OBSTETRICS

Postponing Early intrauterine Transfusion with Intravenous immunoglobulin Treatment; the PETIT study on severe hemolytic disease of the fetus and newborn

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BACKGROUND: Intrauterine transfusion for severe alloimmunization in pregnancy performed <20 weeks' gestation is associated with a higher fetal death rate. Intravenous immunoglobulins may prevent hemolysis and could therefore be a noninvasive alternative for early transfusions.

OBJECTIVE: We evaluated whether maternal treatment with intravenous immunoglobulins defers the development of severe fetal anemia and its consequences in a retrospective cohort to which 12 fetal therapy centers contributed.

STUDY DESIGN: We included consecutive pregnancies of alloimmunized women with a history of severe hemolytic disease and by propensity analysis compared index pregnancies treated with intravenous immunoglobulins (n = 24) with pregnancies managed without intravenous immunoglobulins (n = 28).

RESULTS: In index pregnancies with intravenous immunoglobulin treatment, fetal anemia developed on average 15 days later compared to previous pregnancies (8% less often <20 weeks' gestation). In pregnancies without intravenous immunoglobulin treatment anemia developed 9 days earlier compared to previous pregnancies (10% more <20 weeks), an adjusted 4-day between-group difference in favor of the immunoglobulin group (95% confidence interval, −10 to +18; $P = .564$). In the subcohort in which immunoglobulin treatment was started <13 weeks, anemia developed 25 days later and 31% less <20 weeks' gestation (54% compared to 23%) than in the previous pregnancy. Fetal hydrops occurred in 4% of immunoglobulin-treated pregnancies and in 24% of those without intravenous immunoglobulin treatment (odds ratio, 0.03; 95% confidence interval, 0—0.5; $P = .011$). Exchange transfusions were given to 9% of neonates born from pregnancies with and in 37% without immunoglobulin treatment (odds ratio, 0.1; 95% confidence interval, 0—0.5; $P = .009$).

CONCLUSION: Intravenous immunoglobulin treatment in mothers pregnant with a fetus at risk for hemolytic disease seems to have a potential clinically relevant, beneficial effect on the course and severity of the disease. Confirmation in a multicenter randomized trial is needed.

Key words: alloimmune fetal hydrops, fetal anemia, intrauterine blood transfusion, intravenous immunoglobulin, perinatal loss, red cell alloimmunization in pregnancy

Introduction

Hemolytic disease of the fetus and newborn (HDFN) is caused by maternal alloimmunization against fetal red blood cells. The maternal antibodies can destruct fetal red blood cells and consequently cause fetal anemia, hydrops, and perinatal death.[1,2] Intrauterine blood transfusion (IUT) is currently the only treatment option to prevent fetal death and reduce neurological impairment of these fetuses.[3]

Although relatively safe in experienced hands, IUT remains an invasive procedure, and complications may occur.[4] Early transfusions are technically challenging, especially when performed <22 weeks' gestation, and carry a significantly higher risk of fetal loss compared with procedures performed later in gestation.[5–7] In the largest single-center cohort series from the Leiden University Medical Center (LUMC) (The Netherlands), procedure-related fetal death rates after intravascular IUTs performed either <20 weeks' or >20 weeks' gestation were 8.5% and 0.9% per procedure, respectively.[4] Alternatively, some suggested the use of technically easier intraperitoneal transfusions.[8,9] To date, no other treatment option for fetuses with severe anemia early in pregnancy has been proven to be effective.

The use of intravenous immunoglobulins (IVIg) may postpone or even replace invasive intrauterine treatment in fetuses of mothers with severe alloimmunization in previous pregnancies.[9–11] IVIg may theoretically dilute circulating maternal antibodies and induce competition at the placenta, reducing transplacental transfer of maternal antibodies. Furthermore, it might increase antibody turnover and thus lower maternal alloantibody levels and, after transfer to the fetus, block fetal macrophage function.[12,13] As a result, IVIg might prevent hemolysis, but cannot treat existing fetal anemia.[14]

Administration of IVIg in pregnancy is considered safe, although side effects may include urticaria, myalgia, chills, headache, nausea, or fever.[15] Another

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AJOG at a Glance

Why was this study conducted?

We sought to evaluate whether maternal treatment with intravenous immunoglobulins (IVIg) defers the development of severe fetal anemia and its consequences in pregnancies at risk for severe hemolytic disease of the fetus and newborn.

