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Understanding Preterm Birth in Pregnancies Complicated by Nonimmune Hydrops Fetalis

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Abstract

Objective—Nonimmune hydrops fetalis (NIHF) is associated with poor perinatal outcomes including preterm birth (PTB). However, the frequency and causes of PTB in this population are not well understood. We hypothesized that NIHF frequently results in PTB due to medically indicated delivery for fetal distress.

Study Design—This was a secondary analysis of a prospectively enrolled cohort of pregnancies with NIHF that underwent exome sequencing if standard testing was nondiagnostic. The primary outcome was frequency of PTB at <37 weeks' gestation. Secondary outcomes were reasons for PTB, fetal predictors of PTB, and frequency of neonatal death following PTB.

Results—Fifty-six cases were included, with a median gestational age at delivery of 32.8 weeks (interquartile range [IQR]: 30.3–35.0). Overall, 86% (48/56) were delivered preterm. Among 48 PTBs, 18 (38%) were spontaneous, 9 (19%) were medically indicated for maternal indications (primarily preeclampsia), and 21 (44%) were medically indicated for fetal indications (nonreassuring antenatal testing or worsening effusions). Neither fetal genetic diagnosis nor polyhydramnios was associated with PTB.

Conclusion—More than four-fifths of pregnancies with NIHF result in PTB, often due to nonreassuring fetal status. These data are informative for counseling patients and for developing strategies to reduce PTB in pregnancies with NIHF.

Keywords

preterm birth; nonimmune hydrops fetalis; hydrops; fetal fluid; collections; fetal effusions

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Conflict of Interest

None declared.

Nonimmune hydrops fetalis (NIHF) is a rare complication of pregnancy, but one that is associated with high risks of preterm birth (PTB), fetal genetic disorders, poor neonatal outcomes, and maternal morbidity.[1–4] Given the neonatal risks inherent to PTB and lack of clear evidence to support improved outcomes for hydropic neonates delivered preterm, early delivery is generally not recommended in the absence of fetal or maternal clinical deterioration.[2] However, approximately two-thirds of pregnancies complicated by NIHF result in PTB.[3–6]

It is not known whether PTBs in pregnancies with NIHF are primarily spontaneous or medically indicated, or which of these pregnancies are at greatest risk of this outcome. One factor underlying spontaneous PTB may be polyhydramnios, which is known to complicate NIHF pregnancies and may predispose to PTB.[4,7,8] Preeclampsia is also associated with NIHF pregnancies and its development often necessitates medically indicated delivery.[9] Additional risk factors for PTB may include underlying fetal genetic disorders, fetal distress, and earlier diagnosis of fetal fluid collections.[1,10] To develop strategies to reduce PTB in pregnancies complicated by NIHF, a better understanding of the frequency and reasons for PTB is necessary.

Our objective was to describe the frequency of PTB in a contemporary cohort of pregnancies with NIHF and to identify indications for PTB in this population, fetal risk factors for PTB, and neonatal mortality risk following spontaneous versus medically indicated PTB. We hypothesized that PTB would occur in the majority of pregnancies with NIHF, and that a substantial proportion would result from medically indicated delivery for fetal distress.

Materials and Methods

This is a secondary analysis of a prospectively enrolled cohort study (HyDROPS; Hydrops: Diagnosing and Redefining Outcomes with Precision Study), which was designed to assess the presenting features, genetic etiologies, and postnatal outcomes of NIHF and other abnormal fetal fluid collections.[1] Participants were initially enrolled from the five University of California Fetal-Maternal Consortium sites (UCfC; UC Davis, UC Irvine, UC Los Angeles, UC San Diego, and UC San Francisco [UCSF]), but due to the overall rare prevalence of NIHF, enrollment was further broadened to allow referrals from any other site in the United States. The study was approved by the UC San Francisco Institutional Review Board and participants provided written informed consent.

