ORIGINAL ARTICLE

Nipocalimab in Early-Onset Severe Hemolytic Disease of the Fetus and Newborn

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ABSTRACT

BACKGROUND

In early-onset severe hemolytic disease of the fetus and newborn (HDFN), transplacental transfer of maternal antierythrocyte IgG alloantibodies causes fetal anemia that leads to the use of high-risk intrauterine transfusions in order to avoid fetal hydrops and fetal death. Nipocalimab, an anti–neonatal Fc receptor blocker, inhibits transplacental IgG transfer and lowers maternal IgG levels.

METHODS

In an international, open-label, single-group, phase 2 study, we assessed treatment with intravenous nipocalimab (30 or 45 mg per kilogram of body weight per week) administered from 14 to 35 weeks' gestation in participants with pregnancies at high risk for recurrent early-onset severe HDFN. The primary end point was live birth at 32 weeks' gestation or later without intrauterine transfusions as assessed against a historical benchmark (0%; clinically meaningful difference, 10%).

RESULTS

Live birth at 32 weeks' gestation or later without intrauterine transfusions occurred in 7 of 13 pregnancies (54%; 95% confidence interval, 25 to 81) in the study. No cases of fetal hydrops occurred, and 6 participants (46%) did not receive any antenatal or neonatal transfusions. Six fetuses received an intrauterine transfusion: five fetuses at 24 weeks' gestation or later and one fetus before fetal loss at 22 weeks and 5 days' gestation. Live birth occurred in 12 pregnancies. The median gestational age at delivery was 36 weeks and 4 days. Of the 12 live-born infants, 1 received one exchange transfusion and one simple transfusion and 5 received only simple transfusions. Treatment-related decreases in the alloantibody titer and IgG level were observed in maternal samples and cord blood. No unusual maternal or pediatric infections were observed. Serious adverse events were consistent with HDFN, pregnancy, or prematurity.

CONCLUSIONS

Nipocalimab treatment delayed or prevented fetal anemia or intrauterine transfusions, as compared with the historical benchmark, in pregnancies at high risk for early-onset severe HDFN. (Funded by Janssen Research and Development; UNITY ClinicalTrials.gov number, NCT03842189.)

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*A list of the investigators in the UNITY Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Severe hemolytic disease of the fetus and newborn (HDFN) results from maternal–fetal erythrocyte antigen incompatibility and transplacental transfer of maternal antierythrocyte antigen IgG alloantibodies, which cause fetal hemolytic anemia. Early-onset severe HDFN, defined as severe HDFN occurring at 24 weeks' gestation or earlier, is associated with substantial fetal and neonatal morbidity and mortality.[1-3] Routine anti-RhD prophylaxis has substantially reduced RhD alloimmunization, but early-onset severe HDFN persists owing to missed administration and a lack of prophylaxis for non-RhD antigens.[2,4-9]

The standard care for these high-risk pregnancies is to monitor for fetal anemia by means of middle cerebral artery (MCA) Doppler ultrasonography and fetal blood sampling, followed by timely intrauterine transfusions to avoid fetal hydrops and pregnancy loss.[10] However, complications of intrauterine transfusion include fetal death, preterm (<37 weeks' gestation) prelabor rupture of membranes, and preterm birth.[2,11,12] Early intrauterine transfusions are associated with a particularly high risk of perinatal loss (17% per procedure at <20 weeks' gestation).[11]

Antenatal treatment with intravenous immune globulin (IVIG) with or without plasmapheresis has been reported in case series to delay intrauterine transfusions,[13-15] but it is still associated with poor pregnancy outcomes. Two retrospective studies compared outcomes of standard care alone with those of IVIG treatment added to standard care in pregnant women at high risk for recurrence owing to a previous pregnancy affected by early-onset severe HDFN. With standard care alone, intrauterine transfusions were initiated in all pregnancies at a median of 22 weeks' gestation, 15 to 20% of the pregnancies resulted in fetal loss, and fetal hydrops occurred in 24 to 38% of the pregnancies.[16,17] In another retrospective study comparing pregnancy outcomes between a standard-care–treated and a subsequent IVIG-treated pregnancy in the same women, intrauterine transfusions were administered in 57% of the pregnancies that received standard care alone, starting at a mean of 20 weeks' gestation, with the remaining pregnancies resulting in fetal loss and with fetal hydrops occurring in 50%.[18] With IVIG, 88 to 100% of the participants across these studies received an intrauterine transfusion at a median of 22 weeks' gestation[16,17] or at a mean of 23 weeks' gestation,[18] 6 to 20% had fetal loss, and fetal hydrops occurred in up to 16%.[16-18] Altogether, only 7% of the IVIG-treated pregnant participants (4 of 54) had a live birth without intrauterine transfusions.[16-18]

Nipocalimab, a neonatal Fc receptor (FcRn) blocker, is under development for the treatment of multiple IgG autoantibody- or alloantibody-driven diseases. FcRn is the sole placental IgG transporter and salvage receptor that maintains circulating maternal serum IgG concentrations. FcRn blockade aims to inhibit alloantibody transfer to the fetus and to lower maternal IgG alloantibody titers (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[19-21] In this phase 2, international, open-label, single-group study, we evaluated the safety and efficacy of nipocalimab in delaying or reducing the use of intrauterine transfusions in pregnant persons with previous early-onset severe HDFN.

Methods

Study Oversight

We conducted this study in accordance with Good Clinical Practice guidelines, the principles of the Declaration of Helsinki, and applicable local regulations. Participants provided written informed consent before enrollment. The trial protocol, available at NEJM.org, was approved by the institutional review board or independent ethics committee at each site. A data and safety monitoring board provided oversight and regularly reviewed available data. The sponsor, Janssen Research and Development, designed the trial in collaboration with key investigators; compiled, maintained, and analyzed the data; and engaged the first author for the development of the first draft of the manuscript and all the authors for critical reviews, with the assistance of a medical writing agency. An author who is an employee of the sponsor vouches for the completeness and accuracy of the data and for the fidelity of the study to the protocol.

