Monitoring and Management of Hemolytic Disease of the Fetus and Newborn Based on an International Expert Delphi Consensus

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PII: S0002-9378(24)01130-X

DOI: https://doi.org/10.1016/j.ajog.2024.11.003

Reference: YMOB 15928

To appear in: *American Journal of Obstetrics and Gynecology*

Received Date: 8 September 2024

Revised Date: 6 November 2024

Accepted Date: 7 November 2024

Please cite this article as: Mustafa HJ, Sambatur EV, Shamshirsaz AA, Johnson S, Moise Jr KJ, Baschat AA, Verweij EJT(J), Javinani A, Kilby MD, Lopriore E, Rose R, Devlieger R, Snowise S, Sachs UJ, Khalil A, On behalf of the HDFN Delphi Working Group, Monitoring and Management of Hemolytic Disease of the Fetus and Newborn Based on an International Expert Delphi Consensus, *American Journal of Obstetrics and Gynecology* (2024), doi: https://doi.org/10.1016/j.ajog.2024.11.003.

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The authors report no conflicts of interest.

No external funding has been received for this study.

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Abstract word count: 288

Full-text word count: 2980

Table numbers: 6

Figure numbers: 1

Condensation Page

Tweetable statement: The Delphi method facilitated the development of a consensus-based clinical workflow informing the clinical management of pregnancies at risk or affected by red cell alloimmunization.

Short title: Haemolytic Disease of the Fetus and Newborn Delphi

AJOG at a Glance

Why was this study conducted? To reach a Delphi-generated international expert consensus on the monitoring and the management of hemolytic disease of the fetus and newborn.

What are the key findings?

- The expert panel agreed on using cell-free DNA to determine fetal genotype in pregnancies with red blood cell alloimmunization
- Antibody titers of ≥16 are considered a critical threshold requiring fetal monitoring via ultrasound in non-anti-Kell alloimmunized pregnancies.
- The earliest middle cerebral artery (MCA) Doppler ultrasound assessment is to be started at 16 weeks gestation, to be performed weekly, and to be continued until delivery.
- Intravenous immunoglobulin infusions are to be considered in pregnancies with prior fetal or neonatal death due to hemolytic disease or a history of intrauterine transfusion before 24 weeks in a previous pregnancy. Consensus related to indications, gestational age at initiation, MCA Dopplers, and dosage of infusions was reached.
- The timing of the second and third intrauterine transfusion (IUT) can be determined by a combination of weekly MCA Dopplers and the calculated rate of hemoglobin decline,

which is approximately 0.9 g/dL per day in 10-14 days after the first transfusion and 0.6 g/dL per day in 2-3 weeks after the second transfusion. 78.5% of participating experts perform IUT until a gestational age of $35^{0/7}$ to $35^{6/7}$ weeks.

- Delivery timing in alloimmunized pregnancies in which no IUT was indicated to be between $37^{0/7}$ - $38^{6/7}$ weeks. However, if IUT was performed then timing to be two to three weeks following the last transfusion.
- Regarding postnatal management, the thresholds for phototherapy and exchange transfusion are to be determined by the American Academy of Pediatrics (AAP) 2022 guidelines. Anemia labs should be investigated prior to discharge in all neonates of pregnancies complicated with alloimmunization. If IUT was required, anemia labs should be repeated in one week following discharge if the initial labs were normal.
- The panel agreed that the hemoglobin cut-off level to consider transfusion following hospital discharge is 7 g/dL and the newborns need to be monitored frequently until 2-3 months of age.

What does this study add to what is already known?

The findings of this Delphi can be used to create a standardized approach in the monitoring and management of pregnancies and newborns affected by maternal alloimmunization, particularly related to aspects where clinical and research knowledge gaps exist.

ABSTRACT

The study aimed to develop structured, expert-based clinical guidance on the prenatal and postnatal management of hemolytic disease of the fetus and newborn. A Delphi procedure was conducted among an international panel of experts in fetal medicine, neonatology, and hematology. Experts were selected based on their expertise, relevant publications, and affiliations. The domains were (i) prenatal workup, (ii) prenatal monitoring and management, (iii) intrauterine transfusion, (iv) delivery, and (v) postnatal management. The pre-defined cut-off for consensus was ≥70% agreement. One hundred-seven experts representing 25 countries across six continents completed the first round, and 100 (93.5%) completed the subsequent rounds. 75.3% agreed on using cfDNA to determine fetal antigen status, particularly for RhD, Kell, and Rhc antigens. The critical titer, requiring fetal monitoring via ultrasound, is considered when the threshold of ≥16 is for non-Kell antigens. 70.0% agreed on the use of maternal IVIg in pregnancies with prior intrauterine transfusion (IUT) <24 weeks or fetal/neonatal death due to HDFN. The minimum GA for IUT is 16 to 18 weeks, and the maximum is $35^{0/7}$ to $35^{6/7}$ weeks. Postnatal management consensus was reached for the following: anemia labs should be investigated in the affected neonates before hospital discharge (92.0% agreement), and if they received IUT, the labs should be repeated within one week of discharge (84.0% agreement). 96.0% agreed that exchange transfusions should be centralized in hospitals with sufficient exposure and experience, and 92.0% agreed that the hemoglobin cut-off level to consider transfusion following hospital discharge is 7g/dL, and the newborns need to be monitored until 2-3 months of age (96.0% agreement).

Keywords: Fetal; Erythroblastosis; Pregnancy; Delphi; Consensus, IVIg, IUT, anemia, hemolytic disease, cordocentesis, PUBS

INTRODUCTION

Red blood cell (RBC) alloimmunization has historically been an unknown and tragic cause of perinatal death. Still, its trajectory has significantly changed with the worldwide implementation of prenatal screening and the administration of Rho(D) Immune Globulin (RhIG)[1]. However, the RhD antigen is not the only RBC antigen that can cause alloimmunization; numerous other antigens can cause hemolytic disease of the fetus and newborn (HDFN)[2,3]. The mortality and morbidity of HDFN in the post-RhIG era are heavily determined by prenatal screening, monitoring, and management, which are shown to be directly related to the socioeconomic status of the countries[4].

