Long-term neurodevelopmental outcomes after intrauterine transfusion for alloimmune hemolytic disease of the fetus and newborn

Klink, J.M.M. van; Winter, D.P. de; Oever, R.M. van 't; Tan, R.N.G.B.; Verweij, E.J.T.; Haas, M. de; Lopriore, E.

Best Practice & Research Clinical Obstetrics & Gynaecology 103 (2025) 102680

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics & Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

Long-term neurodevelopmental outcomes after intrauterine transfusion for alloimmune hemolytic disease of the fetus and newborn

Jeanine M.M. van Klink [a,*], Derek P. de Winter [a,b,c], Renske M. van 't Oever [b], Ratna N.G.B. Tan [a], E.J.T. Verweij (Joanne) [b], Masja de Haas [c], Enrico Lopriore [a]

[a] Department of Pediatrics, Division of Neonatology, Willem-Alexander Children's Hospital, Leiden University Medical Center, the Netherlands
[b] Department of Obstetrics, Division of Fetal Medicine, Leiden University Medical Center, Leiden, the Netherlands
[c] Department of Immunohematology Diagnostics, Sanquin Diagnostic Services, Amsterdam, the Netherlands

A B S T R A C T

The mainstay for the management and treatment of severe alloimmune hemolytic disease of the fetus and newborn (HDFN) is based on timely detection and intrauterine transfusions (IUT) in cases with severe fetal anemia. Although long-term neurodevelopmental outcomes in children born following IUT for HDFN are nowadays considered 'favorable', reliable long-term outcome data remain scarce. Several studies suggests that children with a history of severe hydrops, cerebral injury, and preterm birth are at increased risk for neurodevelopmental impairment (NDI). However, follow-up studies are limited by small sample sizes, the absence of control groups, inconsistent criteria for neurodevelopmental outcome, and a lack of standardized developmental assessments. The prevalence of NDI in the literature to date is reported to be around 5 % but varies from 0 % to 18.8 %, depending on the studied cohort. When interpreting the data and extrapolating conclusions to the general population, consideration must be given to the fact that the majority was born moderate to late preterm, a population inherently at increased risk for adverse neurodevelopmental outcomes. Future research should incorporate more subtle impairments, as mild to moderate cognitive deficits, learning problems and socioemotional and behavioral difficulties can substantially impact long-term care needs and socioeconomic potential. A deeper understanding of the effects of fetal anemia and IUT on neurodevelopmental trajectories will enable effective screening and the implementation of timely, targeted interventions to optimize developmental outcomes for children at risk. In addition, the impact of the complicated pregnancy on the wellbeing of parents and the child-caregiver relationship is an underexposed and understudied outcome measure. With the introduction of new non-invasive therapies, international collaborative efforts are of utmost importance to reliably investigate not just survival or neonatal outcome but also long-term neurodevelopment and wellbeing of children and caregivers.

1. Introduction

Alloimmune hemolytic disease of the fetus and newborn (HDFN) is a condition caused by maternal alloantibodies targeting fetal red blood cells (RBCs), leading to severe morbidity and mortality in the fetus and newborn [1]. Effective screening programs have enabled timely prevention and intervention, resulting in a significant decline in the incidence of the disease over the past decades [2]. Intrauterine intravascular transfusions (IUTs) have, since their introduction in 1981, developed into the cornerstone for the treatment of severe fetal anemia [3]. In experienced centers, the perinatal survival rate nowadays exceeds 95 %. Despite these advancements, a prolonged state of profound anemia or severe fetal hydrops may result in cerebral injury and eventually long-term

* Corresponding author. Department of Pediatrics, Division of Neonatology, Willem-Alexander Children's Hospital, Leiden University Medical Center, PO box 9600 2300 RC Leiden, the Netherlands.
E-mail address: j.m.m.van_klink@lumc.nl (J.M.M. van Klink).

https://doi.org/10.1016/j.bpobgyn.2025.102680
Received 20 May 2025; Received in revised form 5 August 2025; Accepted 19 October 2025
Available online 25 October 2025

neurodevelopmental impairment (NDI) [4].

