Immune Anti-D in Pregnancy n=54 24

Authors: Susan Robinson and Jane Keidan

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.

Key SHOT messages

- Cases of immunisation are still occurring even where current best practice is being followed
- Cases of alloimmune anti-D found for the first time in pregnancy should be reported to SHOT, aiming to provide a complete data set after delivery
- Obesity and delivery beyond 40 weeks remain as risk factors for sensitisation in cases which are otherwise ideally managed
- Although managed in accordance with current guidelines, postpartum fetomaternal haemorrhage (FMH) >4mL, is an emerging possible risk factor
- Following large FMH, every effort should be made to confirm all fetal cells are cleared, whilst balancing maternal contact and the upheaval of attending hospital repeatedly
- There is a continued need to audit the anti-D pathway and provide ongoing education to clinical staff and pregnant women, and tools to support best practice

Abbreviations used in this chapter

APH	Antepartum haemorrhage	**NHSBT**	NHS Blood and Transplant
BMI	Body mass index	**NICE**	National Institute for Health and Care Excellence
BSH	British Society for Haematology	**NIPT**	Non-invasive prenatal testing
cffDNA	Cell-free fetal deoxyribonucleic acid	**NPP**	No previous pregnancies
FMH	Fetomaternal haemorrhage	**PP**	Previous pregnancies
HDFN	Haemolytic disease of the fetus and newborn	**PPP**	Postpartum prophylaxis
Ig	Immunoglobulin	**PSE**	Potentially sensitising event
IT	Information technology	**RAADP**	Routine antenatal anti-D Ig prophylaxis
NHS	National Health Service	**UK**	United Kingdom

Introduction

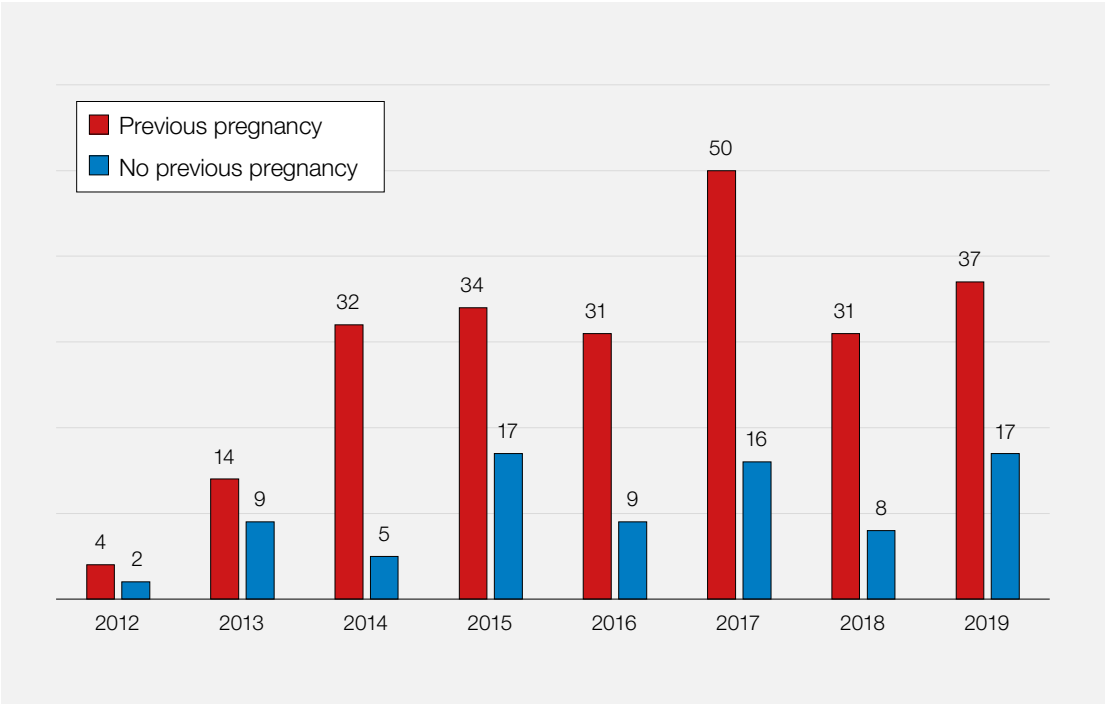
To improve understanding of the causes of continuing anti-D immunisations, since 2012 SHOT has been reviewing cases where immune anti-D has been detected for the first time in the current (index) pregnancy. The reporters are requested to provide data on booking weight, management of sensitising events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

Results

In 2019 a total of 54 cases were reported, 17 cases occurred in women with no previous pregnancies (NPP), and 37 in women with previous pregnancies (PP). It is reassuring to note that the downward trend in reporting has reversed this year, as the available data would suggest that anti-D immunisation 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 83 women with NPP and 233 women with PP.

