BJOG: An International Journal of Obstetrics & Gynaecology

WILEY

BJOG An International Journal of Obstetrics and Gynaecology

SCIENTIFIC IMPACT PAPER

The Use of Novel Therapies in the Management of Haemolytic Disease of the Fetus and Newborn (HDFN)

Scientific Impact Paper No. 75

V. Cordell | A. Soe | T. Latham | V. L. Bills | the Royal College of Obstetricians and Gynaecologists

Correspondence: Royal College of Obstetricians and Gynaecologists, 10–18 Union Street, London SE1 1SZ. | (Email: clinicaleffectiveness@rcog.org.uk)

Funding: All those involved in the development of Scientific Impact Papers, including the Scientific Advisory Committee, Scientific Advisory Committee chair, developers, peer reviewers and other reviewers, are unpaid volunteers and receive no direct funding for their work in producing the paper. The only exception to this are the Scientific Advisory Committee members who receive reimbursement for expenses for attending Scientific Advisory Committee meetings for standard RCOG activities; this is standard as per RCOG rules.

Plain language summary

Haemolytic disease of the fetus and newborn (HDFN) is a rare condition that causes a baby to develop anaemia while growing inside the woman; or after birth. Left untreated, this may lead to stillbirth or neonatal death.

HDFN is caused when the pregnant woman's antibodies cross the placenta, enter the baby's circulation, and attach to proteins called antigens (inherited from the father) on the baby's haemoglobin containing red blood cells, and cause them to break apart, causing fetal anaemia.

Women routinely have their blood tested at the start of pregnancy to assess their ABO blood group and Rh antigens. There are five main Rhesus antigens: D, C, c, E, e; with anti-D being responsible for most cases of HDFN. If a woman is found to be Rh D negative; a 'non-invasive' blood test is performed to assess if the fetal blood group is the same as the woman's. If a woman is found to be Rh D negative, and the baby is found to be D positive, the baby is at risk. This is because the baby has inherited the D antigen from the father; so-called Rhesus incompatibility. Other red blood cell antibodies such as anti-Kell or anti-Duffy can also cause fetal anaemia. Women at highest risk of developing HDFN are those who have had at least one previous birth or a sensitising event (such as abdominal trauma) in a current or previous pregnancy, causing the woman and baby's blood to mix.

Current treatment for haemolytic disease of the fetus involves giving fetal blood transfusions, with a small risk of early labour or pregnancy loss. If anaemia develops later in pregnancy, early delivery of the baby may be recommended; which could lead to complications of prematurity. In cases of mild HDFN, the baby may only require light therapy for neonatal jaundice. However, if the anaemia occurs earlier in pregnancy and is severe, the baby may need blood transfusions while still in the womb - and after birth may require an exchange transfusion, to remove the woman's antibodies from their circulation and to treat the anaemia.

Intravenous immunoglobulin (IVIG) is a potential non-invasive method to prevent or delay the onset of severe anaemia. It is a blood product given intravenously every week to women who have been deemed at very high risk of early onset HDFN. It can be started at the end of the first trimester until birth, or until anaemia develops. This paper will discuss the evidence behind IVIG and other novel therapies during pregnancy, including the risks and the benefits. The developers of the paper include obstetricians, neonatologists and haematologists to provide different opinions on this topic.

Please cite this paper as: Cordell V, Soe A, Latham T, Bills VL, on behalf of the Royal College of Obstetricians and Gynaecologists. The Use of Novel Therapies in the Management of Haemolytic Disease of the Fetus and Newborn (HDFN). RCOG Scientific Impact Paper No. 76. BJOG 2024; [DOI: 10.1111/1471-0528.18008].

1 | Background

Haemolytic disease of the fetus and newborn (HDFN) occurs when there is transplacental passage of maternal immunoglobulin G (IgG) red cell antibodies, which bind to paternally-derived antigens on fetal red blood cells, or alternatively those of a donor gamete (either egg/sperm) following in-vitro fertilisation. The fetal red blood cells coated with IgG alloantibodies become attached to Fc receptors of macrophages mainly in the spleen, and are phagocytosed. This leads to fetal haemolysis, anaemia, and if left to progress, can cause hydrops from high-output cardiac failure and fetal death. Fetal haemolysis can also cause jaundice postnatally, secondary to high unconjugated bilirubin levels from haemoglobin breakdown, and subsequent neurological damage.[1] This process usually occurs following a sensitising event such as a fetomaternal haemorrhage during pregnancy, during birth, or following an incompatible blood transfusion.

Red cell antibodies are found in 2% of all pregnancies, with clinically significant antibodies found in 0.4% of pregnancies.[2] Women at the highest risk of HDFN are those who develop the red cell alloantibodies to the Rhc, RhD, and Kell system blood group antigens.

Fetal mortality is now low following the introduction of routine antenatal blood typing and anti D prophylaxis (RAADP) in the third trimester.[3] However, despite anti D prophylaxis, around 1 in 1000 women still develop D alloimmunisation.[4, 5]

Intrauterine blood transfusion (IUT) is currently the only widely recognised treatment option to prevent fetal death and reduce the neurological impairment of fetuses affected by HDFN.[4] Maternal intravenous immunoglobulins IVIGs, and more recently monoclonal antibodies, have been suggested as non-invasive alternatives to reduce or delay the need for IUT, and will be discussed in this paper.

