Optimising neonatal management of haemolytic disease of the foetus and newborn

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Chapter one

Neonatal management and outcome in alloimmune haemolytic disease

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Expert Review of Hematology 2017;10(7):607-616.

Abstract

Introduction

Haemolytic disease of the foetus and newborn (HDFN) occurs when foetal and neonatal erythroid cells are destroyed by maternal erythrocyte alloantibodies, it leads to anaemia and hydrops in the foetus, and hyperbilirubinaemia and kernicterus in the newborn. Postnatal care consists of intensive phototherapy and exchange transfusions to treat severe hyperbilirubinaemia and top-up transfusions to treat early and late anaemia. Other postnatal complications have been reported such as thrombocytopenia, iron overload and cholestasis requiring specific management.

Areas covered

This review focusses on the current neonatal management and outcome of haemolytic disease and discusses postnatal treatment options as well as literature on long-term neurodevelopmental outcome.

Expert commentary

Despite major advances in neonatal management, multiple issues have to be addressed to optimise postnatal management and completely eradicate kernicterus. Except for strict adherence to guidelines, improvement could be achieved by clarifying the epidemiology and pathophysiology of HDFN. Several pharmacotherapeutic agents should be further researched as alternative treatment options in hyperbilirubinaemia, including immunoglobulins, albumin, phenobarbital, metalloporphyrins, zinc, clofibrate and prebiotics. Larger trials are warranted to evaluate erythropoietin, folate and vitamin E in neonates. Long-term follow-up studies are needed in HDFN, especially on thrombocytopenia, iron overload and cholestasis.

Introduction

Haemolytic disease of the foetus and newborn (HDFN) is a condition in which foetal and neonatal erythroid cells are destroyed by maternal erythrocyte IgG alloantibodies that are transported across the placenta.[1,2] Maternal alloimmunisation can be triggered by more than 50 different erythrocyte antigens, but most severe cases involve the Rhesus D antigen (RhD) and cause Rh-mediated haemolytic disease.[3] The effects of the incompatibility of maternal and foetal erythrocytes range from anaemia and hydrops in the foetus, to hyperbilirubinaemia and kernicterus in the newborn.[2] Management of HDFN is therefore a two-way effort, concerning both antenatal as well as postnatal strategies. The most successful step in antenatal care of HDFN was the introduction of RhD immunoprophylaxis in 1968.[4] Before immunoprophylaxis became available, HDFN affected 1% of all newborns worldwide and the mortality rate in affected foetuses was up to 50%.[4] The incidence of Rh haemolytic disease is now approximately 0.5% in RhD-negative women in industrialised countries.[2,4] However, despite adequate RhD immunoprophylaxis, 1 to 3 in 1000 RhD negative women still develop anti-D antibodies.[5] Antenatal care not only involves immunoprophylaxis, but also the monitoring of high-risk cases by laboratory testing and ultrasound-based techniques in order to detect foetal anaemia. If necessary, severe foetal anaemia is treated with intrauterine blood transfusions (IUTs) to prevent or treat foetal hydrops.[6,7] At least equally important in the management of HDFN is postnatal care. Postnatal care involves the management and stabilisation of the ill and frequently premature newborn[8], but revolves around the treatment of hyperbilirubinaemia and prevention of kernicterus by intensive phototherapy and exchange transfusions. Except for hyperbilirubinaemia, other postnatal complications of HDFN and their respective treatments have been reported and studied such as early and late anaemia. To date, however, little attention has been devoted to complications such as thrombocytopenia, iron overload and cholestasis. The long-term neurodevelopmental outcome has only recently been investigated in large cohorts. With the ongoing research on HDFN, it is important to highlight and summarise recent developments and to point out the remaining challenges for the future. This review focuses on the current postnatal management and outcome of HDFN. Recent literature is reviewed and discussed in a clinical point of view to assess current and future care of these neonates. The main issues addressed in this paper are the various postnatal treatment options of hyperbilirubinaemia and anaemia, as well as long-term outcome.

