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# Chronic villitis in untreated neonatal alloimmune thrombocytopenia: An etiology for severe early intrauterine growth restriction and the effect of intravenous immunoglobulin therapy

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**KEY WORDS**
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**Objective:** The objective of the study was to examine placental histopathology in intravenous immunoglobulin-treated and untreated neonatal alloimmune thrombocytopenia and correlate pathological findings with clinical outcomes.

**Study design:** Placentas from 14 neonatal alloimmune thrombocytopenia–affected pregnancies were identified. Maternal antepartum treatment with intravenous immunoglobulin and pregnancy outcomes were abstracted from medical records. Placental histopathology and clinical outcomes were compared between intravenous immunoglobulin and no intravenous immunoglobulin treatment groups using Fisher's exact test. One subject, treated only after an intracranial hemorrhage (ICH) was diagnosed, was excluded from the analysis. $P < .05$ was considered significant.

**Results:** Untreated pregnancies demonstrated a lymphoplasmacytic chronic villitis not seen in the intravenous immunoglobulin–treated pregnancies ($P = .005$). Intrauterine growth restriction and intrauterine fetal demise occurred as frequently as ICH in the untreated group. No ICH, intrauterine growth restriction, or intrauterine fetal demises occurred in the treated group, although the $P$ value was not significant.

**Conclusion:** Chronic villitis is frequently manifest in neonatal alloimmune thrombocytopenia, with intravenous immunoglobulin alleviating this inflammatory immunologic response. We suspect a more universal role for the maternal antibody, such as fetal endothelial cell damage, in the sequelae of neonatal alloimmune thrombocytopenia.



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Neonatal alloimmune thrombocytopenia (NAIT) is an immune-mediated process whereby fetal platelets are destroyed by maternal antibodies directed against fetal platelet antigens. Although many couples display genotypic differences in their platelet surface antigens that could lead to NAIT, only a fraction results in sensitized pregnancies. The reported incidence of NAIT is 1 in 1000 to 2000 pregnancies, although it is likely higher, because of incomplete ascertainment.[1] Increasing use of assisted reproductive technologies may ultimately lead to an increased incidence of NAIT by exposing gestational carriers to additional foreign antigens.[2] Unlike the natural history of red cell alloimmunization, NAIT can affect a first pregnancy,[3] with the diagnosis often made only after a severe hemorrhagic complication has occurred. Intrauterine fetal demise is also a recognized complication of this disorder.[4]

Current treatment for NAIT is administration of maternal antepartum intravenous immunoglobulin (IVIG) with or without steroids, but optimal dosing regimens have yet to be established.[5] Moreover, although IVIG treatment has greatly reduced the incidence of severe sequelae, little is known about immunoglobulin's mechanism of action, and much remains to be learned.[6]

Few studies of the placenta in NAIT-affected pregnancies exist, with most research efforts focused on treatment of NAIT,[1,7] applicability of population screening,[8,9] and prevention of the devastating fetal hemorrhages that can occur.[10] Placental findings are frequently reported within the context of case reports, but no systematic analysis of placental findings has been reported to date.[11] This study's purpose was two-fold: to describe histological findings in NAIT-affected placentas and determine what if any effect IVIG exerts on the process.

## Material and methods

A search of clinical files in the Department of Gynecology and Obstetrics at the Johns Hopkins Hospital identified 14 consecutive cases of pregnancies that were complicated by NAIT between 1989 and 2003. The medical records of each case were comprehensively reviewed, and in all cases, demographic characteristics as well as clinical and laboratory variables potentially associated with NAIT were abstracted and entered into an Excel database (Microsoft, Redmond, WA). The diagnosis of NAIT was established by the documentation of neonatal hemorrhage and/or thrombocytopenia and the subsequent detection of fetal-maternal alloantigen incompatibility and associated maternal antiplatelet antibodies. Clinical and laboratory variables included maternal age and ethnicity, gestational age at delivery, fetal growth indices, fetal hemorrhagic events, fetal platelet counts, maternal antiplatelet antibody identification, fetal adverse outcomes, and treatment with weekly maternal IVIG (1 g/kg).

Paraffin-embedded placental tissues from all 14 patients were retrieved from the pathology archives of the Johns Hopkins Hospital or from outside sources if the delivery occurred at another hospital. Hematoxylin and eosin-stained histologic sections were prepared for each patient and all samples reviewed by experienced pathologists who were blinded to treatment and clinical outcomes (E.W. and F.A.). Histologic findings of 10 placentas from uncomplicated term pregnancies served as controls. STATA software (7.0 Stata Corporation, College Station, TX) was used for data analysis. We sought to determine IVIG's effect on preventing hemorrhagic sequelae and any differences that prophylactic use of IVIG might have on placental histopathology; therefore, 1 subject, not treated with maternal IVIG until after fetal intracranial hemorrhage was diagnosed at 21 weeks, was excluded from IVIG treatment analysis. $P < .05$ was considered significant. The Johns Hopkins University Internal Review Board approved all methods of data acquisition and analysis.

## Results

Fourteen NAIT-affected pregnancies were identified in 8 different women (Table I). Eleven of 14 patients resulted in a second- or third-trimester delivery of a live-born infant; 1 subsequently died at 18 days of life. There were 3 intrauterine fetal demises (IUFDs). Six of the pregnancies had been treated with maternal IVIG as described earlier, 4 beginning at 13 weeks, and 1 at 17 weeks; in 1 case, weekly IVIG was begun at 21 weeks after referral for in utero intracranial hemorrhage. Although we cannot rule out with absolute certainty for 3 of our patients' prior pregnancies (delivered elsewhere) the possibility of any additional fetal hemorrhages, there were none described in the relevant medical records. No other fetal or neonatal hemorrhages were found in patients under our care other than those cited (Table II).

A substantial chronic inflammatory infiltrate was seen in the villous stroma surrounding the fetal vessels of 5 of 14 (35.7%) placentas (Figure). The presence of chronic villitis did not correlate with maternal age, gestational age at delivery, ethnicity, or fetal gender. Other placental findings included advanced villous maturation (5 of 14), increased syncytial knots (2 of 14), infarctions (4 of 14), and necrosis (1 of 14). Five placentas had no specific pathologic changes. The particular maternal platelet alloantibody involved did not appear to alter the findings.

The effect of treatment with weekly IVIG was striking. All placentas with chronic villitis were in the untreated group, a statistically significant difference