The aim of this review is to summarize the neurodevelopmental outcomes of children treated with IUTs for alloimmune HDFN as reported in the literature to date. Risk factors for adverse outcomes will be highlighted as well as recommendations for future research, clinical practice and care.

2. Methods

Medline, ClinicalTrials.gov and EMBASE were searched using the MESH terms: Fetal erythroblastosis, intrauterine, time, prognosis, epidemiologic studies, human development, neurobehavioral manifestations and morbidity. The search was limited to English language articles and included the period from 1981 to January 2025. All reference lists of primary articles and reviews were examined to search for additional references. Then, a manual search of identified articles was conducted. The following inclusion criteria were applied: children and adolescents treated with intrauterine intravascular transfusion for Rhesus or Kell mediated HDFN, assessment of neurodevelopmental, socio-emotional and/or behavioral outcomes and the conduct of statistical tests. Case reports, dissertations, reviews, qualitative studies, book chapters, guidelines and commentaries were excluded. Two independent reviewers extracted and tabulated the data to assess the methodological quality of the included studies (JK and EL). Data on neurodevelopmental outcomes, visual or hearing impairments, socio-emotional, school and/or behavioral functioning were extracted from the data as well as risk factors for an adverse outcome. Data from individual studies were pooled within subgroups defined by outcome [5]. The primary outcome of interest was the incidence of NDI subdivided into mild to moderate and severe. Severe NDI was defined as at least one of the following: severe neurological dysfunction or cerebral palsy $\geq$ grade 2 according to the Gross Motor Function Classification System (GMFCS) [6], cognitive impairment (psychometric test scores below 70 or -2 SD), severe visual and/or hearing impairment. Mild to moderate NDI was defined as psychometric test scores below 85 or -1 SD, minor neurological dysfunction or CP grade 1 and/or mild visual or hearing impairment.

3. Results

Eleven studies met the inclusion criteria. The main findings of each follow-up study are summarized below, in chronological order.

3.1. Long-term neurodevelopment after IUTs for HDFN

The first study on neurodevelopmental outcome following IUT for HDFN was published in 1993 b y Doyle and colleagues (Australia) [7]. At 2 years of age, 38 survivors had a psychological assessment, including the mental development index of the Bayley and/or Griffiths scales, and a standardized neurological examination. Two children (5.3 %, 2/38) were diagnosed with severe impairment; one child had severe developmental delay (more than 2 SD below the mean) and multiple minor motor seizures and one child was diagnosed with CP (spastic hemiplegia) with a Griffiths developmental quotient of 81. One (2.6 %) child had mild motor disability and a mental development index of 72. The rate of disability was not significantly different compared with a normal birth weight cohort. According to the authors, in neither case were complications of an IUT the likely explanation for the disability. The two children with severe NDI were diagnosed with West syndrome at four months of age and severe cerebral injury, respectively. The child who developed CP had severe fetal hydrops and neonatal morbidities including respiratory distress syndrome requiring mechanical ventilation, bilateral intraventricular hemorrhages, three exchange transfusions and phototherapy (highest serum bilirubin level 358 mmol/L). The remaining 35 children (92.1 %) had no disability. The Bayley mental development index was not related to fetal hemoglobin level, gestational age at first IUT or hydrops at first IUT.

The study group of Stewart and colleagues (United Kingdom (UK), 1994) comprised eight children treated with IUT for alloimmune hemolytic disease between 1986 and 1988 compared to eight contemporary controls matched for gestational age [8]. The controls were diagnosed with alloimmune hemolytic disease and treated with postnatal exchange transfusions but no IUT. The Cattell infant intelligence test and a neurological examination revealed no differences between the groups (mean 97.6 (95 % confidence interval (CI) 87.2–108.1) versus 101.1 (91.2–111.1)) nor the population as a whole. At the time of examination none of the children had any motor disorder, all were making satisfactory developmental progress. However, the small sample size ($n = 8$) lacks the statistical power to detect meaningful differences. Additionally, a follow-up period of 18–24 months, is too short to reliably assess conditions such as CP or severe cognitive impairment.