Eligibility Criteria

Eligible participants were 18 years of age or older, pregnant with a singleton fetus, and had all three of the following characteristics. First, participants had to have had a previous qualifying pregnancy during which they presented at 24 weeks' gestation or earlier with documented severe fetal ane-

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mia (hemoglobin level, <0.55 multiples of the median[10]) as assessed by means of cordocentesis, fetal hydrops with an MCA peak systolic velocity of at least 1.5 multiples of the median, or a previous stillbirth with fetal or placental pathologic features indicative of HDFN.[22] (A multiple of the median was used to indicate how far an individual test result deviated from the median normal hemoglobin value for gestational age.) Second, participants had to have a critical alloantibody titer in the current pregnancy for anti-D (i.e., ≥32) or anti-K (i.e., ≥4), and third, they had to have a cell-free fetal DNA level that was consistent with a D-positive or K-positive fetus.[23,24] Persons who had received IVIG or plasmapheresis in the current pregnancy were excluded (Table S1).

STUDY DESIGN AND TREATMENT

Screening occurred between 8 weeks' gestation and enrollment at 14 weeks' gestation (with a window of ±6 days; baseline). Weekly intravenous infusions of nipocalimab were administered to the maternal participants from baseline until the planned last dose at 35 weeks' gestation. This study was originally designed to evaluate nipocalimab at a dose of 30 mg per kilogram of baseline body weight. Subsequently, according to a protocol amendment, the dose regimen was increased to 45 mg per kilogram of baseline body weight in all current and future participants to ensure coverage of receptor occupancy (i.e., the binding of a monoclonal antibody to a target) to account for a 1-day delay in administration. A further modification in which the total dose calculation was based on the current body weight (determined every 2 weeks) in order to optimize receptor occupancy coverage to account for pregnancy weight gain was applied to all current and future participants. Thus, the dose regimens that we evaluated included 30 mg per kilogram of baseline body weight, 30 mg followed by a switch to 45 mg per kilogram of baseline body weight (i.e., in those treated during a per-protocol dose increase), 45 mg per kilogram of baseline body weight, and 45 mg per kilogram of current body weight (as assessed by measurement every 2 weeks).

Treatment was discontinued in accordance with safety stopping rules or with stopping criteria related to the initiation of intrauterine transfusion. Planned delivery was at 37 weeks' gestation, or earlier if indicated. IVIG (500 mg per kilogram, administered as a single bolus) was given 48 to 72 hours before delivery to maternal participants who had completed nipocalimab treatment and at birth to neonates who had an IgG level below specified thresholds.

The primary analysis was conducted when the last maternal participant–infant pair reached postpartum week 4. Study completion was at postpartum week 24 for maternal participants and at week 96 of life for infants.

Fetal anemia was monitored by means of weekly Doppler ultrasonography of the MCA. An intrauterine transfusion was performed after the occurrence of cordocentesis-confirmed fetal anemia, which was defined as an MCA peak systolic velocity of at least 1.5 multiples of the median.[10] Ultrasonographic monitoring of fetal growth was performed every 2 weeks. Neonates (<28 days of age) and infants (≤1 year of age) received standard care. Details of the nipocalimab doses, stopping rules, and treatment criteria are provided in Table S2.

END POINTS

The primary efficacy end point was live birth at 32 weeks' gestation or later without an intrauterine transfusion. Secondary efficacy end points included the antenatal and postnatal outcomes of live birth, gestational age at the time of the first intrauterine transfusion, live birth without intrauterine transfusion at 24 weeks' gestation or earlier, the number of intrauterine transfusions received, gestational age at delivery, fetal hydrops, and among neonates or infants, receipt of phototherapy, receipt of an exchange transfusion, and receipt of a simple erythrocyte transfusion in the first 12 weeks of life (Table S3). Additional secondary pharmacodynamic or pharmacokinetic end points included maternal or infant serum IgG concentrations and alloantibody titers, as well as maternal monocyte FcRn–receptor occupancy and serum nipocalimab pharmacokinetics.

Safety end points included the incidence, severity, and treatment relatedness of adverse events; electrocardiographic data and vital signs; laboratory values; and physical examinations. Adverse events of special interest included infections that led to anti-infective treatment, unexpected or unusual illnesses in the neonate or infant, decreases of the IgG level in the neonate or infant below age-specified thresholds, and maternal hypoalbuminemia of grade 3 or higher (albumin level, <20 g per liter). Safety outcomes in fetuses and infants included fetal-growth re-

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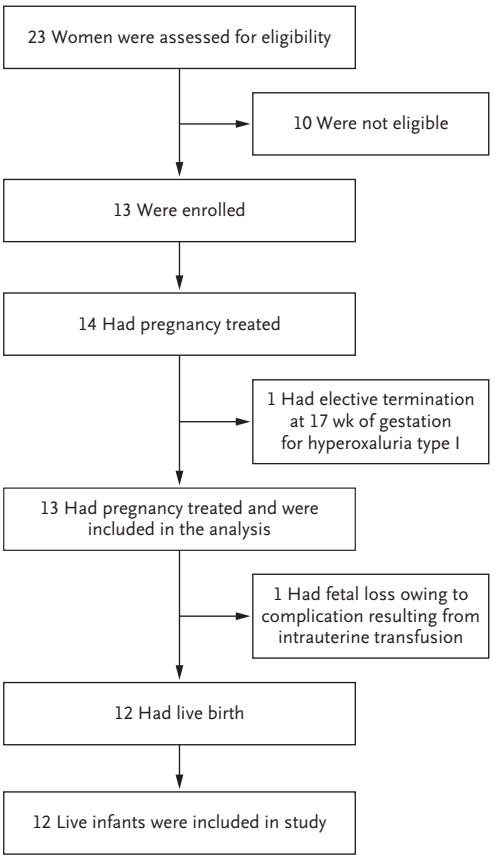

Figure 1. Study Participants.

As of the data-cutoff date for the primary analysis (November 1, 2022), 11 of 13 maternal participants had completed the study and 2 maternal participants and 6 infants remained in the follow-up period. Ten women did not pass screening owing to the absence of cell-free fetal DNA consistent with an antigen-positive fetus (in 5); to the absence of evidence for mumps, measles, rubella, or varicella immunization (in 2); to not meeting the inclusion criteria for a previous pregnancy involving early-onset severe hemolytic disease of the fetus and newborn (in 1); and to meeting the exclusion criteria for a clinically significant medical condition (in 2; 1 with a history of genital herpes and 1 with a history or presence of a clinically significant medical condition). In 1 participant, the pregnancy was terminated at 17 weeks' gestation (after the receipt of three weekly doses of nipocalimab) owing to a familial genetic disorder unrelated to hemolytic disease of the fetus and newborn or to treatment; this participant was included only in the summaries of exposure, adverse events, and clinical abnormalities. The participant enrolled again for the next pregnancy, and data from that pregnancy were summarized for the safety, efficacy, pharmacokinetic, pharmacodynamic, and immunogenicity analyses.

striction, placental insufficiency, fetal heart-rate abnormalities during nipocalimab infusions, birth weight, and Apgar scores. Pharmacodynamic analyses included maternal and neonatal total IgG levels and the maternal alloantibody titer at prespecified and available time points.