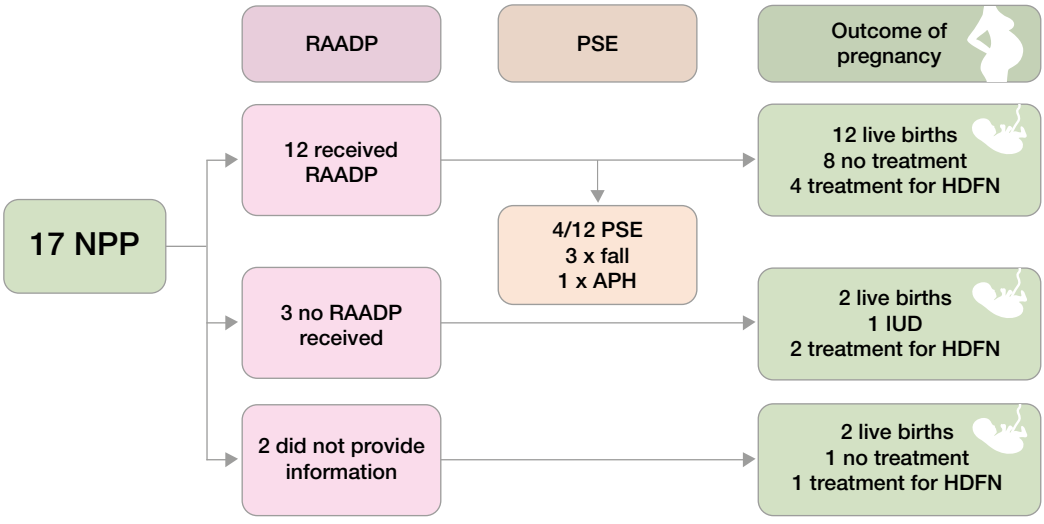
Figure 24.1: Number of reports of anti-D immunisation in pregnancy by year, 2012-2019



No previous pregnancy (NPP) n=17

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-2019/).

Figure 24.2: Summary of 2019 NPP data n=17



Note: The 4 PSE cases did not result in treatment for HDFN

NPP=no previous pregnancy; RAADP=routine antenatal anti-D Ig prophylaxis; PSE=potentially sensitising event; APH=antepartum haemorrhage; HDFN=haemolytic disease of the fetus and newborn; IUD=intrauterine death

Illustrative cases

Case 24.1: Detection of alloimmune anti-D in the third trimester

A primiparous woman in her 20s, was booked at 19 weeks gestation (booking weight 70kg) and no alloantibodies were detected. A group and antibody screen was taken at 27 weeks and routine antenatal anti-D Ig prophylaxis (RAADP) given prior to the result being received. Alloimmune anti-D was detected, quantification 0.1IU/mL. The laboratory biomedical scientist and midwife checked the records with the woman to confirm this was prior to RAADP and no prophylaxis had been administered earlier in pregnancy. The peak quantification was 6.5IU/mL at 34 weeks. The baby was delivered at 37 weeks gestation and required phototherapy.

Alloimmune anti-D was detected at routine follow up at 27 weeks in a first pregnancy, with no prior potentially sensitising events (PSE). This case highlights the need to ensure antibody screening at 28 weeks to identify cases presenting for the first time in the third trimester.

Case 24.2: Ideal treatment

A primiparous woman in her late 20s, with a booking weight of 63kg was booked at 9 weeks gestation. She was D-negative, and no alloantibodies were detected. RAADP was given at 28 weeks, then, following a fall at 31 weeks gestation, received an additional 1500IU dose of prophylactic anti-D Ig within 24 hours. The FMH was <2mL. Serology was performed at 32 weeks gestation and detected anti-D, with a quantification of 0.1IU/mL. A further sample was taken at 40 weeks gestation; anti-D quantification 0.4IU/mL. A D-positive baby was delivered at 40 weeks and the baby required no interventions for haemolytic disease of the fetus and newborn (HDFN).

Ideal management may not always prevent sensitisation and further work is needed to explore this.