The perinatal mortality of HDFN has been reported to be 20-25%, meaning that one out of five pregnancies diagnosed with RBC alloimmunization can still lead to the perinatal death of the fetus or newborn[4]. Moreover, it is estimated that nearly one-third of the patients are diagnosed with hydrops at the time of diagnosis[4]. This significantly highlights the importance of screening in at-risk populations, the optimal prenatal management of pregnancies diagnosed with fetal anemia, and the meticulous postnatal care of affected newborns.

The prenatal screening, diagnosis, and monitoring of patients with HDFN have been addressed in several clinical guidelines from different scientific societies[5,6]. These include strategies for implementing and interpreting screening antibodies, fetal genotyping, middle cerebral artery (MCA) Doppler evaluation, and fetal blood sampling. Regarding the treatment of patients with fetal anemia, intrauterine transfusion (IUT) has been the standard of care, but maternal administration of intravenous immunoglobulin (IVIg) has also been reported[7]. The postnatal care of affected newborns has also been the subject of debate among neonatologists and hematologists.

The Delphi methodology has been recommended as a qualitative method for reaching a consensus on topics where existing literature cannot quantitatively address unresolved challenges[8]. This method has been widely used in fetal medicine, as the rarity of conditions and ethical challenges make it unlikely to run clinical trials to resolve controversies[9-11]. Accordingly, in the current study, we aim to address the controversies in screening, monitoring, and prenatal and postnatal management of HDFN with consensus from a multidisciplinary and international panel of experts.

Delphi Methodology and Participants

Delphi design

The Delphi methodology was used. This methodology consists of scoring a series of structured statements that are revised, fed back to the participants, and repeated in multiple rounds in increasing detail until consensus has been reached.[12] This procedure aims to refine participating experts' opinions while minimizing confounding factors present in other group response methods.[13] The rationale for its use is that it is a well-established instrument with which to reach a consensus from a panel of experts on research questions that cannot be answered with empirical evidence and complete certainty. Participants provided informed consent before commencing the first round and were reminded of their right to anonymity, and the ability to withdraw before each subsequent round. Institutional Review Board (IRB) exempt approval was obtained from Indiana University with IRB # 21347

Panel selection

The study core group (the authors of this study) identified key stakeholder experts (working group) who consisted of general obstetricians, maternal-fetal medicine specialists, neonatologists, and hematologists. Eligibility for experts' participation was based on at least one of the following inclusion criteria: expertise in the management of HDFN, based on a relevant publication record. Second, membership in pertinent scientific organizations, including the Society for Maternal-Fetal Medicine (SMFM), the North American Fetal Therapy Network (NAFTNet), the International Fetal Medicine and Surgery Society (IFMSS), and the International Society for Prenatal Diagnosis (ISPD). Lastly, invitees were asked to nominate other specialists with relevant expertise. Potential

participants were sent an invitational email with a detailed description of the background, goals, methodology, and selection criteria. The intended sample size was above 50 participants to ensure sufficient international representation of expert views.

First round

Five domains were used to structure the first round: (i) prenatal workup (ii) prenatal monitoring and management (iii) IUT (iv) labor and delivery, and (v) postnatal workup and management.

Response options included multiple choice answers or a 5-point Likert scale (with 1 representing Strongly Agree and 5 as Strongly Disagree). A pre-defined cut-off for group consensus on an item or group of similar answers was ≥70%[14]. Items with 60-69% agreement were reconsidered in the next round, while those with <60% agreement reflected a lack of consensus, and follow-up questions regarding these items were not posed in the subsequent round unless rewords were felt to be necessary. Participants were able to provide feedback or suggest additional items which were used to adjust the questions and answer choices by the research core group.

Subsequent round

Items that reached consensus were presented to the panel for confirmation in the second round. Items with significant agreement (60-69%) were reconsidered following rephrasing the question-and-answer options, or a new question was added to clarify. Items with <60% agreement were determined to be no consensus items. Additional suggested items were discussed among the steering group before introduction in the next round.

Data collection and analysis

Data were collected in each round using online questionnaires that were presented to panelists through a unique token-secured link for each round. Responses were captured in REDCap version 13.7.19 (Vanderbilt University, Nashville, TN). Non-responders received reminder emails after two and four weeks and were excluded from subsequent survey rounds if no response was obtained. The panel categorized and considered newly suggested items carefully for their applicability in this procedure. Experts' demographics and practice characteristics were collected. Analyses were performed using REDCap and presented in frequency tables.

Participants

One hundred and seven experts participated in the first round of which 100 (93.5%) completed the subsequent round. Experts' demographic characteristics are outlined in Table 1. The expert panel represented 25 countries across six continents. Among our panel, 76 (71.0%) were maternal-fetal medicine specialists, 22 (20.6%) neonatologists, and 9 (8.4%) hematologists. Experts that had more than 20 years of practice experience made up 48.6% of the expert panel. 53.3% of the experts assessed 15 or more cases of fetal anemia per year (Table 1).

Prenatal Workup of Pregnancies at Risk or Complicated with Alloimmunization

The expert panel agreed on using cell-free DNA (cfDNA) to determine fetal genotype (75.3% agreement). Related to the use of cfDNA, experts agreed (>70% agreement) on using cfDNA for RhD, Kell, and Rhc antigens and agreed on using it in all twin gestations, both monochorionic and dichorionic (89.2% agreement). Additionally, while there was no consensus, there was a significant agreement to not continue monitoring antibody titers (63.3% agreement)

and to not initiate or continue MCA Dopplers monitoring (66.7% agreement) if cfDNA showed fetus is not at risk for HDFN (Table 2). We conducted a subgroup analysis on the responses from US, non-US (including Europe), and Europe. In pregnancies with maternal alloimmunization, if cfDNA suggests that the fetus is not at risk for HDFN, the proportion of experts who agreed that monitoring maternal antibody titers is not required was 71.4%, 59.6%, and 57.5%, respectively. In pregnancies with RBC alloimmunization and elevated titers, if cfDNA testing suggests that the fetus is not at risk for hemolytic disease, the following percentages of experts from the mentioned regions agreed not to perform MCA Doppler for fetal anemia surveillance: 64.3%, 66.0%, and 70.0%.