STATISTICAL ANALYSIS

Assuming that the underlying percentage of pregnant participants treated with nipocalimab who met the primary end point would be at least 40%, we estimated that a planned sample of approximately 15 pregnant participants would provide the study with 78% power to rule out a 10% or lower possibility of success regarding the primary end point, at a two-sided alpha level of 0.05. The value of 10% was determined as a clinically meaningful difference (i.e., margin) from the historical data set we used in which no persons (0%) met the primary end point, according to the published literature and to unpublished data obtained with permission before the initiation of the study (Fig. S2).[13,15,16] A primary end point outside the 10% clinically meaningful margin as determined on the basis of a 95% confidence interval (Clopper–Pearson) would be identical to a two-sided exact test for binomial proportions at the 0.05 level of significance.

For qualitative comparisons, we used descriptive statistics or counts with percentages prespecified for selected secondary end points in the study pregnancies and the same end points in the most recent qualifying pregnancies. The same identification numbers are used to describe maternal participants and their infants reported in this study. Additional details are provided in the statistical analysis plan (available with the protocol).

RESULTS

PARTICIPANTS

From April 23, 2019, to November 1, 2022, a total of 19 national or regional HDFN referral centers screened 23 women with singleton pregnancies. Among these women, 13 were enrolled in the study, with 14 pregnancies, at 8 centers in seven countries (Fig. 1). One participant was enrolled twice, with the first pregnancy excluded from the efficacy analysis owing to early elective termination because of hyperoxaluria type I. According to sequential dose adjustments, nipocalimab was administered at a dose of 30 mg per

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Table 1. Demographic and Baseline Clinical Characteristics of the Participants and Their Qualifying Pregnancies.*

Characteristic	Participants (N=13)
Demographic characteristics at enrollment	
Age — yr	35.8±4.8
White race — no. (%)†	12 (92)
Body-mass index‡	26.4±6.2
Median gravidity, excluding study pregnancy (range)	3 (2–11)
Median time between study pregnancy and last qualifying pregnancy (range) — yr§	3.9 (0.3–10.9)
Median time between study pregnancy and last HDFN-affected pregnancy (range) — yr¶	1.3 (0.1–7.5)
Most recent qualifying pregnancy	
Live birth — no. (%)	5 (38)
Median gestational age at delivery (range)	23 wk 6 days (18 wk 3 days–36 wk 6 days)
Vaginal delivery — no. (%)	7 (54)
Fetal hydrops — no. (%)	7 (54)
Median gestational age at first intrauterine transfusion (range)	20 wk 4 days (17 wk 1 day–23 wk 5 days)
Median no. of intrauterine transfusions (range)	3 (1–11)
D alloantibody type — no. (%)	11 (85)
Intravenous immune globulin — no. (%)	5 (38)

* Plus–minus values are means ±SD. HDFN denotes hemolytic disease of the fetus and newborn.
† Race was reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The time between the study pregnancy and the last qualifying pregnancy was defined as the elapsed time in years between delivery in the last qualifying pregnancy and the date of conception of the study pregnancy. The date of conception of the study pregnancy was defined as the date of informed consent minus the gestational age at informed consent.
¶ The time between the study pregnancy and the last HDFN-affected pregnancy was defined as the elapsed time in years between delivery in the last HDFN-affected pregnancy (if the last qualifying pregnancy was not the last HDFN-affected pregnancy) or the last qualifying pregnancy (if the last qualifying pregnancy was the last HDFN-affected pregnancy) and the date of conception of the study pregnancy. An HDFN-affected pregnancy was defined as pregnancy with an antigen-positive fetus.

kilogram of baseline body weight in three participants; at a dose of 30 mg per kilogram initially but switched to 45 mg per kilogram of baseline body weight in the next 2 participants; at a dose of 45 mg per kilogram of baseline body weight in the following 5 participants (including the participant with an early termination of pregnancy); and at a dose of 45 mg per kilogram of current body weight in the last 4 participants.

At the time of this primary analysis, 11 maternal participants (85%) had completed all study visits, and all 13 (100%) had completed the week 4 postpartum visit. Of 12 live-born infants, 5 (42%) completed all the study visits, 6 (50%) completed the week 48 visit, and 10 (83%) completed the week 24 visit. Two maternal participants and 6 infants were continuing in the study for safety monitoring (Table S4).

The baseline characteristics of the maternal participants and neonates are shown in Table 1 and Tables S5 and S6. A total of 11 participants (85%) had anti-D alloantibodies, and 2 (15%) had anti-K alloantibodies. Three participants had anti-D alloantibodies alone, 7 participants also had anti-C alloantibodies, and 1 had additional anti-C, anti-Fy^a, and anti-Jk^a alloantibodies. The 2 participants with anti-K alloantibodies had no other alloantibodies. These alloantibody characteristics indicate a high risk of fetal anemia.[25]

The median gestational age at the start of nipocalimab treatment was 14 weeks and 1 day (range, 13 weeks and 1 day to 15 weeks and 3 days). The median number of nipocalimab administrations was 21 (range, 6 to 23), and the median duration of treatment was 20 weeks (range, 5 to 22).

PRIMARY END POINT

Live birth at 32 weeks' gestation or later without an intrauterine transfusion (the primary efficacy end point) occurred in 7 of 13 study pregnancies (54%; 95% confidence interval, 25 to 81), which was significantly higher than the 10% clinically meaningful difference from the historical benchmark (P<0.001) (Table 2). All 7 pregnant women who met the primary end point had been treated until 35 weeks' gestation; 5 of these participants (71%) had received 45 mg per kilogram of baseline or current weight (Fig. 2).