Management of hyperbilirubinaemia

In severe hyperbilirubinaemia, unconjugated bilirubin can cross the blood-brain barrier and can potentially lead to bilirubin neurotoxicity. A condition defined as bilirubin-induced neurologic dysfunction (BIND) occurs, of which kernicterus or chronic bilirubin encephalopathy is known as its most severe and permanent clinical manifestation.[9] In the acute phase of BIND, symptoms include lethargy, hypotonia and feeding problems. Untreated, hyperbilirubinaemia can cause fever, a high-pitched cry and hypertonia, eventually leading to apnoea, coma, seizures and death. In kernicterus, the most affected brain tissues are the basal ganglia, cerebellum and various brainstem nuclei. Long term morbidity in surviving infants include athetoid cerebral palsy, hearing loss and intellectual disability.[10,11]

Standard care of hyperbilirubinaemia consists of intensive phototherapy and, if indicated, exchange transfusions. Improvement of these treatments remains a constant and recurring focus of research, as well as the search for alternative treatments such as pharmacotherapeutic agents that might enhance treatment of hyperbilirubinaemia in HDFN.

Intensive phototherapy

Since its introduction in the 1970s, phototherapy has been the main treatment for neonatal hyperbilirubinaemia. Phototherapy causes photo isomerisation of bilirubin in the skin to water-soluble isomers that can be excreted by the kidneys and stool without further metabolism by the liver. The efficacy of phototherapy depends on several factors, including the wavelength of the light used, the intensity of the light source, the total light dose (time under phototherapy and amount of skin exposed), and/or the threshold at which phototherapy is commenced.[12-15] The light used in phototherapy needs to penetrate the skin and be absorbed by bilirubin, which happens with blue or green light with an optimal wavelength range of 460-490 nm.[12] The intensity or irradiance (energy output) of the light source is measured with a radiometer in units of watts per square centimetre or in microwatts per square centimetre per nanometre over a given wavelength band.[12] Light emitting diodes (LEDs) are the most commonly used phototherapy lamps, but also halogen lamps and fiberoptic systems such as biliblankets are used.[10] A recent systematic review by Woodgate et al. recommends close phototherapy (distance of 20 cm above the neonate) over distant light-source phototherapy (40 cm above the neonate), and double over single phototherapy, thus increasing the light irradiance. No clear benefit was found for continuous over intermittent phototherapy in neonates more than 2000 g or term infants, or for higher skin exposure by removing the diaper. Phototherapy should be applied once serum bilirubin levels reach predefined thresholds.[15]

In HDFN, the use of intensive phototherapy is recommended. Intensive phototherapy defined by the American Academy of Pediatrics (AAP) as a spectral irradiance of at least 30 µW per square centimetre per nanometre over the same bandwidth delivered to as much of the body-surface area as possible. In practice, intensive phototherapy is continuous with at least two lamps closely above the neonate and a biliblanket covering the whole body and back side of the neonate.[10]

Phototherapy is generally considered a safe procedure and reports of significant toxicity are exceptionally rare and mostly limited to case reports.[10,16] Recently, two studies were published on a possible link between phototherapy and development of cancer. Specifically, the risk for myeloid leukaemia and kidney cancer seemed slightly increased. However, after correcting for congenital and chromosomal abnormalities, the associations were no longer statistically significant.[17,18] Additionally, previous studies could not find an association between phototherapy and skin cancer.[16,19] Phototherapy does seem to be associated with the development of allergic diseases.[20]

Fluid supplementation/hydration

Fluid supplementation during phototherapy may help the excretion of photoproducts through both urine and bile and to overcome the increased insensible water loss.[21] However, with the increased use of LED lights, the beneficial effect of fluid supplementation in neonates without dehydration becomes questionable, as LED lights have a much lower heat output and therefore less insensible water loss.[12,14] Intravenous fluid support has no effect on the rate of decrease in serum bilirubin and decrease in duration of phototherapy in healthy term newborns with no dehydration.[22,23]

Exchange transfusion

In the 1940s, treatment of neonatal hyperbilirubinaemia with exchange transfusions was introduced, initially as specific treatment for Rh haemolytic disease.[24] Exchange transfusions lower the serum bilirubin level and remove the antibody-coated neonatal erythrocytes and circulating maternal antibodies to reduce further erythrocyte destruction. Approximately 85% of the neonatal blood is replaced by irradiated donor blood, which has the additional benefit of providing new albumin with bilirubin binding sites and directly treating anaemia.[25,26] However, exchange transfusions are not without risk. Current mortality rates are less than 0.3% in term neonates, but increases above 10% in preterm neonates.[27,28] Morbidity rates are still high (up to 24%), even in term neonates and include cardio-respiratory instability, apnoea, catheter-related complications, thrombocytopenia and infections.[27-29]