There was consensus that 16 should be the critical titer threshold for all antigens known to cause HDFN, except Kell (86.4% agreement). While there was no consensus for Kell antigens, experts had 62.9% agreement on using titers of 4 to define critical titers requiring fetal anemia imaging monitoring (Table 2). 64.2% of experts agreed on not repeating antibody titers once they reach a predefined critical level but rather initiating MCA Dopplers for fetal anemia monitoring. The MCA Doppler assessment should be started at 16 weeks gestation (80.2% agreement), weekly assessment (61.7% agreement), to be continued until delivery (93.8% agreement) (Table 2). Regarding ultrasound parameters to assess for fetal anemia, experts did not reach consensus on the use of prenatal surveillance with non-stress tests (NST) or biophysical profile (BPP) (44.4% agreement).

A few items that did not reach consensus include anti-M management and how often to repeat titers. Further practices related to prenatal testing and monitoring that were included in the Delphi can be seen in Table 2.

We included anti-M alloimmunization due to controversy in the literature about its role. It's crucial to determine if it leads to alloimmunization, using lab methods like serological testing, RBC phenotyping, and molecular genotyping. Although consensus wasn't reached, this topic is vital for accurate diagnosis and management.

There are varying recommendations in current clinical guidelines concerning the prenatal assessment of fetal anemia risk using cfDNA. The American College of Obstetrics and Gynecology (ACOG) states that the use of cfDNA is a "reasonable alternative" for fetal RhD testing in patients who are at risk and decline amniocentesis to perform PCR on fetal amniocytes.[15]

Guidelines recommend screening for RBC alloimmunization by testing for antibodies to RBC antigens and measuring titer levels.[5,16] ACOG indicates that critical titer thresholds, which prompt further assessment, range from 8 to 32 due to laboratory variations. Typically, titers of 8 or less may warrant monitoring titers every 4 weeks.[5] The Royal College of Obstetricians and Gynaecologists (RCOG) identifies critical thresholds for anti-D antibodies as >15 IU/mL, though this is not recommended as best practice. Additionally, RCOG recommends referral to a fetal medicine center with anti-D levels ≥ 4 IU/mL. Their recommendation of best practice for anti-Kell antibodies is that referral should occur as soon as they are detected due to the risk of severe anemia at lower titer levels.[16] It is important to note the difference in methodology of alloimmunization assessment between the ACOG and RCOG guidelines. ACOG uses titers which are a dilution of the antibody level in maternal serum to a level where agglutination is not seen and RCOG reports

the autoanalyzer method which directly measures the antibody level in the maternal serum. [5,16] In a 16-year unselected cohort of 1026 Kell-immunized pregnancies, a titer of ≥ 4 was determined to be used as the target for regular clinical monitoring.[17] A Canadian study verifies that their results correspond with the current "critical titer threshold" of 8-32.[18,19] The expert panel agreed on the critical titer threshold of non-Kell antibodies as 16 and significant agreement but not consensus for Kell critical threshold ≥4. Although consensus was reached on the critical antibody titers, the provider must be certain of their lab methodology as the consensus from this study applies only to titers generated from the indirect Coombs test, unlike the various other methodologies used to determine maternal alloantibody titers/levels.

In addressing the differences in Rh antibody assessment methods, it is crucial to emphasize that our Delphi study findings are based solely on the indirect Coombs method. It is recommended that readers be fully aware of the specific methodology used by their laboratories. Additionally, there are various methods for Rh antibody detection, including gel microcolumn agglutination assay and automated solid phase, as well as autoanalyzer measurements. Notably, some European centers utilize an autoanalyzer measurement of maternal serum Rh antibodies ≥15 IU/ml to identify fetuses at risk for moderate-severe anemia, while others suggest lower thresholds (≥ 6 IU/ml and ≥3.5 IU/ml) based on recent studies.[20] These differences underscore the importance of understanding the specific methods and cutoffs used in practice to accurately interpret and apply our findings.

Prenatal Management of Pregnancies with Alloimmunization

Regarding the maternal administration of IVIg, 54/77 (70.0%) experts agreed that it should be considered an option for managing pregnancies with HDFN. Based on our results, IVIg is indicated in pregnancies with prior fetal or neonatal death due to HDFN or a history of IUT before 24 weeks in a previous pregnancy. It is recommended to be started at 10-14 weeks of gestation, (77.4%) with no loading dose and a maintenance dosage of 1 g/kg per week (75.5%) . MCA Doppler monitoring needs to be done weekly while receiving IVIg, and if it suggests fetal anemia, IVIg should be stopped and IUT needs to be offered (92.5%) (Table 3).

With regard to monitoring these patients, American Medical Society guidelines do not have a recommendation for an exact gestational age at which to initiate MCA Doppler assessments. The SMFM guideline suggests that MCA Doppler assessment be initiated at a GA when fetal blood sampling procedures or IUTs are technically feasible, such as 18-20 weeks gestation. However, weekly assessment has been recommended following 24 weeks gestation.[5,21] RCOG mentions that if the fetus is antigen-positive and maternal antibody titers are at a critical level, MCA Dopplers should be initiated and monitored weekly. ACOG and RCOG advised caution with monitoring MCA Doppler beyond 34-35 and 36 weeks gestation, respectively, due to their decreased sensitivity for the detection of fetal anemia beyond this gestational age.[5,16] Our expert panel agreed on the initiation of MCA Doppler assessments starting at 16 weeks and continuing weekly until delivery.

Intrauterine Transfusion

Consensus was not reached regarding the minimum gestational age (GA) for intravenous (IV) IUT. There was consensus that the maximum GA should be $35^{0/7}$ to $35^{6/7}$ weeks (78.5% agreement). The expert panel was asked if the threshold of MCA peak systolic velocity (PSV) is similar in early IUT (<20 weeks) as IUT >20 weeks and the panel recommended that IUT should be offered for pregnancies less than 20 weeks when the MCA PSV is persistently higher than 1.5 MoM (92.9% agreement). In patients where cord IV IUT is not feasible, our panel agreed that intra-peritoneal (IP) and intra-hepatic access should be considered. However, a combination of intra-peritoneal transfusion (IPT) and intravascular transfusion (IVT) should not be routinely used in the same procedure (92.3% agreement) (Table 4).

