15 Immune Anti-D in Pregnancy: Cases reported up to the end of 2017

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New questions arising from these data:

- Now that the majority of women receive routine antenatal anti-D prophylaxis (RAADP) in the form of one injection of 1500 international units (IU) of anti-D immunoglobulin (Ig) between 28 and 30 weeks gestation, if the pregnancy extends beyond 40 weeks, especially beyond late term (41-42 weeks), is an additional dose of prophylactic anti-D Ig required, particularly in obese women?
- Does obesity pose an increased risk of sensitisation, especially in the presence of other risk factors?
- Do placenta accreta and other pathological placentae pose an increased risk of fetomaternal haemorrhage (FMH) in the absence of overt antepartum bleeding?

Recommendations

- Clearer advice for healthcare professionals and women on the use of anti-D immunoglobulin (Ig) in early pregnancy
  - United Kingdom (UK) guidance of the use of anti-D Ig prophylaxis (BSH Qureshi et al. 2014) should be reviewed to avoid conflicting and thus confusing advice, especially in early pregnancy. The definition of 'early pregnancy' should be harmonised (National Institute for Health and Care excellence (NICE) defines this as <13 weeks, and British Society for Haematology (BSH) as <12 weeks

Action: BSH Transfusion Task Force and NICE

- Informing and empowering women
  - All primiparous women and multiparous women with unknown D status who are identified as D-negative from booking bloods, should be informed of the results as soon as possible so that prophylaxis for early potentially sensitising events is not overlooked. This should include, as a minimum, discussion with a healthcare professional about the implications of D-negative status, explanation of potentially sensitising events and how to seek appropriate and timely advice and prophylaxis. It should include written patient information

Action: Royal College of Obstetricians and Gynaecologists, Royal College of Midwives

- Errors resulting from cell free fetal deoxyribonucleic acid (cffDNA) testing should be reported to SHOT
  - The introduction of cffDNA analysis to identify pregnancies with D-negative babies (where the mother does not require prophylaxis with anti-D Ig), while reducing unnecessary exposure of these women to blood products, has the potential to result in new types of error. SHOT has worked in collaboration with National Health Service Blood and Transplant (NHSBT) to add additional questions to the alloimmunisation questionnaire specifically related to cffDNA testing. The initial data will be reported next year

Action: All healthcare professionals involved in the management of D-negative women in pregnancy

- Accurate and complete datasets on women who become alloimmunised.
  - All healthcare professionals, including laboratory staff, are responsible for ensuring that women who become immunised to the D antigen in pregnancy are reported to SHOT with an accurate and complete dataset

Action: All healthcare professionals involved in the management of women in pregnancy

Introduction

To improve understanding of the causes of continuing anti-D immunisations, SHOT is conducting a prospective study of women who have produced immune anti-D 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 prophylaxis, both in the index pregnancy and the pregnancy immediately before the index pregnancy (if applicable).

Results

In 2017 a total of 68 cases were reported, 16 cases occurred in women with no previous pregnancies (NPP) and 52 in women with previous pregnancies (PP), 1 case was excluded as immunisation had occurred several years ago and 1 case was excluded as there was insufficient information available for the case to be informative. Cumulatively SHOT now has data on 58 women with NPP and 165 women with PP.