While in the primary study, cases of NIHF as well as single abnormal fluid collection were included (including enlarged nuchal translucency), for this study only cases of NIHF with two or more abnormal fluid collections were included. Cases enrolled in the primary cohort had standard evaluations recommended for NIHF including karyotype and/or chromosomal microarray, and those that were unexplained after these standard evaluations received exome sequencing.[2] Hydrops cases due to alloimmunization, viral infection, or twin-twin transfusion syndrome were excluded from the primary study. For this study, because the primary outcome was frequency of PTB, we further excluded cases that resulted in termination or pregnancy loss as this would be a competing outcome for PTB, as well as multifetal gestations given their strong association with PTB. We also excluded two cases

that declined exome sequencing to completely assess the role of underlying fetal genetic diagnoses.

The primary outcome of this study was frequency of PTB, defined as delivery before 37 weeks' gestation. Secondary outcomes were (1) reasons for PTB (including spontaneous PTB due to preterm labor, spontaneous PTB following preterm premature rupture of membranes [PPROM], medically indicated PTB for maternal indications, or medically indicated PTB for fetal indications), (2) fetal predictors of PTB (including underlying genetic diagnosis and polyhydramnios), and (3) frequency of neonatal death following spontaneous PTB versus medically indicated PTB. Spontaneous PTB included cases of spontaneous preterm labor as well as labor augmentation following PPROM, while medically indicated PTB included cases delivered preterm in the absence of spontaneous labor or PPROM for either maternal or fetal indications.

The study database included detailed information regarding demographics; obstetric, medical, and family history; pregnancy complications; genetic testing; ultrasound findings; delivery data; and postnatal outcomes until discharge from the birth hospitalization. Neonatal demise was defined as death during the initial birth hospitalization, or if discharged home, death within the first 30 days of life. Our study team reviewed clinical records to extract detailed data on the diagnosis of abnormal fetal fluid collections, evaluations performed, and reasons for delivery. Maternal race/ethnicity was collected from participants directly based on self-identification. Polyhydramnios was defined as amniotic fluid index ≥24 cm and/or deepest vertical pocket ≥8cm.[11] Fetal anomalies and types of fetal fluid collections were recorded as documented in prenatal imaging reports.

All cases in the primary cohort had standard karyotype and/or chromosomal microarray performed. For a handful of cases, a gene panel sent by local providers identified a single gene disorder in the fetus. For the remainder of cases that were not explained, exome sequencing was performed through the UCSF Genomic Medicine Laboratory. The diagnostic yield of exome sequencing for abnormal fetal fluid collections in this cohort was previously reported as 29% in cases with nondiagnostic results of standard testing.[1] Genetic variants identified with exome sequencing were reviewed by a multidisciplinary team of bioinformaticians, geneticists, perinatologists, pathologists, and other subspecialists and were classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines.[12] Cases with a pathogenic or likely pathogenic finding on karyotype, microarray, gene panel, or exome sequencing were categorized as having a known or suspected fetal genetic diagnosis. In a few cases, a highly suspicious variant was identified on exome sequencing that did not meet ACMG criteria for pathogenicity or likely pathogenicity; these were considered to have a "suspected fetal genetic diagnosis."

Frequencies for the primary and secondary outcomes were calculated. Univariable analyses were performed using chi-square, Fisher's exact, and Kruskal–Wallis tests as appropriate, with proportions reported for categorical variables and median values with interquartile range (IQR) for continuous variables. Multivariable logistic regression was performed to generate odds ratios (ORs) and directed acyclic graphs were designed to adjust for

confounders. Statistical analyses were performed using STATA version 15.1 (StataCorp, LLC, College Station, TX).

Results

A total of 201 cases were enrolled in the primary cohort. Of these, we excluded 2 due to incomplete delivery documentation, 96 pregnancy losses (12 miscarriages before 20 weeks' gestation, 24 stillbirths after 20 weeks' gestation, and 60 pregnancy terminations), 6 multifetal gestations, and 2 that declined exome sequencing following nondiagnostic results of standard testing. We also excluded 39 cases of isolated fetal effusion (21 with enlarged nuchal translucency only). Fifty-six cases were therefore included in these analyses (►Fig. 1); their demographics are shown in ►Table 1 and included participants who received care in 19 states. Details of ultrasound findings such as types of fetal effusions and structural anomalies are described in ►Table 2.