There is no clear benefit for the use of single volume exchange transfusion as opposed to double volume exchange transfusion; double volume exchange transfusions is current practice.[30] Two-stage exchange transfusions showed to be more efficient than one-stage exchange transfusions in term neonates in single-volume transfusions. In the two-stage procedure, a first exchange transfusion is given with a three hour resting period (allowing for equilibrium of bilirubin to be established between the intravascular and extravascular compartments), followed by a second stage. Two-stage exchange transfusion significantly lowered rebound serum bilirubin and the need for repeated exchange transfusions. There was no difference in mortality and morbidity between the two groups.[31]

The frequency of exchange transfusions sharply declined since its introduction due to the emergence of phototherapy, the development of RhD immunoprophylaxis and improved monitoring, and care for hyperbilirubinaemia.[28] Exchange transfusions are now recommended if bilirubin levels remain above exchange transfusion thresholds despite intensive phototherapy, or if signs of acute bilirubin encephalopathy occur.[10] The rate of exchange transfusion in HDFN decreased to around 20% after these more restrictive guidelines were published by the AAP.[10,32]

In our centre, the exchange transfusion rate in HDFN dropped from approximately 70% before 2005[33] to approximately 15% thereafter.[32] This reduction was due to the implementation of a more restrictive guideline for exchange transfusions in terms of bilirubin cut-off values, especially by introducing cut-off values for different risk groups, compared to the more liberal guideline used at our centre before 2005.

Intravenous immunoglobulin

Some studies have shown a reduced need for exchange transfusions in HDFN with the use of intravenous immunoglobulins.[34] Immunoglobulins seem to block Fc receptors on macrophages, which reduces the breakdown of antibody coated erythrocytes and lowers the circulating unconjugated bilirubin levels.[35] Administration of intravenous immunoglobulin (0.5-1 g/kg) is currently recommended by the AAP if the total serum bilirubin is rising despite intensive phototherapy or the bilirubin level is within 2 to 3 mg/dL (34-51 μmol/L) of the exchange level. If necessary, a repeated dose can be given in 12 hours.[10,34]

Despite current recommendations, a recent randomised controlled trial by Santos et al. and a recent randomised controlled trial in our centre by Smits-Wintjens et al., could not support the efficacy of intravenous immunoglobulins in HDFN.[32,36] As efficacy is questioned, it is important to point out that although intravenous immunoglobulins are considered a safe

treatment, rare but serious side effects have been reported, including transfusion transmitted diseases, anaphylaxis, hypersensitivity, thrombosis, pulmonary emboli and renal failure.[37] A possible association with necrotising enterocolitis (NEC) was found in a retrospective study comparing near-term infants with Rh haemolytic disease treated with immunoglobulins with a control group without immunoglobulin treatment.[38] In a meta-analysis by Yang et al., immunoglobulins showed an increased risk for NEC (odds ratio 4.53; 95%-confidence interval 2.34-8.79; $p<.001$), but not for final mortality.[39] A recent systematic review advocates further well designed studies before conclusive advice can be given about the treatment of HDFN with intravenous immunoglobulins.[40]

Alternatives

Several pharmacotherapeutic agents have been studied as possible treatment options in neonatal hyperbilirubinaemia. The main focus is on albumin, phenobarbital, metalloporphyrins, zinc, clofibrate and prebiotics. None of these agents is currently recommended as standard care in hyperbilirubinaemia.[10]

Albumin

As albumin binds bilirubin, it is thought that extra administered albumin can lower serum bilirubin levels. However, sufficiently powered trials on the clinical benefits are lacking and albumin administration is not recommended as standard care at this moment.[10] A small randomised controlled trial in India by Shahian et al. showed evidence that albumin administration prior to exchange transfusion is beneficial to lower total serum bilirubin levels post-exchange and lower the mean duration of phototherapy.[41] A subsequent randomised controlled trial did not show the same effects.[42] The AAP marks it as an option to measure the serum albumin level in neonates with hyperbilirubinaemia and to consider an albumin level below 3.0 g/dL as an extra risk factor to lower the phototherapy threshold. Furthermore, if an exchange transfusion is being considered, the serum albumin level should always be measured and with the bilirubin/albumin ratio used in determining the need for exchange transfusions. Albumin supplementation is not recommended.[10]

