22 Immune Anti-D in Pregnancy: cases reported up to end of 2015

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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. Such cases should be notified to SHOT via the website so that the reporter can download a questionnaire requesting 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).

Going forward, SHOT is exploring a potential collaboration with the NHSBT AIR (alloimmune resource) study: this is a research project to determine genetic influences that predispose women to developing red cell alloantibodies during pregnancy. This will be of particular interest in those cases where apparently 'ideal' care has been delivered.

Results

In 2015 a total of 51 cases were reported, although some datasets were incomplete.

- 17 cases occurred in women with no previous pregnancies (NPP)
- 34 in women with previous pregnancies (PP)

SHOT now has a total of 33 NPP cases and 84 PP cases reported 2012–2015.

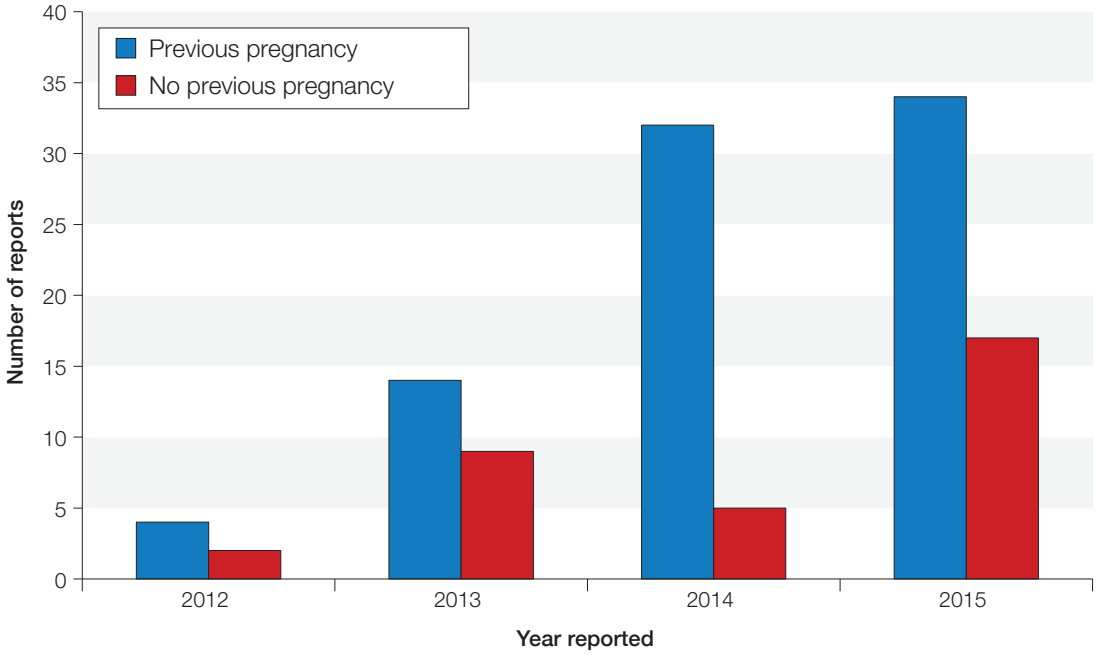

Figure 22.1: Number of reports of anti-D immunisation in pregnancy by year, 2012–2015

No previous pregnancy (NPP) n=17 in 2015, cumulative n=33 cases

When was the anti-D detected?

Time of anti-D detection	Number of new cases 2015	Number of cases cumulative
Before 28 weeks	3*	4**
At or after 28 weeks, before delivery	2	7
At delivery	11	21
No information	1	1
Total	**17**	**33**

Table 22.1: When immune anti-D was detected NPP

One case at 13 weeks in intravenous drug user, 2 cases before 12 weeks with no known cause for immunisation

***All received RAADP before the result showing immune anti-D became available*

What was the booking weight?

Weight at booking in kg	Number of new cases 2015	Number of cases cumulative
<68	8	16
68–80	1	4
>80 (obese)	2	4
No information	6	9
Total	**17**	**33**

Table 22.2: Booking weight NPP

Did the women receive appropriate RAADP?

