Antenatal therapy to prevent severe gestational alloimmune liver disease

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The condition known as *Neonatal Hemochromatosis* is the result of severe fetal liver injury, which in most cases is due to alloimmune injury called *Gestational Alloimmune Liver Disease*. The risk of recurrence in pregnancies subsequent to one affected with NH is approximately 90%. A woman who has had a baby affected with NH should be treated through any and all subsequent pregnancies to prevent recurrence of severe GALD and NH.

Suggested guidelines for the assessment and care of the mother during gestation and child after birth

I. Pooled Human Immune Globulin (IVIG)

A. Purpose: Aimed at preventing or reducing alloimmune injury to the fetal liver (Whitington PF, Kelly S. Outcome of pregnancies at risk for neonatal hemochromatosis is improved by treatment with high dose intravenous immunoglobulin. Pediatrics 2008;121:e1615-21).

B. Contraindications and complications: IgA deficiency, hypogammaglobulinemia, and cardiac disease constitute relative contraindications. There are no controlled trials upon which to base an estimate of risk of complications. In our cumulative experience, minor complications of treatment have included headache, malaise, fatigue and transient hypertension. One major complication has been recorded: aseptic meningitis in a single patient. One patient developed hemolytic anemia, judged by her care providers to possibly be secondary to IVIG therapy. No fetal complications have been recorded.

C. Pre-therapy lab evaluation: IgA level to rule out IgA deficiency. This should be performed in every patient to receive IVIG, but need only be performed once in the event of repeat pregnancies.

D. Dose: 1 gm/kg IV. Base the dose on weight at 14 – 18 weeks and do not adjust with further weight gain. Maximum dose should be 60g. <u>The current recommended dosing schedule is based on our accumulative experience:</u> **dose at 14 weeks, 16 weeks, and 18 weeks, then weekly until 1-week prior to EDC. At <u>minimum</u> we recommend to continue treatment through 35 weeks, for a total of 20 doses.**

E. Monitoring for side effects and complications: Look for signs of allergic reaction, anaphylaxis, aseptic meningitis, injection site reaction, fever, and hypotension. Adjusting infusion rate will usually abrogate reactions other than anaphylaxis.

II. Maternal surveillance

A. The cumulative experience with this treatment suggests that prenatal care and surveillance as routinely provided by the local obstetrician is sufficient.

B. Local (institutional) protocols for monitoring patients receiving IVIG for any purpose should be adhered to.

C. Suggested schedule of observation and surveillance

- Every four-week visits from first trimester to 24 weeks gestation. At each visit, vital signs, estimate of uterine size, evaluation of fetal life, urinary protein assessment, urinary glucose assessment, maternal weight assessment.
- Weekly visits from 24 weeks gestation until delivery. At each visit, vital signs, estimate of uterine size, evaluation of fetal life, urinary protein assessment, urinary glucose assessment, maternal weight assessment, and general well being assessed.

III. Fetal surveillance

A. We recommend no monitoring beyond that normally provided for high-risk pregnancies.

B. Experience has shown that detecting NH en utero is not possible unless the fetus is severely involved.

- Key signs of involvement are: reduced fetal movement; impaired fetal growth; oligohydramnios.
- Ultrasound findings of fetal liver disease including a contracted hyper echoic fetal liver, ascites, and blood flow abnormalities have been described in untreated NH.
- None of the above signs of involvement have been encountered during treated gestations.

IV. Time of delivery

A. Delivery at term is recommended: Our cumulative experience indicates that it is safe for pregnancy to continue to term even though the IVIG treatment may be discontinued after 35 weeks.

B. No reason to perform cesarean delivery for indications other than standard obstetric indications.

C. Iatrogenic prematurity may be planned to avoid progressive liver injury due to NH. Any evidence of gestational problems or fetal distress, liver disease or growth failure should lead to assessment of fetal maturity and planned early delivery if possible.

V. Postpartum maternal surveillance

A. Routine

VI. Postpartum neonate evaluation

A. Well over 95% of treated gestations have resulted in neonates with no clinical evidence of being affected. In general, a healthy appearing neonate is indeed healthy. The following testing may be performed for the indications given. Testing should be performed day 1 of life (**not** to be performed using cord blood)

1. Testing for clinical significant liver disease.

Prothrombin time (INR): INR ≥ 2.0 is considered indicative of liver dysfunction. The test should be performed after parenteral vitamin K administration.

Blood glucose for detection of hypoglycemia (which if present may have cause other than GALD)

2. Testing for involvement specifically of GALD. We consider these tests to be unessential in clinical management, but the results may point to whether the baby would have been severely affected had the mother not been treated.

Serum ferritin: values above 800ng/ml are considered abnormal in the newborn.

α-fetoprotein: values > 80,000ng/ml in >37 week gestation and > 200,000 in 32 week gestation are considered abnormal. Values for 32-37 week gestation are not well established: linear extrapolation is suggested.

Over 80% of infants born after IVIG treatment for GALD will have abnormal AFP and/or ferritin levels.

VII. Care of an affected baby

A. An otherwise healthy baby with only biochemical evidence of NH (i.e. elevated serum ferritin and/or AFP) needs no therapy or special follow-up.

B. A baby with significant liver dysfunction (i.e. INR ≥ 2.0 and/or hypoglycemia) should be cared for and supported in a newborn intensive care unit if at all possible to assure that other complications of liver disease (i.e. hypoglycemia) do not imperil the baby's health. The baby should be treated IVIG ± double volume exchange transfusion as published (Rand EB, Karpen SJ, Kelly S, Mack CL, Malatack JJ, Sokol RJ, Whitington PF. Treatment of neonatal hemochromatosis with exchange transfusion and intravenous immunoglobulin. J Pediatr 2009;155:566-71.) The baby may also be administered vitamin E (α-Tocopherol polyethylene glycol succinate (TPGS) - 25 IU/kg/d divided twice daily p.o.) and N-acetycysteine (Mucomist - 200 mg/kg/day, divided three times daily, p.o. for 17-21 doses) as a liver-protective maneuver.

C. We <u>do not recommend</u> the full antioxidant/chelation cocktail as reported in the literature. Some of its components, especially the deferoxamine, are potentially toxic, and the value of its use is not supported by medical evidence.