This guidance is for healthcare professionals who care for women, non-binary and trans people. Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex recorded at birth.

2 | Pathophysiology of HDFN

Antibodies of the IgG class are the only immunoglobulins to cross the placenta, via the transmembrane protein – the fetal/neonatal Fc Receptor (FcRn)[4], and cause haemolysis of the fetal red blood cells if the fetus is positive for the corresponding red cell antigen. Corresponding erythropoiesis from the fetus is often insufficient to prevent anaemia. Although the primary maternal immune response to the Rh D antigen is often weak, it is the secondary immune response to the antigen if the fetus is Rh D positive in a subsequent pregnancy that causes a greater and earlier degree of anaemia. If there is parental Rh incompatibility, anaemia tends to present at earlier gestations with each subsequent pregnancy.[6] Fetal medicine specialists should always be aware of cases of non-paternity when assessing risk of HDFN.

Red cell antibodies to antigens of the Kell system can also damage the erythroid progenitor cells, meaning erythroblastosis cannot occur and subsequent early fetal anaemia can follow.[6]

Fetal haemoglobin should increase during pregnancy to around 150g/L by term. As fetal anaemia occurs, the peak systolic blood flow velocity in the fetal middle cerebral artery (MCA PSV) will be seen to rise[7], and as the anaemia progresses further it can cause reduced tissue perfusion and hypoxia leading to end organ dysfunction.[1] Late findings of severe disease include fetal hydrops, fetal cardiomegaly, and eventually fetal death if left untreated.[7] Hydrops can occur with a fetal haemoglobin of <40g/L at 18 weeks to <80g/L at term.[1]

Haemolysis also leads to raised bilirubin, which in pregnancy is excreted via the placenta but postnatally can cause severe damage to the fetal nervous system, known as kernicterus. Even after birth the haemolysis can continue and the immature neonatal liver is unable to conjugate the excess bilirubin. This bilirubin can be deposited in the basal ganglia and brain stem nuclei causing athetoid cerebral palsy, hearing problems/ psychomotor impairment.[5]

3 | Current Antenatal Screening and Testing

All pregnant women are screened for their blood group, D status and presence of antibodies in the first trimester and again at 28 weeks of gestation to identify pregnancies at risk of Rh incompatibility. D negative women are screened for fetal RhD status via non-invasive prenatal testing (NIPT); whereby cell-free fetal DNA present in maternal blood is analysed for the fetal RHD genotype. Accuracy of this test has been validated by numerous studies and approved by NICE.[8] If clinically significant alloantibodies are detected, titres are determined.[2] Pregnancies with alloantibody levels above a certain threshold are referred to a fetal medicine service for serial ultrasound scans to screen for the development of fetal anaemia via middle cerebral artery (MCA) Doppler velocities. An MCA – Peak Systolic Velocity (PSV)≥ 1.5 Multiples of the Median (MoM) predicts moderate-severe fetal anaemia with a sensitivity of 100% for a false positive rate of 12% in the landmark study by Mari et al.[7]

There are no specific symptoms of HDFN in pregnancy or the neonatal period. Decreased fetal movements and sudden fetal death are non-specific markers, as is neonatal jaundice.[6] However if a woman presents with reduced fetal movements in the third trimester she will receive antenatal cardiotocograph (CTG) monitoring; fetal anaemia may be identified on the CTG by the presence of reduced variability with a sinusoidal pattern.

Women with a previous pregnancy history of HDFN or rising antibody levels/titres, a level/titre above a specific threshold

should be referred in early pregnancy to fetal medicine. The Royal College of Obstetricians and Gynaecologists provides reference ranges for when to refer to fetal medicine in Green Top Guideline 65.[2]

Non-invasive fetal genotyping by cffDNA can be performed on maternal blood to determine the risk of HDFN by assessing for antigens for D, e, E, c, C and K. This test has high sensitivity and specificity. RhD, c, e, C, and E can be detected with good sensitivity after 11 weeks' gestation. Regarding Kell, genotyping can occur after 20 weeks in UK practice due to the risk of false negative results if performed earlier.[6] If cffDNA NIPT is not available it may be useful to undertake paternal genotyping to determine if the father is homozygous or heterozygous; if the father is homozygous then the parents can be informed that all pregnancies will be at risk of HDFN. However this approach is limited by the potential for non-paternity.

Following a sensitising event in a pregnancy to a Rhesus D negative woman carrying a Rh D positive fetus, a Kleihauer-Betke maternal blood test is recommended to check for mixing of maternal and fetal red cells, as is the administration of routine Anti D immunoglobulin prophylaxis.[6] If alloimmunisation has already occurred no further anti-D is required, and secondary prevention of HDFN includes pregnancy surveillance with serial MCA Doppler ultrasound assessment.[6]

At delivery of a woman with clinically significant antibodies, a cord direct antiglobulin test (DAT) should be taken to assess if the infant's red cells are coated with antibody, as well as haemoglobin and bilirubin levels. This should be followed by subsequent monitoring for neonatal jaundice and anaemia.[9]

3.1 | Invasive Testing

On discovery of raised middle cerebral artery peak systolic velocities, referral to a tertiary fetal medicine service for direct fetal blood sampling is the most accurate method of diagnosing fetal anaemia. However this invasive procedure carries a 1.3% risk of miscarriage or preterm birth.[10] It also carries a risk of further sensitisation.