Phenobarbital

Phenobarbital was used in an attempt to increase biliary flow in the 1970s. Phenobarbital increases hepatic uridine diphosphate (UDP)-glucuronosyl transferase (UGT) activity and the conjugation of bilirubin, and has a possible positive effect on hepatic uptake of bilirubin.[43,44] A recent randomised clinical trial by Kaabneh et al. in neonates with HDFN showed a minor

advantage of adding phenobarbital to phototherapy treatment.[45] However, phenobarbital acts slowly and is therefore not the treatment of choice when adequate phototherapy and exchange transfusions are available. There might be a role for antenatal maternal administration of phenobarbital, as positive results (decreased need for exchange transfusions) were found in a retrospective study by Trevett et al., although these results are yet to be confirmed.[46]

Metalloporphyrins

Metalloporphyrins inhibit heme-oxygenase, the rate-limiting enzyme in the catabolism of haem to bilirubin. In this manner, metalloporphyrins decreases the production of bilirubin, rather than increasing the excretion of bilirubin.[47] Treatment with metalloporphyrins may reduce neonatal bilirubin levels and decrease the need for phototherapy and hospitalisation. Sufficient evidence is lacking however to recommend routine treatment of hyperbilirubinaemia with metalloporphyrins.[48]

Zinc

Oral zinc is thought to reduce the serum bilirubin by decreasing the enterohepatic circulation of bilirubin.[49] However, recent systematic reviews by Mishra et al. and Sharma et al. concluded that there is currently no role for zinc in the treatment of neonatal hyperbilirubinaemia. There seems to be no effect on duration of phototherapy, incidence of phototherapy, or age of starting of phototherapy.[50,51]

Clofibrate

Clofibrate induces glucuronosyl transferase that changes bilirubin in a water-soluble form that can be excreted. It seems that clofibrate in combination with phototherapy lowers the level of bilirubin and shortens the duration of phototherapy in term neonates[52,53], but larger trials are needed to evaluate its effect. Further research is especially needed in haemolytic-caused hyperbilirubinaemia, as these neonates were excluded in some of the trials.[54]

Prebiotic supplementation

Recently, the role of prebiotic supplementation was focus for research on the treatment of neonatal hyperbilirubinaemia. Prebiotics are thought to increase gastrointestinal motility and stool frequency, decrease viscosity of stool and the enterohepatic circulation of bilirubin, and improve feeding tolerance and growth of beneficial bacteria in the gut. Results seem promising in both preterm and term neonates with hyperbilirubinaemia on total serum bilirubin levels as well as duration of phototherapy.[55,56]

Antenatal corticosteroids

Antenatal treatment with corticosteroids has been shown to accelerate lung maturation in preterm infants and reduce the risks of respiratory disorders, especially in those born before 34 weeks' gestation.[57] Although antenatal betamethasone given after 34 weeks' gestation does not appear to decrease the risk of respiratory disorders, recent studies reveal that betamethasone reduces the risk of neonatal jaundice requiring phototherapy, possibly because of acceleration of liver maturation.[58]

Management of anaemia

Haemolysis of the foetal erythrocytes by maternal alloantibodies causes anaemia. These alloantibodies remain in the neonatal circulation after birth for several months and can cause prolonged anaemia. Anaemia in haemolytic disease is divided in early anaemia (onset at birth up to 7 days of age) and late anaemia. Late anaemia occurs in 83% of neonates of a gestational age of 35 weeks or more with HDFN and is further split into "late hyporegenerative anaemia" and "late anaemia of haemolytic disease".[59] Late hyporegenerative anaemia is caused by depressed erythropoiesis and is characterised subsequently by low reticulocyte counts. Underlying mechanisms are proposed to be the following: intramedullary destruction of erythrocyte precursors, bone marrow suppression from intrauterine and postnatal transfusions, erythropoietin (EPO) deficiency, shortened half-life of transfused erythrocytes and relative anaemia due to the expanding intravascular volume of the growing neonate. Late anaemia of haemolytic disease is characterised by age-appropriate or elevated reticulocyte counts, reflecting an active bone marrow to compensate for the shortened erythrocyte survival. This form of late anaemia is thought to be due to a combination of continuing haemolysis by remaining antibodies, shortened survival of transfused erythrocytes, natural decline of the haemoglobin level and the expanding intravascular volume of the growing neonate.[59,60] Interestingly, although late anaemia was already described before IUTs were available, IUTs seem to actually increase the risk of postnatal anaemia. The pathophysiological mechanism is not entirely understood, but treatment with repeated IUTs possibly lead to persistent anaemia due to suppression of erythropoiesis.[33]

Primary treatment of anaemia in HDFN is administering erythrocyte transfusions, known as top-up transfusions. In addition, several pharmacological agents are used to stimulate erythropoiesis.