One participant (Participant 8) discontinued treatment at 35 weeks' gestation (at the week 34 visit) and delivered at 36 weeks' gestation because of anxiety that was due to a transitory decrease in fetal movements. Among the six study pregnancies (46%) in which the primary end point was not met, fetal anemia leading to intrauterine transfusion occurred in five. Three participants discontinued because of stopping criteria related to intrauterine transfusion. Two participants met stopping criteria owing to adverse events (one adverse event of grade 3 fetal anemia resulting in emergency delivery 2 weeks after the only intrauterine transfusion and one adverse event of fetal demise within 1 day after the only intrauterine transfusion). The remaining

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Table 2. Antenatal and Postnatal End Points in the Most Recent Qualifying Pregnancy and the Study Pregnancy.*

End Point	Most Recent Qualifying Pregnancy (N=13)	Study Pregnancy (N=13)
Primary efficacy end point		
Live birth at ≥32 wk of gestation without intrauterine transfusion — no. (%)	0	7 (54)
Antenatal outcomes		
Live birth — no. (%)†	5 (38)	12 (92)
Median gestational age at delivery (IQR)	33 wk 0 days (32 wk 0 days–35 wk 0 days)	36 wk 5 days (36 wk 0 days–37 wk 1 day)
Median no. of intrauterine transfusions per participant (IQR)	5 (5–5)	0 (0–3)
≥1 Intrauterine transfusion — no. (%)	11 (85)	6 (46)
Median gestational age at first intrauterine transfusion (IQR)	20 wk 4 days (18 wk 2 days–22 wk 1 day)	27 wk 1 day (24 wk 1 day–29 wk 4 days)
Median gestational age at delivery (IQR)	23 wk 6 days (21 wk 0 days–32 wk 0 days)	36 wk 4 days (35 wk 6 days–37 wk 1 day)
Fetal hydrops — no. (%)†	7 (54)	0
Postnatal outcomes in neonates and infants		
Phototherapy in neonates — no./total no. (%)	4/5 (80)	11/12 (92)
Exchange transfusion in neonates — no./total no. (%)	0/5	1/12 (8)
Simple erythrocyte transfusion in neonates and infants — no./total no. (%)	4/5 (80)	6/12 (50)

* IQR denotes interquartile range.
† Fetal loss (stillbirth) and fetal hydrops related to HDFN in the qualifying pregnancy were options for inclusion.

participant discontinued owing to a subchorionic hematoma and fetal-growth restriction but received intrauterine transfusions 4 weeks later (Fig. 2B).

SECONDARY END POINTS

Results for secondary end points in the study pregnancies and in the most recent qualifying pregnancies are shown in Figure 2 and Table 2. Intrauterine transfusions occurred less often and at a later gestational age in the study pregnancies than in the most recent qualifying pregnancies. More live births occurred in the study pregnancies than in the qualifying pregnancies.

Exchange transfusion was performed in 1 of 12 neonates from the study pregnancies (who also received one simple transfusion) and in none of the 5 from qualifying pregnancies. As compared with the 4 infants from the 13 qualifying pregnancies, a smaller proportion of infants in the study had simple transfusions, and all the simple transfusions during the study occurred at more than 2 weeks of age. Among the 7 study pregnancies in which the primary end point was met, 6 maternal–infant pairs (i.e., 46% of the 13 pregnancies) received no antenatal or postnatal transfusions; 1 neonate received one simple transfusion.

DELIVERY OUTCOMES FOR LIVE BIRTHS IN STUDY PREGNANCIES

The median birth weight was 2.8 kg (range, 0.9 to 4.0). Ten of 12 participants (83%) delivered at 34 weeks' gestation or later. Apgar scores at 5 minutes and 10 minutes ranged from 8 to 10, except for one newborn who had scores of 5 and 7, respectively (Table S7). The median duration of neonatal intensive care was 5 days (range, 2 to 64).

PHARMACODYNAMICS

At 18 weeks' gestation, maternal IgG levels had decreased by 85% from baseline; the levels remained low during treatment and began returning to baseline levels at 1 to 2 weeks after receipt of the last dose of nipocalimab. The IgG level had returned to the normal range by postpartum week 4 among participants who received IVIG and by postpartum week 24 among those who did not receive

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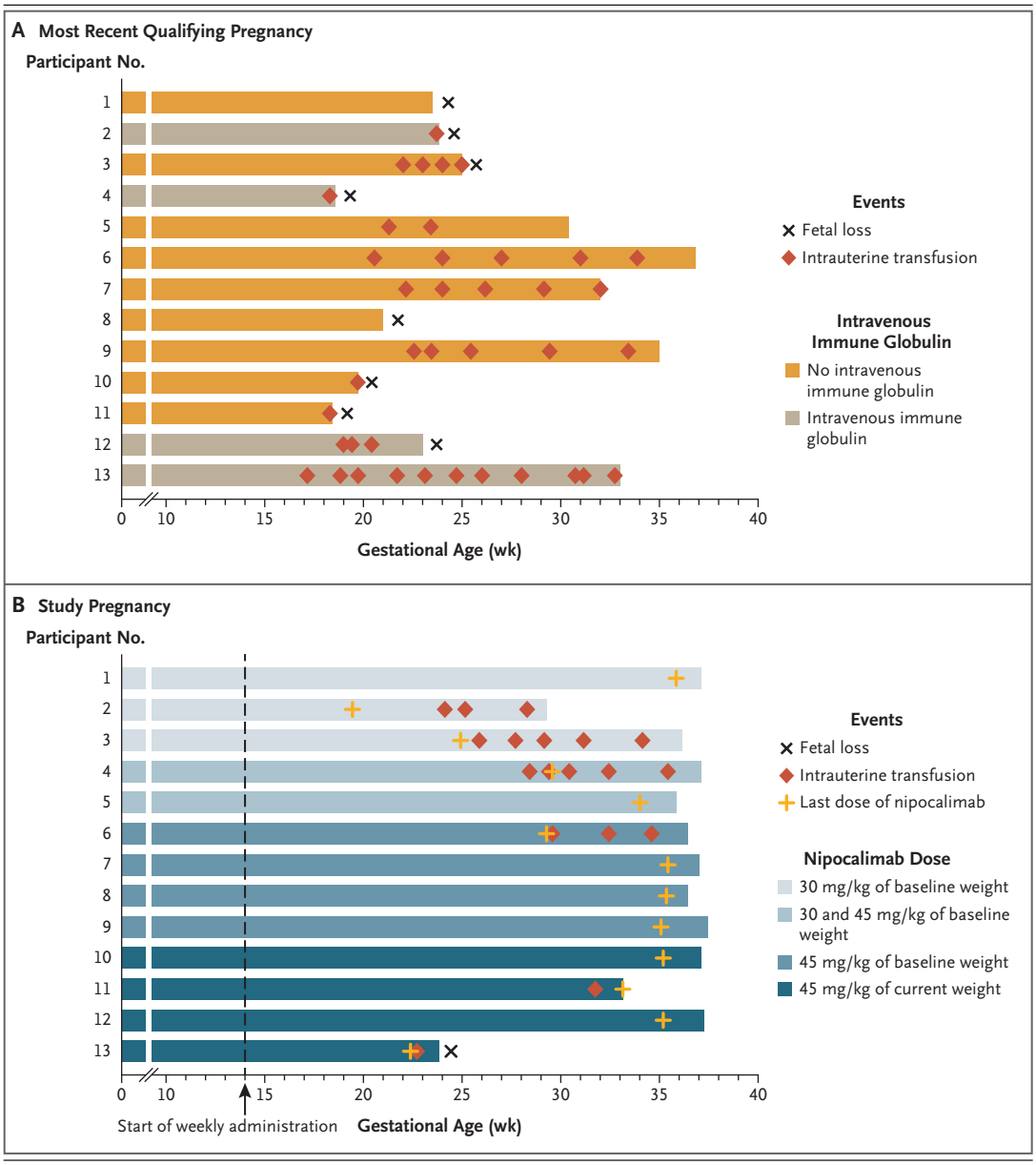

