Anti-D immunisation in pregnancy

Clinical case studies and emerging themes from SHOT reports 2012-2017

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No conflicts of interest to declare
Pathophysiology of haemolytic disease of fetus and newborn (HDFN)
Causes of feto-maternal haemorrhage (FMH) during pregnancy

- Abdominal trauma
- Threatened or actual miscarriage
- Termination of pregnancy
- Ectopic pregnancy
- Antepartum haemorrhage (APH)
- Invasive prenatal diagnosis or other intra-uterine procedures eg amniocentesis
- Stillbirths and intrauterine death
- NORMAL pregnancy
Prevention of HDFN

ÂPassively administered anti-D immunoglobulin (anti-D Ig) can prevent immunisation following exposure to D positive red cells after a potentially sensitising event (PSE), including delivery, if given in sufficient dose and within 72 hours of exposure.

ÂRoutine antenatal anti-D prophylaxis (RAADP) given to all D negative women at 28+weeks gestation further reduces the rate of immunisation.
SHOT reporting of anti-D Ig errors

Late or missed administration of anti-D immunoglobulin prophylaxis is commonly reported to SHOT (350-400 cases annually) but without knowledge of the consequences.

In 2012 SHOT began a prospective study of women who develop immune anti-D detected for the first time in their current pregnancy.

Following detection of immune anti-D in pregnancy, reporters complete a questionnaire detailing booking weight, management of sensitising events in pregnancy, administration of routine antenatal anti-D immunoglobulin (Ig) prophylaxis (RAADP) and post partum anti-D Ig, both in the current (index) and in the pregnancy immediately preceding it.
Reports of anti-D immunisation in pregnancy by year, 2012-2017
Completeness of reporting to SHOT

Å NICE analysis (HTA 2003) for RAADP quoted a reduction in sensitisation rate from 0.95% to 0.35% (of which 30-40% are true treatment failures)

Å Systematic review in 2004 (Jones et al) showed that % sensitised women fell from 1.9-2.2% to 0-0.2% with antenatal prophylaxis

Å There were 636401 births recorded in England on HES up to March 2017, of which 17% will be D neg mothers ie 108188, of which 59% will carry D pos babies ie 63831 pregnancies at risk

Å If we use failure rate of 0.2%, then would expect 128 immunisations per year from RAADP failures

PLUS

Å There were 327 reports to SHOT of omission or late administration of anti-D Ig in 2017

Å Anti-D immunisation in pregnancy remains UNDER-REPORTED
No previous pregnancy (NPP)  
n=58

- 7 out of 41 cases with available information were noted to be obese (>80kg)
- Alloimmune anti-D was detected after 28 weeks gestation in 50 women
- 83% of eligible women received RAADP (most receiving single dose anti-D Ig 1500iu at 28-30 weeks)
- Gestation was >40 weeks in 13/26 cases where anti-D was first detected at delivery
- All 58 pregnancies resulted in live births, 37 with no complications, 13 required phototherapy and 6 required exchange transfusion
CASE STUDIES from 2017
No previous pregnancy

**CASE 1: Ideal care and delivered at term**

Booking weight 59kg. Received RAADP (single dose of 1500IU anti-D Ig at 28 weeks). No potentially sensitising events (PSE). Alloimmune was anti-D detected at term delivery (2.7IU/mL). Baby required no interventions for haemolytic disease of the fetus and newborn (HDFN)

**CASE 2: Gestation >40 weeks**

Booking weight 61kg, body mass index (BMI) 24. Received RAADP (single dose of 1500IU anti-D Ig at 28 weeks). No PSE. Delivered at 42 weeks. Alloimmune anti-D detected at delivery (2.4IU/mL). Baby required no interventions for HDFN

**CASE 3: Gestation >40 weeks**

Booking weight 64kg, BMI 22. Received RAADP (single dose of 1500IU anti-D Ig at 28 weeks). No PSE. Delivered at 42 weeks. Alloimmune anti-D detected at delivery (7.4IU/mL). Baby required no interventions for HDFN

