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The rhesus incompatible pregnancy and its consequences for affected fetuses and neonates

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ABSTRACT

Rhesus incompatibility in pregnancy may result in haemolytic disease of the fetus and newborn (HDFN). This review discusses the fetal, neonatal and long-term consequences of HDFN and its management. Untreated, the fetal and neonatal prognosis of HDFN is poor. Provision of intravascular intrauterine transfusion (IUT) in a dedicated referral centre significantly reduces perinatal loss. Early-onset, severe fetal anaemia carries a greater risk of adverse fetal and neonatal outcomes and is less amenable to treatment with IUT. Interventions to prevent and treat severe, early onset disease have been investigated, however evidence from randomised controlled trials is required. Neonatal consequences of Rhesus haemolytic disease include early and late postnatal anaemia, and hyperbilirubinaemia leading to bilirubin-induced neurological dysfunction. Neurodevelopmental impairment and adult cardiovascular disease are long-term complications that have been reported in association with severe fetal anaemia. Strategies to prevent fetal hydrops, and further research into the long-term impacts of fetal anaemia may improve health outcomes for adult survivors of HDFN.

1. Introduction

Rhesus incompatibility in pregnancy is the discordance between maternal and fetal red cell antigens belonging to the Rhesus blood group system (most commonly D, E, e, C & c). Maternal alloimmunisation to antigens on fetal erythrocytes can result in the significant and potentially fatal consequence of haemolytic disease of the fetus and newborn (HDFN). A significant reduction in the prevalence of maternal alloimmunisation to the D antigen has resulted where widespread use of anti-D immune globulin prophylaxis has been implemented for Rhesus-D negative pregnant women. Despite this, Rhesus incompatibility in pregnancy continues to contribute to perinatal morbidity and mortality worldwide. With the availability of modern surveillance techniques and expert therapeutic interventions, consequences of the disease and its treatment are minimised, and the overall outcomes for the fetus and neonate are favourable [1].

2. Pathogenesis and natural history of HDFN

The pathophysiology underlying HDFN stems from discordance between maternal and fetal red cell antigens. Fetal red cells with paternally inherited surface antigens may enter the maternal circulation during pregnancy or at the time of delivery. Some episodes of fetal-maternal haemorrhage occur in sufficient volumes to cause a maternal immune response to the foreign antigens on fetal erythrocytes. This is well recognised where a Rhesus-D negative woman forms antibodies to a paternally inherited D antigen from a Rhesus-D positive fetus. The initial maternal IgM antibodies are unable to cross the placenta due to their size and are of no consequence to the fetus. Subsequent IgG antibodies can access the fetal circulation via placental transfer, and if a critical titre of IgG is reached, the fetus is at risk of anaemia due to haemolysis of the erythrocytes bearing this antigen. The fetal anaemia that ensues leads to a number of physiologic responses in the fetus [2], including enhanced erythropoiesis, increased fetal cardiac output and, if left untreated, progression to hydrops fetalis and fetal death in utero.

There is clear evidence of enhanced fetal bone marrow production in response to anaemia. Study of the bone marrow biopsies of 14 infants with haemolytic disease of the newborn by Dillon et al., showed marked erythroid hyperplasia in those infants where anaemia was found to be severe (haemoglobin <7.0 g/dL) [3]. In 1988, through sampling of umbilical cord blood in fetuses affected by alloimmunisation, Nicolaides et al. demonstrated increasing reticulocyte then erythroblast counts

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with worsening fetal anaemia. Their findings suggested that mild anaemia leads to stimulation of medullary haematopoiesis, and that recruitment of extra-medullary sites of haematopoiesis, such as the fetal liver, was stimulated by severe anaemia (haemoglobin concentration deficit >7.0 g/dL) [4].

Fetal cardiac output increases in response to low oxygen levels secondary to anaemia, and progression to high-output cardiac failure may occur. When fetal haemoglobin levels fall below 8 g/dL, leading to tissue hypoxia and lactate production, cardiac compensatory mechanisms become less effective [5].