IVIG (Table S8). During treatment, maternal alloantibody titers decreased by 4 to 32 times from baseline; titers returned to near baseline or above by postpartum week 4 in 6 participants who had not received an intrauterine transfusion and for whom titer measurements at week 4 were available. Titers in the third trimester of pregnancy increased from their lowest levels by at least 4 times during treatment in two participants who did not receive an intrauterine transfusion and by at least 128 times after a first intrauterine transfusion in three participants — findings consistent with increased risks of fetomaternal hemorrhage in the third trimester and after intrauterine transfusion, respectively.[12,26,27] Details are provided in Figure S3.

In a result consistent with the inhibition of transplacental IgG transfer by nipocalimab, 6 of 10 neonates (60%) had an IgG level of less than 200 mg per deciliter at birth, after nipocalimab treatment was completed to 35 weeks' gestation, despite the use of maternal IVIG supplementation before delivery. In six pregnancies in which alloantibody titers in cord blood were measured at delivery (2 to 3 weeks after the completion of nipocalimab treatment), titers were low and were below maternal titers (Table S9). In three pregnancies in which

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Figure 2 (facing page). Antenatal Outcomes in the Most Recent Qualifying Pregnancy and the Study Pregnancy.

Panel A shows antenatal outcomes in the most recent qualifying pregnancies, and Panel B antenatal outcomes in the study pregnancies, among the 13 participants in the study. In each panel, the length of bars corresponds to the gestational age at delivery. A qualifying pregnancy was one in which the participant presented at 24 weeks' gestation or earlier with documented severe fetal anemia, fetal hydrops with an MCA peak systolic velocity of at least 1.5 multiples of the median, or a previous stillbirth with fetal or placental pathologic features indicative of HDFN. In the current study, Participants 4 and 5 initially received 30 mg per kilogram of baseline weight (with the total dose calculated on the basis of baseline weight), and the dose was escalated to 45 mg per kilogram of baseline weight later in gestation in accordance with a protocol amendment. Participants 11 and 13 had the nipocalimab dose switched from 45 mg per kilogram of body weight at baseline to 45 mg per kilogram of current weight (as assessed every 2 weeks); these two participants were counted in the group that received 45 mg per kilogram of current body weight. The median number of administrations of nipocalimab was 11 (range, 6 to 22) among the three participants who received 30 mg per kilogram of body weight at baseline, 20 (range, 17 to 23) among the two participants who received 30 mg followed by a switch to 45 mg per kilogram of body weight at baseline, 22 (range, 19 to 22) among the four participants who received 45 mg per kilogram of body weight at baseline, and 21 (range, 10 to 22) among the four participants who received 45 mg per kilogram of current body weight. The median duration of weekly treatment was 10 weeks (range, 5 to 21), 19 weeks (range, 16 to 22), 21 weeks (range, 17 to 21), and 20 weeks (range, 9 to 21), respectively. Among participants who discontinued nipocalimab treatment in association with the initiation of intrauterine transfusions, the last dose of nipocalimab was administered between 7 days before and 10 days after the first intrauterine transfusion.

treatment was discontinued more than 7 weeks before delivery, the titers at birth were substantially higher in both cord and maternal blood than those in the six pregnancies in which treatment was discontinued 2 to 3 weeks before delivery.

SAFETY

Serious and Severe Adverse Events

Serious adverse events occurred in 5 of 13 maternal participants (38%), and severe adverse events (of grade ≥3) occurred in 6 (46%); combined, a serious or severe adverse event occurred in 6 maternal participants (46%) (Table 3 and Table S10). A subchorionic hematoma with fetal-growth restriction at 20 weeks' gestation occurred in Participant 2, who had had fetal-growth restriction in the previous pregnancy; this participant discontinued nipocalimab therapy. At 27 weeks' gestation, periodic fetal heart-rate decelerations that were associated with mild, irregular preterm contractions led to hospitalization and delivery at 29 weeks' gestation in this participant.

Participant 7, who had mild polyhydramnios starting at 34 weeks' gestation, received an amniotomy for induction of labor; placental abruption developed, which led to cesarean delivery with postpartum abdominal pain. Participant 13 had complications from an intrauterine transfusion at 22 weeks' gestation, with stillbirth and retained placenta at 23 weeks. Participants 3, 6, and 11 had at least one serious adverse event or severe adverse event of fetal anemia related to HDFN (Table 3). Nipocalimab resulted in mild infusion reactions in 1% of the infusions (3 of 234). All the postinfusion adverse events were mild (Table S11).

Among the 12 neonates and infants, a serious adverse event occurred in 5 (42%) and a severe adverse event in 4 (33%); combined, 8 neonates or infants (67%) had a serious or severe adverse event (Table 3). These events were related to HDFN (jaundice, hyperbilirubinemia, or anemia), prematurity (respiratory distress), and a grade 3 low IgG level at birth in 1 neonate (Table 3 and Table S12). The additional 4 neonates or infants who were born with a grade 1 low IgG level were not reported as having a serious or severe adverse event.