Overall, 86% of cases (48/56) were delivered at <37 weeks' gestation. The median gestational age at delivery was 32.8 weeks (IQR: 30.3–35.0). Median latency from initial effusion diagnosis to delivery was 8.1 weeks (IQR: 2.0–14.2). Of those who delivered preterm, 38% (18/48) resulted from spontaneous PTB, while 63% (30/48) were medically indicated (►Fig. 2). Among those with spontaneous PTB, 72% (13/18) experienced preterm labor with or without intact membranes, and 28% (5/18) had PPROM after which labor was augmented. Most cases of medically indicated PTB (70%, 21/30) occurred for fetal indications, including new or worsening effusions and nonreassuring antenatal testing. Only 30% (9/30) of medically indicated PTB were for maternal indications; most of these were development of a hypertensive disorder of pregnancy (89%, 8/9). Timing and etiology of delivery are detailed in ►Fig. 2.

At least one fetal procedure was performed in 27% (15/56) of cases. These included 11 percutaneous in utero thoracoamniotic shunt placements (one with concurrent amnioreduction), 2 thoracenteses (one with concurrent amnioreduction), 1 in utero transfusion, and 1 tracheoscopy with amnioinfusion. Latency from procedure to delivery was a median of 3.5 weeks, with an IQR of 1.1 to 8.7 weeks. Spontaneous PTB followed 33% (5/15) of cases that underwent a procedure, while medically indicated PTB followed 60% (9/15).

In terms of fetal risk factors for PTB, polyhydramnios was more common in pregnancies resulting in PTB (present in 50% of deliveries resulting in PTB compared with 25% of term deliveries, ►Table 1), though this was not statistically significant (unadjusted OR: 3, 95% confidence interval [CI]: 0.5–16.4). This remained true when considering only the 42 pregnancies with no history of prior PTB (OR: 6.4, 95% CI: 0.7–58.4). Among 24 pregnancies with polyhydramnios resulting in PTB, 38% (9/24) delivered spontaneously (6 in the setting of preterm labor and 3 with PPROM); the remainder were delivered for fetal (46%, 11/24) or maternal (17%, 4/24) indications. A known or suspected fetal genetic diagnosis was also more common among pregnancies resulting in PTB than those resulting in term birth (50 vs. 15%), but again this was not statistically significant (OR: 3, 95% CI: 0.5–16.4). This finding persisted among the subset of pregnancies with no history of PTB

(OR: 2.6, 95% CI: 0.5–15.5). Among the 24 pregnancies with a known or suspected fetal genetic diagnosis resulting in PTB, 25% (6/24) delivered spontaneously, 50% (12/24) were delivered for fetal indications, and 25% (6/24) were delivered for maternal indications (all hypertensive disorders of pregnancy). These genetic conditions included aneuploidy (4%, 1/24), copy number variants (8% (2/24), and numerous single gene disorders (88%, 21/24).

Finally, neonatal death was significantly associated with PTB, following 73% (35/48) of preterm deliveries but only 17% (1/6) of term deliveries (OR: 13.5, 95% CI: 1.4–126.4). This remained significant after adjusting for known or suspected fetal genetic diagnosis (adjusted OR: 13.6, 95% CI: 1.3–138.6). The risk of neonatal death did not differ following spontaneous versus medically indicated PTB (OR: 0.6, 95% CI: 0.2–2.2). Other perinatal outcomes such as route of delivery, birthweight, and neonatal death are included in ►Table 3.

Discussion

In this secondary analysis of the HyDROPS cohort, PTB complicated 86% of all cases with NIHF, two-thirds of which were delivered for medically indicated reasons (primarily for worsening effusions or nonreassuring fetal status). While polyhydramnios and known or suspected fetal diagnosis were both more common in pregnancies resulting in PTB, these findings did not reach statistical significance.