Fetal hydrops is a marker of severe fetal anaemia and has been defined as the pathologic accumulation of excessive fluid within two or more fetal compartments, including ascites, pleural effusion/s, pericardial effusion, or skin oedema. Other features that may be detected on antenatal ultrasound include polyhydramnios and placental thickening [6]. Fetal hydrops typically occurs when the fetal haemoglobin deficit is greater than 7 g/dL below the mean for gestation [4] and represents the most severe end of the disease spectrum, prior to fetal death. A number of mechanisms underlying the development of fetal hydrops have been proposed, including: impaired synthetic liver function resulting in fetal hypoalbuminaemia; excessive capillary permeability secondary to tissue hypoxia; endothelial dysfunction due to free-radical formation in the setting of haemolysis-related iron overload, and impaired fetal lymphatic drainage due to elevated fetal central venous pressures [2].

Further pathological sequelae observed in the setting of severe, untreated haemolytic disease of the fetus secondary to alloimmunisation include fetal thrombocytopenia and neutropenia. Koenig et al. assessed the incidence and mechanisms of thrombocytopenia and neutropenia occurring in neonates with Rhesus haemolytic disease prior to exchange transfusion. They noted that whilst fetal erythropoiesis was markedly increased, this could be accompanied by a 'down-modulation' of production of neutrophils and platelets [7]. In a retrospective review of platelet counts from 314 pregnancies undergoing fetal blood sampling and intrauterine transfusions for Rhesus-D alloimmunisation in a single centre in the Netherlands, van den Akker et al. found that 23 % of severely hydropic fetuses had severe thrombocytopaenia (platelet count less than 50×10^9/L) [8]. A separate cohort study found severe thrombocytopaenia on cordocentesis in 6% of fetuses at first sampling, prior to intrauterine transfusion [9]. Whilst potential mechanisms for thrombocytopaenia in anaemic fetuses prior to treatment have been postulated, including decreased production, increased consumption, or excessive destruction of platelets, the aetiology remains unclear [8].

The typical sequelae in the first affected pregnancy differs from that of subsequent pregnancies, with generally fewer consequences for the fetus and neonate in the pregnancy where the primary episode of alloimmunisation occurred. In a retrospective review of patients with Rhesus-D alloimmunisation, Markham and Moise found that in pregnancies where antibodies were first detected, one third were affected by significant HDFN, whilst the remaining two thirds either maintained a low titre or developed a critical titre but no adverse fetal or neonatal sequelae [10]. The course in successive pregnancies is usually associated with more severe fetal anaemia, occurring at an earlier gestational age than in the first alloimmunised pregnancy [11]. Fetuses exposed to multiple maternal red cell antibodies have also been reported to be at greater risk of developing haemolytic disease, suggesting a potentially synergistic effect of multiple antibodies, and warranting close surveillance for adverse fetal and neonatal outcomes [12,13].

3. Fetal and postnatal outcomes associated with HDFN and its management

Whilst the natural history of severe Rhesus alloimmunisation confers a poor outlook for the fetus and neonate, the trajectory of the disease has been significantly altered by modern management. Significant reduction in the prevalence of Rhesus-D alloimmunisation has occurred as a result of anti-D prophylaxis. Widespread screening for maternal alloantibodies during pregnancy allows for surveillance of at-risk pregnancies and earlier detection of fetal anaemia. Advances in non-invasive surveillance for fetal anaemia using ultrasound assessment of the middle cerebral artery peak systolic velocity has improved the detection rate of fetal anaemia (Fig. 1), whilst ameliorating the risk associated with the previously employed invasive technique of amniocentesis for assessment of amniotic fluid Delta OD 450 values [14]. With the transition from intraperitoneal intrauterine transfusion to intravenous fetal transfusion in the 1980s, the outcomes of in utero correction of fetal anaemia have improved significantly [15]. Advances in neonatal intensive care have led to improved outcomes for affected infants. Subsequently, reporting on consequences for the fetus and neonate as a result of Rhesus incompatibility centres predominantly on the outcomes of intrauterine transfusion and other potentially beneficial therapies in the management of HDFN.

