Review article

Therapeutic management of fetal anemia: review of standard practice and alternative treatment options

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Abstract

Fetal anemia, mainly due to red cell alloimmunization, is still a significant cause of fetal and neonatal mortality and morbidity. The focus of current clinical research has shifted from an invasive approach to non-invasive management and treatment of affected pregnancies, and the progress in this field is associated with a major improvement in perinatal outcome. During the last 50 years, intrauterine red cells transfusion (IUT), first via the intraperitoneal route and later directly to fetal circulation, is the standard practice in most centers, with survival rates that exceed 90%, particularly if anemia is diagnosed early and treated in a timely manner. In addition, plasmapheresis and intravenous administration of high-dose immunoglobulin have been implicated in the treatment of pregnancies complicated with early-onset severe red cell alloimmunization, alone or in combination with IUTs before the 20th week of pregnancy, but there are still issues to be clarified further. This review article aims to provide an overview of the current standard therapeutic management and alternative treatment modalities in pregnancies complicated by fetal anemia.

Keywords: Fetal anemia; intrauterine red cells transfusion; intravenous immune globulin; plasmapheresis; red cell alloimmunization.

Introduction

Fetal anemia is a serious complication of pregnancy that may result from immune-associated conditions, with rhesus D (RhD) sensitization being the most common cause. Hemolytic disease of the fetus/newborn (HDFN) secondary to red cell alloimmunization is characterized by severe fetal anemia that could cause increased cardiac output, tissue hypoxia, lactic acidosis, fetal hydrops, and eventually intrauterine death. The introduction of intravenous RhD immunoglobulin (IVIG) prophylaxis in 1968 has dramatically decreased the incidence of hemolytic disease from 2% to 0.1%; however, this condition still affects a large number of pregnancies (approx. 6 cases in every 1000 live births), with significant health and financial implications [33, 49]. Antibodies to other red cell antigens of the Rh blood group system and antigens of non-rhesus blood group systems (Kell, Duffy, etc.) may also be implicated in HDFN. There are also non-immune etiologic factors of fetal anemia such as parvovirus B19 infection, fetomaternal hemorrhage, homozygous thalassemia, and placental chorioangioma [8, 30, 70, 84].

Standard evaluation of fetuses at risk of moderate and severe fetal anemia was based on invasive procedures such as amniocentesis to evaluate bilirubin levels in the amniotic fluid and cordocentesis for direct determination of fetal blood count. Non-invasive evaluation with serial ultrasound monitoring and indirect Coombs maternal titers was also included in the standard monitoring of these pregnancies [59]. Several ultrasound parameters have been evaluated as predictors of fetal anemia (Table 1), but none of them could reliably distinguish mild from severe anemia [6, 52, 89], with the exception of fetal ascites, which is compatible with advanced disease and severe anemia [hematocrit (Hct) 15% /hemoglobin (Hgb) 5 g/dL].

The decoding of the human genome showed that the responsible loci for the determination of Rh are on chromosome 1 (OMIM 111680) [57]. This knowledge allowed us to modulate modern management of the Rh-affected pregnancies with the determination of fetal RhD genotype with the use of cell-free fetal DNA and the follow-up of antigen-positive fetuses [33, 60, 77]. The latter is successfully carried out with the use of Doppler, evaluating the peak systolic velocity in the middle cerebral artery (MCA-PSV), which is considered to be the most reliable tool to provide sensitive prediction of the severity of fetal anemia.

Intrauterine transfusion (IUT) for fetuses with severe anemia is the main therapeutic intervention in affected pregnancies and represents one of the greater achievements of fetal therapy...
associated with survival rates of more than 90% in non-hydropic fetuses [47, 49]. Fortunately, only 10% of affected pregnancies will require transfusion in utero, while the remaining 90% will be well-monitored with MCA-PSV [44]. Doppler ultrasonography has also been very useful in monitoring posttransfusion fetuses and determining the next IUT.

In addition, alternative treatment options such as plasmapheresis or administration of adjuvant maternal IVIG to achieve maternal immunomodulation have been reported lately, mainly for treatment in early pregnancy, alone or in combination with intraperitoneal transfusions between 16 and 20 weeks of gestation, as presented below. In this review article, we aim to present the principles of the current therapeutic approach of fetal anemia in terms of standard practice and alternative treatment options, with emphasis on red cell-sensitized pregnancies.