Top-up transfusions

Late anaemia usually resolves by the third month of life; until then erythrocyte transfusions may be necessary to treat postpartum anaemia.[59,61] The mean postnatal age for a first top-up transfusion in HDFN is 18 days (range 1-34).[62] At least one top-up transfusion is reported to be required in 68 to 83% of neonates with HDFN.[33,59,63] Some neonates need up to 6 top-up transfusions in the first three months of life.[62] In neonates that were treated with IUTs, the top-up transfusion rate is significantly higher (77-89%), than in neonates that were not treated with IUTs (27-67%).[33,59,63] In the IUT group, the median number of top-up transfusions was 1 (range 0-4), compared to 0 (range 0-2) in non-IUT group ($p<.001$).[33] This difference can be explained by a depressed erythropoiesis and is correlated with a significantly lower reticulocyte count at birth in transfused neonates.[33,62,64] Variations in the percentage of neonates requiring top-up transfusions may be explained by various factors, including differences in transfusion guidelines and thresholds for erythrocyte transfusions. In our centre, a top-up transfusion of 15 ml/kg irradiated erythrocytes is indicated in term neonates with HDFN when haemoglobin levels fall below 7.2 g/dL (4.5 mmol/L) or below 8.8 g/dL (5.5 mmol/L) when clinical symptoms of anaemia are present (increased oxygen need, poor feeding, tachycardia and/or tachypnoea).

Exchange transfusion

Exchange transfusions not only have a positive effect on the clearance of bilirubin in haemolytic disease, but as mentioned before, it also treats anaemia as the neonatal blood is replaced by immunologically compatible donor blood and decreases plasma ferritin and iron levels.[25] The reduced need for exchange transfusion in the last decades seems to be associated with an increased need for top-up transfusions. This is probably explained by longer lasting haemolysis due to a reduced clearance of maternal antibodies.[33,63]

Delayed cord clamping

Delayed cord clamping at birth allows additional placental blood transfusion. In a term newborn this transfusion can consist up to one-quarter to one-third of the total neonatal blood volume.[65] In anaemia secondary to erythrocyte alloimmunisation, a significant increase in haemoglobin levels at birth was observed, as well as a longer delay between birth and first transfusion, and a decrease in the number of postnatal exchange transfusions, with no notable adverse effects.[66,67]

Pharmacotherapeutic options

In erythropoiesis, sufficient amounts of EPO, folate, iron and vitamin E are essential. To enhance erythropoiesis, administration of these nutrients may have a beneficial effect in the treatment of anaemia in HDFN.[68,69]

EPO

EPO is the principle growth factor responsible for foetal and neonatal erythropoiesis and is primarily developed in the foetal liver.[70] Since over a decade, recombinant human EPO has been applied in small studies and casuistic reports, with different outcomes for the occurrence of anaemia and the need for top-up transfusions in neonates with HDFN.[71-74] Due to limited clinical importance of observed beneficial effects, routine use of EPO is currently not recommended.[75] A well-designed randomised controlled clinical trial of sufficient sample size is required to establish the role of EPO in the treatment of HDFN[69] and will be carried out by our centre in the near future. In this trial, included neonates will be randomised at birth to treatment with darbepoetin alfa (Aranesp®) or conventional care. The intervention group will receive darbepoetin alfa subcutaneously once a week in 10 U/kg/dose for 8 weeks.

Folate

Folate plays a role in the proliferation of erythroblasts during their differentiation.[68] Very limited data is available on its therapeutic efficacy, although a small effect has been seen in the addition of both vitamin B12 (3 microg/kg/day) and folate (100 microg/kg/day) to EPO as treatment in anaemia of prematurity.[76] Due to the prolonged anaemia often seen in HDFN, folate is supplemented in our centre from 3 months postpartum in a dosage of 250 µg/day.