**CASE 4: D negative mother with no antibodies at booking. Alloimmune anti-D at 5 months when she presented with severe pre-eclampsia. Father D negative. Baby delivered at 28 weeks for HELLP syndrome and shown to be D positive**

In vitro fertilisation with egg donor
Previous pregnancy (PP)  
n=165

Â Booking weight in previous pregnancy was >80kg in 26 of 86 (30%) women where data were provided

Â 95/147 who carried to at least 28 weeks received RAADP in previous pregnancy, 21 did not and in 31 information was missing

Â 21/101 women where data were provided delivered beyond term in the preceding pregnancy, compared to a national figure of 17.5%

Â 87/100 eligible women where information was provided received appropriate postpartum anti-D Ig prophylaxis

Â In 2017 there were 45 live births, 12 required phototherapy and 4 intrauterine/exchange transfusion

Â Alloimmune anti-D was detected at booking in 68/165 (41%) indicating that immunisation had probably occurred in the preceding pregnancy. Anti-D was found at or after 28 weeks in 50 (30%) and in 24 (14%) at delivery, 9 of whom delivered beyond term
CASE STUDIES from 2017
Previous pregnancy

Case 4: Ideal care in previous pregnancy, not obese, alloimmune anti-D present at booking (11 weeks) in index pregnancy

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 (PPP)-500IU anti-D Ig. Found to have alloimmune 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.

Case 5: Ideal care with no complications

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 into deltoid). No PSE. Delivered healthy baby at 39 weeks and found to have alloimmune anti-D. The baby required no interventions for HDFN.

Case 6: Obese, APH in index pregnancy

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.
Previous pregnancies

Case 7: Stillbirth at 34 weeks gestation in preceding pregnancy

Booking weight 67kg, BMI 27. Seven previous pregnancies. In the pregnancy immediately prior to index pregnancy received RAADP (single dose of 1500IU anti-D Ig at 28 weeks). Stillbirth at 34 weeks gestation, cause unknown, Kleihauer negative. Given 1500IU anti-D Ig. Antibody screen at booking of index pregnancy negative, alloimmune anti-D detected at 28 weeks. No PSE. No interventions for HDFN

Case 8: Large feto-maternal haemorrhage (FMH)

Previous pregnancy ended in intrauterine death at 40+6 weeks following placental abruption. Large FMH (165mL). Received 20,000IU anti-D Ig 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

Case 9: Placenta accreta

Previous pregnancy managed correctly. In index pregnancy alloimmune anti-D 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 diagnosed at 36 weeks and the woman was found to have alloimmune anti-D (21.7IU/mL). The baby required phototherapy
Previous pregnancies

Â Case 10: Obese. APH at 6 weeks, developed alloimmune anti-D in third trimester

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. Baby required no interventions for HDFN

Â Case 11: Obese, external cephalic version (ECV)

Booking weight 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 subsequent pregnancy. The baby required intrauterine transfusion and exchange transfusion after delivery at 36 weeks gestation

Â Case 12: Obese. Alloimmunisation after correctly managed FMH

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

Â Case 13: Multiple risk factors: twin pregnancy, APH, obesity

Weight 95kg, BMI 34. Index pregnancy complicated by twins, APH at 21 and 23 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
Previous pregnancies

Case 14: Variant D typed as D-positive in previous pregnancies

In first pregnancy typed as D-positive (strong reaction). Received transfusion with D-positive blood for PPH. In second pregnancy typed as D-positive with no antibodies. In index pregnancy alloimmune anti-D was detected at 6 weeks and International Blood Group Reference Laboratory showed her to have a D-variant (weak D type 1 and 2 alleles were not detected by deoxyribonucleic acid (DNA) amplification).

Case 15: Early miscarriage of a non-viable pregnancy with repeated bleeding, confusing guidance

First pregnancy, D-negative baby. Second pregnancy early miscarriage of a non-viable pregnancy followed by bleeding for 5 weeks but received no anti-D Ig.