To calculate the transfusion volume, hemoglobin and/or hematocrit can be used (92.9% agreement), and for IVT, the same calculation formula should be used regardless of GA (88.5% agreement). Concerning monitoring, the timing of the second and third IUT should be determined by a combination of weekly MCA-PSV and the calculated rate of hemoglobin decline, which is approximately 0.9 g/dL per day in 10-14 days after the first IUT and 0.6 g/dL per day in 2-3 weeks after the second IUT (75.7% agreement). Repeat intrauterine transfusions are typically considered when the MCA-PSV exceeds 1.5 MoM. This indicates moderate to severe fetal anemia. As for the Hb level, repeat transfusions are usually considered when the Hb level falls below 10 g/dL.

In dichorionic-diamniotic twin pregnancies, fetal blood sampling should not be performed on both fetuses when only one has an abnormal MCA Doppler finding (85.9% agreement) (Table 4).

The Dodd et al. clinical trial, in 2018, concluded that both MCA-PSV and estimation of fetal hemoglobin drop calculation can be used to determine the timing of the second IUT due to the lack of statistically significant differences in outcomes and complications between the two groups.[22] In line with this study, our expert panel also recommended that the timing of the subsequent IUT should be determined by a combination of weekly MCA-PSV and hemoglobin drop calculations. Additionally, it is important to note that while the expert panel reached significant agreement on the target hemoglobin concentration for intrauterine transfusions (IUT) at 14-16 g/dL, evidence in the literature suggests that, in cases of severely anemic fetuses, it is advised not to increase the fetal hemoglobin by more than four-fold the starting hemoglobin level in one IUT session. Instead, these patients should undergo a subsequent IUT 48 hours later to achieve the target hemoglobin concentration.

Procedural-related practices, the panel agreed on using a 20 gauge needle after 22-24 weeks, while 22 gauge prior to that (81.4% agreement). Type and first line of maternal anesthesia is not affected by GA (85.9% agreement) with local or local with maternal sedation is the most commonly used type (88.5%). While no consensus was reached, 67.1% agreed that fetal paralytic medicine should be considered in IUT, 68.1% agreed on using hemoglobin of 14-16 g/dL or hematocrit of 40-45% as a target level for transfusion, and to proceed for emergency cesarean delivery only if no improvement in fetal status following a trial of intrauterine resuscitation for fetal bradycardia (90.0%) (Table 4).

Regarding IPT, experts who performed at least 5 procedures (49/78, 62.8%) were given open-ended questions given that the procedure is infrequent. Practices were variable related to IPT volume of transfusion and timing of transfusion following IPT. Still, overall experts are

considering between 5-10 mL of transfusion for pregnancies at ≤20 weeks and considering MCA Doppler monitoring 1-2 weekly to trigger possible repeat transfusion after one week.

Delivery Management

Regarding delivery, the route needs to be determined by obstetric indications (98.7%). The timing of delivery for patients with critical antibody titer and no IUT is recommended to be $37^{0/7}$ - $38^{6/7}$ weeks (100.0%) and if IUT was needed to be two to three weeks following the last IUT (89.6%). The panel agreed on delayed cord clamping (71.4%) but not cord milking in pregnancies that had IUT (85.7%) (Table 5).

Based on the results outlined in the sections above, the participating experts were able to generate a monitoring and clinical management workflow as seen in Figure 1.

Postnatal Workup and Management

In this section, 18 statements were presented to 25 experts from various fields and specialties involved in the postnatal care of these neonates (Table 6). Our panel agreed that the postnatal treatment of fetal anemia should include intensive phototherapy, blood transfusion, and exchange transfusion, without the routine administration of IVIg. The thresholds for phototherapy and exchange transfusion should be determined by the American Academy of Pediatrics (AAP) 2022 guidelines (72% agreement). Anemia labs should be investigated in neonates of pregnancies complicated with alloimmunization before hospital discharge (92.0% agreement) and if IUT was needed for the labs to be repeated in one week following discharge if they were not anemic at birth (84.0% agreement). In newborns of pregnancies that had critical titers but did not require IUT,

96% agreed that anemia labs should be performed before hospital discharge. 96.0% agreed that exchange transfusions should be centralized in hospitals with sufficient exposure and experience and 92.0% agreed that they do not use erythropoietin-stimulating agents in the first weeks of life to reduce the need for blood transfusion. The panel agreed that the hemoglobin cut-off level to consider transfusion following hospital discharge is 7 g/dL (92.0% agreement), and the newborns need to be monitored frequently until 2-3 months of age (96.0% agreement) (Table 6).

Regarding the postnatal management of neonates affected by HDFN, the 2022 AAP guidelines mentioned that the use of IVIg is an optional therapy, and similarly, our panel did not reach a consensus on its routine use.[23] It is important to note that with updates to AAP guidelines, the relevance of the consensus reached on the use of neonatal IVIg may be altered.

Although 92% of the expert panel stated that they are not routinely using erythropoietin-stimulating agents in the first few weeks of life to reduce the need for transfusion, a recently published randomized controlled trial showed that darbepoetin alfa decreased the number of transfusion episodes.[24]

Strengths and Limitations

The strengths of our study include the use of the well-established Delphi procedure and the inclusion of a diverse group of international experts. Our selection criteria based on clinical and academic experience resulted in a high degree of expertise among our participants. Moreover, a relatively low attrition rate was achieved across rounds. We were able to provide insight into how experts synthesize conflicting data, and demonstrate choices that are made when no high-quality data exist, and build on current knowledge gaps alloimmunization monitoring and management.

This may drive the further collection of evidence for treatment efficacy but also provide a useful guide for shared decision-making and treatment assessment.

Limitations include that the Delphi output reflects the contemporary interpretation of existing literature which can change over time. As a summary of expert opinion, it also provides different insight than that provided by a systematic review or society guidelines. Additionally, given the presentation of consensus results in follow-up rounds, participants may have altered their initial thoughts to prioritize the consensus views to emphasize group unanimity[25]. This was minimized by masking individual expert opinions that could steer the group in a particular direction, adding relevant questions raised by individual participants guided by a working group, and the independent nature of the questionnaire itself. Another limitation is the overrepresentation of Western world countries and the underrepresentation of countries from Africa, Asia, and South America. This represents the views of a selected group of participants, and it cannot be known how representative it is of the wider community. Lastly, this Delphi consensus can be used as a guideline for areas where consensus was reached. However, in areas where consensus was not reached, providers should apply a patient-by-patient approach to determine the clinical course of action.

