

# Red-cell iso-immune disease

Dr Elizabeth McCarthy  
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“ In red cell isoimmunisation, the fetus has red cell antigens that the mother does not possess. ”



**Transcribed directly from MOGCAST Episode 19. Listen here:**

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Hello, my name's Dr Elizabeth McCarthy, known as Liz, and I'm a maternal fetal medicine subspecialist, which is an obstetrician who deals with various high-risk scenarios, including fetal diseases. And one of the fetal diseases which is very interesting and treatable is red cell isoimmunisation.

Now, I, like many, many specialists and subspecialists around Australia, learnt a lot of what I know about this from Professor Michael Permezel. He's now emeritus, which means he's very busy and hard to pin down for a lecture. But you students are in the fortunate position that his words are there in his textbook. So, I thought I wouldn't make up my words. I thought I could read to you from the chapter which Michael wrote. Enjoy.

So we'll start with pathophysiology. In red cell isoimmunisation, the fetus has red cell antigens that the mother does not possess. The mother is able to make an anti-red blood cell antibody that does not affect her but can cause haemolysis in the fetus.

Which antigens? The most common red cell antigen that is responsible is the D antigen at the rhesus locus. Approximately 85% of all red cell immunisation is related to the capital D antigen. Some of the more common antigens that may be responsible are listed in a table in the textbook, including little c, capital E, big C, Kell, Kidd, Duffy, M,N, S, either capital S or small s. And these are in the left-hand column, headed red cell antigens associated with haemolytic disease of the newborn.

Conversely, there are a set of antigens under the column, headed red cell antigens not associated with haemolytic disease of the newborn or only mild disease. And these include rhesus antigen little e, ABO antigens: A and B, Lewis, abbreviated as LE, or P, or P1.

The rhesus, or antibodies against other antigens, may not cause clinical problems different from D for the fetus, either because they are predominantly IgM, as in anti-A, anti-B, and anti-capital P, or the fetal red cell does not express that antigen as an anti-LE or anti-Lewis.

The rhesus, or Rh factor, in D antigen is present in approximately 85% of Caucasians, 95% of African Americans, and 99% of Asians, and is so named because it is present in the rhesus monkey. In the preprophylaxis era, it was responsible for 98% of all cases of red cell isoimmunisation affecting pregnancy. But now as many as 15% are caused by other non-D, anti-red blood cell iso-antibodies, particularly anti-c, Kell, E, and Duffy.

Next question how did the mother acquire the anti red blood iso-antibody. There are two main ways. One is blood transfusion. The second is fetal maternal haemorrhage.

Blood transfusion. Although all blood administered is ABO and Rh group compatible, there may not be matching for all the other red cell antigens capable of initiating an immune response. The mother will not have a 'transfusion reaction' as such when she is first exposed to that antigen.

However, this will serve as a primary immune stimulus and antibody production will be initiated that might impact on a current or future pregnancy.

Second way in which a mother acquires anti-red blood cell isoantibody can be fetal maternal haemorrhage.

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“Accumulation of unconjugated bilirubin in the neonatal period can have serious consequences for the neonate.”



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The fetus will usually inherit one or more major blood group factors from the father, which are absent in the mother. When fetal red cells leak across the placenta into the mother's circulation, she may react to these 'foreign' red cell antigens by forming isoantibodies. As little as 0.1 ml of fetal blood may lead to a maternal primary immune response.

Next, consequences of anti-red blood cell isoantibodies. If anti-red blood cell isoantibodies are IgG in type, these will pass across the placenta from the mother to the fetus and cause agglutination and destruction of red blood cells. Transfer of antibody across the placenta increases as gestation advances and is minimal before about 16 weeks gestation. In late pregnancy, there is a surge of antibody transfer to equip the neonate with antibodies to fight infection.

The breakdown of fetal erythrocytes has two consequences. First, bilirubin is a breakdown product of haemoglobin and while not a problem in utero (as the mother will clear the bilirubin from the fetus) accumulation of unconjugated bilirubin in the neonatal period can have serious consequences for the neonate with the possible development of 'Kernicterus'. And there is more on this in the neonatal chapters.

