Anti-D errors and immunisation: Lessons from SHOT

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D-sensitisation is dangerous

- A woman who is D-negative is likely to make antibodies to D if exposed in pregnancy or by blood transfusion
- Once sensitised this can never be undone
- Anti-D can cause severe harm and death to a D-positive fetus



Anti-D lg saves lives



Traceability and adverse reactions to anti-D Ig

- Anti-D Ig is made from human plasma and must be traceable
- In the past hepatitis C was transmitted to many women in Ireland and Italy
- Clinical adverse reactions (e.g. allergy) to anti-D are reported via the MHRA Yellow Card scheme
- Procedural errors associated with anti-D Ig are SHOTreportable



Cumulative data for all SHOT categories 1996 to 2017 n=19815





Trend in anti-D lg reports



SERIOUS HAZARDS OF TRANSFUSION

SHC



Sometimes, red cells from the fetus can enter the circulation of the mother and mix – this is known as a fetomaternal haemorrhage (FMH).



How common is FMH?

- The D antigen is well expressed by 7 wks
- Fetal red blood cells (typically <0.1mL) are found in:









The immune system of the mother may recognise the blood groups on the fetal cells as being "different" and can respond by making antibodies – this is known as sensitisation (of the mother).



HDN: haemolytic disease of the newborn



The antibodies made by the mother can *cross the placenta* and cause breakdown (haemolysis) of red cells in the fetus. This can result in HDN with anaemia and jaundice which can be mild or severe.

Very severe HDN can cause hydrops and fetal death in the womb or brain damage after birth from kernicterus due to very high bilirubin levels.





Prevention of HDN

- Identify D-negative women, check for immune anti-D
- Give right blood components to D-negative women
- Counsel about sensitising events in pregnancy
- Give right dose of anti-D Ig at the right time: (it binds to D pos red cells which are removed from circulation)
 - Sensitising events
 - Routine antenatal prophylaxis and post delivery
- Do a test for FMH after 20 weeks gestation



Sensitisation Events in Pregnancy

1 st and 2 nd trimester	After 20 weeks
Miscarriage	Antepartum haemorrhage
Ectopic pregnancy	Placental abruption
Therapeutic TOP	Abdominal trauma
CVS and amniocentesis	Amniocentesis
	External cephalic version
Small volume and infrequent:	More frequent:





What SHOULD we be doing.....

- <12/13 weeks gestation, give at least 250iu anti-D Ig for surgical interventions (ectopic, molar, TOP) or persistent painful bleeding, within 72 hrs of the event
- 12/13 20 weeks, give at least 250iu anti-D Ig for sensitising events such as bleeding, trauma etc
- >20 weeks give at least 500iu anti-D Ig for sensitising events and Kleihauer test in case more is needed
- 1500IU would cover a 12ml bleed if given IM or a 15ml bleed if given IV
 The 250iu vial is no longer available so use 500iu

Why 72 hours ?

 The usual response time to produce a new blood group antibody following exposure to a foreign antigen is 72 hours, so intervening before then offers the best possible chance of avoiding that sensitisation occurring



What if we're not sure ?

- If detectable anti-D in the woman's plasma is immune or the remains of prophylactic anti-D
 – Give anti-D Ig until confirmed
- If the woman has not had her D-status confirmed one way or the other
 Give anti-D Ig until confirmed
- Even if the confirmation results mean you stop giving anti-D Ig, it was not an error to give it before – you go with the information you have at the time, and don't exercise 20/20 hindsight





Common misconceptions about anti-D

- 'We only need to give anti-D Ig at delivery of a fetal death'
 - No you don't you should give anti-D Ig at DIAGNOSIS of the fetal death AND at delivery – the two events may be days apart
- 'You can give too much anti-D lg'
 - You would need to give 15,000 IU anti-D Ig at once, IV, and more than 20,000 IU IM, to get to a maternal plasma level which MIGHT cause problems in the baby



Why are there so many errors?