### Intraterine transfusion

HDFN used to be one of the most common causes of perinatal mortality in the Western world, as affected fetuses were usually delivered early and needed serial exchange transfusions, leading to low perinatal survival rates, particularly for hydropic fetuses. In the early 1960s, William Liley performed the first IUT via the intraperitoneal route; the donor cells were absorbed into the fetal circulation via the subdiaphragmatic lymphatics and thoracic duct, which, in conjunction with the use of amniotic fluid analysis for bilirubin levels, markedly improved the management of Rh-sensitized pregnancies [40]. Intraperitoneal technique had an overall perinatal survival rate of 50% and a procedure-related risk of 7.2% [26]. Historically, intraperitoneal transfusion remained the mainstay of fetal therapy for almost 20 years, until Rodeck et al. in 1981 [64] first described the technique of intravascular transfusion by needing the umbilical cord with the use of fetoscopy. Nowadays, intraperitoneal transfusion does still have a place in case of severe anemia detected before 18–20 weeks’ gestation. Since the mid-1980s until now, the standard method for fetal transfusion in most centers is the direct access to fetal circulation by puncturing the umbilical cord under ultrasound guidance. This form of in utero transfusion allows the definite diagnosis of anemia and direct intravascular infusion of packed red cells into the fetal circulation. Intravascular transfusion is clearly advantageous compared with intraperitoneal approach in cases with fetal hydrops. Some centers continue to perform a combined approach incorporating both procedures so as to achieve a more stable fetal Hct and a more prolonged interval between transfusions. The main indication for IUT continues to be fetal anemia due to red cell alloimmunization, but successful use of this procedure has also been reported in pregnancies with parvovirus B19 infection, fetomaternal hemorrhage, placental chorioangiomas, and others [8, 30, 65, 70, 84].

### Technical aspects

As with all ultrasound-guided invasive procedures, the success of IUT depends on the experience and technical skills of the operator who should have adequate training with more simple invasive procedures such as amniocentesis and chorionic villous sampling. In general, fetal blood transfusion has a duration of about 10–15 min and is performed by a team of at least two or three members. The main operator performs the procedure and monitors the fetal condition with the aid of ultrasonography, while the other assistants provide the various medications needed and perform the on-site blood tests and calculations. At the start of the intravascular transfusion, the initial fetal Hct is estimated after sampling of the chosen vessel, classifying the severity of the anemia immediately during the procedure. Although IUT is the standard treatment for anemia for more than 25 years, there are still different approaches regarding some technical aspects of the procedure. For example, there is no clear evidence if the administration of fentanyl to the fetus to reduce fetal stress and pain or the use of paralyzing agents such as pancuronium, vecuronium, or atracurium for cessation of fetal movement are necessary and from what gestational week and onward their use should be indicated [24].

The red cells transfused are typically from an O-negative unrelated donor who needs to be screened for hepatitis B and C, cytomegalovirus (CMV), and HIV, cross-matched with maternal blood to prevent sensitization to new red cell antigens and collected in the previous 72 h. The unit undergoes 25 Gy of γ-irradiation to avoid graft-vs.-host-like complications and packed to an Hct of 75–85% to prevent volume overload in the fetus. Also, the unit is leukocyte depleted so as to decrease CMV transmission because the virus usually remains inactive in the polymorphonuclear leukocytes. Another potential source is maternal blood after it has been tested for the infectious diseases mentioned above. In addition, the management of pregnancies with sensitization to uncommon red cell antigens could require serial blood donations from the mothers because matched blood is extremely rare [42]. Nevertheless, the source of transfused blood does not affect the rate of consumption of transfused red blood cells in pregnancies at least until 33 weeks’ gestation [21]. Most centers perform top-up transfusions, and this procedure is well tolerated by the fetus. The total amount of red cells to transfuse is calculated by a formula incorporating initial Hct, fetoplacental volume, and Hct of the donor blood so as the posttransfusion Hct will be 40–50% to achieve a longer interval until the next procedure. A simple method to estimate the appropriate volume of red cells to transfuse, given
that the donor unit has Hct of approximately 75\%, is to multiply the estimated fetal weight by 0.02 to achieve an Hct increment of 10\%. The used formula is \( V = (Hct\, desired - Hct\, recipient) \times 150\, mL/kg \) divided by the donor’s Hct. The rate of transfusion should be 5–10 mL/min. The target of a single IUT is to reach Hct 48–55\% in non-hydropic fetuses. In pregnancies with a severely anemic fetus, the initial Hct should not be increased by more than four-fold; otherwise, the fetal cardiovascular system will not compensate for the acute changes in volume and viscosity [49]. In this circumstance, a repeat procedure is recommended 48 h later to normalize the fetal Hct. Usually the aim in fetuses with Hct of ≤15\% before IUT is to reach a posttransfusion Hct of 25\% with the first IUT and 50\% after a second trial, which is usually carried out 24–48 h later [47, 62].