Adverse Events of Special Interest

Maternal adverse events of special interest occurred in 5 of 13 participants (31%) as single instances, except in Participant 4, who had two such events (Table 3). In 4 of these 5 participants, grade 1 or 2 urinary tract infection or bacteriuria occurred, including in Participant 4, who had two urinary tract infections of grade 2. Three of these participants had a urinary tract infection or bacteriuria at 20 to 32 weeks' gestation, when the serum IgG level was 1.6 to 1.9 g per liter. Two additional participants had one adverse event of special interest when the serum IgG level was normal (urinary tract infection at baseline and mastitis at 7 weeks post partum, in 1 participant each).

No cases of hypoalbuminemia as an adverse event of special interest (defined as an albumin level of <20 g per liter) occurred. Expected asymp-

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Table 3. Safety Analyses, According to Nipocalimab Dose Group.*

Event	30 mg/kg of Baseline Weight	30 and 45 mg/kg of Baseline Weight†	45 mg/kg of Baseline Weight	45 mg/kg of Current Weight	Total
In maternal participants					
No. of maternal participants	3	2	4	4	13
Serious adverse event — no. (%)	2 (67)	0	1 (25)	2 (50)	5 (38)
Severe adverse event — no. (%)	2 (67)	0	2 (50)	2 (50)	6 (46)
Serious adverse event or severe adverse event — no. (%)	2 (67)	0	2 (50)	2 (50)	6 (46)
Any pregnancy, puerperium, or perinatal condition	1 (33)	0	1 (25)	1 (25)	3 (23)
Fetal death	0	0	0	1 (25)	1 (8)
Retained placenta or membranes	0	0	0	1 (25)‡	1 (8)
Premature separation of placenta	0	0	1 (25)	0	1 (8)
Fetal-growth restriction	1 (33)	0	0	0	1 (8)
Subchorionic hematoma	1 (33)	0	0	0	1 (8)
Fetal heart-rate deceleration abnormality	1 (33)	0	0	0	1 (8)
Abdominal pain	0	0	1 (25)§	0	1 (8)
Fetal anemia	1 (33)	0	1 (25)§	1 (25)	3 (23)
Adverse event of special interest — no. (%)	1 (33)	1 (50)	1 (25)	2 (50)	5 (38)
Any infection leading to treatment with oral or intravenous anti-infective agent	1 (33)	1 (50)	1 (25)	2 (50)	5 (38)
Urinary tract infection	1 (33)	1 (50)	0	0	2 (15)
Bacteriuria	0	0	0	1 (25)	1 (8)
Mastitis	0	0	1 (25)	0	1 (8)
Streptococcal urinary tract infection	0	0	0	1 (25)	1 (8)
Hypoalbuminemia¶	0	0	0	0	0
In infants					
No. of infants	3	2	4	3	12
Serious adverse event — no. (%)	2 (67)	1 (50)	1 (25)	1 (33)	5 (42)
Severe adverse event — no. (%)	1 (33)	1 (50)	1 (25)	1 (33)	4 (33)
Serious adverse event or severe adverse event — no. (%)	3 (100)	2 (100)	2 (50)	1 (33)	8 (67)
Neonatal respiratory distress syndrome	1 (33)‡	0	0	1 (33)	2 (17)
Jaundice, hyperbilirubinemia, or neonatal hyperbilirubinemia	2 (67)	1 (50)	1 (25)	1 (33)§	5 (42)
Anemia or neonatal anemia	1 (33)§	2 (100)‖	1 (25)§	1 (33)	5 (42)
Upper respiratory tract infection	0	0	0	1 (33)‡**	1 (8)
Blood IgG decreased	0	0	1 (25)§	0	1 (8)
Adverse event of special interest — no. (%)	1 (33)	2 (100)	0	1 (33)	4 (33)
Infection resulting in treatment with oral or intravenous anti-infective agent	1 (33)	1 (50)	0	0	2 (17)
Oral candida infection	0	0	0	1 (33)	1 (8)
Ear infection††	0	1 (50)	0	0	1 (8)
Otorrhea††	0	1 (50)	0	0	1 (8)
IgG decreased‡‡	1 (33)	2 (100)	0	0	3 (25)
Unusual childhood illness	0	0	0	0	0

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Table 3. (Continued.)

* For participants whose dose was based on baseline weight, the total dose was calculated on the basis of the body weight at baseline. For those whose dose was based on time-adjusted weight, the total dose was calculated on the basis of the current body weight (assessed every 2 weeks). The number of participants was counted only once for any given event, regardless of the number of times the participant actually had the event. Adverse events were classified on the basis of the Common Terminology Criteria for Adverse Events, version 5.0, of the National Cancer Institute and were coded with the use of the *Medical Dictionary for Regulatory Activities*, version 26.0.
† Participants 4 and 5 initially received 30 mg per kilogram of baseline weight, and the dose was escalated to 45 mg per kilogram of baseline weight later in gestation in accordance with a protocol amendment.
‡ The event was classified only as a serious adverse event.
§ The event was classified only as a severe adverse event of grade 3 or higher.
¶ Hypoalbuminemia was defined as an albumin level of less than 20 g per liter.
‖ One participant had a serious adverse event only, and one participant had a severe adverse event only.
** This event of upper respiratory infection was a grade 2 adverse event and thus was not assessed as severe. However, the event was considered to be serious because the infant was hospitalized in accordance with the mother's request. No pharmacologic intervention was administered.
†† A decrease in the IgG level (defined below) and infections (adverse events of special interest) developed in the infant, but the infections occurred more than 1 year after the IgG level decreased.
‡‡ A decreased IgG level as an adverse event of special interest was defined as a level of less than 200 mg per deciliter at weeks 24 to 47 of age or as a level of less than 300 mg per deciliter at weeks 48 to 96 of age.

tomatic, clinically nonsignificant hypoalbuminemia that was related to nipocalimab treatment was observed, and the albumin level trended toward baseline after receipt of the last dose of nipocalimab (Fig. S4).