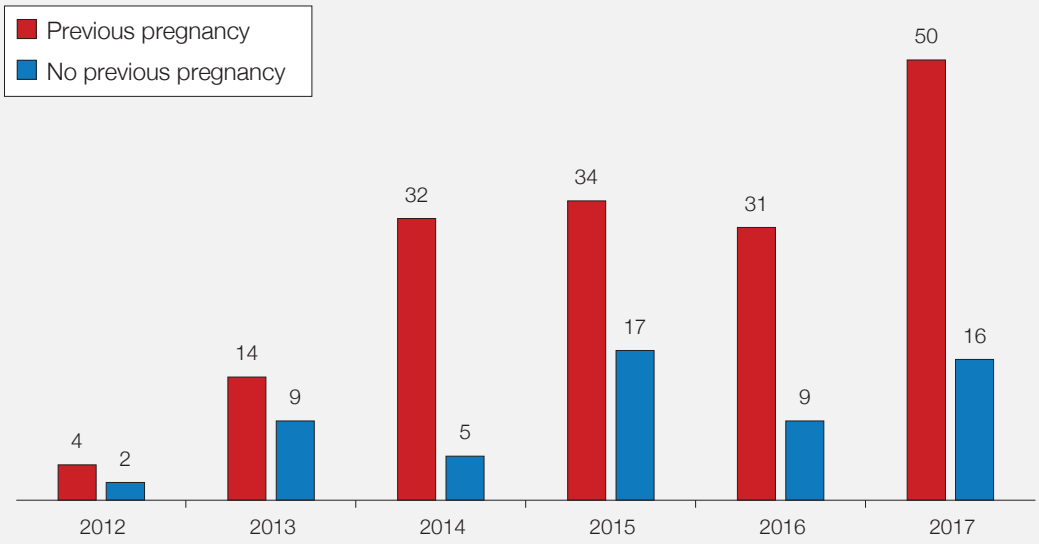

Figure 15.1: Number of reports of anti-D immunisation in pregnancy by year, 2012-2017

No previous pregnancy (NPP) n=16 in 2017, cumulative n=58

When was the alloimmune anti-D detected?

	Number of new cases 2017	Number of cases cumulative to 2017
Before 28 weeks	2	6
At or after 28 weeks, before delivery	4	15
At delivery	10	35
Other	0	1*
No information	0	1
Total	**16**	**58**

Table 15.1: Time of detection of alloimmune anti-D NPP

**Alloimmune anti-D was detected 6 months postpartum after large FMH of 12.7mL at delivery managed correctly*

What was the booking weight?

Table 15.2: Booking weight NPP

Weight at booking in kg	Number of new cases 2017	Number of cases cumulative to 2017
<68	8	29
68-80	1	5
>80 (obese)	0	7
No information	7	17
Total	**16**	**58**

Did the women receive appropriate RAADP?

Table 15.3: Details of RAADP for eligible NPP cases n=15 (2017) n=54 cumulative

RAADP regimen	Number of new cases 2017	Number of cases cumulative 2017
Single dose 1500IU at 28-30 weeks	11	44
Two dose regimen 500IU	0	1
Not given	4*	9
Total	**15**	**54 (eligible cases)**

**1 late booking, 1 refused, 1 already in labour, 1 case no reason given*

One case already had alloimmune anti-D present before RAADP was due to be given.

The route was specified in 4 cases from 2017 as intramuscular (IM) into deltoid, 1 case into gluteal region and the rest were not specified.

Details of potentially sensitising events (PSE)

Table 15.4a: Details of potentially sensitising events NPP n=15

Number of cases	PSE	Management
14	None	
1	Fall at 22 weeks	Kleihauer negative, 1500IU anti-D Ig given

One case had no information on PSE supplied.

Table 15.4b: Details for all NPP cases reported since 2012

PSE	Number of cases
None	44
7 antepartum haemorrhage (APH) 2 interventions (chorionic villous sample, amniocentesis) 2 falls 1 large FMH at delivery 1 twin pregnancy	Some women had more than one PSE

Pregnancy outcomes

In 2017 all 16 pregnancies resulted in live births of which 8 women were delivered at or before 40 weeks and 6 at more than 40 weeks. In 2 cases the gestation at delivery was not supplied. In 6/10 pregnancies where alloimmune anti-D was detected only at delivery the gestation was >40 weeks.

One baby was D-negative, but septic so did require medical intervention at birth. Ten babies had no complications, 2 required phototherapy, 2 cases required both phototherapy and exchange transfusion. In 1 case no information was submitted.

Cumulatively, all 58 pregnancies resulted in 59 live births, of which 37 had no complications, 13 babies required phototherapy and 6 cases required exchange transfusion. No details in 2 cases.

Case studies

Case 15.1: Ideal care and delivered at term

Primipara (primip) in her 30s. Booking weight 59kg. Received RAADP (single dose of 1500IU anti-D Ig at 28 weeks). There were no PSE. Alloimmune anti-D detected at term delivery (2.7IU/mL). The baby required no interventions for haemolytic disease of the fetus and newborn (HDFN).

Case 15.2: Gestation >40 weeks

Primip in her 30s. Booking weight 61kg, body mass index (BMI) 24. Received RAADP (single dose of 1500IU anti-D Ig at 28 weeks). Delivered at 42 weeks. Alloimmune anti-D detected at delivery (2.4IU/mL). There were no PSE. The baby required no interventions for HDFN.

