

Blood and the fetus



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The fetus makes the various constituents from around 21 days post-conception. The volume of blood increases through the pregnancy. The blood volume is greater than expected for the fetal size as blood also circulates around the placental vessels.

As will be explained later, this can provide a significant advantage when a transfusion is required. The fetal blood group and platelet type is usually different to the mother's as it is inherited from both the mother and father. This is the basis of the problems encountered in fetal anaemia secondary to maternal red cell antibodies and fetal thrombocytopenia secondary to maternal platelet antibodies.

Access to the fetal circulation has become possible with the advent of high resolution gray scale ultrasound. This has allowed fetal blood sampling for many reasons and administration of various blood products and medications directly to the fetus. It is not without risk, however, and there needs to be clear justification.

Fetal blood sampling

Indications

Fetal blood sampling (FBS) is not commonly indicated in pregnancy. However, there is a range of indications. FBS may be indicated for prenatal diagnosis. Some conditions require red cells for accuracy of diagnosis. In the case of a mosaic cell line result in an amniocentesis, FBS may help counselling. FBS may be used to diagnose fetal infection, though in most cases, polymerase chain reaction (PCR) examination of the amniotic fluid is sufficient. In the case of cytomegalovirus (CMV) infection, fetal thrombocytopenia has been shown to be usefully correlated with outcome. In some endocrine disorders, for example, hypothyroidism with goitre, where intramniotic drugs are being given, FBS may be necessary to confirm treatment efficacy. Where there is non-immune fetal hydrops, FBS may be part of the work-up.

The most common reason for FBS is where anaemia is suspected. This may be secondary to red cell antibodies or parvovirus. The treatment of anaemia is covered later in this article.

Procedure

FBS is done as a sterile procedure. A needle is inserted into the uterus under ultrasound guidance. If the placenta is anterior, usually the access is transplacental into the base of the cord. The umbilical vein is the vessel chosen as there is a risk of spasm of the umbilical artery. If the placenta is posterior, then the amniotic cavity will need to be traversed to allow access to the umbilical vein. This can be technically more challenging. This procedure should be performed or supervised by someone with expertise and carries a higher risk than amniocentesis or chorionic villus sampling (CVS).

Haemolytic disease of the fetus and newborn (HDFN)

Pathophysiology

HDFN is much less common now compared to 20 years ago prior to the advent of routine anti-D at times of immunisation risk.

During normal pregnancy trophoblast and fetal cells enter the maternal circulation. These are usually destroyed. Some particular red cell antigens are highly immunogenic and during the process of clearing them from the maternal circulation result in antibody production. In addition to the immunogenicity of the antigen, the volume of spill is also important. Therefore a large spill of fetal cells of a highly immunogenic type is more serious. The antibodies are of benefit to the mother as they clear the 'foreign' material away.

Red cell antigens are complex and are grouped in systems. Some are inherited in pairs or triplets. The most common red cell antigens to cause problems are the Rhesus antigens (50 per cent HDFN), Kell antigens (30 per cent) and less commonly those of the MNS system, Duffy system (anti-Fya) and Kidd system (anti-Jka and anti-Jkb). The Rhesus antigens comprise the D, C, c, E and e alleles. Anti-D antibodies are most common and those which most doctors are aware of. Anti-c and anti-Kell antibodies deserve special mention as they cause the worst fetal anaemia.

In the case of HDFN, in the index pregnancy, there is a spill which results in production of antibodies. The first antibodies are IgM. These are large and cannot cross the placenta. It takes some time for B-cell memory to develop in the case of red cell antibodies and this usually means that IgG antibodies are not present in the index pregnancy.

In the next pregnancy, if there is a fetal red cell spill into the maternal circulation which triggers an antibody response (fetus red cell antigen opposite to mother for antibody detected), then IgG may be produced. The IgG can cross the placenta and enter the fetal circulation.

Once in the fetal circulation, the IgG attaches to fetal red cells and triggers the fetal reticuloendothelial system to destroy the red blood cells. As a result, the fetus becomes increasingly anaemic. This is compounded by the fact that as the fetus grows more red cells are needed. There is a rise in bilirubin which is cleared effectively through the placenta. The degree of anaemia is dependant on the amount and type of the antibodies and the ability of the fetus to produce reticulocytes.

Management antenatally

When a red cell antibody is detected on the booking bloods, the transfusion service will normally give quantification and a comment. In New Zealand, the titre is given as a maximal dilution at which the antibody is still detected (for example, one in 64) and in Australia a quantitative value (for example, 4iu/ml). Local circumstances will vary as to the cut-offs used for management. Essentially, titres should be repeated at least every four weeks and sometimes more often. Once a critical level is reached referral should be made to the local expert. In many cases, this will be a subspecialist in maternal fetal medicine but local circumstances will vary.