Janssens and colleagues (The Netherlands, 1997) investigated the neurodevelopmental outcome of 69 children treated between 1987 and 1993 with IUTs for HDFN in comparison with a high-risk and a healthy control group [9]. Neurodevelopment was assessed with Gesell, Touwen and the Denver Developmental Screening Test [9]. Follow-up time ranged from 6 months to 6 years, and 35 % (24/69) had a history of hydrops. The total number of children with severe NDI was 10.1 % (7/69), which compared favorably with a group of high-risk, very low birth weight children (18 %), and less favorably with a healthy control group (6 %; no p-values reported). Mild NDI was observed in six children (8.7 %). The likelihood of severe neurological dysfunctions was significantly higher in the presence of perinatal asphyxia ($p < 0.05$) and with a lower cord hemoglobin level at birth ($p = 0.03$).

In a prospective, observational study of Hudon and colleagues (United States of America (USA), 1998), neurodevelopment was assessed using auditory evoked-response tests in 21 neonates ($n = 1$ with bilateral deafness), the Gesell Developmental Schedules between 9 and 18 months of age in 22 children (all within normal range, 101.9 ± 9.5) and the McCarthy Scales of Children's Abilities between 36 and 62 months in 11 children (all within normal range, 107.6 ± 9.4) [10]. One case of severe bilateral deafness (1/21; 4.8 %) and 1 case (1/22; 4.6 %) of right spastic hemiplegia were diagnosed. Regression analysis revealed no correlation between the

developmental outcome and gestational age at first IUT (mean 26.4 ± 3.7 w0eeks), gestational age at birth (mean 35.6 ± 2.2 weeks) or the severity of HDFN expressed as median number of IUTs (4, range 1–8), lowest fetal hematocrit (20.2 % ± 7.8 %), peak fetal bilirubin (7.1 ± 2.1 mg/dL) and hydrops fetalis (18/40; 45 %). One of the major limitations of this study is the lack of follow-up for all children until 62 months of age (29/40; 72.5 % loss to follow-up).

Neurodevelopmental outcome at age 6 was uneventful in the study cohort of Grab and colleagues (Germany, 1999) including 35 children treated with IUT, of which 7 (20 %) with a history of immune hydrops [11]. The authors report that the fetuses with hydrops tended to have higher perinatal mortality and a significantly increased risk of preterm delivery ($p = 0.03$). Unfortunately no psychometric testing was performed; the study relied on hospital charts and questionnaires sent to the family physicians or pediatricians.

Farrant and colleagues al. (New Zealand, 2001) followed 36 children treated with IUT for HDFN. The authors did not provide information regarding the presence or absence of hydrops. One child (1/36; 2.8 %), born at 28 weeks following fetal death of the monochorionic co-twin, was diagnosed with IVH and ventricular dilatation on the left side, CP and severe developmental delay at two years of age [12]. Two other children had abnormal cranial ultrasounds, but no other child had NDI. However, no formal psychometric assessments were conducted and the age of the children at follow-up was not specified.

The study group of Harper and colleagues (USA, 2006) investigated the long-term neurodevelopmental outcome of 16 immune hydrops survivors treated with IUT between 1985 and 1995 [13]. At a mean age of 10 years, neurodevelopment was severely affected in 18.8 % (3/16) of the children including, sensorineural hearing loss following kernicterus ($n = 1$), static encephalopathy and CP ($n = 1$) and severe cognitive impairment with neuropsychological test scores below 70 ($n = 1$). According to the authors these sequelae had other likely explanations that is, iatrogenic preterm delivery, procedural complications, and fetal alcohol and drug exposure, respectively. Of note, 37.5 % (6/16) of the children had a minor impairment including articulation disturbance, unilateral conductive hearing loss, extroversion of the left foot, bilateral toe-walking, slight clumsiness and a right esophoria. There were no relationships detected among gestational age at hydrops, number of IUTs, Apgar score, number of postnatal red blood cell transfusions, and neuropsychological outcomes. Although the mean test scores, obtained with the Wide Range Assessment of Visual Motor Ability, Memory and Learning, and the Differential Ability Scales, were lower than those of their sibling control subjects ($n = 8$), all scores were in the same clinical-interpretive range (i.e., average). Despite the fact that the authors included a control group ($n = 8$), the study group was too small to demonstrate statistical differences.