Case 24.3: Detection of low-level alloimmune anti-D with no reported cause

A teenager presented at 8 weeks gestation, with no prior transfusion or pregnancy history. Anti-D was detected with a quantification 0.1IU/mL, which did not increase during pregnancy. A D-positive baby was delivered at 39 weeks gestation, there were no PSE, and the baby required no interventions for HDFN.

The significance of this low anti-D quantification is unclear. Where alloimmune anti-D is detected in NPP at booking, there may have been a preceding 'undeclared', or even unknown, early pregnancy.

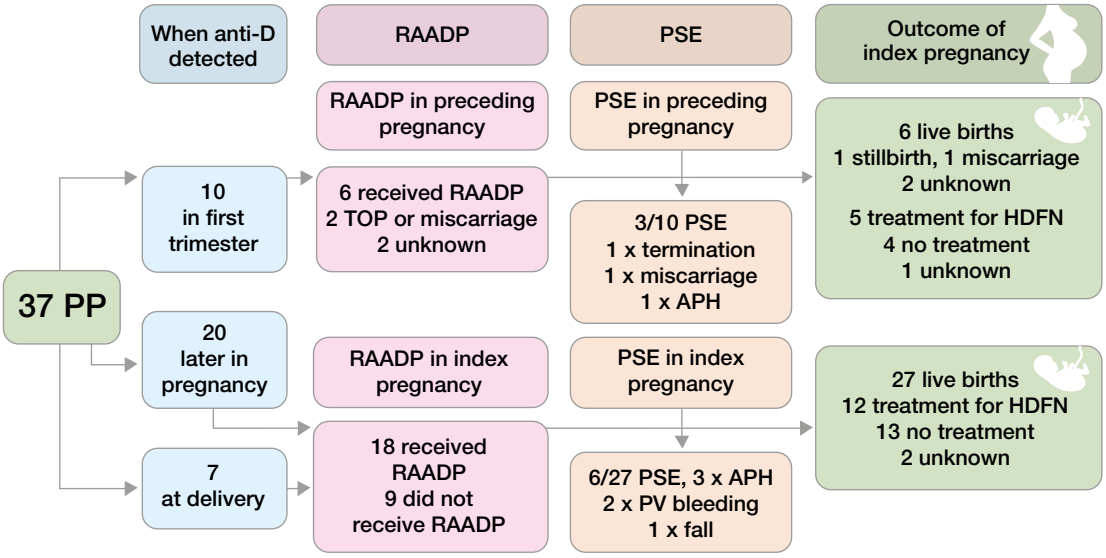
Previous pregnancies (PP) n=37

The index pregnancy in these cases refers to the current pregnancy i.e. the pregnancy in which alloimmune anti-D was first detected. Where alloimmune anti-D is 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 this demographic).

Where anti-D is detected later in the index pregnancy, the relative contribution of events in the previous and index pregnancy is less certain.

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-2019/).

Figure 24.3: Summary of 2019 PP data n=37



PP=previous pregnancy; RAADP=routine antenatal anti-D Ig prophylaxis; TOP=termination of pregnancy; PSE=potentially sensitising event; APH=antepartum haemorrhage; PV=per vaginum; HDFN=haemolytic disease of the fetus and newborn

Illustrative cases

Case 24.4: Large FMH where clearance of fetal cells was not checked

A woman in her 30s, gravida 2 para 1 (booking weight 48kg) had anti-D detected at 7 weeks gestation with a quantification of 7.2IU/mL, which peaked at a quantification of 23.3IU/mL. A cell-free fetal deoxyribonucleic acid (cffDNA) test at 16 weeks gestation predicted a D-positive fetus. A fetal intrauterine transfusion was given, and she delivered at 34^{+6}. Neonatal treatment for HDFN included phototherapy, immunoglobulin and exchange transfusion. In the preceding pregnancy vaginal bleeding occurred at 16 weeks gestation and she received 1500IU anti-D Ig. RAADP was given at 28 weeks gestation. She delivered at 35^{+6} by emergency caesarean section. A FMH of 79mL was confirmed by flow cytometry. She received 12000IU intravenous anti-D Ig, and the follow up FMH test at 48 hours showed 1mL fetal cells. She received a further 1500IU anti-D Ig, but it was not subsequently checked if the fetal cells had cleared completely.

In the preceding pregnancy, a large FMH occurred and was treated with anti-D Ig and follow up but did not check fetal cells were completely cleared, Subsequent sensitisation may suggest a non-linear pharmacokinetic relationship between a follow up FMH test in this setting showing <2ml fetal cells and the expectation that a further 1500IU anti-D Ig would clear the remaining fetal cells; other possibilities include chronic recurrent small FMH before delivery etc.