Adverse events of special interest occurred in 4 of 12 neonates or infants (33%). These events primarily were single infections that resolved after treatment or were events of decreased IgG levels (Table 3). In Infant 10, a grade 2 adverse event of special interest of oral candida occurred at 1 to 2 weeks of life along with an adverse event of a grade 1 decrease in the IgG level (1.3 to 1.8 g per liter). Infant 5, who had a decreased IgG level (1.6 g per liter) at birth before IVIG supplementation, later had three grade 1 ear infections. The onset of the first ear infection occurred at 53 weeks of life, when the IgG level was 3 g per liter (near the lower limit of the normal range [3.45 g per liter]). The resolution of the last ear infection was at 85 weeks of life (with no available IgG values). Two additional infants with low IgG levels at 25 weeks of life (Infant 3 [IgG level, 1.8 g per liter] and Infant 4 [IgG level, 1.9 g per liter]; lower limit of the normal range, 1.7 g per liter) had no concurrent or previous infections. No unusual childhood illnesses were observed.

DISCUSSION

The results of the primary analysis of this study support the efficacy of nipocalimab therapy in pregnancies at high risk for recurrent early-onset severe HDFN. Live birth at 32 weeks' gestation or later without intrauterine transfusion (the primary end point) occurred in 54% of the pregnancies, which exceeded the 10% margin for the historical benchmark. Almost half the maternal–infant pairs received no antenatal or neonatal transfusions.

In qualitative comparisons, outcomes in nipocalimab-treated pregnancies appeared to be substantially better than those of the most recent qualifying pregnancies or those reported in publications regarding the current management of early-onset severe HDFN.[16-18] In previous studies of similarly high-risk pregnancies with similar live-birth rates, the median gestational age at the first intrauterine transfusion was 20 to 22 weeks (with or without IVIG), as compared with 27 weeks for nipocalimab-treated pregnancies.[16-18] The delayed onset of severe fetal anemia or avoidance of intrauterine transfusions with nipocalimab, if confirmed, may substantially improve outcomes in this at-risk population.

IVIG is used in some cases of early-onset severe HDFN on the basis, in part, of its competitive FcRn inhibition, which is similar to nipocalimab,[28] but intrauterine transfusions are still used in the large majority of cases, despite the use of IVIG.[16-18] The favorable outcomes that we observed with nipocalimab therapy are probably due to its FcRn-binding affinity, which is more than 1000 times that of IVIG and thus potentially affords greater inhibition of transplacental alloantibody transfer and lowering of the maternal alloantibody titer.[19,29] The decrease in the maternal alloantibody titer of 4 to 32 times that was observed with nipocalimab, as compared with the decrease of 35 to 43% that was reported with IVIG,[17,30,31] supports this hypothesis.

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In a finding consistent with the anticipated mechanisms of nipocalimab, we observed substantial decreases in the maternal IgG level (85% below baseline) and low cord-blood IgG levels. However, nipocalimab treatment is not expected to affect non-IgG immunoglobulins, key immune-cell functions, or IgG production, nor is it expected to result in pharmacologically significant transplacental transfer of nipocalimab.[19-21,32] In general, immune and vaccine responses are retained with FcRn blockers.[21,33] Such responses are being evaluated in an ongoing phase 3 trial (ClinicalTrials.gov number, NCT05912517).

Potential blunting of passive immunity may be mitigated by breast-feeding and other strategies.[34,35] Infections that led to the use of antibiotic agents (adverse events of special interest) were low-grade and typical for perinatal and neonatal periods, with an incidence in the study population similar to that previously reported in a general pregnancy population (38% vs. 37%[36]) or in a pediatric population (17% vs. 14%[37]), respectively. Overall, no unusual or serious infections were observed in our study. However, given the small sample size, further data are needed to better inform the risks of infection associated with this agent.

Limitations of this study other than the small sample size include the lack of blinding, randomization, placebo comparator, and representation of non-White patients (Table S13). The historical cohort and qualifying pregnancies were managed outside a study protocol, possibly under different standards of care and with care obtained not at experienced referral centers. The incidence of fetal death or hydrops in qualifying pregnancies was high. However, outcomes are commonly similar or worse in pregnancies that occur after antecedent early-onset severe HDFN.[30]

In this single-group study, the use of nipocalimab in pregnancies at high risk for early-onset severe HDFN resulted in a substantially higher percentage of pregnancies with live birth at 32 weeks' gestation or later without intrauterine transfusions than the historical benchmark. These preliminary efficacy results, together with the preliminary safety data and evidence of the anticipated drug mechanisms, support the further evaluation of nipocalimab in severe HDFN.