Case 15.3: Gestation >40 weeks

Primip in her 20s. Booking weight 64kg, BMI 22. Received RAADP (single dose of 1500IU anti-D Ig at 28 weeks). There were no PSE. Delivered at 42 weeks. Alloimmune anti-D detected at delivery (7.4IU/mL). The baby required no interventions for HDFN.

Summary of 2017 NPP data update

The majority of women (10/16) were found to be immunised at delivery, and 6/10 of these cases were delivered beyond 40 weeks, all received apparently 'ideal' care, with timely RAADP and no identifiable sensitising episodes. One case was obese, and in 1 the weight was not reported.

Review of all previous years shows that there have been 26 NPP cases where alloimmune anti-D was detected only at full term delivery and 13 of these (50.0%) were delivered at >40 weeks.

***Question**:*

Now that the majority of women receive RAADP in the form of one injection of 1500IU between 28 and 30 weeks gestation, if the pregnancy extends beyond 40 weeks, is an additional dose of prophylactic anti-D Ig required and if so, when should this be given?

Previous pregnancies (PP) n=50 in 2017, cumulative n=165 cases

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

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

Time of anti-D detection	Number of new cases 2017	Number of cases cumulative total	
At booking (if first trimester)	18	68	(41.2%)
After booking to 28 weeks (includes late booking)	11	15	(8.9%)
At or after 28 weeks	11	50	(30.3%)
At delivery	8	24	(14.5%)
Other	2*	8**	(4.8%)
Total	**50**	**165**	**(100%)**

Table 15.5: When alloimmune anti-D was detected PP

**1 postpartum follow up, 1 unknown*

*** 2 preoperative assessment following pregnancy, 3 at planned follow up of large FMH at delivery where correct dose of anti-D Ig had been given, 2 unknown*

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. In the 8 women who had alloimmune anti-D detected for the first time at delivery, 3 had gestation >40 weeks.

Alloimmune anti-D was first detected at delivery in the index pregnancy in 24 pregnancies: 9 of these cases (37.5%) were delivered after 40 weeks gestation, suggesting that gestation beyond term may be a risk factor for alloimmunisation.

Information about the pregnancy immediately preceding index (current) pregnancy

One woman underwent surgical termination of her early pregnancy, 1 woman had medical termination at 6 weeks gestation (no anti-D Ig required), 3 women had miscarriages at <12 weeks, 1 woman had a stillbirth at 34 weeks, and 1 woman had an intrauterine death with large FMH at 40 weeks. Forty women had live births of which 3 resulted in D-negative babies. Twelve of these 40 live births were delivered >40 weeks gestation. In 3 cases no information was available.

Did the women receive appropriate anti-D Ig prophylaxis for pregnancy loss in preceding pregnancy?

One case received an appropriate dose (250IU) of anti-D Ig after early surgical termination at 9 weeks. Four cases required no anti-D Ig after early (<12 weeks) miscarriages (3) or medical termination (1). After the stillbirth at 34 weeks, the Kleihauer test was negative and 1500IU anti-D Ig was given. The woman whose pregnancy was complicated by an intrauterine death had a large FMH of 165mL and received a correct dose of anti-D Ig and follow up at 72 hours showed full clearance of fetal cells.

What was the booking weight of preceding pregnancy? (Cases where previous pregnancy resulted in live birth)

Table 15.6: Booking weight PP

Weight at booking in kg	Number of new cases 2017	Number of cases cumulative total
<68	12	48
68-80	1	12
>80 (obese)	12	26
No information	18	59
Total	**43**	**145**

Cumulatively, 26 out of 145 total women reported were clinically obese in the preceding pregnancy, and, of the 86 women where booking weight was provided, 26/86 (30.2%) were obese.

Did the women who carried to term receive RAADP in preceding pregnancy?

Table 15.7: Details of RAADP in preceding pregnancy

RAADP	Number of new cases 2017	Number of cases cumulative total
Single dose	25	85
Two doses	3	10
Not given	5*	21**
No information	12	31
Total	**45**	**147**

**1 case typed incorrectly as D-positive, 1 case omitted in error, 3 cases refused*

*** Learning difficulties, concealed pregnancy, needle phobic, prior to RAADP introduction (3), delivered abroad (3), no reason given (5), declined (5), typed incorrectly (1), midwife error (1)*

Note: these numbers are different from Table 15.6 as mothers with early fetal loss will not receive RAADP

In 10 cases the route was specified as deltoid, in 3 cases intravenous, in the other cases it was not specified/known.