3.1. Intrauterine transfusion – consequences and outcomes

Intravascular intrauterine transfusion (IUT) has been associated with a number of complications for the fetus, including fetal bradycardia, need for emergency delivery, premature rupture of the membranes, chorioamnionitis, preterm birth, worsening of alloimmunisation and fetal death [16–18]. The possibility of fetal cerebral pathology secondary to in utero transfusion has been posed, supported by a case of fetal porencephalic cyst reported post-IUT in 1991 [19], although this has not been observed in other studies.

Despite potential complications, overall survival rates have been reassuring since the early years of intravascular IUT, with reports of survival ranging from 82 % to 96 % in the years 1988–1997 [16,20,21]. Where extensive experience has been acquired through the concentration of procedures into dedicated referral centres, very low rates of perinatal loss have been observed. In 2017, Zwiers et al. published outcomes from 1678 IUT procedures performed at the national referral centre for fetal therapy in the Netherlands. For IUTs performed after the year 2000, overall survival was 97 % [22]. Whilst a proportion of fetal loss in the setting of IUT is related to disease severity at the time of transfusion, a number of fetal deaths are the direct consequence of the procedure itself. Zwiers et al. reported a procedure related complication rate of 1.2 % (per procedure), and a procedure related perinatal loss rate of 1.8 % per fetus [22].

The likelihood of survival post-IUT is linked to the severity of anaemia at the time of the procedure. Multiple studies have noted the link between fetal hydrops at time of IUT and reduced survival rates. In 1992, Radunovic et al. observed that, despite an apparently technically successful procedure, almost 37 % of hydropic fetuses died within 72 h of their first IUT. This outcome was attributed to the adverse effects of acute elevations in fetal haematocrit and blood viscosity in the severely anaemic fetus [23]. In their report of outcomes of 288 IUTs between 1984 and 1993, Sampson et al. reported a significantly worse survival rate amongst fetuses found to be hydropic at the time of IUT compared with non-hydropic fetuses (60.6 % vs 86.7 % survival, respectively) [20]. Similarly, Janssens et al. found that 35 % of hydropic fetuses died despite intrauterine transfusion [21]. More recently, data from Zwiers et al. demonstrate a decline in frequency of fetal hydrops and improvement in survival of hydropic fetuses, highlighting the fetal and neonatal advantage conferred by introduction of widespread screening for alloimmunisation in early pregnancy, and concentration of procedures in a centralised referral hospital, allowing for comprehensive surveillance of affected pregnancies and expert, individualised management [14].

3.2. Severe, early-onset fetal disease – consequences of disease and management

From early in the second trimester maternal IgG antibodies to fetal red cell antigens can cross the placenta and access the fetal circulation