Where the amount of haemolysis is great, the accelerated erythropoiesis will not be able to keep up with the rate of haemolysis and anaemia will occur. Where anaemia is severe, the fetus will develop congestive cardiac failure with widespread accumulation of fluid subcutaneously and in the peritoneal, pleural, and pericardial cavities. This is called fetal hydrops. Further haemolysis will produce fetal death.

Next, ABO incompatibility. ABO incompatibility is numerically three to four times more common than rhesus incompatibility. However, it is very rarely, if ever, responsible for fetal death or even severe anaemia. The usual clinical problem is early jaundice, which may require phototherapy or possibly exchange transfusion. This condition is further characterized by fetal involvement in first pregnancies and unpredictable severity in future pregnancies. And these two features make it different from de-isoimmunization.

The next heading is prevention of red cell isoimmunization. This is by two methods. First, blood transfusion compatibility. And second, passive administration of anti-D.

So more on blood transfusion compatibility. When a woman needs a blood transfusion, it is impractical to transfuse only blood that is antigenically fully compatible with the woman for all possible red-cell antigens. In practice, no D-negative person should receive D-positive blood. Kell-positive blood is generally only given to males or women beyond childbearing age. No specific efforts are generally made to avoid blood transfusion causing a primary immune response to the minor incompatibility agents.

Second, passive administration of anti-D. To prevent the development of anti-D antibodies, passive administration of anti-D was introduced in the late 1960s. As illustrated in figure 22.2 in the textbook, passively administered anti-D binds to the D antigen on the fetal red cells and prevents recognition by the maternal immune system, therefore preventing primary immunization as a consequence of fetal maternal haemorrhage. It should be noted that there is no similar process for preventing anti-little c, anti-Kell, or any other red cell isoimmunization.

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This is simply because the high frequency of anti-D isoimmunization makes the passive anti-D program cost-effective, whereas the program to prevent immunization to other antigens would not be cost-effective. Note that the passive administration of anti-D is only effective to prevent primary immunization and has no impact in preventing a fetal maternal haemorrhage-induced titre increase in a woman who's already immunised with anti-D.

Few more features to be considered are; when to administer it, when the partner could be tested, how much passive anti-D to give, and what is the effectiveness of passive anti-D.

First, when to administer anti-D. Anti-D is generally administered at times of likely fetal maternal haemorrhage. There are broadly four such occasions.

One; bleeding in pregnancy, including miscarriage, abortion, ectopic pregnancy, and antepartum haemorrhage. Two; trauma, including amniocentesis chorionic villus sampling, external cephalic version, major fall, or motor vehicle accident. Three; third trimester routine administration at 28 and 34 weeks as part of routine antenatal care. Four, following birth.

In that last fourth circumstance, there is the opportunity to test the neonate to determine if the neonate is capital D positive. In the event that the neonate is D negative, unnecessary wastage of anti-D can be avoided by withholding passive anti-D.

Second, a comment on testing the partner. This isn't routine practice, but occasionally women will tell you that their partner is D negative, and if this can be understood to be the fact, then she doesn't need anti-D.

Third, what amount of passive anti-D is given? There are a number of different formulations of anti-D currently available. For sensitizing events prior to 12 weeks, 250 international units would commonly be administered.

After 12 weeks, prophylaxis occurs with 625 international units of anti-D. In some countries, a single dose of 1,500 international units of anti-D will be given at 28 weeks instead of two doses of 625 international units at 28 and 34 weeks. Kleihauer testing of maternal blood is able to detect the presence and amount of fetal erythrocytes and permits a more scientific approach to prophylaxis.

A Kleihauer should be performed in the presence of a sensitizing event in late pregnancy to see if more than one ampoule of anti-D is required to neutralize the amount of fetally derived D antigen in maternal blood. In the case of a massive fetal maternal haemorrhage, a large amount of passive anti-D will be needed. Then the next point concerns effectiveness of passive anti-D.