Iron

Iron is required for haemoglobin synthesis by erythroblasts. The use of iron in anaemia associated with HDFN has been studied most extensively in combination with EPO. Administration of EPO without, or with, low iron supplementation can lead to iron deficiency and ineffective erythropoiesis.[69,77] However, neonates with HDFN tend to have an iron overload due to the combination of prolonged haemolysis and treatment with multiple IUTs and erythrocyte transfusions. Based on current knowledge, iron supplementation should be withheld, especially in transfused infants as it is associated with numerous potential adverse effects.[78,79]

Vitamin E

It is unclear whether vitamin E acts as an antioxidant that protects the erythrocyte membrane or as an erythropoietic factor, but shortage of vitamin E might be an additional cause of anaemia.[80] Limited data are available on the therapeutic effects of vitamin E. A pilot study of Pathak et al. showed that oral supplementation at 50 IU/day does not enhance the response of preterm neonates to erythropoietin and iron, compared to placebo.[81]

Management of other complications

BIND and kernicterus

Although rare, BIND and kernicterus are still occurring in the industrialised world. According to rough estimates based on national registration systems, a severely high bilirubin count (>420 µmol/l) occurs in 100-200 infants a year in the Netherlands (i.e. 0.5-1 per 100 live births). Although cases of kernicterus are reported several times a year, precise estimates on the prevalence of kernicterus are not available.[82] Alarmingly, throughout the 1990s, a significant rise in case reports of kernicterus occurred compared to previous years. This rise was attributed to a combination of reduced concern for jaundice in newborns, early discharge with inadequate follow-up and a decreased awareness of the long-term complications of hyperbilirubinaemia. Guidelines were then updated and implemented accordingly.[83] Cornerstone of the management of BIND and kernicterus is timely and adequate treatment of hyperbilirubinaemia. Rather than applying phototherapy and exchange transfusions when necessary, the treatment of hyperbilirubinaemia is a complex interplay of adequate screening of at-risk pregnancies, anticipation of the hyperbilirubinaemic neonate, and the combination of antenatal and postnatal management. The importance of this interplay is also reflected in the nonlinear relationship between neonatal bilirubin levels and the risk of BIND and kernicterus and the wide variety of clinical manifestations, varying between neurodevelopmental difficulties (including developmental delay, cognitive impairment, and disordered executive function), and behavioural and psychiatric disorders.[84]

Thrombocytopenia

In severe HDFN, thrombocytopenia is believed to be caused by increased erythropoiesis as it can suppress the other cell lines and potentially cause leukopenia and thrombocytopenia.[85] A retrospective study in our centre showed a 26% incidence of thrombocytopenia (platelet

count <150·10^9/L) in neonates treated with IUT for RhD haemolytic disease. The occurrence of thrombocytopenia was an independent risk factor for perinatal mortality.[86] A more recent retrospective observational study was carried out in our centre and also showed a similar incidence of 26% of thrombocytopenia in all neonates with HDFN at birth. Severe thrombocytopenia was found in 6% of neonates. Three risk factors were independently associated with thrombocytopenia at birth: treatment with IUT, being born 'small-for-gestational-age' (defined as a birth weight below the 10th percentile) and lower gestational age at birth.[87] Thrombocytopenia in HDFN is usually a self-limiting disease, but treatment with platelet transfusions may be needed if platelets drop below transfusion-threshold.

Iron overload

As mentioned before, neonates with Rh haemolytic disease tend to have an iron overload. This is caused by the combination of prolonged haemolysis and treatment with multiple IUTs and erythrocyte transfusions.[72,73,88] Although iron is essential in early brain development and function, iron overload can have detrimental health effects as well. It causes damage to the liver, heart, and endocrine organs, alters immune response and increases susceptibility to infection.[89] Iron deficiency in the first 3 months of life is very rare in HDFN and has not been described in neonates that received postnatal top-up transfusions. Iron overload occurs in 70% of neonates with HDFN at birth, 50% at the age of 1 month and 18% at the age of 3 months. In neonates with HDFN that received IUTs, ferritin levels were twice as high compared to controls at birth (mean 598 ± 249 µg/l vs 270 ± 111 µg/l, p<.001).[73] The use of iron supplementation in the first 3 months of life in neonates with severe HDFN is strongly discouraged, particularly after IUTs.