Where no RAADP was given in preceding pregnancy (5 cases), in 2 cases alloimmune anti-D was detected at booking and in 2 further cases alloimmune anti-D was detected before RAADP had been given in the current pregnancy. Where no information on RAADP in preceding pregnancy was provided (12 cases) in 8 cases alloimmune anti-D was detected before 28 weeks (before RAADP) in the current pregnancy, and in 4 cases at booking.

Details of potentially sensitising events in preceding pregnancy for cases reported in 2017

Sixteen PSE were reported, 18 cases had no PSE and 16 had no information about PSE.

For the 16 PSE, 4 occurred at <12 weeks so no anti-D Ig was indicated or given. Eight cases were correctly managed, and 4 cases were not correctly managed. The details are given below.

- **4 cases occurred <12 weeks, no anti-D Ig indicated or given**:
  1 medical termination of pregnancy (MTOP)
  3 miscarriages
- **8 cases correctly managed:**
  1 surgical TOP, 250IU anti-D Ig
  3 APH at 14 weeks, given 250IU anti-D Ig
  1 abdominal trauma at 19 weeks, 250IU anti-D Ig
  1 APH at 36 weeks, Kleihauer indicated 2.2mL FMH, 500IU anti-D Ig
  1 intrauterine death in third trimester, Kleihauer indicated 165mL FMH, 20,000IU anti-D Ig given intravenously, no fetal cells detectable at 72 hours
- **4 cases incorrectly managed:**
  1 APH at 13 weeks, no anti-D Ig given
  1 APH at 20 weeks, unknown if anti-D Ig given but not recorded
  1 large FMH (176mL) at 33 weeks, given correct dose of anti-D Ig but not followed up to check for clearance of fetal cells
  1 external cephalic version at 38 weeks, 500IU anti-D Ig given, no test for FMH performed

Table 15.8: Details of 16 potentially sensitising events in the preceding pregnancy

Since reporting began in 2013, 44 PSE have been reported in the preceding pregnancies of which 27 (61.4%) were correctly managed.

Method of delivery of preceding pregnancy

Type	Number of new cases 2017	Number of cases cumulative total
No information	4	44
Vaginal	23	60
Instrumental	1	7
Elective caesarean section (El CS)	5	13
Emergency CS (Em CS)	10	21
Total	**43**	**145**

Table 15.9: Mode of delivery for PP cases

Gestation more than 40 weeks at delivery of preceding pregnancy

Gestation at delivery (weeks)	Number of new cases 2017
40 weeks or less	30
More than 40 weeks	12 cases in total, of which 7 cases >41 weeks
No information	1
Total	**43**

Table 15.10: Gestation >40 weeks PP

Cumulatively (data collected from 2015 onwards), 21 out of 101 previous pregnancies (20.8%) lasted longer than 40 weeks. National Health Service (NHS) maternity statistics 2014-2015 indicate 17.5% pregnancies extended beyond 40 weeks. *http://content.digital.nhs.uk/catalogue/PUB19127.*

Postpartum prophylaxis (PPP) in preceding pregnancy

Table 15.11: Details of postpartum anti-D Ig prophylaxis PP

What happened?	Number of new cases 2017	Number of cases cumulative total
Kleihauer test and appropriate dose of anti-D Ig	25	87
No prophylaxis	4*	10**
Incorrect dose/timing of anti-D Ig	1	3***
No information	9	36
D-negative baby	4	9
Total	**43**	**145**

**1 case typed in error as D-positive, 1 case refused, 2 cases missed anti-D Ig in error*

***2 from overseas, 1 learning difficulties, 1 needle phobic, 2 declined, 1 case typed in error as D-positive, 2 cases missed anti-D Ig in error*

**** 1 dose 250IU, 2 doses given late*

Anti-D detected at first trimester booking of index pregnancy n=18

The details of the preceding pregnancy may provide information on the cause of immunisation in these cases.