The introduction of anti-D in the late 1960s reduced the incidence of the mother becoming immunised with anti-D. At that stage, as many as 10% of pregnancies were affected and then following introduction of passive anti-D, this reduced to 1% of pregnancies with a D positive fetus and a D negative mother. With passive anti-D also being administered prophylactically at 28 and 34 weeks gestation as was introduced in the 1990s in Australia, the number of women developing anti-D antibodies may drop to as low as 0.1%. These persisting cases may result from spontaneous fetal maternal haemorrhage before the prophylactic anti-D is administered

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“Ensure that maternal antibodies, if present, are detected by routine antenatal testing.”



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at 28 weeks or an unusually large fetal maternal haemorrhage that has not been administered sufficient anti-D or failure to appropriately administer anti-D globulin due to blood group oversight, blood group error, or refusal by the woman.

So some will question whether the passively administered anti-D can cause problems in the fetus. And it's true, in fact, the anti-D does cross the placenta and bind to fetal red cells. But the amount of anti-D is very small and the amount of haemolysis occurring is clinically insignificant.

Next major heading is detection of anti-red blood cell antibodies. Apart from seeing that anti-D prophylaxis is appropriately carried out in D-negative women, the other major task of the obstetric attendant is to ensure that maternal antibodies, if present, are detected by routine antenatal testing. All women are screened at the first antenatal visit for the presence of anti-red blood cell antibodies.

If no antibodies are present at the first visit, further checks are made in D-negative women at 28 weeks prior to the administration of passive anti-D. Some units will do repeat screening on all women at 28 weeks, but the cost effectiveness is less in those women that are D-positive as the proportion that become immunised during pregnancy, for example, with little c, e, or Kell, will be less than that of D-negative women with capital D. If antibodies are present at any time, the woman must be referred to a specialist or special centre dealing with this problem. A number of complex decisions and therapeutic measures will be required if moderate or severe haemolysis is occurring in the fetus.

So, the next section concerns management of a woman with anti-red blood cell antibodies, and the steps are first to allocate risk at the first antenatal visit, and then there's some information on managing low-risk immunised pregnancy and a brief introduction to managing moderate or high-risk immunised pregnancy. So first, allocating risk at the first antenatal visit. Approximately 1% of women will be found to have anti-red blood cell antibodies at the first antenatal visit.

These women have become immunised as a consequence of a previous pregnancy or a blood transfusion. As a first step, it's necessary to determine the likely risk of this antibody to the fetus. This can be done with three complementary approaches.

One is to determine the partner's antigen status. Two is to quantify the amount of antibody in the maternal plasma. And three, to ask the question whether the specific antigen affects risk.

With respect to the partner, in this case, it's not routine care, but once you have a woman with red cell antibodies, it can be helpful to determine the partner's phenotype and genotype of their red cells. In some cases, he might also have a negative blood group, and the woman's anti-D antibodies have been from some other source, perhaps a child of a previous relationship, and a current child is not at risk. So, you can read in the textbook more about a homozygous capital D, capital D situation, and the heterozygous capital D blank, and how this predicts whether the fetus is at 100% risk or whether there is a 50% chance that the fetus is not at risk at all.

The second contributor to quantifying risk at the first antenatal visit where a woman has anti-red blood cell

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antibodies is to quantify. Now, this is usually done by titres, and for most antibodies, a titre of 16 or less is low risk, of 32 to 256 is moderate risk, and a titre of 512 or higher is high risk. There are also, in some settings, a different quantification using international units per litre, but I'm using titres as they're most commonly used in Victoria, and I refer you to the textbook, which has Table 22.3, which converts to international units per litre.

The third question to ask when we're stratifying the risk is, does the specific antigen affect risk? And the management of an affected pregnancy is largely dependent upon the amount of antibody rather than the particular antibody. The exception to this, however, is anti-Kell which may be more serious than others at the same antibody level because the Kell antigen is particularly expressed on the erythroblast. That is the precursor to red cells.

Okay, the next two sections, one is on managing low-risk immunised pregnancy, and then the following one on managing moderate or high risk. So, for women with low-risk immunised pregnancies, maternal isoantibody levels should be estimated every four weeks until 28 weeks, and fortnightly thereafter until birth. While the antibody level remains in the low-risk range, antenatal management can generally remain with the chosen model of care.

If the titre was to rise, the woman should be managed as for moderate or high risk and referred appropriately. If the antibody is anti-D, there is no value in administering prophylactic passive anti-D. However, anti-D should still be administered to Rh negative women with another isoantibody.