4 | Current Treatment for HDFN

4.1 | Antenatal Treatment

Intrauterine blood transfusion (IUT); the administration of blood into the fetal umbilical vein at the placental insertion, into its intrahepatic course, or a free loop of cord under ultrasound guidance, is the current mainstay of treatment for HDFN.[9] This invasive procedure carries a risk of preterm birth and miscarriage depending on the gestation at which it is performed. These risks are highest under 22 weeks' gestation with early onset fetal anaemia.[4] Miscarriage rates have been quoted as 8.5% at under 20 weeks and 0.9% at over 20 weeks.[11] Complications include intrauterine infection (0.1%), rupture of membranes (1.4%) and iatrogenic preterm birth (when performed after 24 weeks). Fetal distress, perhaps from bleeding of the umbilical cord leading to emergency caesarean section, and accidental intraperitoneal transfusion are also possible. Other complications include contractions requiring tocolysis and bleeding at the maternal puncture site.[9] The overall procedure-related complication rate is 3-5%. In the absence of hydrops, survival following IUT is greater than 90%.[1] However, before 22 weeks, two case series of 30 and 29 transfusions demonstrated procedure-related complications to be much higher with an overall perinatal loss rate of 20-24%.[4, 12, 13] The higher fetal loss rates associated with early IUTs before 22 weeks are attributable to the need for intraperitoneal transfusion rather than intravascular transfusion, as the fetal vasculature is too small to accommodate cannulation at early gestations. Therefore, in order to improve outcomes it is preferable to delay the timing of the first IUT to as late as gestational age as possible. IVIG has the potential to enable this.

4.2 | Postnatal Treatment and Outcomes

Vaginal birth is possible following intra-uterine transfusion if the fetus is not compromised, with units offering induction of labour at 36-37 weeks following IUT. The accuracy of MCA-PSV in predicting anaemia diminishes after the first transfusion so cannot be solely relied upon for its prediction later in the third trimester.[14]

The postnatal treatment for HDFN is neonatal phototherapy or exchange transfusions; to correct fetal anaemia and lower the fetal bilirubin.[6] This is guided by a direct agglutinin test from the umbilical cord. Maternal antibodies can remain for 6 months requiring ongoing monitoring of the neonate for kernicterus.[1] Recombinant erythropoietin and IVIG are no longer used in the neonatal period as they have not been found to be effective, and carry an additional potential increased risk of necrotising enterocolitis (NEC) in infants with HDFN.[5, 9, 15] Around 20% of neonates receiving exchange transfusion suffer a complication such as infection, electrolyte imbalance, thromboembolism, cardiac arrhythmia and necrotising enterocolitis.[5]

Neurodevelopmental outcomes are normal in 95% of children undergoing IUT.[6] Of children born after IUT the rate of cerebral palsy is 2.4%[16], in contrast to global cerebral palsy rates of 1.6/1000 livebirths in high income countries and 3.4 per 1000 in low/middle income countries.[17]

5 | Intravenous Immunoglobulin (IVIG) Mechanism of Action, Risks and Benefits

Although fetal transfusion was first described by Lilley et al in 1963, it has long be recognised that severe early onset fetal anaemia cannot always be treated by transfusion owing to the difficulty in cannulating narrow early umbilical vessels, coupled with a reduced capacity of the sub-24 week fetus to withstand anaemia and hydrops. Furthermore, the tendency for anaemia to occur around 3 weeks sooner in any affected subsequent pregnancy means that alternative treatment options to transfusion need to be investigated.[18]

Intravenous immunoglobulin has been used as a treatment for autoimmune diseases since 1981[4] and interest in this for fetal

anaemia soon developed. IVIG is a concentrate of immunoglobulins; derived from the pooled plasma of 1,000-10,000 healthy human blood donors. The IVIG product is composed of very similar immunoglobulins to normal human plasma: 90% is IgG, but it also includes IgA, cytokines and soluble receptors. The basic structure of an immunoglobulin (IgG) is a Y shape consisting of two identical polypeptide heavy chains making up the trunk of the Y shape (this is the Fc portion that binds to Fc gamma receptors on immune cells and complement); and two identical polypeptide light chains forming the arms of the Y shape (this is the Fab fragment that binds the antigen). The IVIG-Fc portion binds to Fc receptors which are present on almost all immune cells and can be either inhibitory or activatory. Immunoglobulins play a key role in adaptive humoral immunity. Their mechanisms of action are numerous and involve the dilution of maternal circulating antibodies and competitive blockage of the placental Fc receptor, hence reducing the maternal transplacental transfer of pathogenic IgG.[11] They also stimulate the inhibitory Fc-gamma receptors on macrophages to down regulate function. IVIG is known to block the antibody receptors located on the surface of red blood cells.[4] They can also block the Fc receptors of phagocytic cells to decrease the uptake of autoantibody coated cells.