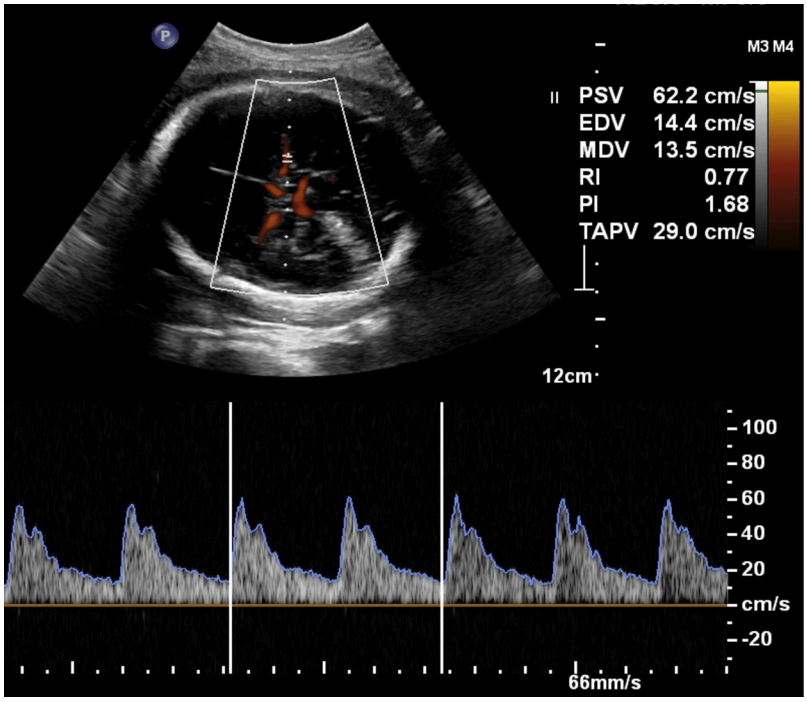

Fig. 1. Ultrasound colour Doppler interrogation of the fetal Middle Cerebral Artery to assess peak systolic velocity (PSV) at 32 weeks' gestation, in a fetus under surveillance for anaemia due to maternal Rh-D alloimmunisation. The PSV of 62.2 cm/s is < 1.5 multiples of the median (MoMs) for gestation and is indicative of a low risk of severe fetal anaemia (Patient consent was obtained for use of the image displayed).

[24]. Early-onset haemolytic disease arising prior to 20 weeks' gestation carries greater risk of adverse consequences for the fetus and neonate. This scenario is more commonly seen amongst patients who have had a previously severely affected alloimmunised pregnancy [25]. The earlier onset of disease is not only associated with more severe anaemia, higher risk of fetal hydrops and in utero demise, but a greater degree of difficulty in management with the standard therapy of intravenous IUT. Safe access to fetal or umbilical cord vasculature is rarely possible at such early gestations [26]. A number of strategies to delay progression to severe fetal anaemia and prolong pregnancy to a gestation where intravascular IUT is possible have been investigated, including maternal plasmapheresis and intravenous immunoglobulin (IVIg), and serial fetal intraperitoneal transfusion.

Administration of IVIg to women during Rhesus alloimmunised pregnancies is thought to competitively block the placental transfer of the maternal antibodies responsible for fetal haemolysis, and potentially suppress the formation of new maternal IgG antibodies to fetal red cell antigens [27]. The role of plasmapheresis is to remove red blood cell antibodies from the maternal circulation, thus decreasing the number of antibodies that can cross the placenta and destroy fetal erythrocytes [28]. Small retrospective case series have suggested potentially beneficial effects of these therapies. Ruma et al. reported a retrospective case series of 9 patients with either a previous early second trimester pregnancy loss due to red cell alloimmunisation (7 cases), or high levels of maternal antibodies early in pregnancy (2 cases). Patients were treated with serial plasmapheresis followed by weekly IVIg infusions. All fetuses subsequently underwent transfusion in utero, with a survival rate of 100 %, and a mean gestational age of 34 weeks at the time of delivery [29]. Nwogu et al. published a case series of five women who delivered healthy infants between 33 and 38 weeks' gestation after severe HDFN was managed with plasma exchange and IVIg, followed by intrauterine transfusions commencing between 21 and 27 weeks' gestation [30]. In a larger retrospective cohort study, Zwiers et al. evaluated whether the development and sequelae of severe fetal anaemia in pregnancies at high risk for HDFN could be delayed with the administration of maternal IVIg therapy. The outcomes for recipients and non-recipients of IVIg in the index pregnancy were compared, as well as outcomes between the index and previous pregnancy in the two groups. IVIg appeared to have a beneficial effect, with clinically significant fetal anaemia arising 15 days later in the index pregnancy treated with IVIg compared with the previous untreated pregnancies. This delay extended to 25 days in those women commencing IVIg prior to 13 weeks' gestation. Fetal hydrops occurred less frequently in the IVIg treated pregnancies [26]. Whilst IVIg appears to offer some benefit for fetuses affected by Rhesus incompatibility, the financial costs of treatment are significant, and a randomised controlled trial is required to clarify the clinical effectiveness of this therapy.