Review of BSH guidance (2014) shows there is potential for confusion in such cases. 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.’ As the bleeding was repeated in this case anti-D Ig may have been indicated, although the pregnancy was very early and non-viable. 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’
Obesity (booking weight >80kg)

Obesity was not seen in any NPP cases this year, but cumulatively since 2012, 7 of 41 (17%) NPP cases where the booking weight was known were obese.

26/86 PP(30%) cases where booking weight was known were obese. Statistics from the Health and Social Care Information Centre (HSIC) for 2015 show 20% of 36000 pregnant women, who attended their first appointment, were classed as obese, similar figure for MSDS data 2016/17.

The important question as to whether obese women should receive anti-D Ig intravenously cannot yet be answered by the SHOT dataset.
Why should obesity reduce effectiveness of anti-D Ig?

• Lack of efficacy in obese patients could be due to inadequate absorption, inadequate distribution or both.

• Drug absorption may be delayed if injection only reaches the subcutaneous tissues and if a woman is overweight then the depth of fat will be greater and the needle may not reach the muscular layer, so the absorption of the anti-D will be lower. To avoid this it has been suggested that anti-D Ig can be given intravenously.
Obesity and anti-D levels

Drug absorption may be delayed if injection only reaches the subcutaneous tissues.

Anti-D concentration after post partum prophylaxis in women with a BMI less than or equal to 27 kg per m² (clear) or higher than 27 kg per m² (shaded) 1, 2 and 3 days, and 2 weeks after its injection. Results are presented as box plots that show the median as a horizontal bar, the range between the first and the third quartiles as a box, and the total range of data as whiskers.

TRANSFUSION 2004;44:512-517
Intravenous versus intramuscular route

Delivery beyond term

Â In 26 NPP cases alloimmune anti-D was detected only at delivery and 13 of these (50%) were delivered at >40 weeks.

Â In PP cases 21 of 101 previous pregnancies (21%) lasted longer than 40 weeks, and of 24 women where alloimmune anti-D was first detected at delivery in the index pregnancy, 9 cases (38%) were delivered after 40 weeks gestation.

Â Most women now receive prophylaxis as a single dose at 28-30 weeks gestation, so if the pregnancy extends beyond 40 weeks is an additional dose of prophylaxis required and when should it be given?

Â Twelve weeks after injection of anti-D IV or IM, mean residual circulating anti-D is 0.6- 1.0 ng/mL (representing 5 g to 8 g of anti-D), not enough to protect against a volume of FMH of greater than 1 mL and some women have no residual anti-D.
Repeat dosing at 40 weeks

Society of Obstetricians and Gynaecologists of Canada

There is insufficient evidence at this time to make a recommendation for or against administering another dose of anti-D to an unsensitized D-negative woman who remains undelivered at 40 weeks

J Obstet Gynaecol Can 2018 40 e1-10
Confusing UK guidance

Cases were reported this year where women became immunised after a PSE, despite apparently adequate anti-D Ig prophylaxis, raising concerns that current recommendations for prophylaxis maybe inadequate (in medical termination where prophylaxis is not currently recommended) or confusing (the correct management of PSE in early pregnancy).

NPP women 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 and its implications 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 other pathological placentae, may increase the risk of occult FMH. Further work should be considered to clarify this risk.
New source of errors?

The introduction of cell free fetal (cff) DNA 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.
References


Note: Royal College of Obstetricians and Gynaecologists green top guideline on use of anti-D has been archived and replaced by BSH guideline.

• National Institute for Health and Care Excellence (NICE). Routine antenatal anti-D prophylaxis for women who are rhesus D negative. Technology Appraisal Guidance No. 156. 2008 https://www.nice.org.uk/Guidance/TA156


• Canadian guidelines J Obstet Gynaecol Can 2018;40(1):e1–e10

• LiumbrunoG M, D’Alessandro A et al The role of antenatal immunoprophylaxis in the prevention of maternal-foetal anti-Rh(D) alloimmunisation (2010) Blood transfusion 6 (1) 8-16 EXCELLENT REVIEW