Maternal administration of intravenous immunoglobulin to reduce severe early onset anaemia emerged as a potential treatment strategy in the 1990s and a number of case series have been published over the last 30 years. One of the earliest came from Marguiles et al in 1991, in which 24 severely D-sensitised pregnant women (initial anti-D levels over 10iu/ml) were treated with 0.4g/kg for 4-5 consecutive days and again 2-3 weeks later until birth. IVIG resulted in a fall in anti-D titres and intrauterine haemolysis.[19] In 1997, the same authors published a study involving 69 women in which they demonstrated that IVIG before 20 weeks followed by IUT after 21 weeks resulted in fewer severely anaemic fetuses and a 36% decrease in fetal mortality compared to standard treatment of IUT from 20 weeks.[20] In 1996, Deka et al published a small case series of 6 women treated with 100mg/kg IVIG from the early second trimester, all of whom had a history of RH immunisation causing preterm fetal hydrops. Repeated IVIG was given every 3-4 weeks until birth or until evidence of anaemia requiring IUT developed. Anaemia was defined as the appearance of cardiomegaly, placentomegaly, hepatomegaly, or raised amniotic fluid bilirubin on amniocentesis. None of the fetuses developed hydrops and only two required IUT. All survived the postnatal period.[21] The following year, there was a case report of a grand multiparous woman with worsening severe early onset RhD haemolytic disease who had suffered two consecutive perinatal deaths from severe anaemia causing hydrops at 26 and 18 weeks. She was commenced on weekly 1g/kg IVIG from 14 weeks. She received multiple IUTs starting at 21 weeks and delivered a live baby at 33^{+5} weeks who did well following phototherapy and an exchange transfusion.[22]

The benefits and risks of IVIG have been investigated more recently in the PETIT study - an international retrospective multicentre cohort study published in 2018. It investigated 52 women from 12 fetal centres in Europe, North America, Australia and New Zealand, in a pregnancy following severe HDFN (defined as fetal death or need for IUT before 24 weeks) in women who did or did not receive IVIG. The IVIG (0.5-1g/kg) was given weekly, before 13 weeks.[11]

Overall, IVIG delayed the development of fetal anaemia by 15 days compared to the previous pregnancy.[11] Conversely, pregnancies not receiving IVIG developed fetal anaemia on average 9 days earlier compared to the previous pregnancy.

In a subgroup of pregnancies in whom IVIG was started before 13 weeks, IVIG delayed the onset of anaemia by 25 days, with a reduction in the occurrence of fetal hydrops: 4% versus 24% in fetuses who did and did not receive IVIG (OR 0.03, 95% confidence interval 0-0.5; $P=0.01$) respectively. Exchange transfusions were required in 9% of neonates if IVIG was used versus 37% if not (OR 0.1, confidence interval 0-0.5, $p=0.009$).[11]

The PETIT study did not comment on adverse reaction rates, neurodevelopmental outcome, or preterm birth rates. There are a number of other limitations to the PETIT study: firstly, it is a retrospective cohort study of a relatively small number of women (due to the rarity of the condition). Secondly, there was heterogeneity of patients and treatments. Thirdly, there was no difference in overall infant survival between treatment and no treatment. Finally, 11 of the 28 fetuses not receiving IVIG also had a later onset of fetal anaemia than the previous pregnancy, so causation cannot be assumed.

Further evidence that IVIG can delay the onset of the first IUT to a later and safer gestation was presented in a case control study from Canada in 2022. These authors presented their 19-year experience of 22 women with history of prior severe HDFN (defined as fetal loss or IUT before 22 weeks) treated with 2g/kg IVIG in the subsequent pregnancy starting at a mean gestational age of 13.3 weeks every 3 weeks, until the first IUT was performed. IVIG delayed the timing of the first IUT by an average of 16.5 days. Two of the 22 women treated with IVIG did not require IUT. Use of IVIG in six women with previous IUD due to HDFN, resulted in 100% live births in their subsequent pregnancy. In these six women the fetal haemoglobin was significantly higher at the first IUT after IVIG treatment with an increase of 36.5g/l compared to their previous pregnancy – this implies the disease process had been ameliorated by the IVIG.[23]

There is evidence that IVIG can be used in combination with concurrent IUT to ameliorate the disease process and space out the subsequent IUTs. In 2007 Kriplani et al published a series of four cases in which IVIG was administered directly to the fetus at the same time as the IUT to treat severe anaemia.[24] The addition of IVIG at the time of IUT resulted in the ability to space out the subsequent IUTs due to amelioration of the disease. All four pregnancies resulted in live births with only postnatal phototherapy required. The logic behind this practice was to reduce the rate of intravascular haemolysis. Although IVIG is considered a prophylactic treatment and may not be highly effective once fetal anaemia has occurred[4], this study implied that it might have a role even after anaemia has developed. This practice may be especially beneficial for low- and middle-income countries in which expensive resources are more difficult to access.