Weisz and colleagues (Israel, 2009) obtained their long-term neurodevelopmental outcome data from parents of 40 children treated with IUT for fetal anemia due to alloimmunisation [14]. Information on motor, cognitive, language and behavioral development (hyperactivity and inattention) was gathered using a computerized questionnaire. The need for physiotherapy, occupational therapy, speech therapy and psychological treatment was also reported. The authors characterized normal motor development by reaching the defined milestones at the appropriate age e.g., sitting upright by 8 months and standing by 12 months. Normal cognitive development was defined by speaking single words by the age of 12 months and short sentences by 24 months as well as studying in the formal education system. Fifteen percent (6/40) of children did not reach the predefined motor milestones by the age of 1 year. One or more paramedical treatments were required for 41 % (14/34) of the children between the ages 1–9 years. Abnormal cognitive development was reported in 13.5 % (5/37) of the children aged ≥1 year. All 26 children who had reached the age of mandatory formal education (≥ age 4) attended normal schools without the need of special assistance. Neurodevelopmental outcomes did not differ between children with a history of severe versus mild-moderate fetal anemia.

The largest follow-up study, from our center (The Netherlands, 2025), concerns a 35-year single-center, retrospective analysis of neurodevelopmental outcomes among 363 children treated with IUT for HDFN [15–17]. Follow-up data were aggregated from three previously published studies on long-term outcomes in HDFN performed at the Leiden University Medical Center (LUMC) including LOTUS [15], LIVIN [16] and EPO-4-Rh [17] as well as data from neurodevelopmental assessments as part of routine follow-up care at the LUMC outpatient clinic. We demonstrated that children with severe hydrops at first IUT were 3.36 times (95 % CI 1.07–10.53) more likely to have NDI, which was observed in 5.0 % (18/363) of the children [15–17]. Every additional week in gestational age at birth was associated with a 29.6 % decrease in the likelihood of NDI (12.1–43.7), being the lowest when gestational age was over 37 weeks. Children with NDI showed a greater disease severity compared to those without NDI as reflected by a lower gestational age at first IUT, lower hemoglobin at first IUT, a higher frequency of severe hydrops at IUT, the need for more IUTs, and a lower gestational age at birth. Median full scale IQ score was 101 (interquartile range 91–110) at a median age of 6.7 years (range 2.0–16.8). Severe cognitive impairment (IQ score below 70) was detected in 2.5 % (9/362) and mild to moderate cognitive impairment (score below 85) in 14.6 % (53/362). In comparison, and according to the normal distribution of IQ scores, 2.3 % of the general population has an IQ score below 70 and 16 % below 85. CP was diagnosed in 2.5 % (9/363) of the children and bilateral deafness in 0.8 % (3/363).

3.2. Patient reported outcome measures of health related quality of life, behavioral functioning and school performance

Using patient reported outcome measures (PROMS), our research group (2015) evaluated health related quality of life (HRQoL), social-emotional and behavioral outcomes in 285 children and adolescents treated with IUT for HDFN between 1988 and 2008 at a mean age of 10.5 years (range 3–21.5 years) [18]. Compared to Dutch norm data, parents reported lower HRQoL scores in the cognitive domain for their children aged 6–11 years ($p < 0.00$). Both children and adolescents did not self-report more difficulties in their cognitive functioning compared to norms. All other parent-, child- and adolescent-rated HRQoL domains, including physical, motor, autonomy, social, positive and negative emotions, were not different from norms. Using the Strengths and Difficulties Questionnaire (SDQ), parents reported behavioral difficulties in the clinical range for 15 % (37/246) of the children aged 3–16 years, which was significantly higher compared to the 10 % instrument norm.

In a more recent study conducted by our research group (2021), school performance and behavioral functioning of 70 children

(aged 5–12 years) treated with IUTs for HDFN between 2008 and 2015 were compared to the general Dutch population [19]. School performance levels in the HDFN group, including reading comprehension, spelling and mathematics according to the Dutch National Pupil Monitoring System, were similar to Dutch norm data. None of the children attended special-needs education. However, grade repetition occurred more often in the HDFN group that is, in 13/70 (19 %) of cases versus 10.3 % in the general Dutch population ($p = 0.020$). The incidence of behavioral problems as reported by parents using the Child Behavioral Checklist (CBCL) was similar to the Dutch norm data. The teachers reported fewer behavioral difficulties in the HDFN group, as assessed by the Teacher Report Form (TRF).