Case 24.5: Ideal management of large FMH

A woman in her 20s, gravida 2 para 1, booked at 8 weeks gestation, with a booking weight of 75kg. Anti-D was detected with a quantification of 0.3IU/mL. The peak quantification at 23 weeks gestation was 68.5IU/mL and an intrauterine transfusion was performed. The pregnancy was further complicated by maternal medical complications and resulted in a stillbirth. The previous pregnancy was booked at 9/40, RAADP was received at 29 weeks gestation, and she delivered at 40^{+1}. There was 16mL FMH, she received 3000IU anti-D Ig, and a follow up FMH test demonstrated complete clearance of fetal cells.

This case demonstrates even in cases where management is apparently ideal sensitisation may still occur.

Case 24.6: Delivery at 42^{+3} weeks in preceding pregnancy which was otherwise ideally managed

A woman in her 30s, gravida 2 para 1, booked at 9^{+5} weeks gestation, with a booking weight of 61.8kg. Anti-D was detected at booking with a quantification of 0.7IU/mL. Peak quantification in the pregnancy was 0.9IU/mL, and a D-negative infant was delivered. In the preceding pregnancy the woman received RAADP and experienced no PSE. However, she delivered vaginally at 42^{+3} weeks and the baby was D-positive. No test for quantitation of FMH was performed, and a standard dose of anti-D Ig was given into the deltoid within 24 hours of delivery.

The only risk factor in this case was delivery at 42^{+3} weeks in the preceding pregnancy.

Case 24.7: Home birth

A woman in her 20s, gravida 2 para 1, had no details available for her preceding pregnancy of booking weight or serology, RAADP administration, PSE or delivery except that it was a home delivery with no FMH test postpartum. Postpartum prophylaxis (PPP) was administered 3 days after delivery. In the index pregnancy, alloimmune anti-D was found at 10 weeks when the woman attended for termination of pregnancy.

The care offered to women who deliver at home should comply with best practice to avoid alloimmunisation.

Case 24.8: Obese, previous miscarriage, antepartum haemorrhage (APH) in index pregnancy

A woman in her 30s, gravida 2 para 1, experienced an early miscarriage at 5-6 weeks in her previous pregnancy. No anti-D Ig was given and was not indicated. She booked for the index pregnancy at 8^{+5} weeks gestation, with a booking weight of 97kg and body mass index (BMI) of 32. An APH occurred at 22 weeks, the flow cytometry was negative, and 1500IU anti-D Ig was given intramuscularly within 24 hours. Follow up testing at 25 weeks showed low level anti-D (0.1IU/mL) which was thought to be due to prophylactic anti-D Ig given to cover the APH. Blood Service advice was to continue with prophylactic anti-D Ig, so RAADP was given at 28 weeks and the anti-D level was monitored every 2 weeks. The level peaked at 2.9IU/mL at 38 weeks. A healthy D-positive baby was delivered and required no treatment for HDFN.

Despite optimal management of APH, an obese woman became immunised.

Case 24.9: Failure to inform the laboratory of a PSE

Woman in her 30s, gravida 2 para1, received RAADP in the preceding pregnancy at 29 weeks. She experienced spotting at 35^{+2} weeks, but the midwife did not inform the laboratory so no prophylaxis was issued or given. She was delivered by elective caesarian section at 38^{+1} weeks and received appropriate PPP. In the index pregnancy alloimmune anti-D was detected at 28 weeks (not present at booking) and the infant was born at 38^{+2} weeks and required phototherapy.

The midwife failed to take appropriate action when the woman reported spotting at 35 weeks.

Case 24.10: Twin pregnancy

A woman in her 30s had a preceding pregnancy that was ideally managed. In the index pregnancy she booked at 13 weeks with a twin pregnancy. Due to a hospital error she did not receive an appointment for RAADP. The twins were delivered at 36 weeks when the woman was found to have alloimmune anti-D of 0.75IU/mL. Despite the low titre, the infants required treatment for HDFN.

Twin pregnancies may be at increased risk of sensitisation as previously observed but in this case, there was also omission of RAADP due to hospital administration error.