Scope for future research:

1. **Prevention Strategies:** Exploring new preventive measures, such as novel immunoglobulin therapies or vaccines, to reduce the incidence of HDFN. This includes awaiting the completion of the phase III randomized, double-blind, placebo-controlled trial of nipocalimab to prove the potential benefit in preventing the need for serial IUTs in HDFN.

2. **Long-term Outcomes:** Studying the long-term health impacts on children who were affected by HDFN, including neurodevelopmental outcomes and quality of life.
3. **Global Health Initiatives:** Addressing disparities in HDFN care by conducting research in low-resource settings and developing cost-effective treatment protocols.
4. **Ethical and Social Considerations:** Investigating the ethical, legal, and social implications of HDFN management, including informed consent and access to care.

Conclusions

Although experts agreed on many aspects of monitoring and management of red cell alloimmunization and HDFN, the results of this Delphi show apparent practice variations worldwide. This Delphi survey facilitated the development of a consensus-based clinical workflow that can be used to enhance clinical practice, improve outcomes, and facilitate future research. Non-consensus items should be viewed as areas where clinical judgment remains crucial, and where further evidence and expert discussion are needed to develop more definitive guidelines.

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The following are members of the HDFN Delphi working group that provided consent to be included in the acknowledgment:

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407 **ACKNOWLEDGEMENTS**

408 We would like to thank our expert panel for participation in our Delphi procedure.

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410

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480 **Table 1: Experts demographics and practice characteristics**

Characteristic	Respondents (n=107)
Age	
25-44	23 (21.5)
45-54	45 (42.1)
55-64	30 (28.0)
65+	9 (8.4)
Region of practice ǂ	
United States	30 (28.0)
Germany	15 (14.0)
Netherlands	12 (11.2)
United Kingdom	9 (8.4)
Each of Australia, Brazil (total N=8)	4 (3.7)
Each of France, Finland, Belgium, Slovenia (Total N=12)	3 (2.8)
Each of India, Japan, Canada, South Africa, Sweden, Mexico (Total N=12)	2 (1.9)
Each of Argentina, Austria, Bulgaria, China, Denmark, Italy, Portugal, Singapore, Switzerland (Total N=9)	1 (0.9)
Speciality	
Obstetrics	76 (71.0)
Maternal-Fetal Medicine, performing intrauterine transfusion	71 (66.4)
Maternal-Fetal Medicine, not performing intrauterine transfusion	5 (4.7)
Neonatology	22 (20.6)
Hematology or immunohematology	9 (8.4)
Academic rank	
Professor	36 (33.6)
Specialist/Consultant	35 (32.7)
Associate / Assistant professor	31 (29.0)
Other	5 (4.7)
Practice setting	
University/Academic hospital-based practice	93 (86.9)
Community academic hospital-based practice	5 (4.7)
Private practice (independently or health system/hospital owned)	7 (6.5)
Other	2 (1.9)
Years in practice	
<5-9	18 (16.8)
10-19	37 (34.6)
>20	52 (48.6)
HDFN related participants' characteristics	
Number of assessments for fetal anemia per annum	
<5	5 (4.7)
5-14	29 (27.1)
15-34	29 (27.1)
>35	28 (26.2)
Uncertain	16 (15.0)
Number of intrauterine transfusions for fetal anemia per annum*	
<5	26 (26.3)

Characteristic	Respondents (n=107)
5-14	42 (42.4)
15-34	22 (22.2)
>35	3 (3.0)
Uncertain	14 (13.1)
Number of individuals who perform intrauterine transfusions at the centre	
1-2	40 (37.4)
3-4	53 (49.5)
>5	14 (13.1)
Number of IVIG procedures per annum**	
None /I do not offer IVIG	26 (26.5)
<5	60 (61.2)
5-24	5 (5.1)
>25	1 (1.0)
Uncertain	15 (14)
Number of deliveries following treatment for fetal anemia per annum*	
None	4 (4.0)
<5	26 (26.3)
5-24	53 (53.5)
>25	12 (12.1)
Uncertain	12 (11.2)
Number of HDFN pediatric cases per annum***	
None	1 (1.1)
<5	18 (19.8)
5-24	46 (50.5)
>25	16 (17.6)
Uncertain	26 (24.3)
Published papers in HDFN	65 (60.7)
Principal investigator and/or First author	46/65 (70.8)

HDFN (Hemolytic Disease of the Fetus and Newborn); IVIG (Intravenous Immunoglobulins)

ǂN=100*; *N=99 as 8 out of 107 participants indicated 'Not appliable to my specialty'; **N=98 as 9 out of 107 participants indicated 'Not applicable to my specialty'; ***N=91 as 16 out of 107 participants indicated 'Not applicable to my specialty',*

All percentages are presented in parentheses ()

487 **Table 2: Prenatal Workup and Monitoring**

	Round in which item was included	
	1	2
	N=81	N=81
cfDNA		
cfDNA to determine fetal genotype in maternal alloimmunization	61/81 (75.3)	
Fetal antigens to test **		
RhD antigen	61/61 (100.0)	
Kell antigen	51/61 (86.9)	
Rhc antigen	44/61 (72.1)	
RhE antigen	36/61 (59.0)	
RhC antigen	31/61 (50.8)	
Rhe antigen	23/61 (37.7)	
Fya antigen	12/61 (19.7)	
JKa antigen	6/61 (9.8)	
Gestational age to initiate testing **		
10 weeks	18/61 (29.5)	
11 weeks	15/61 (24.6)	
12 weeks	16/61 (26.2)	
13 or 14 weeks	4/61 (6.6)	
cfDNA use to determine fetal genotyping in twin gestations	33 (89.2)	
MCA doppler surveillance should not be performed in alloimmunized pregnancies with high titres if cfDNA suggests no risk of HFDN	41/61 (67.2)	40/60 (66.7)
Antibody titers monitoring should not be continued in alloimmunized pregnancies if cfDNA suggests no risk of HFDN	41/61 (67.2)	38/60 (63.3)
Antibody titers		
Critical threshold for all antibodies known to cause HDFN, except Kell		
1:4 or 1:8	7/81 (8.6)	
1:16	54/81 (66.6)	70/81 (86.4)
1:32	10/81 (12.3)	
1:64 or >1:128	10/81 (12.3)	
Critical threshold for Kell antibodies		
Any positive Indirect Coombs test	20/81 (24.7)	
1:4	49/81 (60.5)	51/81 (62.9)
1:16	3/81 (3.7)	
≥1:32	0 (0.0)	
Critical threshold for Anti-M pregnancies		
Quantification of IgM vs IgG to determine high risk pregnancies	28/81 (34.6)	
Any positive indirect Coombs test *ł*	4/81 (14.3)	
1:4	1/81 (3.6)	
1:16	13/81 (46.4)	
1:32	6/81 (21.4)	
1:64	4/81 (14.3)	
Antibody titres should NOT be repeated if they have reached critical threshold	53/81 (65.4)	52/81 (64.2)
Frequency of repeat titres if no critical threshold reached		
Weekly	1/81 (1.2)	