3.3. *Interpretation and discussion*

When the results from the follow-up studies included for review are pooled, the overall rate of severe NDI is 5.1 % (32/627), the rate of CP of any grade is 3.0 % (16/536) and mild to moderate NDI is 14.2 % (72/508) (Fig. 1). Bilateral deafness was diagnosed in 0.8 % (5/627) children. However, these figures should be interpreted with caution, as the studies described exhibit significant variability in design, the (non-)use of psychometric and/or neurological tests, differing definitions and grading of impairment, follow-up duration and the size of the study populations. Moreover, when interpreting the data and extrapolating conclusions to the general population, consideration must be given to the fact that the majority of the children treated with IUTs was born moderate to late preterm, that is 32–36 weeks gestational age. Children born moderate to late preterm are inherently at increased risk for poor neurodevelopmental outcomes [20]. According to a British cohort study, 6.9 % of children born between 32 and 36 weeks exhibit moderate to severe NDI at

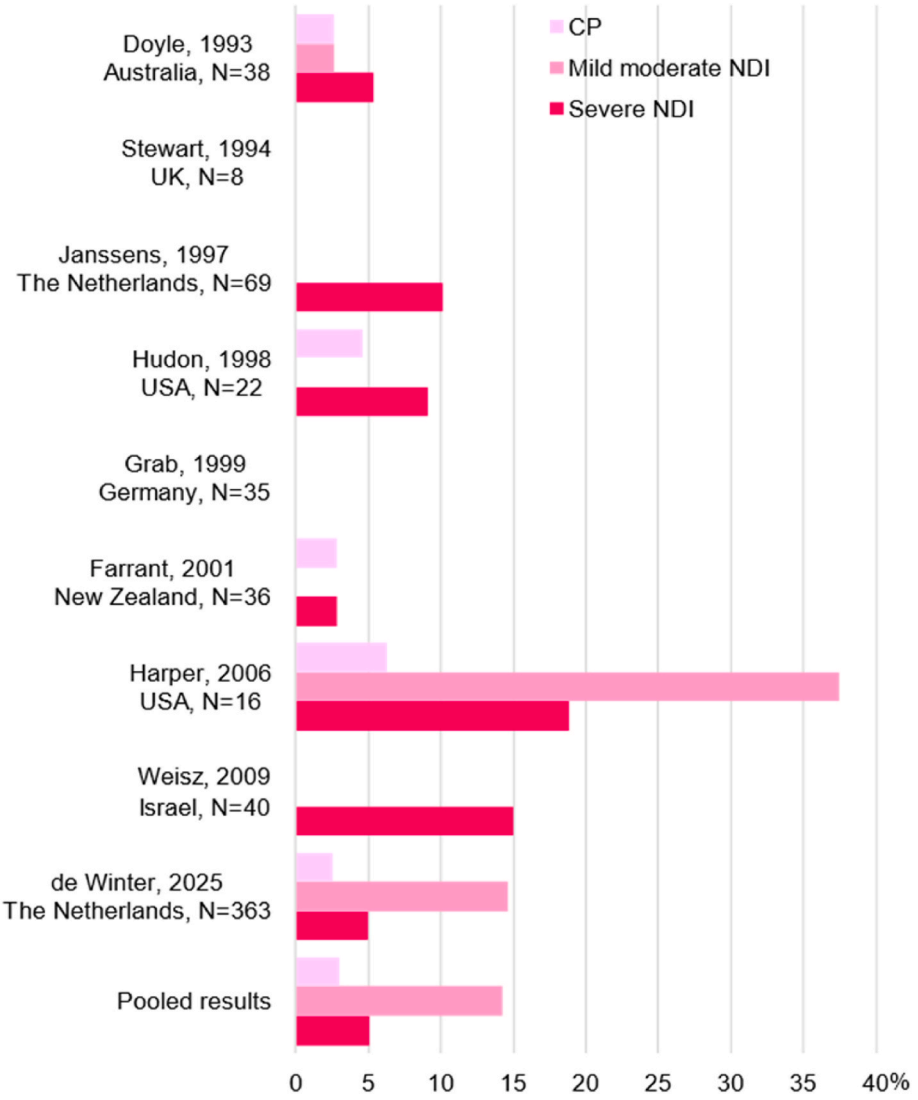

Fig. 1. Pooled outcomes of the included studies for review.