Table 15.12: Details of management in previous pregnancy

Case number	Obese (booking weight >80kg)	RAADP	PSE	Delivery gestation	Delivery route	PPP	'Risk factors' identified
1	Yes (81)	Yes	No	?	Vaginal	Yes	Obesity
2	Yes (102)	Yes	No	39^{+6}	Vaginal	Yes	Obesity
3 in Poland	?	?	?	38	Em CS	?	Em CS
4	?	?	Yes	40	?	?	176 mL FMH at 33 weeks given anti-D Ig, not followed up for clearance of fetal cells
5	No	Yes	No	39^{+6}	Vaginal	Yes	Ideal care
6	No	Refused	?	37	Em CS	Refused	No anti-D Ig-refused
7	?	Yes	No	32	Em CS	No	PPP omitted after Em CS due to midwife error
8	Yes (119)	Yes (2 dose)	Yes	40	El CS	Yes	ECV at 38 weeks, given anti-D Ig but no test for FMH
9	Yes (86)	Yes	?	41^{+6}	Em CS	Yes	Obesity, gestation >40 weeks, Em CS
10	Yes (89.4)	Yes	Yes	38	El CS	Yes	APH at 13 weeks, no anti-D Ig given
11	?	?	Yes	-	-	-	IUD (?gestation) with large FMH, given correct dose of anti-D Ig, full clearance of fetal cells at 72 hours
12	No	Yes	?no	40	Vaginal	Yes	ideal, no record of PSE. Immunised at 11 weeks in index (next) pregnancy
13	No	Yes	?no	41	Vaginal	No	Gestation >40 weeks, PPP omitted in error
14	?	?	?	?	?	?	No information
15	Yes (102)	Yes	No	39^{+6}	Vaginal	Yes	Obesity
16	-	-	-	-	-	-	Miscarriage at <12 weeks
17	No	Yes	?no	41	Vaginal	Yes	Gestation >40 weeks
18	?	No	?	-	?	No	Typed in error as D-positive and managed accordingly
Totals of those cases with sufficient data	6 obese 5 not obese	11 yes 2 no (1 refused, 1 error)	4 yes, 5 no, 7 no/?no	3 delivered >40 weeks	2 ElCS, 4 EmCS	9 yes, 3 no (1 refused, 2 errors)	

Missing data in these cases make analysis difficult, but as in NPP reports, there are cases where apparently 'ideal' management with no risk factors still resulted in immunisation, including cases where management of PSE was correct.

Alloimmune anti-D detected after first trimester in index (current) pregnancy n=30

Further information is requested on the index pregnancy when alloimmune anti-D is detected after the booking (first trimester) sample, as it may be that the sensitisation occurred in the index pregnancy rather than in the preceding pregnancy.

What was the booking weight of index pregnancy?

Weight at booking in kg	Number of new cases 2017	Number of cases cumulative total
<68	11	38
68-80	8	18
>80	7	14
No information	4	19
Total	**30**	**89**

Table 15.13: Booking weight in index pregnancy

7/30 cases were clinically obese.

RAADP in index pregnancy

RAADP given or not	Number
Single dose 1500IU	27
Not given	
Late booker: alloimmune anti-D present at 28-week visit	2
Refused	1
Total	**30**

Table 15.14: Details of RAADP in index pregnancy

Details of potentially sensitising events in index pregnancy

Number of women	Details
7 cases where PSE reported before alloimmune anti-D detected	• APH at 6 weeks, no anti-D Ig • APH at 16 weeks, 1500IU anti-D Ig • APH at 17 weeks, 1500IU anti-D Ig • Twin pregnancy, obese, APH at 21 and 23 weeks, given anti-D Ig • APH at 24 weeks, Kleihauer negative, 1500IU anti-D Ig given • Abdominal trauma (abusive relationship) at 17 weeks, 1500IU anti-D Ig • Frequent epileptic fits, not reported, no anti-D Ig
22 cases no PSE reported	Includes one case of placenta accreta with no reported PSE
1 case no information on PSE	

Table 15.15: Details of potentially sensitising events in index pregnancy PP

In a number of cases PSE were reported but occurred after alloimmune anti-D had been found, with no reported PSE **before** alloimmune anti-D detection.

In 3 cases, where alloimmune anti-D was detected at delivery, antenatal care was ideal but delivery was >40 weeks.