In Auckland, we use a different threshold for referral for anti-c and anti-Kell antibodies and review anyone with these antibodies as they are associated with more severe HDFN. At this point, consideration can be given to whether this particular fetus is at risk from the

antibodies. Paternal testing of phenotype (or ideally genotype) should be offered. If the father of the pregnancy is homozygous for the antigen that the antibody attaches to, then all fetuses are likely to be affected. If the father is heterozygous, there is a 50 per cent chance the fetus will not be at risk. In this case, with the most common antibodies, fetal genotyping with DNA extracted from amniocentesis or CVS samples can be performed (Rhesus and Kell). This allows the pregnancy to be normal and not monitored where the fetus is not at risk. However, there is a risk of pregnancy loss with the invasive test and for some couples this isn't outweighed by the reduction in monitoring. Note that there is a risk of increasing antibody production with CVS and generally amniocentesis is preferred.

As the pregnancy continues, once the antibody levels reach a threshold for closer monitoring, the assessment of peak systolic velocity (PSV) in the middle cerebral artery (MCA) is performed. In an anaemic fetus (whatever the cause) there is an increase in the MCA PSV. This is thought to be due to preferential shunting of the lower oxygen carrying capacity blood to the brain and a change in the blood rheostatics allowing higher speeds.

In the past, the OD450 value of amniotic fluid (a surrogate of bilirubin level) was used. This has been shown in a large randomised controlled trial to be inferior to MCA PSV in predicting fetal anaemia. In addition, amniocentesis is invasive and carries risks.

It should be noted that this study looked at need for first FBS and in-utero transfusion. There is no well-validated test for monitoring the fetal haemoglobin level once the fetus has been given a transfusion. Also, the value of MCA PSV after 35 weeks gestation is not so certain.

Invasive procedures

If the MSA PSV suggests the fetus is anaemic, a FBS and probably an in-utero transfusion (IUT) will be performed. This can be performed from around 18 to 20 weeks and is not commonly performed after 35 weeks when induction of labour is usually indicated. This is a technically challenging procedure which should be done in a medical unit with the expertise to perform it and access to appropriate blood products. The fetal loss rate in series is three per cent when commenced before 32 weeks overall and one per cent when commenced after 32 weeks. If the fetus is hydropic at the first IUT the outcomes are worse (30 per cent loss rate).



Figure 1. In-utero transfusion (IUT). Under ultrasound screening guidance using a sterile technique, a needle is inserted into the umbilical vein.

If the pregnancy is still under 34 weeks but viable, many units will administer steroids for fetal lung maturation prior to the procedure, as very occasionally, emergency preterm delivery may be required during or shortly after the procedure.

In most units, the blood for donation is a fresh unit as the 2,3-diphosphoglycerate (DPG) level is higher and therefore the haemoglobin gives up oxygen more easily to tissues. The blood is irradiated to prevent graft versus host disease and is CMV negative. The blood group is the same as the mother's so that the red cells are not affected by the antibodies. The immature fetal immune system does not mount an antibody response to the transfused red cells. The blood is then centrifuged to remove a large proportion of the plasma so it is very concentrated. This means more red cells are given in less volume, the transfusion volume being the limiting factor.

Under ultrasound screening (USS) guidance using a sterile technique, a needle is inserted into the umbilical vein as described above (Figure 1). A sample of fetal blood is taken and analysed for haemoglobin. In addition, blood will be tested for blood group, bilirubin level and a full blood count to include a reticulocyte count. This helps to guide timing of future transfusions. The concentrated donated blood is attached via a small connector to the needle and injected into the umbilical vein. The fetal heart is monitored throughout. A calculation based on the initial haemoglobin, haematocrit of the donor blood and fetal weight is used to guide the volume to be given. As the placenta has a significant vascular volume, more volume can be given for the expected size of the fetus. Once the IUT is completed a second sample is taken to confirm haemoglobin and check Kleihauer and then the needle is removed.

In many medical units, a muscle relaxant is given to the fetus at the start of the procedure, as it has been shown to reduce the risk of the procedure. This means that after the procedure the fetus may not move for an hour or two.

Once an IUT has been performed, it is likely that further IUTs will be required. This is due to the fact that the remaining fetal red cells continue to be destroyed and that as the fetus grows it requires more red blood cells and quite quickly erythropoiesis slows and stops. There is no clear method to decide the frequency of IUTs and a lot of this requires 'clinical judgement'.

Most units will consider delivery from 35 to 37 weeks in a woman who has required IUTs. There is an argument for nearer to 37 weeks if all remains well, as there is a big improvement in fetal/neonatal liver enzyme function over the last few weeks. This reduces the chance of serious jaundice requiring further intervention. Delivery method is as indicated by the usual obstetric issues.