	Round in which item was included	
	1	2
	N=81	N=81
Every 2 weeks	21/81 (25.9)	
Every 4 weeks	42/81 (51.9)	
Once per trimester	1/81 (1.2)	
Changes with titers and gestational age	17/81 (20.9)	
Antibody titres should be obtained first in the current pregnancy to decide if MCA Dopplers are required, despite the level of the high antibodies in a prior pregnancy without treatment	49/81 (60.5)	54/81 (66.6)
Ultrasound		
Parameters to assess for fetal anemia		
Fetal middle cerebral artery (MCA) Doppler assessments	79/81 (97.5)	
Evaluation for hydrops fetalis	79/81 (97.5)	
Detailed anatomical survey (if not previously obtained)	69/81 (85.2)	
Cardiac function assessment (cardiac size, regurgitation, others)	59/81 (72.8)	
Antepartum surveillance (eg CTG/NST, BPP)	36/81 (44.4)	
UA Doppler assessment, including in the absence of FGR	30/81 (37.0)	
Measurements of fetal liver and spleen	22/81 (27.2)	
Earliest gestational age for MCA Doppler to reliably detect fetal anemia		
14 weeks	6/81 (7.4)	
15 weeks	4/81 (4.9)	
16 weeks	49/81 (60.5)	65/81 (80.2)
17 weeks	3/81 (3.7)	
18 weeks	19/81 (23.5)	
Frequency of MCA Doppler assessment once antibody titre threshold is reached and GA < 28 weeks		
Twice weekly	4/81 (4.9)	
Once weekly	50/81 (61.7)	50/81 (61.7)
Once biweekly	18/81 (22.2)	
Once every four weeks	2/81 (2.5)	
Individualized per titer and gestational age	7/81 (8.6)	
Gestational age at which MCA Doppler monitoring should cease if no IUT is required		
Up to 32 weeks	1/81 (1.2)	
Up to 35 weeks	10/81 (12.3)	
Up to 37 weeks	21/81 (26)	
Until delivery	49/81 (60.5)	76 (93.8)
The frequency of MCA Doppler monitoring should not change after a certain GA	58/81 (71.6)	
It should be increased if there was an incremental rise in MoMs (but this remains <1.5 in absence of other ultrasound signs)	53/81 (65.4)	53/81 (65.4)
MCA dopplers should cease if repeat antibody titres are below critical threshold	56/81 (69.1)	56/81 (69.1)

* *Dark grey shading represents consensus (defined as ≥70% agreement), light grey light grey represents significant agreement (of 60-69%), and white represents no agreement (<60%). A '-' in a cell means that the issue was not addressed in that round.*

GA= Gestational age UA= umbilical doppler FGR= Fetal growth restriction MCA= middle cerebral artery MoMs,

ǂ Test was not available in the region for 16 (19.8%) participants; **N=61; *ł* N=28

All percentages are presented in parentheses ()

494 **Table 3: Prenatal Management with Intravenous Immunoglobulins**

	Round in which item was included	
	1	2
	(N=77)	
For eligible pregnancies, IVIg should be considered	54/77 (70.0)	
Indications in fetal anemia		
Prior fetal or neonatal death due to HDFN	38/53 (71.7)	
History of IUT at <24 weeks in the previous pregnancy	37/53 (70.0)	
Current MCA Dopplers >1.5 MoM at <16-18 weeks regardless of obstetric history	11/53 (20.8)	
Current critical antibody titres at <16-18 weeks + confirmed Current fetal genotype at risk, regardless of obstetric history	7/53 (13.2)	
History of IUT at any GA in the previous pregnancy	7/53 (13.2)	
GA at initiation of IVIg		
6-10 weeks	3/53 (5.7)	
10-14 weeks	41/53 (77.4)	
14-18 weeks or > 18 weeks	9/53 (17.0)	
Maximal GA at which IVIg should not be offered		
>14 weeks	3/53 (5.7)	
>16 weeks	6/53 (11.3)	
>17 weeks	1/53 (1.9)	
>18 weeks	6/53 (11.3)	
>20 weeks	19/53 (35.8)	
No GA limit	18/53 (33.9)	
GA at which IVIg should be stopped, given no signs of fetal anemia		
Up to 24 weeks	9/53 (17.0)	
Up to 26 weeks	2/53 (3.8)	
Up to 28 weeks	1/53 (1.9)	
Up to 32 weeks	9/53 (17.0)	
Up to 35 weeks	13/53 (24.5)	
Up to 37 weeks	7/53 (13.2)	
Until delivery occurs regardless of GA	12/53 (22.6)	
IVIg Dosing		
No loading dose + 1g/kg/week	40/53 (75.5)	
2 g/kg loading dose + 1g/kg/week every week after	5/53 (9.4)	
No loading dose + 2 g/kg every 3 weeks administered as 1 g/kg/day over 2 days	4/53 (7.5)	

	Round in which item was included	
	1	2
	(N=77)	
No loading dose + 0.5 g/kg/week	4/53 (7.5)	
MCA Doppler monitoring once every week while on IVIg	49/53 (92.5)	
If suggestive of fetal anemia, IVIG should be stopped and IUT started	49/53 (92.5)	