In summary, these studies showed that IVIG may increase the gestational age at which clinically significant fetal anaemia

occurs, and may avoid or delay the requirement for an intrauterine transfusion until a gestation where the transfusion risks are lower.[1]

5.1 | Potential Adverse Effects of IVIG

As IVIG is a derived blood product, adverse effects are varied and common. They have the potential to reduce the maternal toleration to therapy and reduce compliance. Adverse effects are typically classified into immediate and delayed. Immediate effects can be mild, moderate or severe. Mild effects include flu-like symptoms such as fever, chills and fatigue and occur in around 80% of people at the time of the transfusion. They are self-limiting and can be reduced by slowing the transfusion. Moderate side effects include dermatological effects (eczema, papules, urticaria) and occur in around 6% of people. Skin lesions usually occur within 2 weeks of IVIG administration and can be managed with corticosteroids. If an adverse reaction occurs, management options include slowing the intravenous administration time, reducing the standard IVIG dose from 1g/kg maternal weight to a lower dose such as 0.4g/kg, giving steroids (for example, 100mg hydrocortisone or 15mg oral prednisolone) at the time of the IVIG administration[23], or switching to a different IVIG product. Different IVIG products contain different concentrations of other IVIG types to IgG such as IgA, different sugars, amino acids and sodium used to stabilise proteins and prevent IgG aggregation. Severe side effects are much less common and occur in around 1% of people.[25] They include hypotension, arrhythmias such as supraventricular tachycardia. Finally transfusion-related acute lung injury (TRALI) is an immediate and severe adverse reaction with high mortality. It manifests within 6 hours and causes pulmonary oedema and acute respiratory distress.[25]

Delayed adverse events are much less common, affecting less than 1% of people. However, they are usually severe and can be life threatening. These include thrombosis – of veins, intracranial vessels and arteries, and can lead to stroke or myocardial infarction. Other delayed adverse effects include neurological (aseptic meningitis, posterior reversible encephalopathy syndrome), renal (impairment from transient ischaemia or acute tubular obstruction) and haematological (haemolysis or neutropaenia).[26]

5.2 | IVIG in Combination With Other Novel Therapies

There is emerging evidence that IVIG can also be used as part of an immunomodulatory package of care for women with severe HDFN, incorporating IVIG with other therapies to improve outcomes. In 2018, Nwogu et al[27] presented a case series of 5 multiparous women who had all received IUTs but despite this suffered second trimester intrauterine deaths from hydrops and severe anaemia. In their subsequent pregnancies all 5 women received 3 therapeutic plasma exchanges (TPE) to remove existing antibodies every other day from between 11 to 13 weeks of gestation followed by a loading dose of 2g/kg IVIG and then weekly IVIG at a dose of 1g/kg until they required their first IUT. The timing of the first IUT ranged from 21 to 27 weeks and all 5 women went on to deliver healthy babies at 33 to 38 weeks. The TPE was shown to acutely decrease the RBC antibody titres 4 fold, which is often transient and often followed by a rebound increase. This rebound phenomenon was prevented by the IVIG; in which administered IVIG replaced the rebound IVIG pool in the woman's vasculature.[28]

Another care package involving IVIG to delay the timing of the first IUT was published in 2008 by Fox et al.[29] This involved intraperitoneal transfusion as well as IVIG from early pregnancy, removing the need to cannulate small fetal vessels. These authors described 6 women all with a history of severe anaemia and hydrops before 20 weeks with 66% fetal mortality, who were managed with fortnightly percutaneous intraperitoneal transfusion and IVIG from 16 weeks. Of the 6 women, one suffered an IUD but 5 delivered live babies in the third trimester (86% survival). The timing of the first intravascular transfusion ranged from 21 to 24 weeks in the live born babies.[29]

5.3 | Economic Implications of IVIG

Financial implications must also be considered because the cost of IVIG is high - around £4,800 per week.[4] Direct economic comparison of IVIG to IUT has not been performed. The cost of a blood transfusion is around £200; but this does not take into account staffing costs.[30] Although IVIG for HDFN is commissioned by NHS England, it is not regarded as a priority, and is distributed on a case-by-case basis after discussion with a haematologist.[31]

5.4 | Logistical Administration of IVIG

The early case control studies and case reports from the 1990s described low doses of IVIG between 0.1g/kg and 0.4g/kg maternal weight with differing frequencies of administration of between every 5 days and every 3-4 weeks.[19, 21] IVIG was initiated between 13 and 20 weeks in these early studies. More recently since 2018, 3 cohort and case control studies have been published in which IVIG was initiated before 13 weeks[4, 23, 32], and one case series of 3 patients in which IVIG was started at 14 weeks.[33] Commencing IVIG before 13 weeks shows a beneficial effect in postponing the timing of the first IUT by an additional 10 days than if it were started after 13 weeks.[4] Three of these 4 recent studies describe a standard dose of 1g/kg maternal weight and repeating the dose weekly until the onset of fetal anaemia, in which IVIG therapy is ceased and IUT therapy is then commenced. There are no randomised controlled trials to demonstrate the optimum gestational age for commencement of IVIG. Vlachodimitropoulou et al presented an alternative regime to this protocol.[23] These authors used 2g/kg over 2 days, repeated this dose every 3 weeks, and stopped therapy at the onset of anaemia in favour of IUT. These studies report a drop in antibody quantification with IVIG use.