Another important technical aspect is the choice of the ideal site of puncture, taking into account the fetal position and placental localization, but this decision depends on the personal preference of the operator as well. Fetal circulation is usually accessed via the umbilical vein, preferably near the placental insertion of the cord, to provide stabilization (Figure 1). Transfusion into the intrahepatic portion of the umbilical vein is associated with an increase in fetal stress hormones, but this technique is related to a lower incidence of fetal bradycardia, as the umbilical artery is unlikely to be punctured in this location and any extravasated blood is absorbed from the peritoneal cavity [53]. In earlier reports [53], the risk of fetal loss rate with such an approach was estimated to be as high as 5\%, but in a more recent study [73], no significant difference in complication rates was found whether the intrahepatic portion of umbilical vein was punctured or its cord root. It is also possible to target a floating loop of the cord, but there is a risk of trauma of the vessel wall during fetal movements or dislocation of the needle and need for second puncture of a free floating loop, which is technically more difficult. Another risk is puncture of the umbilical artery, which may cause prolonged bleeding and is prone to spasm, which could cause fetal bradycardia [86]. Intracardiac transfusion has been practically abandoned in recent years because it carries the risks of hemopericardium, arrhythmia, and even asystole, with a procedure-related complication rate of 5\% at least [4].

**Timing of first and subsequent IUTs**

As in all invasive procedures in fetal medicine, the knowledge of the indication and optimal timing of intervention are of utmost importance for a successful outcome. In pregnancies...
with red cell alloimmunization, obstetric history and maternal antibody titers should be carefully evaluated to identify fetuses at risk for anemia. The challenge is to transfuse in case of moderate to severe anemia but before the fetus develops hydrops, which is associated with low survival rates compared with non-hydropic fetuses [81]. Hydrops is characterized by generalized skin edema and fluid collection in more than one area, such as pericardial, pleural, or ascitic effusions. It develops when the Hgb deficit is >6 SD below the mean for gestational age (i.e., Hct 15%, Hgb 5 g/dL) [55], whereas a transfusion is performed when the fetal Hgb level is 4–6 SD below the mean gestational age, which corresponds to an Hgb deficit of more than 6 g/dL. Hydropic signs will normally reverse after one or two transfusions, but the reversal rate depends on the severity of the disease (88% in fetuses with mild hydrops and 39% in fetuses with severe hydrops) [81]. The precise method of assessing the severity of fetal anemia is by fetal blood sampling, but cordocentesis carries a risk of infection, bleeding, fetal bradycardia, and procedure-related fetal loss of 1% and should be undertaken only if there is strong evidence that the fetus is severely affected [3].

Currently, Doppler assessment of the MCA-PSV on a weekly basis has been established as the clinical gold standard for the detection of moderate to severe fetal anemia [50], with high sensitivity (100%) and low false-positive rate (12%), and therefore invasive testing can be avoided in >80% of isoimmunized pregnancies with high maternal antibody titers [44]. The correlation between Hgb and MCA-PSV becomes more accurate as the severity of anemia increases [45]. A large prospective study has shown that MCA Doppler measurement can safely replace amnionic fluid analysis for bilirubin concentrations (delta OD450) in the prediction of fetal anemia [56]. Current data suggest that an elevated peak MCA velocity (>1.5 SD above the mean for gestational age) is the threshold for the first IUT in affected pregnancies with moderate to severe anemia and a modified cut-off value of 1.69 MoM for severe and 1.32 MoM for moderate anemia can be used to time the second IUT [19]. The MCA-PSV seems to be less predictive for timing the subsequent IUTs, although there is good correlation between MCA-PSV and fetal Hgb [46]. The decreasing sensitivity of the MCA Doppler assessment after several IUTs is possibly explained by the fact that adult donor cells have different rheological properties that contribute to an increased whole blood viscosity and decreased total oxygen carrying capacity [88]. Subsequent IUTs can be performed on fixed intervals that vary among different centers (2 weeks between the second and the third procedure and every 3 weeks for the following IUTs) based on an estimated drop in Hct of 1% per day [55]. Alternatively, a calculated decline in Hgb of 0.4, 0.3, and 0.2 g/dL for the first, second, and third transfusion intervals, respectively, has been used to decide when to carry out the next IUT [67]. A rapid decline in fetal Hct may result from transplacentual hemorrhage, maternal sensitization to new red cell antigens, and bleeding from the umbilical cord puncture site. The use of MCA-PSV is also reliable in pregnancies affected with Kell alloimmunization and it is important because in these pregnancies, maternal antibody titers do not strictly correlate with the severity of the disease, and poor outcomes have been reported with low titers [80].