A further intervention aimed at improving outcomes for fetuses affected by early-onset severe disease is the use of early intraperitoneal intrauterine transfusion (IPT). Historically, the approach to fetal transfusion was via the intraperitoneal route, however intravenous IUT has replaced this as the preferred method of treatment for the anaemic fetus since the 1980′s. Intravascular fetal transfusion has numerous advantages compared with IPT, including improved survival rates (particularly in hydropic fetuses), more advanced gestation at delivery, fewer neonates requiring exchange transfusions, and the ability to perform concurrent fetal blood sampling [15]. However, prior to 20 weeks' gestation, the fetus is at higher risk of death after intravascular transfusion. Lindenburg et al. reported a 24 % perinatal loss rate in a cohort undergoing IUT prior to 20 weeks' gestation, compared with 8% in the group receiving IUT after 20 weeks' gestation. This was due to the greater severity of disease inherent in its earlier onset, along with the technical challenges of administering this therapy in a small fetus [31]. The use of early IPT in fetuses at risk of severe disease prior to 20 weeks' gestation may maintain fetal haemoglobin at sufficient levels to avoid hydrops or fetal demise, until a time when intravascular IUT can be attempted. Fox et al. reported a case series of 6 pregnancies at high risk of early-onset disease, treated with IVIg and early IPT. This resulted in an 86 % survival rate, compared with a 34 % survival rate in the previous pregnancies of the cohort [24]. A ten-year series of 11 fetuses at risk of early onset anaemia due to Rhesus alloimmunisation was reported by Crawford et al. 45 intraperitoneal transfusions were

performed on 11 fetuses prior to 20 weeks' gestation, in the absence of hydrops in any of the fetuses, with decision to treat assisted by findings of middle cerebral artery peak systolic velocity measurements. The survival rate was 91 %, with all surviving fetuses being delivered after 33 weeks' gestation. The one perinatal loss was due to a complication during intravascular transfusion at 26 weeks' gestation [32]. Whilst these are small cohort studies with heterogenous approaches to management, the findings suggest early IPT may offer some improvement in outcome for fetuses at high risk of severe early-onset disease.

3.3. *Rhesus haemolytic disease and the newborn infant: postnatal course and long-term outcomes*

Haemolytic disease of the fetus and newborn secondary to Rhesus incompatibility in pregnancy is associated with high risk of neonatal morbidity and mortality. Fetuses with Rhesus haemolytic disease are at risk of preterm birth and its associated short- and long-term sequelae, including perinatal death. The major clinical challenges for the newborn infant with Rhesus haemolytic disease include anaemia, both early and late in the postnatal period, and hyperbilirubinaemia which, if severe, may manifest with clinical signs of bilirubin-induced neurological dysfunction. A known predictor of postnatal course for the infant born with Rhesus haemolytic disease is history of fetal IUT. Intensive care management of the newborn infant with Rhesus haemolytic disease may include phototherapy, transfusion of blood products, and exchange transfusion. Additional blood transfusions may be required to manage late anaemia observed in a proportion of infants, more likely in those who received blood transfusion in the fetal period.

3.3.1. *Postnatal anaemia*

3.3.1.1. Early anaemia. The use of IUT in the management of Rhesus haemolytic disease reduces the risk of severe early postnatal anaemia [33]. Despite this, a proportion of infants will have symptomatic anaemia, and will receive urgent blood transfusion in the early hours after birth, followed by exchange transfusion [34]. Infants with severe Rhesus haemolytic disease complicated by hydrops are at higher risk of death, and their early management in the delivery room or in intensive care may include drainage of fluid-filled cavities, most frequently pleural effusions and then ascites, and intubation and mechanical ventilation, particularly if pleural effusions have impaired fetal lung growth and development culminating in pulmonary hypoplasia [35,36]. Infants with severe anaemia and/or hyperbilirubinaemia in the early postnatal period may receive exchange transfusion, which may be repeated as indicated by disease progression [34]. For infants with mild, asymptomatic anaemia, blood transfusion may be avoided, and consideration given to treatment with erythropoietin [34]. Judicious use of iron supplementation must be balanced with the risk of iron-overload secondary to haemolysis and fetal and postnatal blood transfusion. At birth, approximately 70 % of infants will have evidence of iron-overload, with the potential to cause liver, cardiac, and endocrine organ injury [37].

