fully as possible.

Recommended resource

SHOT Bite No.29: Differences of reporting errors related to anti-D Ig and immune anti-D
https://www.shotuk.org/resources/current-resources/shot-bites/

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