Outcomes of pregnancies reported in 2017:

Table 15.16: Outcome of pregnancies reported in 2017

Number of cases	Outcome
45	Live births
29	No treatment (4 D-negative babies)
12	Required phototherapy
1	Required intrauterine transfusion and phototherapy
1	Required exchange transfusion
1	Required phototherapy and exchange transfusion
1	Required intrauterine transfusion and exchange transfusion after delivery
2	No information
1	Anti-D detected at 6-month follow up of previous pregnancy with large FMH
2	Early pregnancy loss (1 ectopic, 1 TOP)

Case studies

Case 15.4: Ideal care in previous pregnancy, alloimmune anti-D present at booking (11 weeks) in index pregnancy

Multiparous (multip) in her 40s. Booking weight in previous pregnancy 50kg. RAADP (1500IU anti-D Ig) given into deltoid at 28 weeks. No PSE. Delivered vaginally at 40 weeks with no complications. Postpartum prophylaxis (500IU anti-D Ig) given. Found to have all immune anti-D at 11-week booking appointment in index (next) pregnancy. Fetus required intrauterine transfusion and exchange transfusion was given after birth at 36 weeks gestation.

Comment: This woman appeared to be managed ideally in her previous pregnancy and yet was immunised at early booking in her index pregnancy.

Case 15.5: Ideal care with no complications

Multip woman in her 20s. Booking weight 72kg, BMI 26.1. Four previous pregnancies. In index pregnancy, no alloantibodies detected in booking or 28-week samples. Received RAADP (single dose of 1500IU anti-D Ig at 28 weeks IM into deltoid). No PSE. Delivered healthy baby at 39 weeks and found to have alloimmune anti-D. The baby required no interventions for HDFN.

Comment: This woman was managed in line with current guidance but became immunised.

Case 15.6: Stillbirth at 34 weeks gestation given correct dose of anti-D Ig

Multip in her 40s. Booking weight 67kg, BMI 27. Seven previous pregnancies. In the pregnancy immediately prior to index pregnancy she received RAADP (single dose of 1500IU anti-D Ig at 28 weeks). No PSE until stillbirth at 34 weeks gestation, cause unknown – not HDFN. Kleihauer negative. Given single dose of 1500IU anti-D Ig. Antibody screen at booking of index pregnancy negative, alloimmune anti-D detected at 28 weeks. There were no PSE. The baby required no interventions for HDFN.

Comment: This woman was managed in line with current guidance but became immunised.

Case 15.7: Large FMH

Multip in her 20s. Previous pregnancy ended as intrauterine death at 40^{+6} weeks following placental abruption. Kleihauer showed large FMH and the Blood Centre confirmed bleed of 165mL. The Blood Service recommended the woman should receive anti-D Ig 15000IU intravenous (IV) and 2000IU IM. She was given 20,000IU IV in total. Follow up Kleihauer at 72 hours showed full clearance of fetal cells. Alloimmune anti-D was detected at 9 weeks in the booking sample of the index pregnancy, which was terminated as woman required chemotherapy.

Comment: This woman was managed in line with current guidance but became immunised. It may be that her bleeding was acute on chronic making up 165mL total FMH, so that earlier bleeds would not have been covered by anti-D Ig in time.

Case 15.8: Obese

Multip in her 20s. Booking weight in previous pregnancy 100kg. Received RAADP (single dose of 1500IU anti-D Ig IM at 28 weeks). No known PSE. Delivered spontaneously at 42 weeks. Kleihauer negative. 500IU anti-D Ig as PPP. Booking weight of index pregnancy 98kg. APH at 17 weeks for which she received 1500IU anti-D Ig IM. Alloimmune anti-D detected at 27 weeks gestation. The baby required no interventions for HDFN.

Comment: This woman was managed in line with current guidance but became immunised.

Case 15.9: Variant D typed as D-positive in previous pregnancies

Multip in her 20s. In her first pregnancy she was typed as D-positive (strong reaction) so received no anti-D Ig as RAADP or PPP. She received transfusion with D-positive blood for PPH. In her next pregnancy at booking she was again typed as D-positive with no antibodies so received no anti-D Ig as RAADP or PPP. In her index pregnancy alloimmune anti-D was detected at 6 weeks in the booking sample and she was subsequently investigated by the International Blood Group Reference Laboratory which showed her to have a D-variant (weak D type 1 and 2 alleles were not detected by deoxyribonucleic acid (DNA) amplification).

Comment: D-variants can be erroneously typed as D-positive and this should be considered if the reaction in D-typing is weak, as such cases should be referred for further investigation to exclude D-variants. In this case the reaction in D-typing was strong and the true D-type was only identified when alloimmune anti-D developed.

