The Effects of Gestational Alloimmune Liver Disease on Fetal and Infant Morbidity and Mortality

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Objectives To evaluate pregnancy outcomes in pedigrees of neonatal hemochromatosis to determine the spectrum of gestational alloimmune liver disease (GALD) in a large cohort.

Study design We prospectively collected data from women with a prior offspring with proven neonatal hemochromatosis between 1997 and 2015 and analyzed pregnancy outcomes.

Results The pedigrees from 150 women included 350 gestations with outcomes potentially related to GALD. There were 105 live-born infants without liver disease, 157 live-born infants with liver failure, and 88 fetal losses. Fetal loss occurred in 25% of total gestations. Ninety-seven pedigrees contained a single affected offspring, whereas 53 contained multiple affected offspring. Analysis of these 53 pedigrees yielded a per-pregnancy repeat occurrence rate of 95%. Notably, the first poor outcome occurred in the first pregnancy in 60% of pedigrees. Outcomes of the 157 live-born infants with liver failure were poor: 18% survived, 82% died. Of the 134 live-born infants with treatment data, 20 received intravenous immunoglobulin with or without double-volume exchange transfusion of which 9 (45%) survived; 14 infants (10%) received a liver transplant of which 6 (43%) survived.

Conclusions GALD is a significant cause of both fetal loss and neonatal mortality with a high rate of disease recurrence in untreated pregnancies at risk. Poor outcomes related to GALD commonly occur in the first gestation, necessitating a high index of suspicion to diagnose this disorder at first presentation. *(J Pediatr 2017;■■:■■-■■).*

Gestational alloimmune liver disease (GALD) is a materno-fetal alloimmune disorder directed at the fetal liver, often producing neonatal liver failure.[1-4] The most common presentation is as neonatal hemochromatosis, which is defined as neonatal liver injury accompanied by siderosis of various extrahepatic tissues.[5,6] Although it has been known for some time that neonatal hemochromatosis is a familial disorder, observations of an unusual familial pattern of recurrence in maternal sibships led to the hypothesis that neonatal hemochromatosis is the result of materno-fetal alloimmunity.[7] This led to the initiation of antenatal therapy with high-dose intravenous immunoglobulin (IVIG) in women with an affected offspring to prevent recurrence of the disease in subsequent pregnancies. The results of antenatal treatment have demonstrated the effectiveness of this approach.[8-10]

Increased referrals for gestational therapy led to increased access to pathology materials for research into the mechanisms of fetal liver injury and the relationship between fetal liver injury and iron overload in the newborn. Demonstration of the deposition of complement component C5b-9 complex (membrane attack complex) in most hepatocytes in livers of neonates with neonatal hemochromatosis provided evidence for the alloimmune mechanism of fetal liver injury.[11] The mechanism of iron overload in GALD relates to markedly depressed hepatic expression of hepcidin (*HAMP*) in the injured fetal liver, which leads to dysregulation of placental iron flux.[12,13] The preferential distribution of siderosis occurs in tissues that can uptake, but not expel, nontransferrin bound iron.[12] In sum, these findings and the success of antenatal IVIG treatment provide reasonable evidence that most cases of neonatal hemochromatosis are the result of alloimmune fetal liver injury; GALD is now understood to be the disease causing fetal liver injury that leads to most cases of neonatal hemochromatosis, and that neonatal hemochromatosis is the symptom of fetal liver disease attributable to GALD.[3]

We have maintained an ongoing database of women treated with antenatal IVIG and recently reported the outcomes of treatment in 152 women.[10] This database includes the gestational histories of these women and provides a large cohort of pedigrees from which to tabulate pregnancy outcome. The goal of the current study is to examine these pedigrees to gain a deeper understanding of how GALD affects

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
DVET	Double-volume exchange transfusion
GALD	Gestational alloimmune liver disease
INR	International normalized ratio
IVIG	Intravenous immunoglobulin

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pregnancy, outcomes of GALD in the fetus and newborn, and the clinical presentation of GALD in live-born infants. Our results provide a comprehensive view of GALD, in which there are some surprises in context of what is known about gestational alloimmunity.

Methods

This is a cross-sectional analysis of outcomes of the prior pregnancies of women presenting for their initial antenatal treatment with IVIG to prevent repeat occurrence of GALD. The data were acquired prospectively from 1997 to 2015 at the time of each woman's initial treatment course. Women signed a standard release of medical information consent to have their data and that of their affected offspring included. The Institutional Review Board of the Anne and Robert H. Lurie Children's Hospital of Chicago approved the study and publication of the data by exception.