Key findings

IVIg treatment in mothers pregnant with a fetus at risk for hemolytic disease appears to have a potential clinically relevant, beneficial effect on the course and severity of the disease. For example, IVIg was associated with a reduced risk of hydrops and need for exchange transfusions.

What does this add to what is known?

There is lack of evidence on the effect of IVIg on the course of fetal hemolytic disease. This multicenter study actualizes the issue, adds to the knowledge, suggests beneficial effects, and stresses the need for a randomized controlled trial.

disadvantage is that IVIg treatment is relatively expensive (approximately $6000/wk).[16]

A few single-center case series have reported on the possible effects of IVIg on morbidity and mortality in HDFN.[9,11,17] In the largest study, from the 1990s, IVIg appeared to lead to a major reduction in fetal mortality from 51−20%.[10]

Although several fetal therapy centers occasionally use IVIg treatment in pregnancies at risk for recurrence of severe HDFN, there is still much uncertainty about the indications and true effects of IVIg. In this study, we gathered the international experience of treatment with IVIg to evaluate whether (early) administration in high-risk alloimmunized pregnancies is successful in delaying the onset of severe fetal anemia and thus diminishing its clinical consequences.

Materials and Methods

Study design, setting, and study population

We conducted a retrospective multicenter cohort study. The cohort consisted of pregnancies of women with an earlier pregnancy with severe HDFN ("previous pregnancy"), managed in the first trimester of a new pregnancy from January 2010 through June 2016 ("index pregnancy"). A list of participating centers is provided as Supplemental Data. Patients from the LUMC were included from 2001 onward, as the antenatal management of HDFN has not changed since the early 2000s in our center.[4]

In all included current ("index") pregnancies women were either treated with IVIg or were managed without IVIg. Severe HDFN was defined as either a previous fetal and neonatal death as a result of HDFN, or the need for IUT <24 weeks' gestation in the previous pregnancy.

All eligible pregnancies of all mothers were included. We excluded pregnancies in which a previous fetal or neonatal death was the result of a lack of diagnostic or therapeutic care, rather than caused by severe HDFN.

In the participating centers, 10−140 women with red cell immunization are seen annually, receiving 5−60 IUTs that are performed by 1−4 operators. A 20- or 22-gauge needle was used for intravascular IUT in all participating centers. The preferred transfusion access sites were the placental cord insertion and the intrahepatic part of the umbilical vein.

Treatment with IVIg was preferably started <13 completed weeks' gestation. Most cases were treated with Nanogam (Sanquin Plasma Products B.V., Amsterdam, the Netherlands) or Privigen (CSL Behring GmbH, Marburg, Germany) IVIg. Alternatively, Gammagard (Baxter B.V., Utrecht, the Netherlands), Intragam (CSL Behring Pty Ltd, Broadmeadows, Australia), Vigam (Bio Products Laboratory Limited, Hertfordshire, UK), Flebogamma (Instituto Grifols, S.A., Barcelona, Spain), or a combination was used. Most centers dosed IVIg at 1 g/kg maternal weight and administered it in weekly doses.

We documented patient characteristics, laboratory results, Doppler measurement results, data on additional treatments, IUT details, delivery details, and data on neonatal outcome (up to 3 months of age) from all pregnancies. Furthermore, details on IVIg treatment were collected of all index pregnancies.

Outcome definitions

We chose the difference in gestational age at onset of severe fetal anemia, requiring IUT, between the index and previous pregnancy (delta gestational age) as our primary outcome, because the expert opinion is that fetal anemia tends to occur earlier in gestation in subsequent pregnancies of the same alloimmunized mother.[18] As anemia may be present for days before it is diagnosed, the exact onset of severe anemia is impossible to determine. Therefore, we use "onset of severe anemia" when we mean "diagnosis of severe anemia" throughout this article. The (diagnosis of) onset of severe anemia was defined as the day of IUT, the day fetal death was diagnosed, or the day the Doppler peak systolic velocity in the middle cerebral artery (MCA)[19] was measured >1.5 multiples of the median (MoM), in case fetal death followed at an unknown time point.

We elected the need for IUT <20 weeks as a secondary outcome, because of the clinical relevance of this endpoint due to the associated increased risk for procedure-related complications.[4]

Furthermore, we assessed perinatal survival, fetal hemoglobin (Hb), ZHb, the presence of hydrops at time of the first IUT, the occurrence of complications (premature rupture of membranes, emergency cesarean delivery, and fetal or neonatal death), the number of IUTs per pregnancy, and the proportion of neonates needing exchange transfusions. ZHb is the deviation of fetal Hb from the