Case 15.10: Early miscarriage of a non-viable pregnancy with repeated bleeding

Multip in her 30s. First pregnancy, D-negative baby. Second pregnancy resulted in an early miscarriage of a non-viable pregnancy. She then bled for 5 weeks but received no anti-D Ig. Review of BSH guidance (BSH Qureshi et al. 2014) shows that there is potential for confusion in such cases as the key recommendations section states:

> 'In pregnancies <12 weeks gestation, anti-D Ig prophylaxis is only indicated following ectopic pregnancy, molar pregnancy, therapeutic termination of pregnancy and in cases of uterine bleeding where this is repeated, heavy or associated with abdominal pain. The minimum dose should be 250IU. A test for fetomaternal haemorrhage (FMH) is not required'.

This would suggest that as the bleeding was repeated in this case anti-D Ig may have been indicated, although the pregnancy was very early and non-viable. By contrast, in the same guideline, the relevant section of PSE <12 weeks gestation states:

> 'In cases of spontaneous complete miscarriage confirmed by scan where the uterus is not instrumented, or where mild painless vaginal (PV) bleeding occurs before 12 weeks, prophylactic anti-D immunoglobulin is not necessary because the risk of FMH and hence maternal exposure to the D antigen is negligible'.

Comment: This woman was managed in line with current guidance (if interpreted in one way) but became immunised.

Case 15.11: APH at 6 weeks, developed alloimmune anti-D in third trimester

Multip in her 30s, obese. APH at 6 weeks in index pregnancy. No anti-D Ig indicated or given. Received RAADP at 29 weeks. Alloimmune anti-D found at 34 weeks gestation. The baby required no interventions for HDFN.

Comment: This woman was managed in line with current guidance but became immunised.

Case 15.12: External cephalic version (ECV)

Multip in her 30s, obese 119kg, BMI 39.9. RAADP 500IU anti-D Ig x 2 (at 29 and 36 weeks gestation). ECV at 38 weeks gestation. Given 500IU anti-D Ig IM but no test for FMH performed. Baby delivered by elective CS at 40 weeks, Kleihauer negative, 500IU anti-D Ig given. Alloimmune anti-D found at booking in her subsequent pregnancy. The baby required intrauterine transfusion and exchange transfusion after delivery at 36 weeks gestation.

Comment: Following ECV, no sample was taken to measure size of FMH, and although a dose of prophylactic anti-D Ig was given, the woman became immunised.

Case 15.13: Alloimmunisation after correctly managed FMH

Multip in her 20s. Obese 96kg. Received RAADP (1500IU anti-D Ig at 30 weeks IM). Delivered by emergency CS in index pregnancy and had 4mL FMH and received postpartum prophylaxis (1500IU anti-D Ig IM). FMH volume was checked by flow cytometry and clearance of fetal cells was checked at 72 hours and was complete (as per guidelines). Follow up at 6 months showed woman had developed alloimmune anti-C, anti-D and anti-G.

Comment: Immunised after FMH at delivery.

Case 15.14: Placenta accreta

Multip in her 30s. Previous pregnancy managed correctly with no PSE, and anti-D Ig given as RAADP and PPP following emergency CS at 36 weeks. In index pregnancy anti-D was detected at 28 weeks but mistakenly assumed to be due to anti-D Ig given for RAADP (in fact the blood sample had been taken before anti-D Ig was given). Placenta accreta was diagnosed at 36 weeks and the woman was found to have a significant titre of anti-D (21.7IU/mL). The baby required phototherapy.

Comment: Do placenta accreta and other pathological placentae pose an increased risk of FMH in the absence of overt antepartum bleeding?

Case 15.15: Multiple risk factors: twin pregnancy, APH, obesity

Multip in her 30s. Weight 95kg, BMI 34. Index pregnancy complicated by twins, APH at 21 and 22 weeks for which she received anti-D Ig 500IU. RAADP given IM at 29 weeks (1500IU anti-D Ig). Alloimmune anti-D was first detected at 36^{+5} when the babies were delivered. The babies required phototherapy.

Comment: (as in 2016) Do twin pregnancies pose a higher risk of alloimmunisation during pregnancy as well as the recognised risk of increased FMH at delivery?

Case 15.16: Failed prophylaxis after TOP 10 years ago

Multip in her 20s. Weight 74.2kg, BMI 25.4. Surgical TOP 10 years previously, given anti-D Ig 250IU. Index pregnancy managed correctly with no PSE, and anti-D Ig given as RAADP (1500IU at 28^{+6} into deltoid muscle). No alloantibodies detected in booking or 28-week samples. Alloimmune anti-D was detected at delivery at 40^{+4}. The baby required no interventions for HDFN.