two years of age, compared to 2.5 % among term-born children [21]. A comprehensive meta-analysis showed that the prevalence of CP increases significantly with decreasing gestational age that is, 0.1 % in born children at term, 0.7 % at 32–36 weeks, 6.2 % at 28–31 weeks and 14.6 % at 22–27 weeks [22]. In this light, the number of children with CP, of any grade, in the included studies for review seems increased. When we take a closer look at the data of the children diagnosed with CP (n = 16), the majority had a history of hydrops (n = 9), perinatal asphyxia (n = 3) and/or severe cerebral injury (n = 3). A significant body of research shows a similar association between cognitive scores and premature birth, with evidence of a dose-response relationship with gestational age in weeks [23]. The magnitude of this decrease varies across studies but ranges between 0.9 and 2.3 IQ points per week, with more pronounced effects observed at lower gestational ages [24]. Upon closer examination of the five children with bilateral deafness in the included studies for review, all were born with hydrops, received phototherapy with bilirubin levels above the exchange transfusion level. One child had a diagnosis of bilirubin induced neurological disorder (BIND). Bilateral hearing loss is observed in approximately 1.7 % of all NICU neonates screened in the Netherlands and in up to 0.09 % of healthy Dutch newborns [25].

Important risk factors for severe NDI were HDFN severity (expressed by severe hydrops, lower gestational age at first IUT, lower hemoglobin at first IUT and/or the need for more IUTs), low gestational age at birth, low birth weight, lower cord hemoglobin at birth, perinatal asphyxia and/or severe cerebral injury. Nowadays, effective screening programs have facilitated timely prevention and intervention, leading to a significant decline in the incidence of HDFN, particularly in cases complicated by severe hydrops, over the past decades. Despite their proven efficacy, an international cohort study, including 31 expert centers from 22 countries has shown that such screening programs are not yet universally implemented [2]. Consequently, (unborn) children continue to die unnecessarily from this preventable and treatable condition. The dissemination of knowledge and the availability of appropriate resources are therefore critical to the global prevention and effective management of severe HDFN [2]. From the studies included for review, no decline in NDI could be identified probably due to the lack of psychometric and/or sensorineural tests, different definitions of impairment in the majority of studies as well as large lost-to follow-up rates.

The significance of long-term follow-up studies lies not only in the evaluation of treatment outcomes but also in providing evidence-based counselling for prospective parents. When a center chooses to initiate in utero treatment— acknowledging that a proportion of fetuses develop long-term morbidity—it is responsible that survivors receive appropriate follow-up care [26]. Consequently, long-term follow-up should be considered an integral component of any fetal therapy program. Despite their critical importance, long-term follow-up studies are associated with considerable practical and logistical challenges. Follow-up studies are resource-intensive, requiring sustained financial and organizational support, which can impede their implementation. Maintaining an infrastructure for longitudinal research (e.g. trained staff and databases) is costly. Other key barriers include the transition of care, from a fetal therapy center to local pediatric specialists, and the coordination of standardized neurodevelopmental assessments. Such evaluations must be conducted by trained pediatricians, child physiotherapists, research or specialist nurses and psychologists using validated tools with adequate psychometric properties. Furthermore, ensuring the completeness and quality of data collection and analysis is essential for generating reliable outcomes. A standardized framework for assessing long-term outcomes—encompassing neuro-developmental, functional, and psychological domains—remains lacking. Nevertheless, the investments associated with a follow-up program are minimal in comparison to the substantial expenses and logistical challenges involved in the management of HDFN and the treatment of severe fetal anemia with IUTs.

