

Clinical Outcomes and Treatment Patterns in Hemolytic Disease of the Fetus and Newborn: Evidence from United States Claims Data

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Background

Hemolytic Disease of the Fetus and Newborn (HDFN) is caused by maternal immunoglobulin G (IgG) antibodies that cross the placenta and hemolyze fetal red blood cells, leading to fetal anemia, hydrops fetalis, kernicterus, or even fetal/neonatal death.

HDFN occurs in approximately 3 to 80 per 100,000 pregnancies in the United States annually^{1,2}. Within the last five decades, the incidence of HDFN has dramatically declined due to the availability of prophylactic immunoglobulins and the establishment of antibody screening programs^{3,4}.

Middle cerebral artery (MCA) Doppler ultrasound is the standard noninvasive method for monitoring fetal anemia. Intrauterine transfusion (IUT), the primary treatment for severe fetal anemia, is invasive and associated with procedural risks.

Despite advances in prevention and treatment, there is limited population-level data on the burden, management, and outcomes of severe HDFN in the US. This study aims to address this gap using a large, national claims database.

Objective

 This study aimed to describe the disease burden, treatment patterns, clinical characteristics, and outcomes of severe HDFN among pregnant individuals in a large claims database in the US.

Methods

- A large, retrospective, US population-based cohort study was conducted using the MarketScan® Commercial Claims and Encounters database from January 2010 to July 2024.
- Alloimmunized pregnancies were identified using ICD-9 and ICD-10 isoimmunization diagnosis codes (excluding those for ABO isoimmunization).
- Further, severe HDFN pregnancies were identified by specific criteria: (1) intrauterine transfusion, (2) fetal hydrops, (3) non-first trimester fetal death with at least 2 claims for MCA Doppler ultrasound, or (4) premature delivery by induction with at least 2 claims for MCA Doppler ultrasound.
- Descriptive comparisons of clinical characteristics and maternal monitoring, treatments, and interventions were made between severe HDFN pregnancies and control pregnancies (random sample of 25% of mothers with no evidence of alloimmunization in their maternal claims and no evidence of HDFN in the infant claims linked to them).