Cholestasis

Conjugated hyperbilirubinaemia (cholestasis) has been described in neonates with HDFN[90,91] and can give rise to suspicion of underlying liver disease with additional diagnostic measures. A retrospective study in our centre showed a total incidence of cholestasis in infants with RhD-mediated HDFN of 13% (41/313). Cholestasis in haemolysis might be caused by obstruction of the excretory system by excessive conjugated bilirubin and should primarily be regarded as complication of HDFN. Treatment with one or more IUTs and RhD alloimmunisation were independent risk factors for cholestasis. Cholestasis resolved spontaneously within one week to three months after birth in almost half of the patients, but the authors advocate larger studies to confirm these findings and to determine the exact course and aetiology of cholestasis in HDFN.[92]

Long-term outcome

With the improvements in antenatal and neonatal management over the past decades, survival has significantly improved in HDFN. As mortality rates lower, attention is shifting towards the long-term outcome in the surviving neonates. Adverse prenatal conditions including impaired foetal nutrition and growth can have a profound and long-lasting impact on physical and mental health throughout life, for example increased risk of cardiovascular disease, neuropsychological disorders and metabolic disease.[93,94] The impact of severe foetal and neonatal anaemia, hyperbilirubinaemia and of the (invasive) procedures and treatments foetuses and neonates with HDFN are exposed to is unknown, but seems to justify long-term follow-up studies as current data is limited.[95]

Long-term outcome after IUT

A large long-term follow-up study in our centre, the LOTUS study (Long-Term follow-up after intra-Uterine transfusionS), was performed to determine the incidence of neurodevelopmental impairment (NDI) in children treated with IUT for HDFN (between 1988 and 2008). A total of 291 children were studied at a median age of 8.2 years. NDI was defined as the presence of one or more of the following: cerebral palsy, severe developmental delay, bilateral blindness, and/or deafness. The incidence of severe NDI was 3.1%, comparable to the Dutch normative population (2.3%). The overall rate of NDI was 4.8% (14/291). In a multivariate regression analysis, the number of IUTs, severe neonatal morbidity, parental education and severe prenatal hydrops were independent risk factors associated with NDI.[96]

Health-related quality of life and behavioural functioning in 285 children and adolescents treated with IUT for alloimmune anaemia was recently assessed at our centre.[97] Parents reported lower scores on cognitive functioning in their children aged 6-11 years compared to Dutch norms. Behavioural difficulties were more prevalent than norms and associated with maternal educational level. Overall, in the majority of survivors, long-term outcomes following IUT for alloimmune anaemia appear favourable.

Hypothetically, the chronic anaemia caused by immune haemolysis in the foetus results in the need for increased cardiac output and may lead to myocardial hypertrophy. Limited data show that HDFN treated with IUT may lead to less myocardial mass in childhood, but the long-term cardiovascular consequences in adult life are unknown.[95] However, very recently, a retrospective cohort study by Wallace et al. was published on the cardiac function and cardiovascular risk factors in adults exposed to foetal anaemia and intrauterine transfusion

(n=95), compared to their healthy siblings. The former patients showed smaller left ventricular volumes, increased left ventricular wall thickness, and decreased myocardial perfusion at rest, concluding that cardiovascular development is altered after exposure to foetal anaemia and IUT. It is unknown whether this will have clinical consequences regarding the development of cardiovascular disease as the average age at the time of study was 34 years.[98]

Long-term outcome after immunoglobulins

In a follow-up study of a randomised controlled trial conducted at our centre, we found that the neurodevelopmental outcome in children treated with intravenous immunoglobulins for HDFN was not different from children treated with placebo.[32,99] At a median age of 4 years, NDI was detected in 3% in both the immunoglobulin (1/34) and placebo (1/32) group. After stratification for treatment with or without IUT, similar results were obtained. Standardised long-term follow-up studies with large enough case series and sufficient power are needed to replicate these findings.

Conclusion

Over the years, neonatal management and outcome in HDFN improved significantly. Classical therapies such as intensive phototherapy and exchange transfusions for hyperbilirubinaemia and erythrocyte transfusions for anaemia are well studied, but are still improved upon. Alternative treatments have been suggested such as albumin, phenobarbital, metalloporphyrins, zinc, clofibrate and prebiotics in hyperbilirubinaemia, and EPO, folate, iron and vitamin E in anaemia. These alternative agents have varyingly been studied, but lack evidence to support their use. Although long-term outcome in HDFN seems favourable, neonates with foetal hydrops have a general bad outcome. This emphasises the need for adequate screening and treatment, preferably regulated by nationwide guidelines and monitoring.