Only two studies, by our research group hence from the same center in the Netherlands, reported on socio-emotional, behavioral and school functioning [18,19]. Parents reported lower cognitive scores for their children at primary school age. Grade repetition was reported more often and behavioral difficulties ranged from 5 % to 15 % depending on the questionnaire used. A Dutch community-based longitudinal study, reported emotional and behavioral problems in 14.6 % (118/809) of children born moderate to late preterm (32–36 weeks) at the start of primary school [27]. These problems negatively impact the child's HRQoL and are associated with an increased risk of grade retention, the need for special educational support, and long-term adverse outcomes, including difficulties in employment and interpersonal relationships [28].

The majority of studies included in this review were conducted in high-income countries, where sufficient resources are available for antenatal screening, prophylaxis, preventive measures, and referral to specialized fetal therapy centers [29]. In contrast, long-term outcome data on pregnancies complicated by HDFN in low- and middle-income settings remain scarce to non-existent. This well-recognized bias in outcome reporting highlights a significant evidence gap and underscores the necessity for international collaboration to comprehensively assess the global burden of HDFN. With the introduction of new non-invasive therapies, including Nipocalimab [30], international collaborative efforts are of utmost importance to reliably investigate not just survival or neonatal outcome but also long-term neurodevelopment and wellbeing of children and their caregivers. For all parents, a pregnancy complicated by HDFN and treatment with IUTs is a highly stressful experience, increasing their risk of developing mental health problems. Appropriate guidance, psychoeducation and systematic screening for difficulties during pregnancy, after birth or discharge home, at six months and at structured follow-up points are essential to facilitate early identification of psychological distress, including post-traumatic stress and attachment problems, and ensure timely support and intervention. Since good care for the parents translates directly into good care for the child.

3.4. Practice points

- For all parents, screening for psychosocial difficulties during pregnancy, after birth or discharge to home, at 6 months and at structured follow-up time-points by a psychologist or specialist nurse.
- Where psychosocial difficulties are identified, further assessment is required (by a psychologist) and referral or signposting for additional social or mental health support.

- Implementation of standardized PROMS for parents and children at predetermined time points, for example 6 and 12 months, 2, 5 and 8 years.
- In experienced fetal therapy centers: Tailored neurodevelopmental assessment, guided by a psychologist or suitably qualified professional, in high-risk children that is, with a history of severe hydrops, premature birth (below 30 weeks), small for gestational age at birth (below the 10th percentile) and/or severe cerebral injury.
- In starting, less experienced or low volume fetal therapy centers: Tailored neurodevelopmental assessment, guided by a psychologist or suitably qualified professional, for all children treated with IUT.

3.5. Research agenda

- Structured long-term neurodevelopmental follow-up studies following IUT and exchange transfusions for severe fetal anemia in all fetal therapy centers with:
  - o Uniform, well described outcome criteria and measures,
  - o Incorporation of mild to moderate impairments,
  - o A focus on mental wellbeing of parents/caregivers.
- Future follow-up studies should ideally be set in an international setting.

CRediT authorship contribution statement

Jeanine M.M. van Klink: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Derek P. de Winter:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Renske M. van 't Oever:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Ratna N.G.B. Tan:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Data curation. **E.J.T. Verweij:** Writing – review & editing, Resources, Methodology, Conceptualization. **Masja de Haas:** Writing – review & editing, Resources, Methodology, Conceptualization. **Enrico Lopriore:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors have no conflicts of interest.