At birth, the cord blood should be sent for grouping, bilirubin and haemoglobin determination. The baby should be managed by a doctor experienced in the management of immunised neonates. Early severe jaundice is possible and may follow a quite different course from that of physiological jaundice.

Then the next bit is a brief introduction to management of the moderate or high-risk immunised pregnancy. In general, these women will be referred to an obstetrician in the first instance and then usually have ongoing care with a maternal fetal medicine subspecialist.

In Victoria, there are specialists who visit the Northern. There is a unit at the Western Hospital, Sunshine, at Royal Women's, Monash and Mercy Hospital for Women. So on occasions, women who live rurally or in other regional centres will need to travel for MFM care if they have a moderate or high-risk immunised pregnancy.

So, in this case, it's really important to work out the partner state, whether they're heterozygous. And if the partner is heterozygous, it is pertinent to know whether the fetus inherited the relevant antigen. To do this, we would avoid a CVS or chorionic villus sampling as the actual procedure may provoke fetal maternal haemorrhage and further increase antibody level. Amniocentesis may be safe.

It's less likely than CVS to produce a rise in titre. But there's more and more possibility of using a non-invasive way to assess fetal blood group by isolating free fetal DNA from the maternal bloodstream and typing the fetus on the basis of that DNA. This is the sort of highly specialised test that needs to be ordered from an MFM unit, not in the general maternity units.

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“Fetal anaemia can be corrected with the infusion of donor cell into that fetal vessel.”



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Fetal anaemia can be anticipated on the basis of ultrasound, the peak systolic velocity, or PSV, in the middle cerebral artery of the fetus, the MCA. In severe cases, this may be commenced this sort of ultrasound surveillance as early as 17 weeks and would commonly be performed every one to two weeks. It may be less reliable after 34 to 36 weeks and then would be complemented by fairly frequent cardiotocography, or CTG.

This may initially be non-reactive in fetal anaemia and then as the anaemia gets worse, the abnormalities get even more significant with a sinusoidal pattern, but this is a very late sign of fetal anaemia. To look at a picture of this, go to figure 22.3 in the Beischer & MacKay textbook. If fetal anaemia is thought probable on the basis of the MCA-PSV, fetal blood sampling may be performed under ultrasound control into either the umbilical cord or the umbilical vein as it passes through the liver.

Fetal anaemia can be corrected with the infusion of donor cell into that fetal vessel. The blood infused will be negative for whichever antigen the maternal antibody is directed against. Fetal transfusions are commonly needed frequently at first, so two in the first week, typically, and then with reducing frequency, spaced out as far apart as up to four weekly as the fetal blood type “changes” to that of the donor blood and is no longer susceptible to being destroyed by the maternal antibody.

Delivery. Delivery will be indicated in these high-risk scenarios when the risks of fetal transfusion exceed the risks of prematurity, and it would be uncommon, therefore, to continue to transfuse after 35 weeks gestation.

Then the newborn. The newborn needs to be carefully watched for both severe jaundice and anaemia. If transfusions have not occurred, severe jaundice should be anticipated in these moderate to severely high-risk immunised women. In contrast, the fetus that has had many transfusions may not have jaundice at all but may suffer from later anaemia as the transfusions have suppressed fetal erythropoiesis, which needs to re-establish in the neonatal period.

So, I hope that you've enjoyed that introduction. It really covers all the basics of what medical students in their women's health term need to know about prevention of anti-D disease, how anti-D affects the fetus, and how women with a low risk isoimmune condition or a high-risk isoimmune condition are managed.

If you go to the textbook in Chapter 22, there's further interesting information about analogous but even rarer conditions like antiplatelet immunisation, myasthenia gravis, fetal neonatal grave disease and fetal neonatal systemic lupus erythematosus and congenital heart block.

So, they're all really fascinating. They are really core to maternal fetal medicine rather than to general obstetrics or other aspects of maternity care. But they're great examples of immunology in practice and how pathology is explainable and treatable in this fascinating world of obstetrics where we have two patients, a mother and a fetus.

So, I hope you enjoy that, and we'll see you on the next podcast.