New cases reported in 2015: 14/17 women were eligible for RAADP, as 3 were immunised by booking date.

RAADP regimen	Number of new cases 2015	Number of cases cumulative
Single dose 1500IU at 28 weeks	9	24
Single dose 1500IU at 30 weeks	1	
Two dose regimen 500IU	0	1
Not given	4*	5**
Total	**14**	**30**

Table 22.3: RAADP details for eligible cases n=14 (2015) n=30 (cumulative)

1 error, 3 reason unknown

***1 case delivered at 26 weeks, 1 error, 3 reasons unknown*

The route was specified in 6 cases from 2015 as intramuscular into deltoid, the rest were not specified.

Details of potentially sensitising events (PSE)

PSE	Management
None 12	
Antepartum haemorrhage (APH) 2 cases	1. Bleed at 7,11 and 40 weeks No samples taken and no anti-D Ig given except RAADP 2. Bleed at 30 weeks but already immunised (managed at another Trust/Health Board until 28 weeks: no information provided)

Table 22.4: Details of PSE for 2015: data exclude 3 cases who were sensitised at booking n=14

Table 22.5: Details for all cases reported since 2012

PSE	Number of cases
None	24
7 antepartum haemorrhage (APH) 2 interventions (chorionic villous sample, amniocentesis) 1 fall	6 women had 10 events

Pregnancy outcomes

In 2015: All pregnancies resulted in live births, of which 8 had no complications, 7 babies required phototherapy and 2 cases required intravenous immunoglobulin and exchange transfusion in addition.

Cumulatively, all 33 pregnancies resulted in live births, of which 20 had no complications, 11 babies required phototherapy and 3 cases required exchange transfusion. No details in one case.

Summary of 2015 NPP data

- The majority of women (11/17) were found to be immunised at delivery, of whom 5 women received apparently 'ideal' care with timely RAADP and no identifiable sensitising episodes. They were not overweight and the pregnancies did not go beyond term. Only one of the remaining 6 women had had a sensitising event (for which she did not receive appropriate prophylaxis), 3 women did not receive RAADP, 2 women who did receive RAADP had booking weight >80kg, and 2 who received single dose RAADP at 28 weeks delivered beyond term (one of whom also weighed >80kg)
- 3 cases were immunised at booking despite no previous pregnancies or transfusion, although one case was a known intravenous drug user

Previous pregnancies (PP) n=34 in 2015, cumulative n=84 cases

When was the anti-D detected?

Table 22.6: Time of anti-D detection for PP cases

Time of anti-D detection	Number of new cases 2015	Number of cases cumulative
At booking	15 (44%)	41 (49%)
Booking to 28 weeks	2	2
At or after 28 weeks	12	29 (35%)
At delivery	3	7 (8%)
Other	2*	5**
Total	**34**	**84**

**1 at planned follow up of large fetomaternal haemorrhage at delivery where correct dose of anti-D Ig had been given, 1 unknown in ectopic pregnancy*

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

Where anti-D was detected at booking in the index pregnancy, only the events in the preceding pregnancy are relevant to the sensitisation. Where anti-D is detected later in the index pregnancy, the relative contribution of events in the previous and index pregnancy is less certain.

Information about the pregnancy immediately preceding index pregnancy:

In 2015, the previous pregnancy ended in miscarriage in 2 cases, and one case underwent a termination at 6 weeks, leaving 31 previous pregnancies that went to term.

What was the booking weight?

Weight at booking in kg	Number of new cases 2015	Number of cases cumulative
<68	10	28
68–80	4	9
>80 (obese)	3	9
No information	14	28
Total	**31**	**74***

*10 cases did not go to term

Table 22.7: Booking weight for PP cases

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

Three cases were reported in 2015: a spontaneous miscarriage at 11 weeks (anti-D Ig is not indicated), a miscarriage at 10 weeks (no further details) who received 250IU anti-D Ig and a therapeutic termination at 6 weeks where information on whether anti-D Ig was given was not available.

Did the women who carried to term receive RAADP?