** Dark grey shading represents consensus (defined as ≥70% agreement), light grey light grey represents significant agreement (of 60-69%), and white represents no agreement (<60%). A '-' in a cell means that the issue was not addressed in that round.*

GA= Gestational age IVIg= Intravascular immunoglobulins IUT= intrauterine transfusion CS= Caesarean section MoM= Multiple of the Median

All percentages are presented in parentheses ()

505 **Table 4: Intrauterine transfusion**

	Round in which item was included	
	1	2
	(N=78)	(N=70)
Minimum GA for intravascular IUT in a non-hydropic fetus		
14 weeks	1/78 (1.3)	
16 weeks	18/78 (23.1)	
18 weeks	36/78 (46.2)	
20 weeks	16/78 (20.5)	
22 weeks	5/78 (6.4)	
24 weeks	2/78 (2.6)	
Minimum GA for intravascular IUT in a hydropic fetus		
14 weeks	6/78 (7.7)	
16 weeks	27/78 (34.6)	
18 weeks	34/78 (43.6)	
20 weeks	11/78 (14.1)	
IUT should be considered for pregnancies <20 weeks when the MCA is persistently >1.5 MoM	53/78 (67.9)	65/70(92.9)
Interventions in a non-hydropic fetus when intracord IUT is not technically feasible		
Intraperitoneal transfusion	64/78 (82.1)	
Intrahepatic vein transfusion	58/78 (74.4)	
Abort the procedure and re-attempt later	17 (21.8)	
Interventions in a hydropic fetus when intracord IUT is not technically feasible		
Intraperitoneal transfusion	60/78 (76.9)	
Intrahepatic vein transfusion	58/78 (74.4)	
Abort the procedure and re-attempt later	7/78 (9.0)	
Test to determine transfused volume in intravascular IUT		
Hb and/or Hct	47/78 (60.3)	65/70 (92.9)
Hct	17/78 (21.8)	
Hb	14/78 (17.9)	
In intravascular IUT the same calculation should be used if GA <24 weeks	69 (88.5)	
Intraperitoneal transfusion (IPT), experts who have performed at least 5 IPTs answered related open-ended questions (see results text)	49/78 (62.8)	
Use of peri-operative tocolysis in IUT	34/78 (43.6)	
Needle gauge choice should differ depending on GA at the procedure	47/78 (60.3)	42/70 (60)
22 gauge needle		

	Round in which item was included	
	1 (N=78)	2 (N=70)
<20 weeks	21/47 (44.7)	
<22 weeks	10/47 (21.3)	
<24 weeks	7/47 (14.9)	
<26 weeks	3/47 (6.4)	
<28 weeks	6/47 (12.8)	
20 gauge needle should be used following the 22-24 weeks, while 22 gauge prior	30/47 (63.8)	57/70 (81.4)
18 needle gauge should not be used in IUT	36/47 (76.6)	
Maternal anaesthesia methods in IUT		
Methods		
Local or local and maternal sedation	69/78 (88.5)	
Regional	6/78 (7.6)	
General	3/78 (3.8)	
First-line choice for maternal anaesthesia is not influenced by GA	67/78 (85.9)	
Fetal paralytic medication should be considered in IUT	51/78 (65.3)	47/70 (67.1)
Intravascular	30/51 (58.8)	
Intramuscular	21/51 (41.2)	
MCA dopplers should be used to determine timing for the second IUT	52/78 (66.7)	43/70 (61.4)
MCA dopplers should not be used to determine timing for third IUT	44/78 (56.4)	
Timing of second transfusion in a non-hydropic fetus	N=78	
48 hrs	1 (1.3)	
72 hrs	1 (1.3)	
1 week	11 (14.1)	
2 weeks	22 (28.2)	
3 weeks	4 (5.1)	
Decide based on MCA Doppler assessment	33 (42.3)	
None of the above	5 (6.4)	
Timing of third transfusion in a non-hydropic fetus	N=78	
1 week	1 (1.3)	
2 weeks	16 (20.5)	
3 weeks	15 (19.2)	
Decide based on MCA Doppler assessment	29 (37.2)	
Based on MCA and post-transfusion levels	17 (21.8)	
Timing of second transfusion in a hydropic fetus	N=78	

	Round in which item was included	
	1 (N=78)	2 (N=70)
48 hrs	11 (14.1)	
72 hrs	17 (21.8)	
1 week	27 (34.6)	
2 weeks	4 (5.1)	
Based on MCA and post-transfusion levels	19 (24.4)	
Timing of the second and third transfusion should be determined by a combination of weekly MCA-PSV and closing Hb drop calculation (0.9/d after 1st and 0.6/d after 2nd)**	52/78 (66.7)	53/70 (75.7)
Combining intraperitoneal and intravascular IUT should not be routinely used at the same procedure	72/78 (92.3)	
Target level in intravascular IUT		
Between 14-16 g/dl or hematocrit 40-45% regardless of GA	50/78 (64.1)	47 (68.1)
Between 16-18 g/dl or hematocrit 45-50% regardless of GA	28/78 (35.9)	
Maximal gestational age of last IUT		
32-34+6 weeks	9 (11.4)	
35-35+6weeks	49/78 (62.8)	55/70 (78.5)
36-37 weeks	20 (25.6)	
Threshold for emergency caesarean in pregnancies with viable GA that develop fetal bradycardia during IUT		
Trial of intrauterine resuscitation	47/78 (60.2)	63/70 (90)
Trial of intrauterine resuscitation + atropine first	24/78 (30.8)	
Trial of atropine only first	4/78 (5.1)	
Immediately progress into emergency C-Section	5/78 (6.4)	
Setting of IUT with pre-viable GA		
The Office/Fetal Medicine Unit	44/78 (56.4)	
OR/Theatres	34/78 (43.6)	
Phenobarbital should not be used	72/78 (92.3)	
In DCDA twins, fetal blood sampling should not be performed on both fetuses when only one has triggered the MCA Doppler MoM for IUT	67/78 (85.9)	

** Dark grey shading represents consensus (defined as ≥70% agreement), light grey represents significant agreement (of 60-69%), and white represents no agreement (<60%). A '-' in a cell means that the issue was not addressed in that round.*

***Approximately in 10-14 days after 1st IUT and in 2-3 weeks after the 2nd IUT*

ǂ Variability in open responses. See Supplementary material.