During the period of intraperitoneal transfusions in the 1960s, anemic fetuses were routinely delivered at 32 weeks’ gestation, and they often experienced prematurity-associated complications and underwent repeated neonatal exchange transfusions to treat hyperbilirubinemia. Nowadays, in cases that have been transfused before the 32nd week of pregnancy, IUTs, if necessary, may be continued until 34 weeks, while in cases who have not been transfused previously, it is preferable to terminate the pregnancy by the 32nd week and proceed with neonatal exchange transfusions. In the absence of any other factor of delivery, the final IUT is performed at 35–36 weeks’ gestation, and labor induction is suggested at 37–38 weeks’ gestation to allow maturation of the fetal pulmonary and hepatic system [37]. There is also evidence that the antenatal administration of phenobarbital can induce hepatic maturity and prevent the need for neonatal exchange transfusions [78].

**IUT in other diseases**

**Parvovirus B19 infection** Parvovirus B19 infection accounts for about 27% of cases of non-immune hydrops in anatomically normal fetuses, and fetal anemia usually occurs with infection in the second and third trimesters [84]. Parvovirus B19 has the ability to cause inhibition of erythropoiesis at the late normoblast stage and also thrombocytopenia. Most cases are detected upon the finding of fetal hydrops in the ultrasound assessment, although there are also pregnant women referred due to seroconversion for parvovirus B19. Close ultrasonographic surveillance on a weekly basis for 10–12 weeks after the estimated time of exposure for signs of fetal anemia, heart failure, and hydrops and Doppler screening (Doppler examination of the MCA) after initial seroconversion can identify the subgroup with fetal anemia that needs to be transfused [71]. Delle Chiaie et al. observed that a cut-off value of 1.29 MoM for MCA-PSV could predict any degree of fetal anemia induced by parvovirus infection with sensitivity and specificity of 100% [17]. A review of the literature in a total of 82 studies involving 705 cases of fetal parvovirus infection showed a clear benefit of active intervention with IUT over conservative management (82% vs. 55% survival rates); also, the signs of anemia usually resolve after a single transfusion [84]. Interestingly, successful management of fetal anemia secondary to parvovirus B19 infection with intravascular transfusion at 13 weeks’ gestation has been reported in two fetuses [36]. Each fetus received a 3-mL intravenous transfusion of packed red blood cells into the umbilical vein, using a 25-gauge spinal needle. Due to persistence of infection, three more IUTs were performed after 25 weeks. There is inconsistency regarding the long-term outcome after fetal transfusion for parvovirus B19-induced hydrops as both good clinical outcome and some degree of neurological handicap not associated with the severity of anemia have been reported [18, 51]. Because of the association between parvovirus fetal B19 infection and thrombocytopenia, which could be a cause of hemorrhage...
during cordocentesis and transfusion, it may be prudent to have compatible platelets available at the time of fetal blood sampling [69].

**Fetomaternal hemorrhage** Fetomaternal hemorrhage (FMH) is a rare but severe pregnancy complication with an unexpected onset that can lead to severe fetal anemia, hydrops, and fetal death (perinatal mortality ranges from 33% to 50%) [28]. Reduced fetal movements, increased blood flow velocities in the MCA and umbilical vein, and sinusoidal fetal heart rate pattern are considered to be suggestive but not specific signs of this condition [74]. The diagnosis is confirmed by a Kleihau-Betke test showing fetal cells in the maternal circulation, and an IUT could be performed if the fetus is preterm to prevent the life-threatening consequences. Serial IUTs via the endovascular or intraperitoneal route in these cases have been associated with either good clinical outcomes or transient improvement because of the continued passage of fetal blood into the maternal circulation [65, 70].

**Placental chorioangioma** Placenta chorioangiomas are benign tumors of the placenta that complicate 1% of pregnancies and may cause fetal anemia, hydrops, and fetal death. There are few reports of pregnancies with placenta chorioangiomas successfully managed with IUT therapy [30]; moreover, the MCA Doppler assessment seems to be useful in the detection of fetal anemia in these cases [22].

**Complications and short- or long-term outcome**

IUT is now considered as a relatively safe procedure in fetal medicine, with a perinatal fetal loss rate of 2% [49] and an acceptable complication rate. Transient fetal bradycardia is the most common complication occurring in 8% of the procedures and fetal distress caused by rupture, spasm, hematoma of the umbilical cord, hemorrhage from the puncture site, volume overload, or chorioamnionitis can lead to the decision of emergency delivery [49, 55, 87]. Moise in 2002 [48] reported a 2% fetal loss rate per IUT. In 2004, Van Kamp et al. [82] conducted a cohort study to establish the true procedure-related complications of IUT for fetal anemia due to red cell alloimmunization and demonstrated that the procedure-related fatal complication rate was 1.7% per procedure, giving a total loss rate of 4.8%. The overall survival for a total of 593 transfusions in 210 fetuses was 86%. Non-hydropic fetuses had a better outcome as expected, 92%, compared with 78% for hydropic fetuses. In the following year (2005), in an effort to further establish the safety of IUTs, the same center in Leiden analyzed fetal losses after IUTs in procedure related and non-procedure related, in more or less the same study group (254 fetuses/740 IUTs) [83]. The overall survival in this series was even better and was estimated to be at the level of 89%. The study further showed a total procedure-related complication rate of 3.1% resulting in 1.6% total procedure-related fetal loss rate. In the same study, the authors estimated the risks for other complications such as rupture of membranes (0.1%), intrauterine infection (0.3%), emergency cesarean section (2%), fetal death (0.9%), and neonatal death (0.7%). In addition, fetomaternal hemorrhage or alloimmunization for new maternal antibodies can result from repeated procedures. Data on complications rates of IUTs are essential in providing an accurate counseling in patients.