The overall risk of PTB in our study (86%) was higher than previously reported (66–76%).[4,5,13,14] Because many of the previously published studies on outcomes of hydropic pregnancies included smaller cohorts of patients who delivered many years ago, it is possible that changing protocols for antenatal management with serial ultrasounds and nonstress testing are partially responsible for an increase in PTB, particularly given our finding that most PTBs were iatrogenic for fetal indications. Advances in neonatal care and an increasing expertise in the care of premature newborns may also have contributed to the greater frequency of PTB in our cohort. The overall high frequency of delivery for fetal indications is particularly notable, especially in light of the Society for Maternal-Fetal Medicine recommendation to avoid PTB in pregnancies with NIHF when possible, as preterm delivery has not been shown to improve postnatal outcomes.[2] As the role of antenatal surveillance in pregnancies complicated by fetal fluid collections has not been clearly elucidated, further research understanding how different management strategies contribute to the risk of iatrogenic PTB while balancing risks of stillbirth in ongoing pregnancies would be valuable.

Additionally, our findings that one-third of cases with fetal fluid collections deliver spontaneously suggest that poor fetal status could contribute to spontaneous PTB, potentially through the release of cytokines or other mediators that may trigger the preterm labor cascade. Further investigations are indicated to determine how the risks of both spontaneous and medically indicated PTB might be mitigated for pregnancies with NIHF.[2]

Although the association between PTB and known or suspected fetal genetic diagnosis was not statistically significant, the trend toward significance warrants further evaluation in larger cohorts. It may be that fetal distress or growth restriction is more common in fetuses

with genetic diagnoses than in those without, resulting in higher frequency of iatrogenic PTB. It is also possible that increased fetal monitoring in pregnancies with fetal genetic diagnoses results in more iatrogenic preterm deliveries. Additionally, genetic changes also present in the placenta may alter placental pathophysiology and increase the risk of placental dysfunction or spontaneous PTB. Further research on this topic is needed to understand the impact of fetal genetic diagnoses on placental function, fetal distress, or other ultrasound findings that increase the risk of PTB.

Strengths

This study has several strengths. As the data were prospectively collected for the primary cohort, we had the ability to obtain records for missing variables and ensure completeness of the dataset. This study enrolled participants from across the country and includes a geographically diverse population, with included participants receiving care in 19 states. As management decisions were made by the local care teams, it is a pragmatic study and likely represents the variety of practice patterns that exist currently. It provides unique data with respect to PTB risks associated NIHF and is robust in the genetic evaluations performed such that the risk of PTB can be assessed when an underlying fetal genetic diagnosis is present. There are, however, limitations to this study. While our sample size is large given the prevalence of NIHF, we were limited in our ability to identify statistically meaningful findings, particularly fetal risk factors for PTB. Due to broad national recruitment, it is possible that participants enrolled could represent poorer outcomes and thus reduce the generalizability of our findings. Finally, because the primary cohort excluded viral etiologies of NIHF, and all cases that were not explained by standard testing received exome sequencing, we anticipate that our cohort contains a greater proportion of cases with an underlying fetal genetic disease.

Conclusion

In conclusion, we found that PTB occurs in approximately 86% of contemporary cases with NIHF, most commonly for fetal indications. These findings are important for both patient counseling and antenatal management. Further research will be essential to develop strategies for mitigating fetal and maternal risks in these pregnancies, to decrease the risk of PTB and improve outcomes for this highly morbid condition.

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Key Points

- Pregnancies complicated by nonimmune hydrops fetalis often result in preterm birth.
- Preterm birth in these cases is most often medically indicated for fetal benefit.
- Fetal genetic conditions and polyhydramnios may be associated with preterm birth in cases of NIHF.