Case 24.11: Obese woman with previously ideally managed caesarian delivery who developed immune anti-D at term in index pregnancy

A woman in her 30s, gravida 2 para 1, had a booking weight in the preceding pregnancy of 118kg (BMI 42.8). She received RAADP of 1500IU anti-D Ig into the deltoid muscle at 27 weeks gestation and delivered at 42 weeks by emergency caesarian section. No FMH test was performed, and she was given 1500IU anti-D Ig PPP into the deltoid. In the index pregnancy, alloimmune anti-D was

detected at delivery at 40 weeks. The woman had experienced an APH at 17 weeks for which she received 1500IU anti-D Ig into the deltoid. She also received RAADP into the deltoid at 28^{+6} weeks. The infant required no treatment for HDFN.

Despite receiving correct management in preceding and index pregnancies, the woman became immunised, possibly because her obesity made the anti-D Ig she received less effective.

Conclusions

The data this year, detailed online (https://www.shotuk.org/shot-reports/report-summary-and-supplement-2019/), continue to demonstrate issues around ideal management of D-negative women during pregnancy to prevent immunisation, including the correct management of FMH >4mL. Every effort should be made to confirm all fetal cells are cleared following a large FMH, whilst balancing maternal contact and the upheaval of attending hospital repeatedly. Subsequent sensitisation may suggest a non-linear pharmacokinetic relationship between a follow up FMH in this setting of <2mL and the expectation a further 1500IU anti-D Ig would clear the remaining fetal cells; other possibilities include chronic recurrent small FMH before delivery etc.

There are several other emerging questions on ideal management from the cumulative data including the increased risk in obesity, the increased risk of gestation beyond 40 weeks, 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.

Recent introduction of data collection on cffDNA highlights ongoing barriers to implementation and indicates a need to update and expand this section to include distinct response fields relating to:

- High-throughput non-invasive prenatal testing (NIPT) for fetal D genotype as recommended by the National Institute for Health and Care Excellence (NICE) as a cost-effective option to guide antenatal prophylaxis with anti-D Ig
- Fetal blood group D genotyping following the detection of maternal alloimmune anti-D

This will provide further clarity around current practice and identify potential errors which may include inappropriate testing, wrong blood in tube, laboratory testing and resulting errors, transcription of results and interpretation of results.

A United Kingdom (UK) audit is recommended to determine current practice in relation to screening for fetal D type and identify the barriers local services face. Whilst these data reflect UK centres who have submitted cases where sensitisation has been detected, only 1 appeared to have implemented screening. Following NICE recommendations in 2016 (NICE 2016), 58% of services identified in England have either commenced or plan to send samples to National Health Service Blood and Transplant (NHSBT) for cffDNA testing. However, to date the sample volumes received by NHSBT do not represent the anticipated volumes. This might be due to various reasons, which could include partial implementation at Trusts/Health Boards or reluctance of women to have the test, either for personal reasons or fear of genetic tests (personal communication NHSBT).

A further issue with regards to cffDNA reporting is access to the results within hospital information technology (IT) systems. A pilot is in progress to look at the electronic transfer of results for cffDNA to hospital IT systems to enable auditability of data, reduce transcription errors and improve the timely availability of results to clinical staff (personal communication NHSBT).

The British Society for Haematology (BSH) anti-D guideline writing group published an addendum to the website to address both NICE Guidelines NG126 (NICE 2019a) and NG140 (NICE 2019b).

The 2019 data suggest:

- Ideal management does not equal no sensitisation
- Delivery beyond 40 weeks may be a risk factor for sensitisation even when managed appropriately
- A postpartum FMH >4mL may be a risk factor for sensitisation even when managed appropriately
- Women who are obese may not be adequately 'protected' by standard doses of anti-D Ig
- The continued need to audit the anti-D pathway and provide ongoing education and tools to support best practice. Management is not always ideal

Further work needed

A national audit of new practices recently introduced in the management of D-negative pregnancies is recommended, to look at current practice in relation to high-throughput NIPT for fetal D genotype screening and identify the implementation barriers local services face and the pathways are in place to enable fetal blood group D genotyping following the detection of maternal alloimmune anti-D.

The data collected regarding cffDNA testing will be revised to distinguish data regarding high-throughput NIPT for fetal D genotype and fetal blood group D genotyping following the detection of maternal alloimmune anti-D.

A review of the cumulative data with regards to obesity, delivery beyond 40 weeks and FMH >4mL should be undertaken to see if the data provide enough evidence to modify current guidelines.

References

Narayan S (Ed), Poles D, et al. (2019) on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. The 2018 Annual SHOT Report. https://www.shotuk.org/shot-reports/ [accessed 08 June 2020].

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