- Multiple steps
- Different professional groups
 - Midwives and nurses
 - Laboratory staff
 - Medical staff
- Assumptions and failure to check
- So it needs a checklist



SERIOUS HAZARDS OF TRANSFUSION

Key risks in medicine

- Identification
- Documentation manual transcription of results in the laboratory or by midwives into maternity notes is a DANGER point
- Communication several biomedical scientists and different midwives increase risk of missed or mixed messages



Anti-D Ig issued without reference to grouping results

- During the on-call period, the duty BMS issued 1500 IU anti-D Ig to the mother of a baby confirmed to be D-negative
- The BMS was 'very busy' and did not check the LIMS to confirm blood groups before issuing the anti-D Ig



Bedside checking means 'at the bedside'

- Anti-D Ig was issued by the laboratory for a post-natal woman
- The anti-D Ig was checked by two qualified midwives away from the woman and then taken to the wrong woman for administration





Laboratory report misinterpreted

- Anti-D Ig was issued for routine prophylaxis at 28 weeks from clinical stock, after midwives misinterpreted 'Antibody Screen Negative' as 'D negative'
- The laboratory has changed the wording on their grouping reports to 'No antibodies detected' in an attempt to stop this happening again



Messing up anti-D can be disastrous





Case 1

Failure to recognise a complication of pregnancy 1

- A baby was born with unexpected jaundice and haemolytic disease of the fetus and newborn (HDFN) due to anti-D antibodies which had not been anticipated
- The baby required urgent red cell exchange transfusion during which a cardiac arrest occurred, and the baby subsequently died
- This was the second pregnancy in a D-negative woman

How did this happen?



Failure to recognise a complication of pregnancy 2

- There were **multiple errors** in the first pregnancy
- Anti-D antibody was detected prior to the administration of routine anti-D immunoglobulin (Ig) but was misinterpreted on two separate occasions and not followed up
- The first baby was born with HDFN requiring exchange transfusion, but there was then 'no mechanism for ensuring that information was fed into future pregnancies'
- At booking for the second pregnancy the history of jaundice and transfusion at birth for the first baby was noted but this was **not identified as indicating a risk** for the current pregnancy



Failure to recognise a complication of pregnancy 3

- The laboratory staff then misinterpreted the presence of anti-D in the booking bloods at 10 weeks as being due to prophylactic anti-D Ig administration but the midwife did not pick up this error
- The woman was reviewed by an obstetric registrar at 20 weeks who noted that the first baby had required phototherapy for jaundice but missed the history of exchange transfusion
- Anti-D was again detected in blood samples at 28 weeks and was again wrongly assumed to be due to anti-D lg administration (which had not been given) 18 weeks before



Failure to recognise a complication of pregnancy 4

- Five hours after birth (39 weeks) the baby was jaundiced (group O D-positive) and required exchange transfusion
- The baby suffered complications and subsequently died (January 2015)
- The hospital review of this case was signed off by the hospital in June 2015
- The post-mortem report had not been available so the review was unable to determine the cause of death



Laboratory error and poor communication

Baby induced at 36 weeks in local centre: hyperbilirubinaemia Admitted to NICU Group O D pos NICU not aware of this baby prior to delivery; not discussed in obstetric high risk meeting Maternal anti-D and anti-C detected at 17 weeks Advised close follow up with titres Monitored in tertiary centre

Policies not followed

Day 3: Verbal requests for urgentblood for exchange2 BMS did not look at maternalresults so provided wrong group

Given the WRONG BLOOD O D-pos (incompatible), should be O D-neg

The baby required repeat exchange transfusion with O D-neg on day 6





Steps where errors are likely

- Blood sample for group check
 - Is it the correct woman?
- Check the laboratory report
 - If anti-D is detected, what is the cause
 - COMMUNICATION (is the anti-D immune or a result of previous treatment?)
- Check the product and dose (whose responsibility?)
- Record the informed consent



Distribution of anti-D lg-related reports 2016 n=409

- Omission or late administration of anti-D Ig
- Anti-D Ig given to a D-positive woman
- Anti-D Ig given to a woman with immune anti-D
- Anti-D Ig given to the mother of a D-negative infant
- Anti-D Ig given to the wrong woman
- Wrong dose of anti-D Ig given
- Anti-D Ig handling and storage errors





Who makes the errors?