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APPENDIX

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REFERENCES

1. Canlorbe G, Macé G, Cortey A, et al. Management of very early fetal anemia resulting from red-cell alloimmunization before 20 weeks of gestation. Obstet Gynecol 2011;118:1323-9.
2. Lindenburg ITM, van Kamp IL, van Zwet EW, Middeldorp JM, Klumper FJCM, Oepkes D. Increased perinatal loss after intrauterine transfusion for alloimmune anaemia before 20 weeks of gestation. BJOG 2013;120:847-52.
3. Yinon Y, Visser J, Kelly EN, et al. Early intrauterine transfusion in severe red blood cell alloimmunization. Ultrasound Obstet Gynecol 2010;36:601-6.
4. Bhutani VK, Zipursky A, Blencowe H, et al. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res 2013; 74:Suppl 1:86-100.
5. Yu D, Ling LE, Krumme AA, Tjoa ML, Moise KJ Jr. Live birth prevalence of hemolytic disease of the fetus and newborn in the United States from 1996 to 2010. AJOG Glob Rep 2023;3:100203.
6. Brackney K, Labbad G, Hersh A, et al. Missed anti-D immune globulin administration to postpartum patients in 2 health systems: an unrecognized patient safety risk. AJOG Glob Rep 2022;2:100038.
7. Slootweg YM, Zwiers C, Koelewijn JM, et al. Risk factors for RhD immunisation in a high coverage prevention programme of antenatal and postnatal RhIg: a nationwide cohort study. BJOG 2022;129:1721-30.
8. Bowman J. Thirty-five years of Rh prophylaxis. Transfusion 2003;43:1661-6.
9. de Haas M, Finning K, Massey E, Roberts DJ. Anti-D prophylaxis: past, present and future. Transfus Med 2014;24:1-7.
10. Society for Maternal-Fetal Medicine (SMFM), Mari G, Norton ME, et al. Society for Maternal–Fetal Medicine (SMFM) clinical guideline #8: the fetus at risk for anemia — diagnosis and management. Am J Obstet Gynecol 2015;212:697-710.
11. Zwiers C, Lindenburg ITM, Klumper FJ, de Haas M, Oepkes D, Van Kamp IL. Complications of intrauterine intravascular blood transfusion: lessons learned after 1678 procedures. Ultrasound Obstet Gynecol 2017;50:180-6.
12. Tiblad E, Kublickas M, Ajne G, et al. Procedure-related complications and perinatal outcome after intrauterine transfusions in red cell alloimmunization in Stockholm. Fetal Diagn Ther 2011;30:266-73.
13. Colpo A, Tison T, Gervasi MT, et al. Personalized treatment with immunoadsorption and intravenous immunoglobulin in a case of severe Rh alloimmunization during pregnancy unresponsive to plasma-exchange. Transfus Apher Sci 2017;56:480-3.
14. Nwogu LC, Moise KJ Jr, Klein KL, Tint H, Castillo B, Bai Y. Successful management of severe red blood cell alloimmunization in pregnancy with a combination of therapeutic plasma exchange, intravenous immune globulin, and intrauterine transfusion. Transfusion 2018;58:677-84.
15. Ruma MS, Moise KJ Jr, Kim E, et al. Combined plasmapheresis and intravenous immune globulin for the treatment of severe maternal red cell alloimmunization. Am J Obstet Gynecol 2007;196(2): 138.e1-138.e6.
16. Zwiers C, van der Bom JG, van Kamp IL, et al. Postponing Early intrauterine Transfusion with Intravenous immunoglobulin Treatment: the PETIT study on severe hemolytic disease of the fetus and newborn. Am J Obstet Gynecol 2018; 219(3):291.e1-291.e9.
17. Maisonneuve E, Dugas A, Friszer S, et al. Effect of intravenous immunoglobulins to postpone the gestational age of first intrauterine transfusion in very severe red blood cell alloimmunization: a case-control study. J Gynecol Obstet Hum Reprod 2021;50:102119.
18. Vlachodimitropoulou E, Lo TK, Bambao C, et al. Intravenous immunoglobulin in the management of severe early onset red blood cell alloimmunisation. Br J Haematol 2023;200:100-6.
19. Ling LE, Hillson JL, Tiessen RG, et al. M281, an anti-FcRn antibody: pharmacodynamics, pharmacokinetics, and safety across the full range of IgG reduction in a first-in-human study. Clin Pharmacol Ther 2019;105:1031-9.
20. Roy S, Nanovskaya T, Patrikeeva S, et al. M281, an anti-FcRn antibody, inhibits IgG transfer in a human ex vivo placental perfusion model. Am J Obstet Gynecol 2019;220(5):498.e1-498.e9.
21. Moise KJ Jr, Oepkes D, Lopriore E, Bredius RGM. Targeting neonatal Fc receptor: potential clinical applications in pregnancy. Ultrasound Obstet Gynecol 2022;60:167-75.
22. Wentworth P. The placenta in cases of hemolytic disease of the newborn. Am J Obstet Gynecol 1967;98:283-9.
23. Scheffer PG, Ait Soussan A, Verhagen OJHM, et al. Noninvasive fetal genotyping of human platelet antigen-1a. BJOG 2011; 118:1392-5.
24. de Haas M, Thurik FF, van der Ploeg CPB, et al. Sensitivity of fetal *RHD* screening for safe guidance of targeted anti-D immunoglobulin prophylaxis: prospective cohort study of a nationwide programme in the Netherlands. BMJ 2016; 355:i5789.
25. Markham KB, Rossi KQ, Nagaraja HN, O'Shaughnessy RW. Hemolytic disease of the fetus and newborn due to multiple maternal antibodies. Am J Obstet Gynecol 2015;213(1):68.e1-68.e5.
26. Urbaniak SJ, Greiss MA. RhD haemolytic disease of the fetus and the newborn. Blood Rev 2000;14:44-61.
27. Schonewille H, Klumper FJCM, van de Watering LMG, Kanhai HHH, Brand A. High additional maternal red cell alloimmunization after Rhesus- and K-matched intrauterine intravascular transfusions for hemolytic disease of the fetus. Am J Obstet Gynecol 2007;196(2):143.e1-143.e6.
28. Shock A, Humphreys D, Nimmerjahn F. Dissecting the mechanism of action of intravenous immunoglobulin in human autoimmune disease: lessons from therapeutic modalities targeting Fcγ receptors. J Allergy Clin Immunol 2020;146: 492-500.
29. Pyzik M, Sand KMK, Hubbard JJ, Andersen JT, Sandlie I, Blumberg RS. The neonatal Fc receptor (FcRn): a misnomer? Front Immunol 2019;10:1540.
30. Moise KJ Jr. Immunomodulation for early-onset haemolytic disease of the fetus/newborn: can we delay the need for intrauterine transfusions? Br J Haematol 2023;200:11-2.
31. Margulies M, Voto LS, Mathet E, Margulies M. High-dose intravenous IgG for the treatment of severe rhesus alloimmunization. Vox Sang 1991;61:181-9.
32. Ling LE, Tyler S, Beneduce CJ, et al. Nipocalimab's selective targeting of FcRn and IgG clearance preserves key immune functions. Neurology 2022;98:Suppl:S5-S6 (https://www.neurology.org/doi/10.1212/WNL.98.18_supplement.1826).
33. Guptill JT, Sleasman JW, Steeland S, et al. Effect of FcRn antagonism on protective antibodies and to vaccines in IgG-mediated autoimmune diseases pemphigus and generalised myasthenia gravis. Autoimmunity 2022;55:620-31.
34. Meek JY, Noble L, Section on Breastfeeding. Policy statement: breastfeeding and the use of human milk. Pediatrics 2022;150(1):e2022057988.
35. Jones JM, Fleming-Dutra KE, Prill MM, et al. Use of nirsevimab for the prevention of respiratory syncytial virus disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices — United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:920-5.
36. Stokholm J, Schjørring S, Pedersen L, et al. Prevalence and predictors of antibiotic administration during pregnancy and birth. PLoS One 2013;8(12):e82932.
37. Gerber JS, Bryan M, Ross RK, et al. Antibiotic exposure during the first 6 months of life and weight gain during childhood. JAMA 2016;315:1258-65.

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