Our anecdotal data from the Maternal Fetal Medicine Unit of the First Department of Obstetrics and Gynecology of the Athens Medical School for 341 IUTs in 143 pregnancies during the past 20 years showed an overall survival of 83.6%, 90.2% for non-hydropic fetuses, and 71.2% for hydropic. We also observed a 2.8% fetal loss rate per procedure (details available from the authors).

Fetal hydrops is categorized as moderate and severe. Non-reversal of severe hydrops after the first two transfusions is a poor prognostic sign, as shown by Mesogitis et al. [47]. During the neonatal period, these infants often need top-up or exchange red cell transfusions in the first 1–3 months. A recent study demonstrated that infants with rhesus disease treated with IUT required fewer days of phototherapy and more top-up red blood cell transfusions than neonates without IUT [14]. In addition, infants treated with IUTs are characterized by normal growth, although Rhesus disease is related to lower birth weights [63]. Regarding the long-term consequences of fetal anemia, cerebral palsy and developmental delay are more common in fetuses with HDFN when compared with unaffected fetuses, but in more than 90% of cases, the psychomotor development is normal [35]. Normal developmental outcome during standardized developmental assessments in the first 62 months was observed for children treated with IUTs for severe fetal hemolytic disease [32]. In a study of 16 hydropic patients who were evaluated at a mean age of 10 years, the incidence of severe neurologic morbidity was estimated to be 12.5% [31]. In a recent (2012) study by the LOTUS study group [41], a total of 291 children were evaluated at a median age of 8.2 years. Cerebral palsy, severe developmental delay, and bilateral deafness were detected in 2.1%, 3.1%, and 1.0% of children, respectively. The overall incidence of neurodevelopmental impairment was 4.8%, and fetal hydrops was the strongest preoperative predictor for impaired neurodevelopment [41].

**Alternative therapeutic approaches for fetal anemia**

The treatment of severe maternal red cell alloimmunization is thought to be a “challenging” task before 20 weeks’ gestation due to the technically difficult access in fetal intravascular system despite improved ultrasound resolution. The operator has to target the umbilical cord vessels that measure <3–5 mm in diameter and even if the IUT is completed successfully, the premature anemic fetus will not tolerate the acute hemodynamic changes. The estimated overall IUT procedure-related fetal loss rate was 5.6% when performed at <20 weeks’ gestation especially if the Hgb level is <5 SD for gestation associated with fetal hydrops [83]. Furthermore, reliable data regarding the use of MCA-PSV in the monitoring of fetal condition in cases with severe anemia before 18–20 weeks are
insufficient. Therefore, alternative treatment modalities could be proposed in pregnant women with a history of a previously affected pregnancy due to fetal hemolytic disease presenting in the early second trimester or in cases with a markedly elevated maternal antibody titer for a red cell antibody known to be associated with HDFN. As mentioned above, one approach is to manage these pregnancies with intraperitoneal transfusion from 14 weeks’ gestation until an intravascular transfusion can technically be undertaken [27]. Other treatment options include plasmapheresis and administration of IVIG to manipulate maternal immune system from early pregnancy and reach a gestational age at which an IUT is technically feasible. An overview of published clinical evidence for the use of IVIG administration as well as plasmapheresis in pregnancies complicated with red cell alloimmunization is shown at Table 2.

**Intravenous immunoglobulin**

Over 20 years ago, administration of maternal high-dose IVIG for severe, early-onset Rh alloimmunization was offered as a promising therapy but only limited data were available to support its widespread use. The use of IVIG has been evaluated in patients with severe Rh immunization, high maternal antibody titers, and previous pregnancy with early-onset hydrops and intrauterine death and has been related to a reduction in overall IUT requirements and a beneficial effect on pregnancy outcome [25]. Several immunomodulatory mechanisms have been proposed for the action of high-dose IVIG in reducing the volume of fetal hemolysis [10]. In an in vitro perfusion model, IVIG has been noted to decrease the passage of maternal anti-D acting as a ligand for placental Fcγ receptors involved in the uptake of IgG [79]. Other proposed mechanisms include the blockade of activating Fc receptors, the induction of the surface expression of the inhibitory Fcγ-RIB on splenic macrophages, and the inactivation of the FcγR receptor, which prevents the catabolism of IgG, resulting in increased catabolism of the harmful antibodies as well [90]. However, Palli et al. [58] suggested that sole treatment with high-dose IVIG is effective in less severe cases of Rh-immunized women, but a combination with plasmapheresis is indicated in the management of very severe alloimmunization with bad prognosis. In addition, IVIG effect on immunomodulation is variable and unpredictable, and the combination with plasmapheresis can add positively in a good clinical outcome [72].