6 | Neonatal Management With IVIG

The NICE guideline on neonatal jaundice recommends the use of intravenous immunoglobulin (IVIG) (500 mg/kg over 4 hours)

as an adjunct to continuous intensified phototherapy in cases of Rhesus haemolytic disease or ABO haemolytic disease when the serum bilirubin continues to rise by more than 8.5 micromol/litre per hour.[33] It recommends clear communication with parents; specifically explaining why IVIG is being considered and the possible adverse effects of IVIG. Neonatal use of IVIG has been shown to reduce the need for exchange transfusions, reduce duration of stay, and the need for phototherapy.[34]

7 | Other Treatment Options

Other medical treatments for alloimmunised women would either have to reduce the number of circulating antibodies, i.e. by stopping or reducing their production, increasing their elimination from the pregnant woman, or preventing their placental transfer.[4]

Treatment options could include maternal plasma exchange to clear alloantibodies from the maternal circulation, described by Nwogu et al.[27] However, plasma exchange is an invasive procedure with potential severe side effects including alteration of feto-maternal haemodynamics and loss of important proteins, as well as a risk of infection and haematoma formation.[1]

7.1 | Monoclonal Antibodies - Nipocalimab

Specific immunomodulatory therapy in the form of Nipocalimab is now emerging as a potential effective therapy for severe HDFN.

Nipocalimab (also known as M281) is a high affinity, human, aglycosylated, monoclonal antibody that selectively blocks the neonatal Fc receptor (FcRn) to reduce levels of circulating immunoglobulin G (IgG), including auto- and alloantibodies.[35] The Fc receptor is an important transmembrane receptor expressed by syncytiotrophoblast and transports maternal IgG across the placenta. It is also under investigation for other autoimmune conditions such as myasthenia gravis.[36] In the UNITY trial, 13 women at high risk of severe early onset HDFN were treated with weekly intravenous nipocalimab. Of these, 7 (54%) had a live birth at or after 32 weeks without intrauterine transfusion (compared to the control group of 10%), with a median gestational age of 37^{+1} weeks. Six pregnancies required an IUT with a median gestational age of 28^{+3} weeks for the first IUT (range 24-31 weeks). There were no reports of hydrops. There was one intrauterine death due to complications from the IUT and was not deemed to be related to nipocalimab. The drug was generally well tolerated, although 2 of the live births experienced serious adverse effects possibly related to nipocalimab: subchorionic haematoma and premature placenta separation.[37] These data provide the potential for nipocalimab becoming the first anti-neonatal Fc receptor targeted treatment and non-surgical therapy for HDFN. The UNITY trial will become a phase 3 study for pregnancies at risk of HDFN.

8 | Opinion

Intrauterine blood transfusion is currently the only established treatment for fetal anaemia due to red cell alloimmunisation and this can carry significant risks for both the woman and fetus, especially when performed at less than 22 weeks, when the fetal vasculature may be too small and fragile to withstand vascular cannulation. A plausible treatment to reduce these risks is IVIG, for which the available data suggest that it can delay the timing of the first IUT to after 20-22 weeks. Further well-designed trials are needed to confirm this. It is important to test the fetal blood group via cffDNA before considering therapies such as IVIG or monoclonal antibodies, because of the high cost of the medications, intensity of the treatment protocol (weekly hospital visits) and the potential for maternal adverse effects of treatment.

The PETIT study was a retrospective multicentre cohort study that showed that administration of IVIG to pregnant women with a previous pregnancy affected by severe HDFN reduced fetal hydrops and neonatal exchange transfusions compared to those who did not receive IVIG.[11] However, this study had limitations; it was retrospective and unblinded (decisions made by caregivers), potentially adding bias to the results. Finally, half of the women in the non IVIG group did not have worsening HDFN in their subsequent pregnancy. Recent studies suggest that initiating IVIG therapy by 13 weeks at a dose of 1g/kg/week may be beneficial, and stopping therapy at the onset of fetal anaemia, in favour of IUT. Further multicentre randomised trials are warranted to investigate efficacy, optimal timing of initiating treatment and dosing schedules. It is unlikely, however, that better evidence will be forthcoming because of the rarity of the condition and the need for international collaboration. In conclusion, IVIG is unproven, but with some evidence of benefit, and in the absence of alternatives has a reasonable risk-benefit balance for the rare cases where there has been very early onset HDFN in previous pregnancies. A central database to record the national and international use of this treatment would be beneficial for tracking outcomes and adverse effects.

A future alternative therapy to IVIG could be the use of monoclonal antibodies; specifically the anti-neonatal Fc receptor antibody nipocalimab. A multicentre randomised trial into nipocalimab for pregnancies at risk of severe HDFN is currently underway and results should be awaited before introducing this into clinical practice.[37]

Conflicts of Interest

Full disclosure of interests are available on request.

References

1. Joint United Kingdom (UK), "Blood transfusion and tissue transplantation Services Professional Advisory Committee. *Handbook of*," *Transfusion Medicine.* (2013): 110–113 [transfusionguidelines.org/transfusion-handbook]. Accessed 1 February 2024.

2. Royal College of Obstetricians and Gynaecologists, "*The Management of Women with Red Cell Antibodies during Pregnancy*," in *Green-top Guideline No. 65* (London: RCOG, 2014).