Management of the neonate

As HDFN becomes rarer secondary to reduction in anti-D antibodies, the experience of healthcare professionals of managing this condition diminishes. It is therefore important that the obstetrician/gynaecologist caring for a woman who has had HDFN understands the neonatal issues and can actively advocate for best practice.

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Cases arise not infrequently where there is a poor outcome in the neonatal period due to a lack of understanding of this condition. It may be that although a woman has been under the care of a specialised maternal fetal medicine unit for her pregnancy, delivery and postnatal care may be provided at her local hospital.

At birth, a cord sample should be taken to determine blood group; the presence of red cell antibodies which react to the neonatal red cells (a direct antiglobulin test or Coombs depending on the local laboratory); haemoglobin and erythrocyte count; and bilirubin. At this stage, the results should be interpreted in conjunction with a paediatrician.

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The neonate who has had significant haemolysis and continues to do so will be producing large amounts of bilirubin. In fetal life this is cleared by the placenta. In neonatal life liver enzymes do the job. If the enzymes are over capacity, jaundice results. If this rises unchecked, it will reach dangerous levels in the brain and can cause Kernicterus and brain damage. Treatment options include intravenous immune globulin (IVIG) treatment if the bilirubin is not rising too fast or an exchange transfusion. This is where some blood is removed and then donated blood given while carefully maintaining a normal intravascular volume. This is technically challenging and has a significant risk to the neonate. It should only be performed in experienced neonatal units.

After birth, maternal IgG continues to circulate in the fetal circulation for four to six weeks. During this timeframe, the neonate who is not anaemic remains at risk of becoming anaemic and weekly blood counts should be considered. The cord blood results can help to determine the level of risk.

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For the neonate who has had multiple IUTs, there is often complete suppression of erythropoiesis. There is usually no fetal/neonatal red blood cells and the whole blood volume comprises of transfused cells. These cells last around three months and are then destroyed by the neonate as they reach their natural life end. At this stage, the neonate should be producing red blood cells which will now not be destroyed as there are no maternal antibodies left. However, in some cases, there is no resumption of erythropoiesis and the neonate becomes dangerously anaemic and can even die. This all happens at four to 12 weeks of age when the O and G and midwife have often handed care to the general practitioner. It is imperative that the carers understand that often these babies will continue to need weekly haemoglobin counts until three months of age.

Pre-pregnancy counselling

It is good practice to offer pre-pregnancy counselling. This will need to be tailored to the individual and in most regions is offered by the maternal fetal medicine unit. A general rule of thumb is that if the fetus is susceptible and IUTs were needed in the last pregnancy, they are likely to be needed in the next pregnancy. If the paternal phenotype/genotype are not known, this is a good time to arrange testing.

Future developments

In the future, there is likely to be some new developments in this area. Free fetal DNA in the maternal circulation may allow identification of the fetal blood type. Where anti-D is given routinely to Rhesus negative women, this will allow rationing of supplies of anti-D. It will only be given in pregnancies where the fetus is Rhesus positive. In the case of women with antibodies, amniocentesis where there is a heterozygous partner can be avoided as fetal susceptibility can be determined.

One of the problems for maternal fetal medicine specialists performing IUTs is deciding when to perform the next one. In the past, most specialists have used a calculation including a presumed fall in haematocrit or a transfusogram. Some discussion is being given to the role of MCA to detect further anaemia and a randomised controlled trial comparing the two methods is proposed.

The role of intravenous immune globulin (IVIG) in the neonate is new and slowly being adopted into neonatal units. This is likely to become standard first-line management for significant jaundice in the future.

Neonatal alloimmune thrombocytopenia

This condition is rare and should be managed in conjunction with a maternal fetal medicine specialist. Essentially, the pathology is similar to HDFN except that the IgG attacks fetal platelets. The maternal platelets are usually normal.

The main difference is the condition can arise in the first pregnancy and rather than anaemia can result in intracerebral haemorrhages antenatally and postnatally secondary to fetal/neonatal thrombocytopenia. For the general O and G, if there is a history of an intracerebral haemorrhage during or after a previous pregnancy, consideration should be given to this diagnosis if there is no other reason.

Summary

Blood conditions in the fetus are rare. Most will be managed in conjunction with a maternal fetal medicine unit. It is important for the general O and G to have an understanding as their patients will need support and information. Following delivery, the O and G can advocate best care for the neonate and ensure that the appropriate care is continued at handover in the postnatal period.

Reference

1. Oepkes, van Scheltema. Intrauterine fetal transfusions in the management of fetal anaemia and fetal thrombocytopenia. 2007, Seminars in Fetal and Neonatal Medicine.