Before 1990, only case reports were published for the use of IVIG as adjuvant therapy in Rh-sensitized pregnancies [7, 68], while De La Camara et al. [15] presented two cases in which IVIG was the sole treatment resulting in two live births. Margulies et al. [43] conducted the largest prospective series to date in which 24 severely Rh-sensitized pregnant women were treated with IVIG alone until delivery and demonstrated that IVIG use should be initiated before 28 weeks or before the appearance of hydrops. In addition, Voto et al. [85] demonstrated the predominance of the combined treatment with IVIG and IUT over IUT alone, as in the first group, severe fetal anemia was less common and fetal mortality was reduced by 36% compared with the second group. In the more recent case series, Fox et al. [25] described the management of six pregnant women, with a previous pregnancy complicated by severe anemia before 20 weeks’ gestation, with intraperitoneal transfusion at 2-week intervals between 16 and 21 weeks and adjuvant maternal IVIG therapy. In this cohort, the pregnancies that progressed beyond 20 weeks and were further treated with intravascular transfusions all had a successful outcome. In line with previous findings, Connnan et al. [12] reported a case series of six women at high-risk for severe disease who were treated with weekly IVIG infusions and were monitored with MCA Doppler ultrasound to time the required IUTs; all experienced improved perinatal outcomes. However, another research group found IVIG to be of no benefit in the treatment of Rh isoimmunization, reporting that IVIG had no apparent effect on the total number, frequency, or volume of IUTs in four cases of severe Rh sensitization [9]; moreover, the treatment did not prevent fetal hydrops and had no effect on maternal antibody titers. Interestingly, in the same study, it was shown that IVIG treatment reduced the disease severity in one case of Kell isoimmunization. Administration of low-dose IVIG directly to the fetus with severe RhD-hemolytic disease after an IUT did not have any beneficial effect on the transfusion requirements of the fetuses and on the clinical outcome [20].

Although rare, side effects of IVIG treatment vary from mild reactions, such as fever, headache, myalgia, rush, nausea, and vomiting occurring 30–60 min after administration, to more severe complications, including tachycardia, shortness of breath, chest tightness, and hemolytic anemia [5]. IVIG is contraindicated in women with selective IgA deficiency because of anaphylactic reactions, whereas no association has been reported to any fetal defect [5]. Another factor that plays an important role in the decision to use IVIG for maternal red cell alloimmunization is that IVIG costs approximately $6000/week of treatment [76]. Further studies in the form of randomized controlled trials are required to clarify if maternal administration of IVIG alone or combined with intraperitoneal or intravascular transfusion or plasmapheresis can improve the outcome in high-risk red cell-alloimmunized pregnancies.

**Plasmapheresis**

Plasmapheresis is a well-known historical therapeutic approach that has been utilized as the sole treatment of red cell alloimmunization to reduce maternal antibody titer, but it has been replaced by IUT techniques that were associated with a significantly higher rate of perinatal survival. Angela et al. presented a series of 14 cases of anti-D alloimmunized patients who underwent plasmapheresis for a mean duration of 13.5 weeks with successful perinatal outcomes in 75% of the cases [2]. In recent years, plasma exchange treatment appears to be useful in cases of HDFN developed early in pregnancy (before 20 weeks’ gestation). The American Society of Apheresis in 2007 proposed that plasmapheresis should be considered early in pregnancy (from the 7th to 20th week) and continued until IUT can be safely administered (approx. 20 weeks of gestation) [75].
Table 2  Clinical case reports and case series about the use of plasmapheresis and maternal and fetal administration of IVIG in pregnancies complicated with fetal anemia due to red cell alloimmunization.