Expert Commentary

Our clinical experience, as a tertiary referral centre of Neonatology, is in line with the conclusions reported above. The Leiden University Medical Centre is the national referral centre for HDFN in the Netherlands, which allowed us to develop as an expertise centre and to play an important role nationwide in the care for these neonates. Despite major advances in the field of HDFN, multiple issues still need to be addressed in the future to optimise the postnatal management of neonates with HDFN.

Firstly, it is important to emphasise that major improvements could probably be achieved by strict adherence to guidelines. Clear guidelines on screening and management appear to have significant effect, but have to be evaluated continuously and implemented around the globe. Strict adherence to guidelines is recommended to further eradicate kernicterus and treat affected foetuses and neonates effectively.

Secondly, to further assess the extent of the problems in the management of HDFN, it is important to assess its epidemiologic aspect. We need exact and national numbers on the occurrence of hyperbilirubinaemia, exchange transfusions and kernicterus as well as insight in clinical course and pitfalls in these cases. To better asses these cases, the pathophysiologic mechanisms also have to be better understood. For example, not much is known on BIND and why some infants develop kernicterus and others with an equally high serum bilirubin do not. It is also unclear what the exact mechanism of late anaemia is and why some neonates require top-up transfusions up to three months of life.

Thirdly, pharmacotherapeutic agents should be further researched as potential alternatives for and supplements to classical treatments. As pointed out, the role of albumin supplementation (prior to exchange transfusion), phenobarbital (especially antenatal maternal administration), metalloporphyrins, zinc, clofibrate and prebiotics in hyperbilirubinaemia needs to be clarified. Prospective, double-blinded RCTs are necessary to evaluate outcome and adverse effects, ideally in HDFN specific patient groups. The use of immunoglobulins in Rh haemolytic disease should be re-evaluated on efficacy and safety in the prevention of exchange transfusions. Larger trials are warranted to evaluate the use of EPO, folate and vitamin E in neonates with HDFN in the treatment of postnatal anaemia. Due to the low occurrence rate of HDFN, these trials should be multicentre international studies to reach sufficient power.

Lastly, there is a general lack of long-term follow-up studies in HDFN. Especially complications such as thrombocytopenia, iron overload and cholestasis should be studied in terms of short-term and long-term effects.

The ultimate goal in HDFN is timely detection and treatment of maternal alloimmunisation in an effort to lower the occurrence of hyperbilirubinaemia and to completely eradicate kernicterus, with a prosperous long-term prognosis for all affected neonates.

Five-year view

Detection and management of HDFN has vastly improved in the last decades. Unfortunately, it is still a major cause of hyperbilirubinaemia and, on occasion, kernicterus. The eradication of kernicterus has been a worldwide point of interest and can partly be achieved by adequate management of neonates with HDFN. By strict compliance to national guidelines, HDFN can be timely recognised and treated. It would be desirable in the future to obtain more information of the associations between serum bilirubin levels and neurologic damage, as well as epidemiologic information. Much attention is currently focused at identifying new pharmacological agents in HDFN. Some of these have already been used in clinical practice; others are currently under evaluation or await proper designed trials. Studies are needed on the impact of treatment in the long-term follow-up.

Key issues

- Despite RhD immunoprophylaxis, 1 to 3 in 1000 RhD negative woman develop anti-D antibodies, therefore HDFN is still a relevant condition of which treatment needs to be optimised.
- Guidelines for hyperbilirubinaemia and specifically for this group should be implemented worldwide and strictly followed.
- Intensive phototherapy and exchange transfusions are the treatment of choice in haemolytic hyperbilirubinaemia, although alternative pharmacotherapeutic agents are researched.
- Late anaemia is a common problem in neonates with HDFN and can last up to three months of age. In Rh haemolytic disease the majority of neonates needs at least one to up to 6 top-up transfusions.
- HDFN is associated with postnatal thrombocytopenia, iron overload and cholestasis.
- Limited studies are available on long-term outcome in HDFN, but generally show a favourable outcome in neonates that did not develop kernicterus.

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