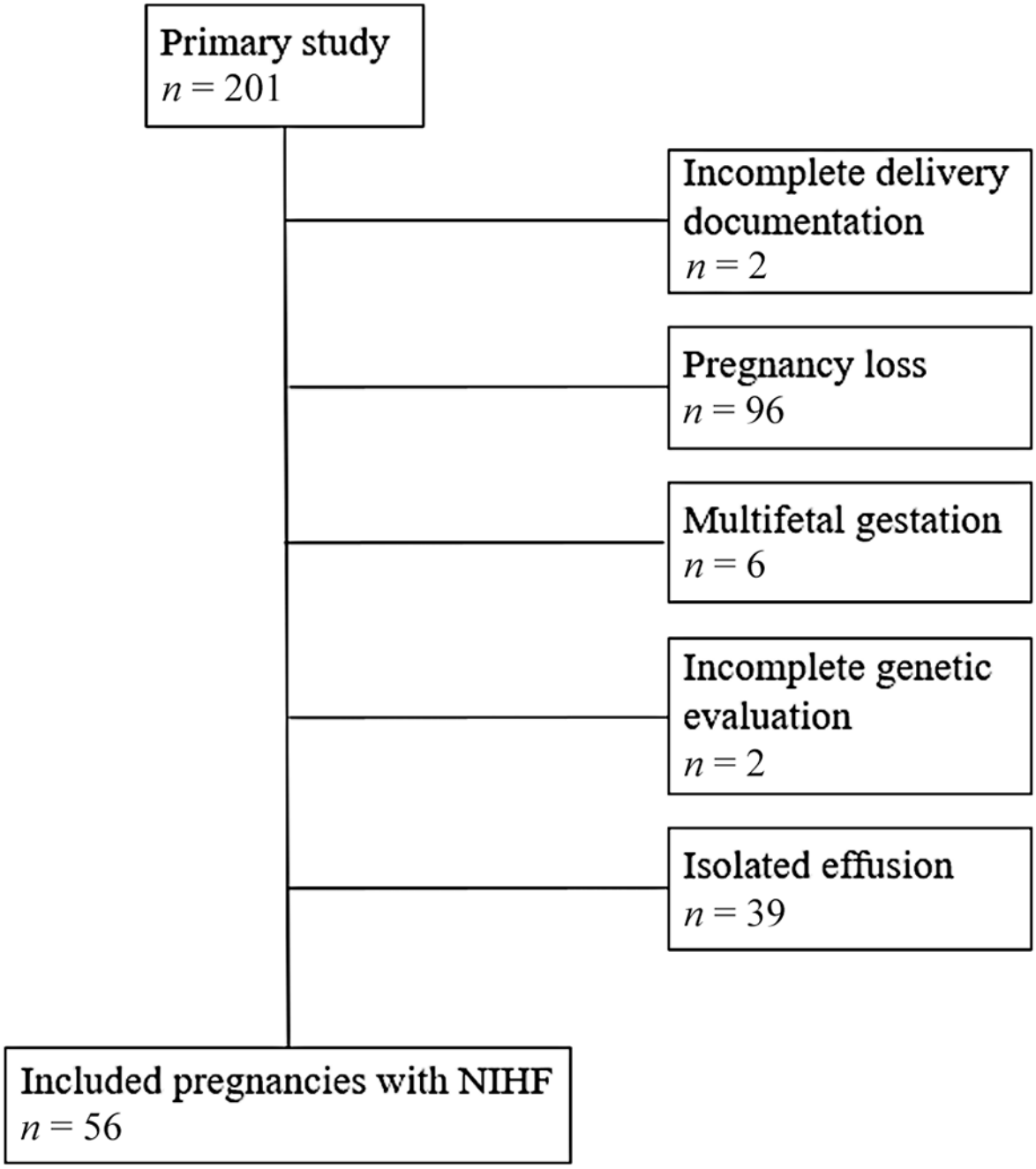

Fig. 1.
Inclusion and exclusion of patients in this secondary analysis.