3. J. Castleman, K. J. Moise, Jr., and M. D. Kilby, "Medical therapy to attenuate fetal anaemia in severe maternal red cell autoimmunisation," *Br J Haematol.* 192 (2021): 425–432.

4. C. Zwiers, J. G. van der Bom, I. L. van Kamp, et al., "Postponing Early Intrauterine Transfusion with Intravenous Immunoglobulin Treatment; the PETIT study on severe haemolytic disease of the fetus and newborn," *Am J Obstet Gynaecol.* 219, no. 291 (2018): e1–291.e9.

5. C. Zwiers, M. E. A. Scheffer-Rath, E. Lopriore, M. de Haas, and H. G. Liley, "Immunoglobulin for alloimmune hemolytic disease in neonates," *Cochrane Database Syst Rev.* 18 (2018): CD003313.

6. M. de Haas, F. F. Thurik, J. M. Koelewijn, and C. E. van der Schoot, "Haemolytic disease of the fetus and newborn," *Vox Sang.* 109 (2015): 99–113.

7. G. Mari, R. L. Deter, R. L. Carpenter, et al., "Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses," *N Engl J Med.* 342 (2000): 9–14.

8. NICE. Review of DG25: High-throughput non-invasive prenatal testing for fetal RHD genotype. [https://www.nice.org.uk/guidance/dg25/evidence/review-decision-april-2021-pdf-9078748237]. Accessed 17 May 2024.

9. H. Shash and S. Alkhater, "Maternal blood group and Routine Direct antiglobulin testing in neonates: is there a role for selective neonatal testing?," *Children(Basel).* 8 (2021): 426.

10. Society for Maternal-Fetal Medicine (SMFM), S. M. Berry, J. Stone, M. E. Norton, D. Johnson, and V. Berghella, "Fetal Blood Sampling," *Am J Obest Gynecol.* (2013): 170–180.

11. K. Fung-Kee-Fung and F. Moretti, "Rh incompatability," *BMJ Best Practice* (2018), https://dev.bp-frontend.tf.aws.bmjgroup.com/topics/en-gb/669.

12. Y. Yinon, J. Visser, E. N. Kelly, et al., "Early intrauterine transfusion in severe red blood cell alloimmunization," *Ultrasound Obstet Gynecol.* 36 (2010): 601–606.

13. I. T. Lindenburg, I. L. van Kamp, E. W. van Zwet, J. M. Middeldorp, F. J. Klumper, and D. Oepkes, "Increased perinatal loss after intrauterine transfusion for alloimmune anaemia before 20 weeks of gestation," *BJOG.* 120 (2013): 847–852.

14. R. J. Martinez-Portilla, J. Lopez-Felix, A. Hawkins-Villareal, J. R. Villafan-Bernal, F. Paz y Miño, and F. Figueras, "Performance of fetal middle cerebral artery peak systolic velocity for prediction of anemia in untransfused and transfused fetuses: systematic review and meta-analysis," *Ultrasound Obstet Gynecol.* 54, no. 6 (2019): 722–731.

15. V. E. Smits-Wintjens, F. J. Walther, M. E. Rath, et al., "Intravenous immunoglobulin in neonates with rhesus haemolytic disease: A randomised controlled trial," *Pediatrics* 127 (2011): 680–686.

16. I. Lindenburg, V. E. Smits-Wintjens, E. Verduin, et al., "Longterm neurodevelopmental outcome after intrauterine transfusion for haemolytic disease of the fetus/ newborn: the LOTUS study," *Am J Obstet Gynaecol.* 206, no. 2 (2012): 141e.1–141e.8.

17. S. McIntyre, S. Goldsmith, A. Webb, et al., "Global prevalence of cerebral palsy: A systematic analysis," *Dev Med Child Neurol.* 64, no. 12 (2022): 1494–1506.

18. R. M. Van't Oever, C. Zwiers, M. de Haas, et al., "Severity of haemolytic disease of the fetus and newborn in patients with a history of intrauterine transfusions in a previous pregnancy: A nationwide retrospective cohort study," *BJOG.* 131 (2024): 769–776.

19. M. Margulies, L. S. Voto, E. Mathet, and M. Margulies, "High-dose intravenous IgG for the treatment of severe rhesus alloimmunization," *Vox Sang.* 61, no. 3 (1991): 181–189.

20. L. S. Voto, E. R. Mathet, J. L. Zapaterio, J. Orti, R. L. Lede, and M. Margulies, "High-dose gammaglobulin (IVIG) followed by intrauterine transfusions (IUTs): a new alternative for the treatment of severe fetal hemolytic disease," *J Perinat Med.* 25, no. 1 (1997): 85–88.

21. D. Deka, K. Buckshee, and G. Kinra, "Intravenous immunoglobulin as primary therapy or adjuvant therapy to intrauterine fetal blood transfusion: a new approach in the management of severe Rh-immunization," *J Obstet Gynaecol Res.* 22, no. 6 (1996): 561–567.