<table>
<thead>
<tr>
<th>Authors and year [reference]</th>
<th>Number of cases</th>
<th>Antibodies present</th>
<th>Treatment period</th>
<th>Therapeutic scheme</th>
<th>IUT (IV/IP)</th>
<th>Pregnancy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin et al., 1985 [7]</td>
<td>1</td>
<td>Anti-D, Anti-C</td>
<td>25 weeks</td>
<td>0.4 g/kg/day for 5 days (single dose)+plasmapheresis</td>
<td>IV</td>
<td>Live birth</td>
</tr>
<tr>
<td>Scott et al., 1988 [68]</td>
<td>1</td>
<td>Anti-D</td>
<td>20 weeks to delivery</td>
<td>0.4 g/kg/day for 5 days Four subsequent fetal IVIG dose (10 mL)</td>
<td>IV</td>
<td>Live birth</td>
</tr>
<tr>
<td>De La Camara et al., 1988 [15]</td>
<td>2</td>
<td>Anti-D</td>
<td>24 and 30 weeks to delivery</td>
<td>0.4 g/kg/day for 4 days every 14 days</td>
<td>–</td>
<td>2 Live births</td>
</tr>
<tr>
<td>Chitkara et al., 1990 [9]</td>
<td>5</td>
<td>Anti-D</td>
<td>15–27 weeks to delivery</td>
<td>1 g/kg/week</td>
<td>IV</td>
<td>1 Fetal death, 4 Live births</td>
</tr>
<tr>
<td>Margulies et al., 1991 [43]</td>
<td>24</td>
<td>Anti-D</td>
<td>&lt;20 weeks (n=8) 20–28 weeks (n=7) &gt;28 weeks (n=9)</td>
<td>0.4 g/kg/day for 4–5 days every 15–21 days</td>
<td>–</td>
<td>3 Fetal deaths, 21 Live births</td>
</tr>
<tr>
<td>Dooren et al., 1994 [20]</td>
<td>10</td>
<td>Anti-D</td>
<td>20–31 weeks to delivery</td>
<td>85.7±11.6 mg/kg of EFW after every IUT (fetal administration)</td>
<td>IV</td>
<td>3 Fetal deaths, 7 Live births</td>
</tr>
<tr>
<td>Alonso et al., 1994 [1]</td>
<td>1</td>
<td>Anti-D</td>
<td>28 weeks to delivery</td>
<td>0.4–0.5 g/kg EFW at 3-week intervals</td>
<td>–</td>
<td>Live birth</td>
</tr>
<tr>
<td>Gottvall and Selbing, 1995 [29]</td>
<td>5</td>
<td>Anti-D</td>
<td>22 weeks if fetal Hb &lt;100 g/L or anti-D ≥ 2.0 µg/mL to delivery</td>
<td>100 g over 4–5 days and repeated after 6 weeks if fetal lung maturity was not ascertained and fetal Hb was &gt;70 g/L 0.1 g/kg 3–4 times/week</td>
<td>–</td>
<td>No perinatal birth reported</td>
</tr>
<tr>
<td>Deka et al., 1996 [16]</td>
<td>6</td>
<td>Anti-D</td>
<td>16–18 weeks (n=5) and 13 weeks (n=1) to IUT or delivery</td>
<td>0.4 g/kg/day for 5 days every 15–21 days</td>
<td>IV</td>
<td>6 Live births</td>
</tr>
<tr>
<td>Voto et al., 1997 [85]</td>
<td>30</td>
<td>Anti-D</td>
<td>&lt;20 weeks to delivery</td>
<td>1 g/kg/week</td>
<td>IV</td>
<td>22 Live births, 6 Fetal and 2 Neonatal deaths</td>
</tr>
<tr>
<td>Porter et al., 1997 [61]</td>
<td>1</td>
<td>Anti-D</td>
<td>14 weeks to delivery</td>
<td>1 g/kg/week</td>
<td>IP+IV</td>
<td>Live birth</td>
</tr>
<tr>
<td>Palfi et al., 2006 [58]</td>
<td>1</td>
<td>Anti-D</td>
<td>12 weeks to delivery</td>
<td>100 g/week+plasmapheresis</td>
<td>IV</td>
<td>Live birth</td>
</tr>
<tr>
<td>Kriplani et al., 2007 [38]</td>
<td>4</td>
<td>Anti-D</td>
<td>22–34 weeks to delivery</td>
<td>1 g/kg EFW at IUT</td>
<td>IV</td>
<td>Live births</td>
</tr>
<tr>
<td>Ruma et al., 2007 [66]</td>
<td>9</td>
<td>Anti-D</td>
<td>6 to 30 weeks</td>
<td>1 g/kg/day (2 doses) followed by 1 g/kg/week+plasmapheresis</td>
<td>IV</td>
<td>9 Live births</td>
</tr>
<tr>
<td>Novak et al., 2008 [54]</td>
<td>1</td>
<td>Anti-D</td>
<td>16+5 weeks to delivery</td>
<td>1 g/kg/week+plasmapheresis</td>
<td>–</td>
<td>Live birth</td>
</tr>
<tr>
<td>Fox et al., 2008 [25]</td>
<td>4</td>
<td>Anti-D</td>
<td>14 weeks to IUT</td>
<td>0.8 g/kg/week</td>
<td>IP+IV</td>
<td>4 Live births</td>
</tr>
<tr>
<td>Connan et al., 2009 [12]</td>
<td>6</td>
<td>Anti-D</td>
<td>8 weeks to delivery</td>
<td>1 g/kg/week</td>
<td>IP+IV (4)</td>
<td>6 Live births</td>
</tr>
<tr>
<td>Isojima et al., 2011 [34]</td>
<td>1</td>
<td>Anti-D</td>
<td>15 weeks to delivery</td>
<td>Plasmapheresis+400 mg/kg/day for 5 days (single dose)</td>
<td>IV</td>
<td>Live birth</td>
</tr>
<tr>
<td>Lakhwani et al., 2011 [39]</td>
<td>1</td>
<td>Anti-Kell</td>
<td>28 weeks to delivery</td>
<td>Plasmapheresis</td>
<td>IV</td>
<td>Live birth</td>
</tr>
</tbody>
</table>