Lack of knowledge results in delay of administration of anti-D lg

- A woman presented with a vaginal bleed at 19 weeks of gestation, but was discharged by a doctor who informed her that anti-D Ig should only be given if a Kleihauer test is positive
- The woman was recalled and given anti-D Ig four days later



Misinterpretation of the Kleihauer test

- A negative Kleihauer test does not exclude a sensitising fetomaternal haemorrhage
- The test is done to ensure that enough anti-D Ig is given to cover the size of any bleed and NOT to decide whether a dose is needed
- The current dose of anti-D Ig should cover a bleed of up to 4mL



Prophylaxis and PSE

Staff should be made aware that national guidelines specifically recommend that RAADP and prophylaxis for PSE should be regarded as **separate events** and anti-D Ig given for both at a dose indicated by the local policy



Catalogue of errors leads to incorrect administration of anti-D lg

- A woman told her consultant that she was D-negative, and anti-D Ig was requested on that basis
- The BMS issued anti-D Ig even though the laboratory information management system record clearly showed the woman to be D-positive ALWAYS CHECK THE LABORATORY RESULT
- The midwife administered the anti-D Ig, knowing the woman was D-positive, because the consultant had prescribed it
 SERIOUS FAILURE OF PROCEDURE

DO NOT DISENGAGE BRAIN

Failure to check historical laboratory records and lack of understanding by the midwife

- A BMS was 'busy' and failed to check computer records before issuing anti-D Ig for a woman known to have immune anti-D
- The midwife assumed that because the laboratory had issued it, it should be given, citing a lack of understanding of the 'science' of anti-D
- She also carried out a 'straw poll' of her midwifery colleagues that indicated every one of them would have administered the anti-D Ig because it had been issued by the laboratory

ASSUMPTIONS



Incorrect route of administration results in an inadequate dose

- A woman required anti-D Ig following a reported TPH of 100 mL fetal cells
- Seven 1500 IU vials of anti-D Ig were sourced from another hospital; the dose was calculated assuming they were to be given intravenously (100 IU/mL)
- Due to unfamiliarity with the particular formulation of anti-D lg in the receiving hospital, all 7 vials were administered intramuscularly (IM)
- Not only was this extremely uncomfortable for the woman, but it also resulted in an underdosing by 2000 IU if calculated according to recommendations for IM route of administration (125 IU/mL)



Student midwife relies on patient to confirm anti-D lg administration

- A student midwife asked a postnatal woman whether she had received her anti-D Ig and the woman confirmed that she had
- The anti-D Ig labelled for the woman was found some days later in the maternity refrigerator, and it transpired that the woman had received an injection of Syntometrine (oxytocin with ergometrine)
- She was recalled and given her anti-D Ig injection a week late

ASSUMPTION





Failure to give anti-D lg in first pregnancy results in sensitisation – multiple errors

- A woman delivered a D-positive baby in 2011. She booked at 17 weeks but did not receive anti-D lg in pregnancy because she did not return at 28 weeks
- She missed some appointments, but many opportunities were missed (at least 8)
- She was delivered by emergency CS but also did not receive her postnatal dose despite it having been ordered and issued

• Anti-D discovered in 2nd pregnancy in 2013



Group change following merger of patient records

- Two patient records with identical names were merged in the laboratory computer, although one patient was O D-negative and the other B D-positive
- The merged record showed the patient as blood group O D-negative, on which basis anti-D Ig was issued
- The current sample from the pregnant woman was erroneously rejected as 'wrong blood in tube' by the laboratory as it grouped as B D-positive and was discrepant with the blood group on record



D problem?