GA= Gestational age Hb=hemoglobin Hct=Hematocrit IVIG= Intravascular immunoglobulins IUT= intrauterine transfusion MoM= Multiple of the Median MCA PSV= Middle cerebral artery peak systolic flow

All percentages are presented in parentheses ()

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515

516 **Table 5: Delivery Management**
517

	Round in which item was included	
	1	2
	(N=78)	(N=77)
GA at which delivery should be opted as opposed to IUT if initial presentation of >1.5 MoM		
32 weeks	1/78 (1.3)	
34 weeks	11/78 (14.1)	
35 weeks	33/78 (42.3)	
36 weeks	23/78 (29.5)	
37 weeks	10/78 (12.8)	
Timing of delivery following last successful IUT in absence of other indications		
2-3 weeks after last IUT	54/78 (69.2)	69/77 (89.6)
3-4 weeks after last IUT	9/78 (11.5)	
Other	15/78 (19.2)	
GA for delivery in pregnancies where critical antibody titres are reached and IUT was not required		
34-36 +6/7 weeks GA	9/78 (11.5)	
37-38 + 6/7 weeks GA	54/78 (69.2)	77 (100.0)
39-40 + 6/7 weeks GA	15 (19.2)	
Route of delivery should follow obstetric indication for vaginal or CS delivery	76/77 (98.7)	
Delayed cord clamping during delivery in an IUT pregnancy	55/77 (71.4)	
Cord milking should not be performed in an IUT pregnancy	66/77 (85.7)	

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519 *agreement (of 60-69%), and white represents no agreement (<60%). A '-' in a cell means that the issue was not*
520 *addressed in that round.*

521 *GA= Gestational age, IUT= intrauterine transfusion CS= Caesarean section MoM= Multiple of the Median*
522 *All percentages are presented in parentheses ()*
523

524 **Table 6: Postnatal Management**

	Round in which item was included	
	1	2
	(N=25)	(N=25)
Postnatal treatments to be considered for fetal anemia	N=25	
Phototherapy	25 (100.0)	
Blood transfusion	25 (100.0)	
Exchange transfusion	23 (92.0)	
IVIg	14 (56.0)	
Treatment with erythropoietin	7 (28.0)	
Bilirubin level at birth to initiate phototherapy treatment	N=25	
<5 mg/dl	4 (16.0)	
5-10 mg/dl	8 (32.0)	
10-15 mg/dl	2 (8.0)	
15-20 mg/dl	2 (8.0)	
None of the above	9 (36)	
Rise in bilirubin should be calculated when monitoring hyperbilirubinemia	18/25 (72.0)	
Rate of rise to start aggressive phototherapy in first 24 hrs		
>0.2 mg/dl	6 (33.3)	
>0.3 mg/dl	3 (16.7)	
>0.4 mg/dl	4 (22.2)	
>0.5 mg/dl	5 (27.8)	
None of the above	7 (28.0)	
All neonates with a history of HDFN requiring IUT should be not started on phototherapy immediately	15/25 (60.0)	15/25 (60.0)
Neonatal IVIG should not be used routinely in cases of HDFN with hyperbilirubinemia in the first few days of life to prevent the need of exchange transfusions	21/25 (84.0)	
Hb threshold for transfusion in term neonates with HDFN who are critically ill	N=25	
<13 g/dl	1 (4.0)	
<12 g/dl	9 (36.0)	
<11 g/dl	2 (8.0)	
<10 g/dl	6 (24.0)	
< 9 g/dl	1 (4.0)	
< 8 g/dl	2 (8.0)	
None of the above	4 (16.0)	
Hb threshold for transfusion in term neonates with HDFN who are not critically ill	N=25	

	Round in which item was included	
	1	2
	(N=25)	(N=25)
< 13 g/dl	1 (4.0)	
< 11 g/dl	2 (8.0)	
< 10 g/dl	8 (32.0)	
< 8 g/dl	5 (20.0)	
< 7 g/dl	4 (16.0)	
None of the above	5 (20.2)	
Hb threshold for transfusion in preterm neonates with HDFN who are critically ill	N=25	
<12 g/dl	13 (52.0)	
<10 g/dl	7 (28.0)	
<8 g/dl	1 (4.0)	
None of the above	4 (16)	
Hb threshold for transfusion in preterm neonates with HDFN who are not critically ill	N=25	
<12 g/dl	2 (8.0)	
<11 g/dl	2 (8.0)	
<10 g/dl	6 (24.0)	
<9 g/dl	2 (8.0)	
<8 g/dl	4 (16.0)	
<7 g/dl	2 (8.0)	
None of the above	7 (28.0)	
AAP 2022 guidance use to determine thresholds of phototherapy and exchange transfusion	18/25 (72.0)	
Prior to discharge, in a newborn, of a pregnancy complicated by maternal alloimmunisation with no evidence of fetal anemia, Hb and bilirubin levels should be determined	23/25 (92.0)	
In a newborn of a pregnancy which has critical titres but did not require IUT, anemia laboratory investigations should be performed	24/25 (96.0)	
In a newborn of a pregnancy which required recent IUT and who was not anaemic at birth, anaemia laboratory investigations should be repeated at 1 week	21/25 (84.0)	
Exchange transfusions should be centralized in hospitals with sufficient exposure and experience	24/25 (96.0)	
Erythropoietin stimulating agent not used in the first few weeks of life to reduce the need for transfusions in neonates treated with IUT	23/25 (92.0)	
The Hb level to consider further transfusions following hospital discharge is <7 g/dl	23/25 (92.0)	
Follow up frequency in infancy		
4-8 weeks	3/25 (12.0)	
2-3 months	15/25 (60.0)	24/25 (96.0)
2- 6 months	5/25 (20.0)	

	Round in which item was included	
	1	2
	(N=25)	(N=25)
6-12 months	2/25 (8.0)	

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*** 2 experts indicated that other erythropoietin analogs may be used in their respective countries*

IVIg= Intravenous immunoglobulins Hb= hemoglobin Hct=Hematocrit AAP: American Academy of Pediatrics
All percentages are presented in parentheses ()