3.3.1.2. Late anaemia. Late anaemia, defined as anaemia presenting after the first postnatal week, occurs in 83 % of infants with HDFN delivered after 34 weeks of gestation [37]. Late anaemia may be due to haemolysis resulting from continued immune destruction of erythroid progenitors, or suppression of erythropoiesis in the infant secondary to fetal or neonatal blood transfusion [34]. With regard to immune destruction of erythroid progenitors and risk of anaemia, maternal antibodies can remain in the infant's circulation for up to 3 months after birth [21]. In infants who had received IUT, transfused donor erythrocytes are eventually replaced by the infant's own erythrocytes which are susceptible to haemolysis in the presence of residual maternal antibodies [38]. Improvement in fetal oxygenation following receipt of donor erythrocytes has been associated with decreased erythropoietin levels in infants [38]. Late hypo-regenerative anaemia, characterised by a low reticulocyte count, contributes to the need for 'top-up' blood transfusions in infants exposed to IUT [37]. De Boer et al. reported a rate of blood transfusion within the first 6 months of age of approximately 58 % in term and late preterm infants with HDFN. For infants who had received IUT, 77 % had 'top-up' transfusions compared with 26.5 % of those who had not received IUT [39]. The effectiveness of administration of erythropoietin to infants in the early postnatal period to reduce the need for top-up transfusions for late anaemia due to HDFN is yet to be established, and therefore its routine use is not currently recommended [37].

3.3.2. *Hyperbilirubinaemia and bilirubin-induced neurologic dysfunction (BIND)*

The immune-mediated destruction of fetal and neonatal erythrocytes by maternal antibodies results in the release of biliverdin from the heme molecules within the red cell cytoplasm, which is then converted into bilirubin [40,41]. Elevated serum bilirubin levels in the newborn infant can manifest as jaundice, and due to the ability of unconjugated bilirubin to cross the blood-brain barrier, may cause bilirubin-induced neurologic dysfunction (BIND) [42]. The initial phase of neurologic injury, acute bilirubin encephalopathy (ABE), presents clinically as poor feeding, lethargy, irritability, and abnormal tone, and later as seizures [34]. Newborn infants are at risk of acute bilirubin encephalopathy when serum bilirubin levels are severely elevated (>360 μmol/L), or when serum bilirubin levels rise at a rapid rate (>8.5 μmol/L/hr) [43]. Following the acute injury, chronic bilirubin encephalopathy (also referred to as classic kernicterus) may ensue. This permanent neurologic damage manifests as athetoid cerebral palsy, sensorineural deafness, Parinaud's phenomenon (failure of upward gaze), seizures, and cognitive impairment [43]. Without rapid treatment, haemolytic disease of the newborn can lead to adverse short- and long-term neurologic injury, and death.