- 2 x 2mL samples were received for group and crossmatch of one unit of red cells for an 11 year old girl (one 5mL sample should have been sent).
- One sample was placed on the automated analyser but was too small to allow complete testing. (The partial grouping results obtained from the analyser gave the D type as D negative but these results were not taken into consideration by the BMS.)
- The sample was then tested manually.
- Positive D typing results of +1 and +2 were obtained
 What should be done next?



Serious outcome - loadsamoney

- According to the laboratory SOP this should have instigated further testing but this was not done.
- No explanation was given in the report as to how/why these 'false' positive results were obtained.
- One unit of D pos red cells was transfused. The error was noticed when a second unit was requested.
- The patient was immediately treated with high dose IV anti-D immunoglobulin but has since produced immune anti-D.





Anti-D When and How Much?

This poster gives recommended dosages of anti-D immunoglobulin at different stages during pregnancy for women with an RhD negative blood type who do not already have immune anti-D antibodies.



 Anti-D is NOT usually indicated unless there has been therapeutic termination, molar or ectopic pregnancy, surgical intervention associated with miscarriage. or continued painful vaginal bleeding (request at least 250iu within 72 hours in these cases)

Between 12 and 20 weeks

Administer at least 250iu anti-D ig within 72 hours of a potentially sensitising event.

Between 20 weeks and delivery

- Administer at least 500iu anti-D ig within 72 hours of a potentially sensitising event.
- Send a sample for a Kleihauer Test in case additional anti-D ig is needed.
- Anti-D ig should be given for potentially sensitising events, even if RAADP has been given already.

Routine Antenatal Anti-D Prophylaxis (RAADP) should be administered between 28 and 30 weeks

- Send a sample for blood group and antibody screen and then administer RAADP according to local policy, even if anti-D ig has been recently given for a sensitising event.
- SINGLE DOSE: Administer 1,500ju anti-D ig at 28-30 weeks.
- TWO-DOSE: Administer at least 500iu anti-D ig at 28 and 34 weeks.

After delivery

- Send 'Mother & Cord' samples for testing.
- Where the baby is RhD positive, administer at least 500lu anti-D lg within 72 hours of delivery.
- Administer further anti-D ig on the advice of the laboratory If the Kleihauer shows a large fetomaternal haemorrhage.

For further information please refer to your local policy

British Committee for Standards in Haematology (BCSH) Guidelines for the use of prophylactic anti-D immunoglobulin 2006.

Royal College of Obstetricians and Gynaecologists (RCOG) Green Top Guideline No 22 The Use of Anti-D Immunoglobulin for Rhesus D Prophylaxis 2011.



- If outside 72 hrs still give anti-D, as a dose up to 10 days may provide some protection
 - Give RAADP in addition to prophylaxis for sensitising events, and vice versa



Anti-D Administration Checklist



Always confirm

- · the woman's identity
- that the woman is D-negative using the latest laboratory report
- · that the woman does not have immune anti-D using the latest laboratory report
- · that informed consent for administration of anti-D Ig is recorded in notes

Potentially Sensitising Events (PSEs) during pregnancy

Gestation LESS than 12 weeks	
Vaginal bleeding associated with severe pain	
ERPC / Instrumentation of uterus	Administer 500i u anti-D within 72 hours of event
Medical or surgical termination of pregnancy	Confirm product / dose / expiry and patient ID pre administration
Ectopic / Molar Pregnancy	
Gestation 12 to 20 weeks	
For any Potentially Sensitising Event (PSE)	Administer 500iu anti-D within 72 hours of event. Confirm product / dose / expiry and patient ID pre administration
Gestation 20 weeks to term	
For any Potentially Sensitising Event (PSE) (Irrespective of whether RAADP has been given)	Request a Kleihauer Test and immediately administer at least 500iu anti-D within 72 hours of event. Confirm product / dose / expiry and patient ID pre administration
Does the Kleihauer Test indicate that further anti-D is required ?	Administer more anti-D following discussion with laboratory
Routine Antenatal Anti-D Prophylaxis (RAADP)	
	Take a blood sample to confirm group & check antibody screen – do not wait for results before administering anti-D
For Routine Antenatal Anti-D Prophylaxis	Administer 1500iu anti-D at 28 – 30 weeks
(Irrespective of whether anti-D already given for PSE)	OR
	Administer at least 500iu anti-D at 28 weeks and then administer at least 500iu anti-D at 34 weeks
	Confirm product / dose / expiry and patient ID pre administration
At Delivery (or Intra Uterine Death >20 weeks)	
Is the baby's group confirmed as D-positive ? OR Are cord samples not available following IUD ?	Request a Kleihauer Test
	Administer at least 500iu anti-D within 72 hours of delivery Confirm product / dose / expiry and patient ID pre administration
Does the Kleihauer Test indicate that further anti-D is required ?	Administer more anti-D following discussion with laboratory