IV=Intravenous, IP=Intraperitoneal.

There are few reports in the literature, based on a small series of patients, that suggest the use of combination treatment with plasma exchange and IVIG in severe pregnancy alloimmunization in an attempt to prolong pregnancy to a gestational age at which IUT is technically possible [1, 16]. This combined approach has first been described in a variety of immune-mediated diseases such as systemic lupus erythematosus, Sjogren disease, and Guillain-Barré syndrome [13]. Ruma et al. [66], in a case series with nine fetuses (five with anti-D and four with anti-K), concluded that the combined immunomodulation could be theorized a successful treatment modality because all the fetuses survived, with a mean gestational age at delivery of 34 weeks, maternal antibody titers were significantly reduced after plasmapheresis.
and remained stable during IVIG therapy, and the serial measurement of peak MCA velocity were below the cut-off value for moderate to severe fetal anemia. Nevertheless, all nine fetuses subsequently required IUTs but to a later gestational age compared with the previous affected pregnancy, and a more pronounced increase in fetal Hct was achieved with the first therapy. These findings are consistent with other reports, which confirm that early plasmapheresis followed by the use of high-dose maternal IVIG could be beneficial in early treatment of severe Rh-alloimmunized pregnancies [16, 34].

There are also three articles reporting a total of eight patients with poor obstetrical history who were treated with both plasmapheresis and IVIG administration according to their antibody titers, and all had live-born infants without undergoing transfusion therapy [23, 54, 91]. A potential explanation for the enhanced perinatal survival reported in these series is that plasma exchange can remove the damaging antibodies but cannot inhibit further antigen stimulation; the adjuvant administration of IVIG would retain this decline in antibody levels, inhibiting a “rebound” effect soon after treatment in the majority of patients [66]. Lakhwani et al. [39] reported a case of a pregnant woman with Kell alloimmunization and severe hemolytic disease of the fetus, which was managed with only one fetal blood transfusion by cordocentesis and repeated plasmapheresis performed between 29 and 33 weeks’ gestation. With this scheme, a newborn with mild anemia was born

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Figure 2  An algorithm of the current approach of the therapeutic management of fetal anemia.
with normal delivery at 34 weeks. This observation is consistent with a previous report of a pregnancy complicated by severe anti-Kell alloimmunization and successfully managed with a highly aggressive course of repeated maternal plasma exchanges beginning at 7 weeks’ gestation followed by serial IUTs until 34 weeks [11]. Similarly, Fernandez-Jimenez et al. [23] used plasmapheresis in combination with IVIG on a weekly basis from 8 weeks in a pregnant woman with anti-P1Ppk and seven previous pregnancies with adverse outcomes and managed to deliver a healthy infant at 36 weeks’ gestation.

Conclusive remarks

Major advances have been observed in the management of fetal anemia over recent decades, but this condition still consists of a significant cause of perinatal mortality and morbidity. The focus of research interest has shifted from the invasive management to a non-invasive monitoring and treatment of fetal anemia with the use of free fetal DNA in maternal circulation and non-invasive estimation of fetal anemia with the use of MCA-PSV. Figure 2 summarizes the current approach of the therapeutic management of fetal anemia. Multicenter studies will prospectively assess the use of MCA velocimetry and validate cut-off points to manage fetuses that have undergone more than two transfusions and cases of severe red alloimmunization with early onset. In the following years, the directed maternal immunomodulation may be a realistic therapeutic option to delay the development of fetal hydrops and decrease or eliminate the need for IUTs. Clinical indications for use of IVIG are derived from isolated case reports or small case series, which might be because severe fetal anemia before 15 weeks is exceptional or unsuccessful cases are not published. Strict protocols should be standardized and should specify several aspects of alternative treatment modalities such as the onset and intervals between interventions, the optimal dosage of IVIG administration, the indications for combination with plasmapheresis, and the end point of the therapy.

References


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