The initial treatment of hyperbilirubinaemia is phototherapy, and where this is unsuccessful or insufficient, exchange transfusion is performed to reduce bilirubin levels and remove maternal antibodies to neonatal erythrocyte antigens [40]. Whilst phototherapy is a safe and effective intervention for lowering neonatal bilirubin levels, exchange transfusion is associated with a high risk of morbidity and mortality for the infant. The frequency with which exchange transfusion is performed has declined markedly in recent years making it a relatively rare procedure in the management of hyperbilirubinaemia. This is a result of diminishing rates of Rhesus-D alloimmunisation due to anti-D prophylaxis, as well as advances in fetal management of the alloimmunised pregnancy. Accordingly, exchange transfusion is now more likely to be used in the setting of more severely affected, preterm infants resulting from Rhesus incompatible pregnancies, who are already at greater risk of morbidity and mortality [44]. Reported mortality rates associated with exchange transfusion range from 0.3 %–10 % in term and preterm infants, respectively [37]. Serious complications associated with exchange transfusion include: metabolic disturbances (metabolic acidosis, hypocalcaemia, hyperkalaemia, and hyperglycaemia); cardiac arrhythmias; need for respiratory support; central line complications, such as vascular or visceral perforation, or thrombosis; sepsis; thrombocytopenia; coagulopathy [45]. Whilst the need for exchange transfusion has declined in more recent years, infants affected by Rhesus haemolytic disease comprise the majority who receive this therapy, accounting for approximately 70 % of neonatal exchange transfusions being performed for Rhesus haemolytic disease of the newborn [44]. The effect of administration of intravenous immunoglobulin to the neonate in an attempt to reduce the need for exchange transfusion was assessed in a 2018 systematic review. The authors concluded there was insufficient evidence to support the use of IVIg in this setting [46].

Of note, a further neonatal complication associated with Rhesus incompatibility in pregnancy is the increased risk of neonatal cholestasis,

or conjugated hyperbilirubinaemia. This is thought to be in part due to the iron overload associated with haemolysis and frequent transfusion. In a review of 313 infants treated with and without IUT, neonatal cholestasis was found to occur in 13 % of neonates with haemolytic disease of the newborn due to red cell alloimmunisation. Investigations for other causes of cholestasis were negative, and six of the 41 affected infants required treatment (medical and nutritional therapy), one of whom underwent iron chelation therapy [47].

3.3.3. Long-term consequences of HDFN and its management

3.3.3.1. Long-term neurodevelopmental outcomes. With improved survival of affected fetuses and neonates due to IUT and other modern interventions, longer term follow-up of neurological sequelae has been the focus of a number of cohort studies.

Doyle et al. reviewed the neurodevelopmental outcomes at two years of age in 38 children who survived IUT between 1984 and 1990, at a tertiary maternity hospital in Australia. The survival rate of fetuses undergoing IUT during this time frame was 73 %. Neurodevelopmental outcomes were classified as: no disability, or mild, moderate, or severe disability, depending on the presence and severity of cerebral palsy, sensorineural deafness, and the mental development index score. The results were compared with a previously described cohort of normal birth weight children. At two years of age, 92.1 % of children who survived IUT were classified as having no disability, and no relationship was found between neurological outcome and the severity of fetal anaemia or presence of hydrops in utero. The rates of disability in the IUT cohort were not significantly different to those in the normal birth weight group [48]. In 1997, Janssens et al. reported on neurodevelopmental outcomes in 69 children from a cohort of 92 fetuses that underwent IUT for severe haemolytic disease between 1987 and 1993. The age of the children ranged from 6 months to 6 years at the time of assessment. The outcomes were compared to those of a high risk and a healthy cohort of children from within the Dutch population. The rate of disability in the IUT cohort was 10.1 %, compared with 18 % in the high-risk comparison cohort. The rate of disability in the IUT group compared unfavourably to the normal 'healthy' population group (6% rate of disability), however this difference was not statistically significant [21].

Hudon et al. followed up 40 children to assess long-term neurodevelopmental outcomes after in utero transfusion for haemolytic disease, up to 62 months of age. They concluded that a normal neurodevelopmental outcome can be expected in around 95 % of cases, even in severe cases of fetal haemolytic disease [49]. Grab et al. reported neurologic outcomes of a cohort of 35 survivors of IUT, followed up for 6 years. One case of mild psychomotor disability was identified in a one year old, which subsequently resolved, and one case of delayed speech development was observed. Favourable long-term neurological outcomes were observed even amongst fetuses presenting with hydrops [50]. In 2006, Harper et al. published long-term neurodevelopmental and neuropsychological outcomes of 16 children treated in utero with intravascular transfusion for profound anaemia and hydrops, followed up to ten years of age. Of the 16 children, 81 % had normal physical and neurologic outcomes. Explanations other than haemolytic disease were probable in those in whom adverse neurological sequelae were present, including preterm birth, a procedural complication, and maternal drug and alcohol use [51].