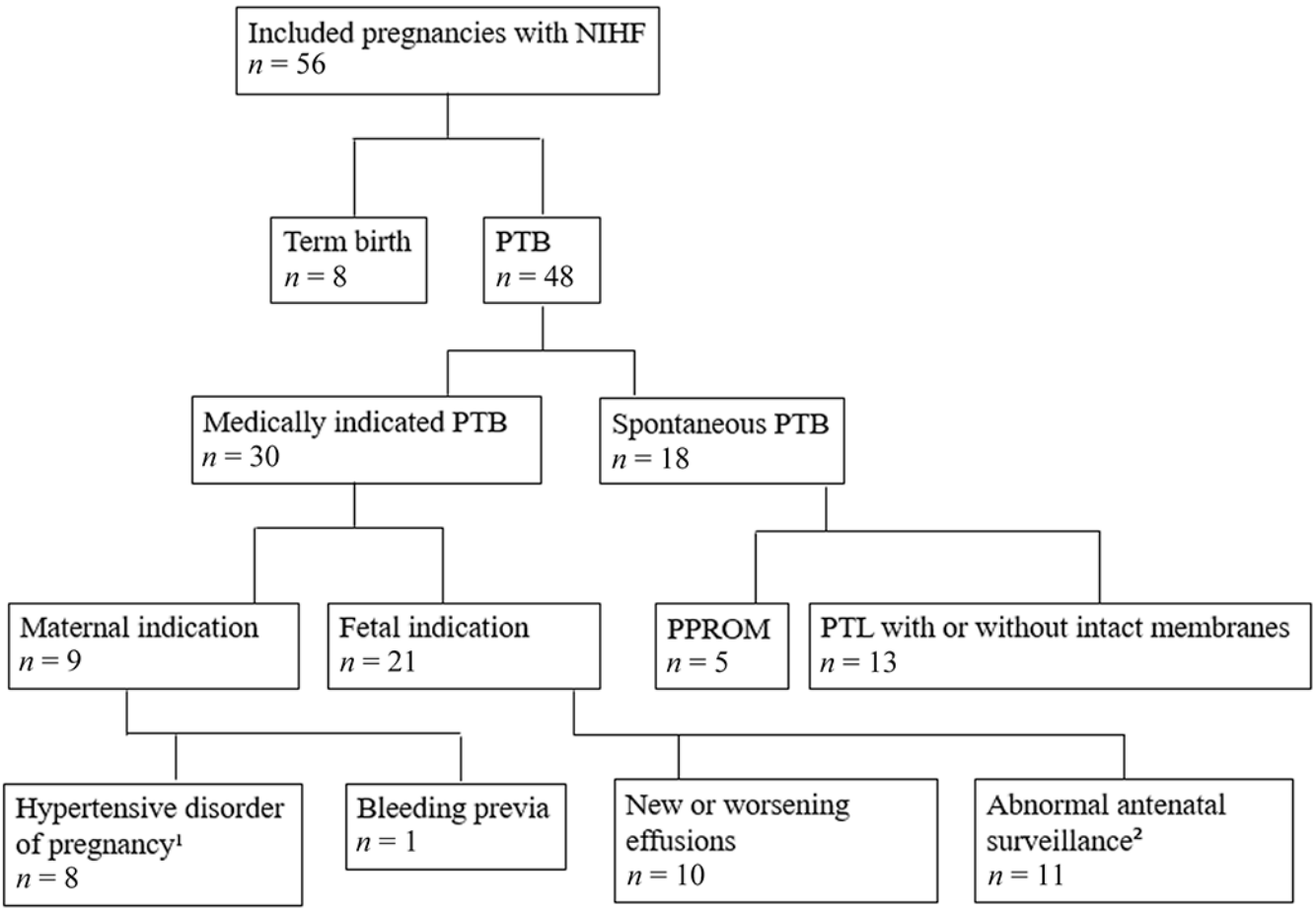

Fig. 2.

Timing and reasons for preterm birth in pregnancies complicated by NIHF. PTB, preterm birth; PPROM, preterm premature rupture of membranes; PTL, preterm labor. [1]Includes cases with gestational hypertension, preeclampsia with and without severe features, and atypical preeclampsia. [2]Includes nonstress test, biophysical profile, and/or umbilical artery Dopplers.