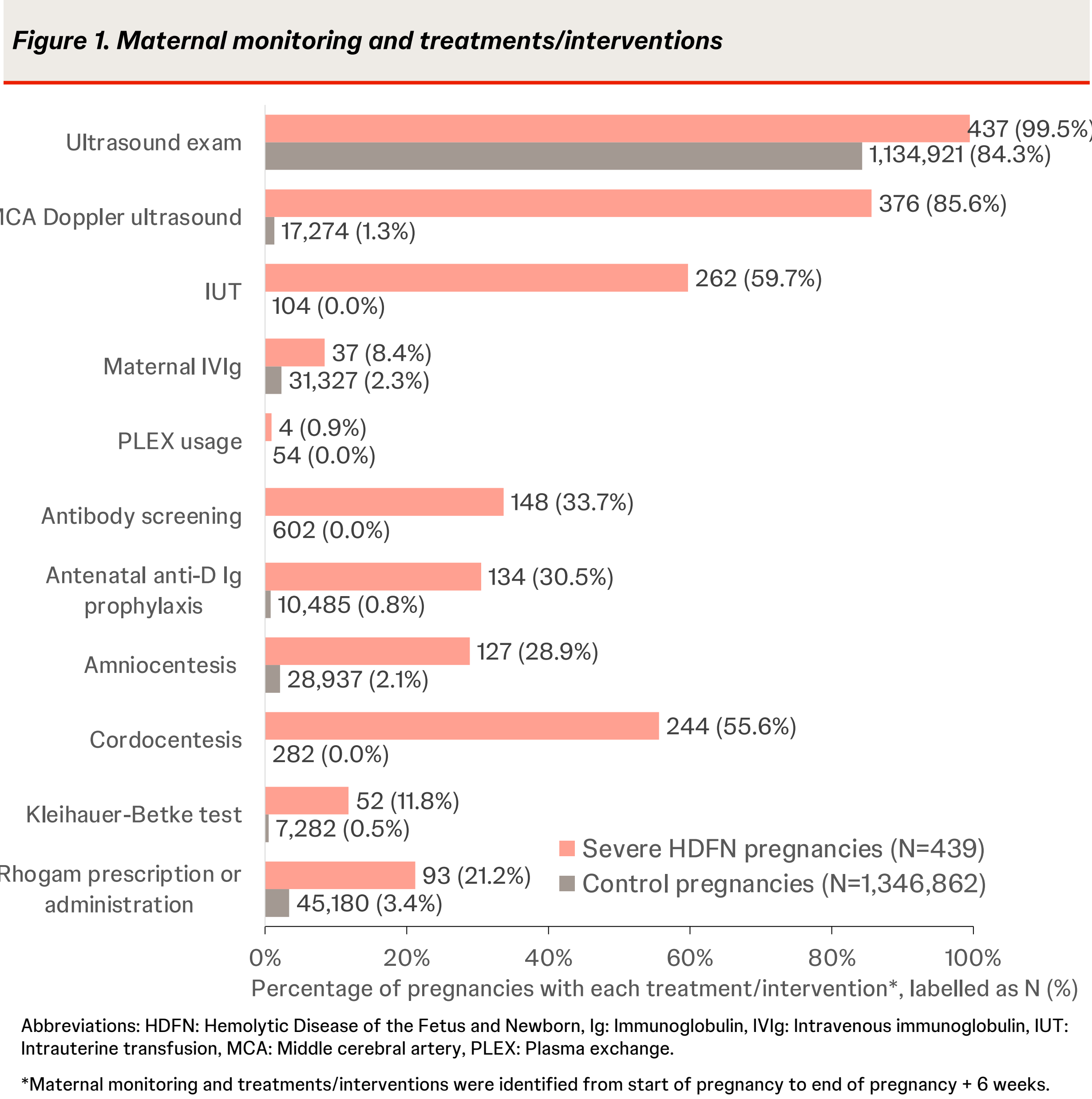
Results

Table 1. Baseline characteristics		
Baseline characteristic	Severe HDFN pregnancies (N=439 pregnancies)	Control pregnancies (N=1,346,862 pregnancies)
Age – Mean (SD)	31.8 (5.0)	30.9 (6.0)
Charlson comorbidity index* – Mean (SD)	0.1 (0.3)	0.1 (0.4)
0 – N (%)	406 (92.5%)	1,260,324 (93.6%)
1 – N (%)	28 (6.4%)	73,762 (5.5%)
≥2 – N (%)	5 (1.1%)	12,776 (0.9%)
Index pregnancy year – Median (Min-Max)	2015 (2010-2024)	2014 (2010-2024)
Duration of index pregnancy in days** – Mean (SD)	155.0 (60.4)	127.1 (93.1)
Region – N (%)		
Missing	-	1,265 (0.1%)
Northeast	71 (16.2%)	237,293 (17.6%)
North Central	109 (24.8%)	286,552 (21.3%)
South	175 (39.9%)	539,382 (40.0%)
West	79 (18.0%)	267,795 (19.9%)
Unknown	5 (1.1%)	14,575 (1.1%)

Abbreviations: HDFN: Hemolytic Disease of the Fetus and Newborn, SD: Standard deviation.
*Identified from 6 months prior start of pregnancy until beginning of pregnancy.
**Duration calculated as days between start of pregnancy (first pregnancy-related claim date) to first delivery or fetal death related claim within 294 days of start of pregnancy.

Table 2. Clinical characteristics		
Clinical characteristic*	Severe HDFN pregnancies (N=439)	Control pregnancies (N=1,346,862)
Maternal death – N(%)	0 (0.0%)	3 (0.0%)
Thrombocytopenia – N(%)	27 (6.2%)	19183 (1.4%)
Premature birth – N(%)	194 (44.2%)	66,892 (5.0%)
Hydrops – N (%)	103 (23.5%)	340 (0.0%)
Polyhydramnios – N(%)	77 (17.5%)	30,818 (2.3%)
Placental abruption – N(%)	16 (3.6%)	12,821 (1.0%)
Chorioamnionitis – N(%)	25 (5.7%)	38,831 (2.9%)
Tachycardia – N(%)	25 (5.7%)	34,219 (2.5%)
Fetal growth restriction – N(%)	44 (10.0%)	51,332 (3.8%)
Preeclampsia – N(%)	59 (13.4%)	121,124 (9.0%)
IUT related maternal outcomes – N(%)		
Cord occlusion	0 (0.0%)	50 (0.0%)
Bradycardia	119 (27.1%)	172,973 (12.8%)
Ruptured membranes	39 (8.9%)	81,549 (6.1%)

Abbreviations: HDFN: Hemolytic Disease of the Fetus and Newborn, IUT: Intrauterine transfusion.
*Clinical characteristics were identified from start of pregnancy to end of pregnancy + 6 weeks.



Key Takeaways

-  The prevalence of alloimmunized pregnancies (N= 317,445) was 5.2% of the total number of pregnancies (N=6,102,538) during the study period. Among these, 439 (0.1%) were classified as severe HDFN.
-  Baseline characteristics were balanced between severe HDFN pregnancies (N=439) and controls (N=1,346,862).
-  Severe HDFN pregnancies had higher utilization of maternal intravenous immunoglobulin (8.4% vs 2.3%), antibody screening (33.7% vs 0%), MCA Doppler ultrasound (85.6% vs 1.3%), and amniocentesis (28.9% vs 2.1%) compared to controls.
-  Severe HDFN pregnancies also had higher rates of IUTs (59.7% vs 0.0%), fetal hydrops (23.5% vs 0%), polyhydramnios (17.5% vs 2.3%), fetal growth restriction (10.0% vs 3.8%), preterm birth (44.2 vs 5.0%), and thrombocytopenia (6.2% vs 1.4%) compared to controls.
-  There was no major difference in the occurrence of ruptured membranes between severe HDFN pregnancies and controls (8.9% vs 6.0%).

Discussion

- This analysis used real-world data from a large US claims database to describe the disease burden, treatment patterns, and outcomes associated with severe HDFN.
- Several proxy-based criteria were used to identify severe HDFN, and comparisons with a large control group yielded patterns across clinical and treatment-related outcomes.
- Findings were consistent with published literature, highlighting the rarity of severe HDFN but underscoring its association with high maternal and fetal morbidity, including elevated rates of preterm births, fetal hydrops, and invasive intervention of intrauterine transfusions.
- Limitations of the study include reliance on administrative claims data, which may under capture certain clinical variables, and potential misclassification due to coding limitations.
- This study contributes new population-level data on the clinical impact and resource use associated with severe HDFN in the US.
- Severe HDFN pregnancies necessitate advanced care and are associated with higher maternal and fetal complication rates compared to controls. These findings highlight the significant disease burden of severe HDFN, emphasizing the need for effective treatment and management strategies to improve outcomes.