References

[1] De Winter DP, et al. History and current standard of postnatal management in hemolytic disease of the fetus and newborn. Eur J Pediatr 2023;182(2):489–500.
[2] de Winter DP, et al. Variations in antenatal management and outcomes in haemolytic disease of the fetus and newborn: an international, retrospective, observational cohort study. Lancet Haematol 2024;11(12):e927–37.
[3] Zwiers C, et al. Intrauterine transfusion and non-invasive treatment options for hemolytic disease of the fetus and newborn - review on current management and outcome. Expert Rev Hematol 2017;10(4):337–44.
[4] van Klink JM, et al. Long-term neurodevelopmental outcome after intrauterine transfusion for fetal anemia. Early Hum Dev 2011;87(9):589–93.
[5] Deeks JJA, D G, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: M.D.S, Egger G, Altman DG, editors. Systematic reviews in health care: meta-Analysis in context. London, UK: BMJ Books; 2001. p. 6–12.
[6] Palisano R, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol 1997;39(4):214–23.
[7] Doyle LW, et al. Sensorineural outcome at 2 years for survivors of erythroblastosis treated with fetal intravascular transfusions. Obstet Gynecol 1993;81(6):931–5.
[8] Stewart G, et al. Developmental outcome after intravascular intrauterine transfusion for rhesus haemolytic disease. Arch Dis Child Fetal Neonatal Ed 1994;70(1):F52–3.
[9] Janssens HM, et al. Outcome for children treated with fetal intravascular transfusions because of severe blood group antagonism. J Pediatr 1997;131(3):373–80.
[10] Hudon L, et al. Long-term neurodevelopmental outcome after intrauterine transfusion for the treatment of fetal hemolytic disease. Am J Obstet Gynecol 1998;179(4):858–63.
[11] Grab D, et al. Treatment of fetal erythroblastosis by intravascular transfusions: outcome at 6 years. Obstet Gynecol 1999;93(2):165–8.
[12] Farrant B, Battin M, Roberts A. Outcome of infants receiving in-utero transfusions for haemolytic disease. N Z Med J 2001;114(1139):400–3.
[13] Harper DC, et al. Long-term neurodevelopmental outcome and brain volume after treatment for Hydrops fetalis by in utero intravascular transfusion. Am J Obstet Gynecol 2006;195(1):192–200.
[14] Weisz B, et al. Outcome of severely anaemic fetuses treated by intrauterine transfusions. Arch Dis Child Fetal Neonatal Ed 2009;94(3):F201–4.
[15] Lindenburg IT, et al. Long-term neurodevelopmental outcome after intrauterine transfusion for hemolytic disease of the fetus/newborn: the LOTUS study. Am J Obstet Gynecol 2012;206(2):141 e1–8.
[16] van Klink JM, et al. Immunoglobulins in neonates with rhesus hemolytic disease of the fetus and newborn: long-term outcome in a randomized trial. Fetal Diagn Ther 2016;39(3):209–13.
[17] de Winter DP, et al. Long-term neurodevelopmental outcomes in infants with haemolytic disease of the newborn treated with darbepoetin. Lancet Haematol 2025;12(3). e169-e170.
[18] van Klink JM, et al. Health-related quality of life and behavioral functioning after intrauterine transfusion for alloimmune anemia. J Pediatr 2015;167(5):1130–5 e2.
[19] Ree IMC, et al. School performance and behavioral functioning in children after intrauterine transfusions for hemolytic disease of the fetus and newborn. Early Hum Dev 2021;157:105381.
[20] Cheong JLY, et al. Neurodevelopment at age 9 years among children born at 32 to 36 weeks' gestation. JAMA Netw Open 2024;7(11):e2445629.
[21] Johnson S, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. Arch Dis Child Fetal Neonatal Ed 2015;100(4):F301–8.

[22] Himpens E, et al. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: a meta-analytic review. Dev Med Child Neurol 2008; 50(5):334–40.
[23] Kerr-Wilson CO, et al. Meta-analysis of the association between preterm delivery and intelligence. J Public Health 2012;34(2):209–16.
[24] Twilhaar ES, et al. Cognitive outcomes of children born extremely or very preterm since the 1990s and associated risk factors: a meta-analysis and meta-regression. JAMA Pediatr 2018;172(4):361–7.
[25] Korver AM, et al. Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. JAMA 2010;304(15):1701–8.
[26] van Klink JM, et al. Long-term neurodevelopmental outcome in monochorionic twins after fetal therapy. Early Hum Dev 2011;87(9):601–6.
[27] den Haan PJ, et al. Risk factors for emotional and behavioral problems in moderately-late preterms. PLoS One 2019;14(5):e0216468.
[28] van Baar AL, et al. Functioning at school age of moderately preterm children born at 32 to 36 weeks' gestational age. Pediatrics 2009;124(1):251–7.
[29] de Winter DP, et al. Hemolytic disease of the fetus and newborn: systematic literature review of the antenatal landscape. BMC Pregnancy Childbirth 2023;23(1): 12.
[30] Moise Jr KJ, et al. Nipocalimab in early-onset severe hemolytic disease of the fetus and newborn. N Engl J Med 2024;391(6):526–37.