Table 1

Maternal and fetal characteristics of the cohort by preterm versus term delivery

	Preterm delivery *N* = 48	**Term delivery *N* = 8**
Median maternal age (IQR), y	31 (29–34)	30 (28–31)
Self-reported race/ethnicity, no. (%)		
White	32 (67)	3 (38)
Hispanic or Latina	11 (23)	2 (25)
Asian	3 (6)	0 (0)
Black	1 (2)	2 (25)
Unknown	1 (2)	1 (13)
Chronic hypertension, no. (%)	1 (2)	1 (13)
Nulliparity, no. (%)	18 (38)	4 (50)
Prior preterm birth, no. (%)	13 (27)	1 (13)
In vitro fertilization, no. (%)	2 (4)	0 (0)
Polyhydramnios, no. (%)	24 (50)	2 (13)
Structural anomalies present on ultrasound, no. (%)	21 (44)	4 (50)
Known or suspected fetal genetic diagnosis[a]	24 (50)	2 (13)
Fetal procedure during pregnancy[b]	14 (29)	1 (13)
Median GA at diagnosis of fluid collection (IQR), wk	25 (21–30)	22 (21–25)

Abbreviations: GA, gestational age; IQR, interquartile range.

[a]Includes aneuploidy, copy number variants, and single gene disorders.

[b]Includes in utero transfusion, shunt placement, and tracheoscopy.

Table 2

Ultrasound findings in pregnancies complicated by nonimmune hydrops fetalis

	Preterm delivery *N*=48	Term delivery *N*=8
Fetal effusions[a]		
Skin edema	39 (81)	6 (75)
Pleural effusion	36 (75)	6 (75)
Ascites	35 (73)	6 (75)
Pericardial effusion	17 (35)	5 (63)
Polyhydramnios	24 (50)	2 (13)
Structural anomalies[b]		
Shortened long bones	6 (13)	1 (13)
Pelviectasis	5 (10)	1 (13)
Club foot	3 (6)	2 (25)
Ventriculomegaly	4 (8)	0 (0)
Micrognathia	4 (8)	0 (0)
Congenital diaphragmatic hernia	3 (6)	0 (0)
Single umbilical artery	2 (4)	0 (0)
Intracranial cyst	1 (2)	1 (13)
Renal cysts	2 (4)	0 (0)
Cataracts	1 (2)	0 (0)
Absent nasal bone	1 (2)	0 (0)
Cleft lip/palate	0 (0)	1 (13)
Congenital high airway obstruction	1 (2)	0 (0)
Rhabdomyoma	0 (0)	1 (13)
Dextrocardia	1 (2)	0 (0)
Atrial septal defect	1 (2)	0 (0)
Ventricular septal defect	1 (2)	0 (0)
Ambiguous genitalia	1 (2)	0 (0)

Note: Data presented as *n* (%).

[a] Twenty-two cases with 2 effusions, 30 cases with 3 effusions, 4 cases with 4 effusions.

[b] Thirty-one cases with no anomalies, 11 cases with 1 anomaly present, 14 cases with more than 1 anomaly present.

Table 3

Perinatal outcomes in pregnancies complicated by nonimmune hydrops fetalis

	Preterm delivery *N* = 48	**Term delivery *N* = 8**
Median GA at delivery (IQR), wk	32.1 (29.9–34.1)	37.6 (37.0–38.7)
Cesarean delivery, no. (%)	34 (71)	4 (50)
Indication for cesarean delivery[a]		
Nonreassuring fetal status or worsening hydrops	19 (56)	2 (50)
Repeat cesarean delivery	5 (15)	1 (25)
Worsening maternal status	4 (12)	0 (0)
Noncephalic presentation	3 (9)	0 (0)
Arrest of labor	2 (6)	0 (0)
Macrosomia	1 (3)	0 (0)
Median birthweight (IQR), g[b]	2,325 (1,620–3,075)	3,227 (2,553–4,125)
Small for gestational age, no. (%)[b,c]	2 (42)	1 (13)
Large for gestational age, no. (%)[b,d]	20 (42)	2 (25)
Neonatal demise, no. (%)	35 (73)	1 (13)

Abbreviations: GA, gestational age; IQR, interquartile range.

[a] indication for cesarean delivery not reported in one case with term delivery, therefore *N* = 37.

[b] Birth weight not reported in 13 cases, therefore *N* = 43.

[c] Defined as <10th percentile for gestational age.

[d] Defined as >90th percentile for gestational age.

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