The study cohort comprises the gestational pedigrees of 150 women from 18 countries (57% from the US) who received antenatal therapy with IVIG to attempt to prevent repeat occurrence of GALD.[10] The index case in each pedigree is defined as the first infant in a maternal sibship diagnosed as having neonatal hemochromatosis and which brought the family under study by being considered for gestational IVIG treatment. For a pedigree to be included in this study, the woman must have been accepted for antenatal therapy, and, thus, the index case had neonatal hemochromatosis without demonstrable alternate etiology.[1,3,4] Diagnosis of neonatal hemochromatosis in the index case was made by standard criteria: clinically by severe liver disease with demonstration of siderosis of extrahepatic tissues by buccal biopsy and/or magnetic resonance imaging, and/or findings from postmortem examination.[4,14] Cases referred for consideration were not accepted for antenatal therapy and inclusion in this cohort if clinical or pathologic findings indicated an alternate etiology for neonatal hemochromatosis. Over the timeframe of the data collection, cases were excluded because of demonstrable viral infection, mitochondrial disease, bile acid synthetic defect, trisomy 21, and hemophagocytic lymphohistiocytosis. GALD is operationally defined in this study as index cases of neonatal hemochromatosis that led to acceptance for antenatal therapy, and poor outcomes in all pedigrees were considered related to GALD.

The principal data collected were the outcomes of all gestations preceding entry into gestational IVIG therapy: the gestational history of natural (untreated) pregnancies in these women. This history was catalogued for each woman as: total gestations (gravity); those with good outcome (ie, newborn with no evidence of liver disease); and those with poor outcomes, including all live-born infants with liver disease/liver failure and all fetal losses. Gestations with elective terminations and ectopic pregnancies were excluded from analysis. It should be noted that identification of the index case in any sibship led to antenatal therapy in the immediate next pregnancy and, thus, was the last affected member of the pedigree. Additional GALD cases in a pedigree were identified from the gestational history provided at the time of initiation of gestational therapy. The gravity at the first gestation with poor outcome in a pedigree is considered to be the point at which GALD first occurred. All poor outcomes in sibships were included in the computation of the occurrence rate, which equals total gestations with poor outcome divided by total gravity (preceding antenatal therapy). Repeat occurrence rate was computed as the number of gestations with poor outcome divided by the number of gestations at risk (ie, untreated gestations after the first with poor outcome in any pedigree).

We also collected clinical information from the hospital course of live-born infants and autopsy reports from live-born infants who died, when available. Laboratory data was available in <15% of live-born infants. We examined the liver sections from autopsies and performed immunostaining for C5b-9 complex in cases where tissue was available.[11] Treatment regimens for the live-born neonatal hemochromatosis patients with GALD were categorized as no specific treatment; application of the chelation/anti-oxidant cocktail[15,16]; IVIG with or without double-volume exchange transfusion (DVET)[17]; and liver transplantation.

Results

Reporting of gestational history was nearly complete, with histories from 148 of 150 women providing full outcome data by gestation. A consort flow diagram of the cohort comprising 364 pregnancies is shown in **Figure 1**. Twelve elective terminations and 2 ectopic pregnancies were excluded from analysis, leaving 350 outcomes potentially related to GALD. Of these, there were 105 healthy live offspring (30% of total gestations) and 245 poor outcomes (70% of total gestations). Of the poor outcomes, 157 (64%) were live-born infants with liver failure. Two sets of twins were recorded, in each case with 1 severely affected and 1 minimally affected, as previously reported.[18] Both twin pregnancies were categorized as poor outcomes. One case included in this series as a poor outcome was subsequently diagnosed by gene analysis of frozen liver tissue to have *GALT* mutations consistent with the diagnosis of hereditary galactosemia. However, it could not be proven that the infant did not have coexistent GALD and the mother went on to have antenatal therapy, as described elsewhere.[10] Eighty-eight fetal losses comprised 36% of poor outcomes, of which 38% occurred at ≥18 weeks of gestation and 62% occurred at <18 weeks or at uncertain gestational age. Fetal loss ended approximately 1 in 4 pregnancies.

Examination of individual pedigrees demonstrates that of the 150 women, 97 (65%) had a single pregnancy with poor outcome (ie, both the first affected and the index case). The **Table** shows the gravity of women at time of the first poor outcome in 148 pedigrees (excluding the 2 women with incomplete gestational data) and how many of these first poor outcomes were the index case. It is remarkable that 89 women (60%) had their first poor outcome in their first pregnancy; of these 61 (69%) were also the index case and, thus, the only untreated gestation of the pedigree. Conversely, in 28 pedigrees (31%), the first affected was not the index case and, thus,

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