22. T. F. Porter, R. M. Silver, G. M. Jackson, D. W. Branch, and J. R. Scott, "Intravenous Immune Globulin in the Management of Severe Rh D Hemolytic Disease," *Obstet Gynecol Surv.* 52, no. 3 (1997): 193–197.

23. E. Vlachodimitropoulou, T. Kin Lo, C. Bambao, G. Denomme, G. R. Seaward, and R. Windrim, "Intravenous immunoglobulin in the management of severe early onset red blood cell alloimmunisation," *Br J Haematol.* 200 (2023): 100–106.

24. A. Kriplani, B. Malhotra Singh, and K. Mandal, "Fetal Intravenous Immunoglobulin Therapy in Rhesus Hemolytic Disease," *Gynecol Obstet Invest.* 63, no. 3 (2007): 176–180.

25. Y. Guo, X. Tian, X. Wang, and Z. Xiao, "Adverse Effects of Immunoglobulin Therapy," *Front Immunol.* 8, no. 9 (2018): 1299.

26. J. Siegel, "The product: All intravenous immunoglobulins are not equivalent," *Pharmacotherapy.* 25, no. 11 Pt 2 (2005): 78S–84S.

27. L. C. Nwogu, K. J. Moise, Jr., K. L. Klein, H. Tint, B. Castillo, and Y. Bai, "Successful management of severe red blood cell alloimmunization with a combination of therapeutic plasma exchange, intravenous immune globulin, and intrauterine transfusion," *Transfusion* 58 (2018): 677–684.

28. Johnson & Johnson Innovative Medicine. New Phase 2 Data Demonstrate Potential Benefit of Nipocalimab for Pregnant Individuals at High Risk of Early-Onset Severe Hemolytic Disease of the Fetus and Newborn (HDFN). *Clinical trial*, last update posted 26 June 2023. [https://www.janssen.com/new-phase-2-data-demonstrate-potential-benefit-nipocalimab-pregnant-individuals-high-risk-early#:~:text=Nipocalimab%20is%20currently%20the%20only%20therapy%20reported%20in,causing%20life-threatening%20anemia%20in%20the%20fetus%20or%20infant]. [Accessed 17 May 2024]

29. C. Fox, W. Martin, D. A. Somerset, P. J. Thompson, and M. D. Kilby, "Early Intraperitoneal Transfusion and Adjuvant Maternal Immunoglobulin Therapy in the Treatment of Severe Red Cell Alloimmunization prior to Fetal Intravascular Transfusion," *Fetal Diagn Ther.* 23 (2008): 159–163.

30. T. Oge, C. H. Kilic, and G. S. Kilic, "Economic impact of blood transfusions: balancing cost and benefits," *Eurasian J Med.* 46, no. 1 (2014): 47–49.

31. *Commissioning Criteria Policy for the use of therapeutic immunoglobulin (Ig)* (England, 2021).

32. E. Maisonneuve, A. Dugas, S. Friszer, et al., "Effect of intravenous immunoglobulins to postpone the gestational age of first intrauterine transfusion in very severe red blood cell alloimmunization: A case-control study," *J Gynecol Obstet Hum Reprod.* 50 (2001): 102119.

33. National Institute for Health and Care Excellence. Jaundice in newborn babies under 28 days. NICE guideline 98. NICE; 2010 [https://www.nice.org.uk/guidance/cg98]. Accessed 23 March 2023.

34. C. Hammerman and M. Kaplan, "Recent developments in the management of neonatal hyperbilirubinemia," *Neoreviews* 1 (2000): e19–e24.

35. A. Choudhury, W. Noël, T. Ebrahim, C. Shu, L. E. Ling, and B. Fattizzo, "Mode of Nipocalimab Action and Pharmacology in Cells and Preclinical Models," *Blood.* 140 (2022): 8161–S2.

36. Johnson & Johnson Innovative Medicine. A Study of Nipocalimab Administered to Adults With Generalized Myasthenia Gravis. *Clinical trial*, last update posted 12 April 2023. [https://clinicaltrials.gov/ct2/show/NCT04951622]. Accessed 17 May 2024.

37. K. J. Moise, Jr., L. E. Ling, D. Oepkes, et al., "Nipocalimab in Early-Onset Severe Hemolytic Disease of the Fetus and Newborn," *New England Journal of Medicine* 391 (2024): 526–553.

This Scientific Impact Paper was produced on behalf of the Royal College of Obstetricians and Gynaecologists by: **Dr V Bills, MRCOG, Bristol; Dr V Cordell, Bath; Dr T Latham, Bristol; Dr A Soe, Medway**.

The following organisations and individuals submitted comments at peer review:

Dr JL Gibson FRCOG, Glasgow; Dr Anwen Gorry, Bart's Health British Society of Urogynaecology; Professor Mark Kilby, FRCOG, Birmingham; RCOG Women's Network

The Scientific Advisory Committee lead reviewers were: Professor K Morris, FRCOG, Birmingham; Professor S Thornton, FRCOG, London.

The chair of the Scientific Advisory Committee was: Professor K Morris, FRCOG, Birmingham.

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

Interested in CPD credits? You can answer CPD questions on this paper at the RCOG CPD ePortfolio.

The paper will be considered for update 3 years after publication, with an intermediate assessment of the need to update 2 years after publication.