RAADP	Number of new cases 2015	Number of cases cumulative
Single dose	15	43
Two doses	4	7
Not given	4*	15**
No information	8	9
Total	**31**	**74**

*Declined (2), no reason (1), before practice adopted (1)

**Learning difficulties, concealed pregnancy, needle phobic, prior to RAADP introduction (2), delivered abroad (3), no reason given (5), declined (2)

Table 22.8: Was RAADP given at term or not?

15 of 74 (20.3%) cases were documented to have not received RAADP.

Number of PSE	Type of event	Management
7 PSE reported	4 APH	3 less than 20 weeks-all received anti-D Ig 1 at 22 weeks, no Kleihauer or anti-D Ig
	1 spontaneous miscarriage	At 11 weeks, no anti-D Ig indicated
	1 miscarriage (no further details)	At 10 weeks, given 250IU anti-D Ig
	1 termination of pregnancy	At 6 weeks, no anti-D Ig given
16 cases had no PSE reported		
11 cases had no information on PSE		

Table 22.9: Details of potentially sensitising events

Method of delivery

Type	Number of new cases 2015	Number of cases cumulative
No information	9	28
Vaginal	12	28
Instrumental	2	4
Elective caesarean section (CS)	3	5
Emergency CS	5	9
Total	**31**	**74**

Table 22.10: Mode of delivery for PP cases

Gestation at delivery >40 weeks (data collected from 2015 onwards)

3 out of these 31 cases delivered beyond 40 weeks

Postpartum prophylaxis

Table 22.11: Details of postpartum anti-D Ig prophylaxis

What happened?	Number of new cases 2015	Number of cases cumulative to date
Kleihauer test and appropriate dose of anti-D Ig	19	50*
No prophylaxis	2	5**
Incorrect dose of anti-D Ig	0	2***
No information	10	15
D-negative baby	0	2
Total	**31**	**74**

**Includes 4 cases requiring higher doses as a result of Kleihauer test*

***2 from overseas, 1 learning difficulties, 1 needle phobic, 1 declined*

****One dose 250IU, one dose given late*

Anti-D detected at booking of index pregnancy n=15

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

Table 22.12: Details of management in previous pregnancy n=15

Details	Management notes for preceding pregnancy
Ideal care 5 cases	Correct RAADP (single dose 1500IU) and postpartum prophylaxis, not obese and no known PSEs 2 cases delivered beyond 40 weeks (41 and 42 weeks)
No RAADP given/documented 4 cases	1 declined 1 no reason for omission 2 no information on RAADP
PSEs documented 3 cases, all APH	2 cases (at 15 and 18 weeks) anti-D Ig given, Kleihauer not indicated 1 case at 22 weeks did not have Kleihauer or receive anti-D Ig (Note: An additional case had spontaneous miscarriage at 11 weeks so anti-D Ig not indicated or given)
Delivery method	4 vaginal 0 instrumental 4 CS (1 elective, 3 emergency) 7 not specified
Postpartum anti-D Ig	6 correct dose within 72 hours of delivery, Kleihauer performed 1 correct dose >72 hours after delivery, Kleihauer performed 2 no Kleihauer, no anti-D Ig given 2 not given, spontaneous miscarriage at 11 weeks, D-negative baby 4 no information

In 2015, 5 of 15 cases (33.3%) received apparently 'ideal' care, although in 2 cases pregnancy continued beyond term.

Cumulatively, 13 out of 41 cases (31.7%) found to be immunised at booking received apparently 'ideal care' in the preceding pregnancy.

Anti-D detected later in index pregnancy n=19

Excluded cases: n=3 (1 ectopic, 1 miscarriage at 22 weeks and large fetomaternal haemorrhage (FMH) follow up) leaving 16 informative cases.

There is further information requested on the index pregnancy in these cases, as it may be that the sensitisation occurred in the index pregnancy rather than in the preceding pregnancy.

What was the booking weight?