The largest of these cohorts published is from the LOTUS study (Long-term neurodevelopmental outcome after intrauterine transfusion for haemolytic disease of the fetus/ newborn). Lindenburg et al. evaluated 291 children treated with IUT for haemolytic disease of the fetus, with a median age at follow up of 8.2 years. The overall incidence of neurodevelopmental impairment, defined as the presence of at least one of cerebral palsy, severe developmental delay, bilateral deafness, and/or blindness was found to be 4.8 %. They reported a 2.1 % rate of cerebral palsy, a 3.1 % rate of severe developmental delay, and a 1.0 % rate of bilateral deafness. An odds ratio of 11.2 (95 % CI, 1.7–92.7; $P = 0.011$) was reported for the independent association between severe hydrops and neurodevelopmental impairment [52]. Whilst overall neurodevelopmental outcomes for affected fetuses and neonates appear to be favourable, long-term outcomes may be improved by interventions to prevent the development of fetal hydrops.

3.3.3.2. Long-term cardiovascular outcomes. The association between a pathological in utero environment and long-term cardiovascular disease is well documented [53]. Exposure to severe anaemia in the fetal period may have deleterious effects on the developing fetal heart, resulting in an increased risk of cardiac complications in adulthood [53]. A case-control study evaluating long-term cardiac effects of fetal anaemia due to red cell alloimmunisation was reported in 2010 by Dickinson et al. 25 children who survived IUT for the treatment of haemolytic disease secondary to maternal red cell antibodies were matched with 25 healthy children, to compare findings from echocardiography performed at a median age of 10.1 years in the case group (10.5 years in the control group). Compared to the control group, children who required transfusion in utero had significantly less left atrial area (9% less) and less ventricular mass (10 % less), which may suggest an adverse impact of fetal anaemia on cardiomyocyte proliferation and differentiation [54].

The impact of fetal anaemia due to Rhesus alloimmunisation and IUT on cardiovascular development and long-term outcomes was investigated in adults by Wallace et al. This retrospective cohort study compared 95 exposed participants with a mean age of 33.7 years to their unexposed siblings, whose mean age was 40.1 years at the time of examination. Subjects underwent assessment of blood pressure, serum lipid profile, and heart rate variability, and were investigated with cardiac MRI. Participants in the exposed group had smaller left ventricular volumes, increased relative left ventricular wall thickness, decreased myocardial perfusion at rest, and less favourable lipid profiles than their non-exposed siblings. Whilst acknowledging the co-existing long-term cardiovascular risk factors of prematurity and lower birth weights in the exposed group, the authors concluded that their findings suggest an association between exposure to fetal anaemia and IUT and altered cardiovascular development, with persistence into adulthood potentially increasing the risk of cardiovascular disease [53]. With improvements in live-birth rates of severely anaemic fetuses, the longer-term cardiovascular consequences of this significant physiologic insult in early development have become more relevant for survivors of the Rhesus incompatible pregnancy.

4. Conclusion

Left untreated, haemolytic disease of the fetus and newborn is associated with significant morbidity and risk of death. With access to current, expert surveillance and interventions for Rhesus incompatible pregnancies, favourable outcomes for the fetus and neonate can be expected. Ongoing investigation of the long-term consequences for fetuses and neonates affected by Rhesus incompatibility will provide further opportunities to optimise the health of adult survivors of HDFN.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Caroline Tyndall: Writing - original draft. **Rocco Cuzzilla:** Writing - review & editing. **Stefan C. Kane:** Supervision, Writing - review & editing.

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