Summary of 2017 PP data

- Eighteen women were found to be immunised at first trimester booking indicating that sensitisation had probably occurred in the preceding pregnancy. In 30 cases alloimmune anti-D was detected later in the index pregnancy so that the relative contribution of previous pregnancies is less clear
- Although the data has gaps, we continue to see cases where despite apparently 'ideal' care in preceding or index pregnancy, sensitisation to anti-D occurs and alloimmune anti-D develops
- Twelve of 43 of the previous pregnancies to term lasted longer than 40 weeks and cumulatively (data collected from 2015 onwards), 21 out of 101 previous pregnancies (20.8%) lasted longer than 40 weeks. NHS maternity statistics 2014-2015 indicate 17.5% pregnancies extended beyond 40 weeks http://content.digital.nhs.uk/catalogue/PUB19127
- Twelve of 25 PP cases where booking weight was known were obese and cumulatively of the 86 PP cases where booking weight was known 26/86 (30.2%) were obese

Conclusion

The dataset continues to grow and 2017 had the largest annual number of immunisation cases reported to SHOT. Some cases can clearly be attributed to omission of anti-D Ig prophylaxis or testing for FMH. In other cases, the management appeared ideal but immunisation still occurred and it is these cases that require careful scrutiny to ensure current guidelines provide adequate prophylaxis.

Obesity was not seen in any NPP cases this year, but cumulatively since 2012, 7 of 41 (17.1%) NPP cases where the booking weight was known were obese. By contrast in this year's reports, 12 of 25 PP cases where booking weight was known were obese and cumulatively of the 86 PP cases where booking weight was known 26/86 (30.2%) were obese. The important question as to whether obese women should receive anti-D Ig intravenously cannot yet be answered by the SHOT dataset.

The cumulative data both in NPP and PP begin to raise questions about pregnancies delivered beyond 40 weeks. There have been 26 NPP cases where alloimmune anti-D was detected only at delivery and 13 of these (50.0%) were delivered at >40 weeks. For PP cases, from 2015 onwards, 21 of the 101 previous pregnancies (20.8%) lasted longer than 40 weeks, and of 24 women where alloimmune anti-D was first detected at delivery in the index pregnancy, 9 cases (37.5%) were delivered after 40 weeks gestation. Cases where alloimmune anti-D was first detected at term will now be analysed in more detail by dividing the cases into four groups: early term (37-38^{+6} weeks), full term (39-40^{+6} weeks), late term (41-42 weeks) and post term (>42 weeks) and adding booking weight and age. This more detailed analysis may enable us to identify women who are at increased risk of developing alloimmune anti-D and who would benefit from an additional dose of anti-D Ig prophylaxis near term.

Several cases were reported this year where despite apparently adequate anti-D Ig prophylaxis women became immunised after a PSE, raising concerns that the current recommendations for prophylaxis may be inadequate, for example in medical termination where prophylaxis is not currently recommended. In addition, several cases highlight the continuing confusion around the correct management of PSE in early pregnancy. There is also a group of NPP women who may experience PSE in early pregnancy before they have been informed of their D-negative status and thus will not seek appropriate advice. There may be a case for informing all NPP (primips) of their D-negative status as soon as the result is available rather than waiting for their booking clinic visit at 16 weeks.

This year a case of placenta accreta was reported where, despite apparently ideal management, sensitisation occurred raising the possibility that placenta accreta, and possibly other pathological placentae, may increase the risk of occult FMH. Further work should be considered to clarify this risk.

The introduction of cffDNA analysis (NICE 2016) to identify pregnancies with D-negative babies (where the mother does not require prophylaxis with anti-D Ig), while reducing the unnecessary exposure of these women to blood products, has the potential to result in new types of error. SHOT has worked in collaboration with NHSBT to add additional questions to the alloimmunisation questionnaire specifically related to cffDNA testing. We hope to present the initial data in next year's report.

All healthcare professionals, including laboratory staff, involved in the care of pregnant women must be encouraged to provide fully completed datasets on newly identified cases of anti-D immunisation in pregnancy, as the SHOT anti-D immunisation database may be the only way the important questions posed at the beginning of this chapter will be answered, particularly why women with apparently ideally managed pregnancies are still becoming immunised.

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