Weight at booking in kg	Number of new cases 2015	Number of cases cumulative
<68	9	18
68–80	2	8
>80	2	2
No information	3	10
Total	**16**	**38**

Table 22.13: Details of booking weight

RAADP in current pregnancy

RAADP given or not	Number of new cases 2015	Number of cases cumulative
Single dose 1500IU	11	25
Not given	5	13
No reason given		*4*
Needle phobia		*1*
Late booker	*3*	*4*
On advice of the Blood Service		*1*
Incorrectly typed as D-positive in past		*1*
Declined	*1*	*1*
Intrauterine death	*1*	*1*
Total	**16**	**38**

Table 22.14: RAADP information in current pregnancy

Sensitising events in current pregnancy occurred in 2 women, one who experienced a fall (gestation not reported) but declined anti-D Ig prophylaxis, and one of whom was an intravenous drug user who booked late following abdominal trauma and was found to have immune anti-D.

Outcomes of pregnancies reported in 2015

Outcome	Number of cases
Live births	26
No treatment (1 D-negative baby)	*13*
Required phototherapy	*10*
Required phototherapy and intravenous immunoglobulin	*2*
Required phototherapy and exchange transfusion	*1*
Miscarriage at 22 weeks	1
Intrauterine death at 14 weeks	1
Ectopic (?gestation)	1
No information	5
Total	**34**

Table 22.15: Outcome of pregnancies reported in 2015 n=34

Summary of 2015 PP data

- In 15 cases, sensitisation must have occurred during the previous pregnancy as anti-D was detected at booking in the index pregnancy. Five of these 15 cases (33.3%) received apparently 'ideal' care in the previous pregnancy, although in 2 cases that pregnancy continued beyond term

Cumulatively since data collection began in 2012, 13 out of 41 PP cases (31.7%) found to be immunised at booking received apparently 'ideal' care in preceding pregnancy.

- In 19 cases sensitisation occurred later in pregnancy so that the relative contribution of previous pregnancies is less clear

COMMENTARY

While errors/omissions in care continue to lead to anti-D immunisation in pregnancy, we again see a small number of cases where apparently 'ideal' care is given, no other risk factors are identified and yet sensitisation occurs, leading to the production of immune anti-D in current or future pregnancies. The cause in these cases is unknown; whether genetic studies will identify women at particular risk of alloimmunisation to explain these findings, and whether such women once identified require a different approach to prophylaxis will be of great interest.

Further work

It is only by gathering sufficient data that we will have a chance of answering questions that persist around the ideal way to prevent alloimmunisation to the D antigen during pregnancy. SHOT is exploring a potential collaboration with NHSBT Alloimmune Resource (AIR) Study* with a view to collating the two databases and, where possible using the SHOT questionnaire for more detailed evaluation of women who have produced anti-D and are already entered into the AIR database.

*The AIR Study for pregnant women with red cell antibodies

The AIR Study is a research project funded by NHSBT to determine genetic influences that predispose women to developing red cell alloantibodies during pregnancy. Only a small proportion of women who have the potential to develop red cell antibodies during pregnancy go on to mount a clinically significant antibody response. The AIR study aims to collect 2000 deoxyribonucleic acid (DNA) samples from alloimmunised women to allow a genome-wide screening study to identify genes that may enhance the likelihood of antibody production. This information will help focus therapies and improve screening for high risk cases. Ethical approval has been given to write to women who are identified by NHSBT laboratories as having red cell antibodies and they will be asked if they are willing to:

- Provide a saliva sample to allow extraction of DNA
- Fill in a questionnaire about their transfusion and pregnancy history

Pregnant women, with antibodies, from any hospital where antenatal testing is undertaken by NHSBT may be asked to take part but we hope that this will not lead to any new workload for clinical teams. If you (or your patients) have any questions about the study, would like to help or would like more information please contact: sarah.morley@nhsbt.nhs.uk.

References

BCSH (2014) **Anti-D guidelines amendment 4.8.14**. http://www.bcshguidelines.com/documents/BCSH_Anti_D_guidelines_-__Amendment_4_8_14_(2).pdf [accessed 28 March 2016]

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National Institute of Clinical Excellence (NICE) (2008). **Routine antenatal anti-D prophylaxis for women who are rhesus D negative. Technology Appraisal Guidance No. 156**. https://www.nice.org.uk/Guidance/TA156 [accessed 28 March 2016]