Use a checklist

Key Messages

- DO NOT wait for the result of a Kleihauer test before giving a standard dose of anti-D lg
- If in doubt GIVE IT !

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From 2012: anti-D sensitisation discovered in pregnancy

- Although SHOT receives many reports of late or missed anti-D Ig prophylaxis, the long-term outcome is rarely reported, despite reminders
- New questionnaire for reporting new anti-D picked up at booking or during pregnancy



Number of reports of anti-D immunisation in pregnancy



Immune anti-D discovered in pregnancy 2012-2017

- 58 women with no previous pregnancies (NPP)
- 165 women with previous pregnancies (PP). The data are incomplete particularly data relating to previous pregnancy
- Cumulative data demonstrates that 13/41 (31.7%) women found to be immunised at booking had apparently ideal management in the previous pregnancy
- Still worth giving anti-D lg >72h and up to 10+ days after a sensitising event (go for it!)



Women with no previous pregnancies

In NPP anti-D was detected in 50/58 (86.2%) between 28 weeks gestation and delivery

Gestation was >40 weeks in 13/26 (50.0%) cases where anti-D was first detected at delivery

7/41 with available information were noted to be obese (>80kg)

44/54 eligible women had received single dose anti-D Ig 1500iu at 28-30 weeks; 9 had not received anti-D Ig

All 58 pregnancies resulted in live births, 37 with no complications, 13 required phototherapy and 6 required exchange transfusion



Women with previous pregnancies

- In 68/165 (41.2%) PP women anti-D was detected at booking, 50 (30.3%) developed anti-D at or after 28 weeks and 24 (14.5%) at delivery, 9 of whom delivered beyond term
- Booking weight in previous pregnancy was >80kg in 26 of 86 (30.2%) women where data were provided
- 95/147 who carried to at least 28 weeks received RAADP, 21 did not and in 31 information was missing
- 21/101 (20.8%) women where data were provided delivered beyond term in the preceding pregnancy, compared to 17.5% nationally. 87/145 PP received appropriate postpartum anti-D lg prophylaxis
- In 2017 there were 45 live births, 12 required phototherapy and 4 intrauterine/exchange transfusion.





Woman sensitised despite prophylaxis

- 29 year old woman, first pregnancy
- Received 1500iu anti-D lg at 28 weeks
- Blood sample at 38 weeks showed anti-D level
 5.9 IU/mL
- Result not available until after delivery
- Baby O Pos, +DCT, bilirubin 318
- Treated with phototherapy

Anti-D Summary

- Effective anti-D Ig prophylaxis is a *partnership* between the laboratory and the clinical area
- Requests for anti-D Ig should be driven by the clinicians, especially in early pregnancy
- The clinical area must be responsive to requests for follow-up from the laboratory, and the laboratory must not assume that action will be taken purely because they have issued a report



This man's blood has saved the lives of two million babies

Harrison's blood is precious. He and Anti-D are credited with saving the lives of more than 2 million babies, according to the Australian Red Cross blood service. Known as 'The Man with the Golden Arm,' nearly every week for the past 60 years he has donated blood plasma from his right arm. "In 1951, I had a chest operation where they removed a lung -- and I was 14," recalls Harrison, who is now aged 78.





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Further information is available in the Annual SHOT Reports at www.shotuk.org

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