Fetomaternal Hemorrhage: A Review

Fetomaternal hemorrhage (FMH) aka maternofetal hemorrhage or fetomaternal transfusion refers to the entry of fetal blood into the maternal circulation before or during delivery that can lead to neonatal anemia. Neonatal anemia is defined by a hemoglobin or hematocrit value that is more than two standard deviations below the mean for age, and hence the value varies by gestational age. FMH leads to fetal blood loss and can be acute and/or chronic. Acute FMH presents with signs including non-reassuring fetal heart tracing, neonatal pallor, hypotension, metabolic acidosis soon after delivery; whereas chronic FMH can present in physiologically compensated manner where plasma volume is expanded despite low red blood cell (RBC) mass or hydrops in severe forms. FMH in small amounts is considered physiological; as occasional RBCs enter the maternal circulation in most pregnancies. Specifically, up to 20-30 ml is considered acceptable as no or minimal neonatal clinical signs or symptoms are seen. Also supporting this cut-off is the clinical practice of using 300 micrograms of RH immunoglobulin (RHIG) to avoid RH alloimmunization, which covers a similar volume of 30ml of fetal blood in maternal circulation. The volume of blood lost by the fetus that is deemed to be a clinically significant amount vary in different studies, most of the studies quote >50ml or >20% of neonatal total blood volume. A larger amount of hemorrhage lead to shock, Hypoxic Ischemic Encephalopathy (HIE), Broncho Pulmonary Dysplasia (BPD), Intraventricular Hemorrhage (IVH) and death due to severe tissue hypoxia, can be further classified into A) Large FMH - >80ml (incidence 1/1000) and B) Massive FMH - >150ml (incidence 1/5000), with severity increasing with the proportional amount of fetal blood loss. However, the incidence may be higher as this condition is difficult to diagnose, making it an under-recognized entity. The proposed pathophysiologic mechanism is of disruption in the trophoblast, allowing entry of fetal RBC's from the higher pressure fetal circulation into the intervillous space and ultimately to the maternal circulation. What triggers the trophoblastic breach remains unknown. Greater numbers of placental lesions have been associated with larger FMH. Placental vascular thrombosis, on the other hand, seems to be a protective mechanism to limit FMH.

Diagnosis: Testing for FMH should be considered in all unexplained cases of 1) Neonatal anemia, 2) Stillbirth, 3) Persistent maternal perception of decreased fetal activity, 4) Hydrops and 5) Elevated middle cerebral artery (MCA) Doppler detected velocity consistent with anemia. As most of the presenting features antenatally are very non-specific, a high index of suspicion is necessary for diagnosis of FMH. Savitz et. al (2013) found that, physician awareness and an educational module in a large group of hospitals, increased the diagnosis of FMH by 8-fold despite the fact that during the same period the incidence of neonatal anemia remained the same. The clinical triad of antenatal signs for diagnosis includes, 1) Reduced or absent fetal movement (most common but non-specific), 2) Cardiotocographic abnormalities like reduced variability and sinusoidal pattern and 3) Sonographic evidence of hydrops (late decompensated/severe phase). Laboratory diagnosis of FMH can also be challenging. In general it is diagnosed by KB (Kleihauer-Betke) stain (described in 1957). This is an acid elution (lysis and removal of antibodies from RBCs) test, which is done after forming a smear of maternal blood on a microscopic slide followed by staining with Erythrosine B. This test works on the principle that fetal RBC (F-cells) with HbF (A2G2) is resistant to acid elution and hence are the only cells stained with Erythrosine B. A larger amount of hemorrhage lead to shock, Hypoxic Ischemic Encephalopathy (HIE), Broncho Pulmonary Dysplasia (BPD), Intraventricular Hemorrhage (IVH) and death due to severe tissue hypoxia, can be further classified into A) Large FMH - >80ml (incidence 1/1000) and B) Massive FMH - >150ml (incidence 1/5000), with severity increasing with the proportional amount of fetal blood loss. However, the incidence may be higher as this condition is difficult to diagnose, making it an under-recognized entity.

Most (82%) cases are idiopathic, but when present, etiologies for FMH can be grouped as follows:

A. Fetal Factors – twin-to-twin transfusion, mono-mono twins, malformations, fetal death
B. Maternal Trauma – Direct trauma (falls), motor vehicle accident, physical or sexual abuse.
C. Placental – Placenta previa, abruption, placental abnormalities, Umbilical vein thrombosis
D. Obstetric Interventions – Cesarean section, amniocentesis, cordocentesis, external cephalic version.
E. Miscellaneous – Substance abuse (cocaine), Hypertensive disorders of pregnancy.

(Adapted from Markham et. al)

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Due to above mentioned reasons; the testing is labor intensive, has longer turnaround time and has subjective variability depending on who is reviewing the stained smears. One of the formulas used to calculate FMH in ml of fetal RBCs is - (number of fetal cells/number of adult cells x maternal RBC volume). Many places use the assumption of average term woman weight of 70Kg and maternal RBC volume of 75ml/kg, giving maternal RBC volume of 5250 mls (=70x75). Practically a wide variation exists and hence can give different results that may reduce accuracy.

Other variables potentially contributing to misinterpretation of amount of FMH can be tabulated as follows:  

A. Overestimation
- Presence of F-cells that are also stained (F-cells are RBCs containing 20%-25% HbF and are present in normal adults at a range of 0.5%-7.0% of circulating RBCs, elevated in inherited hemoglobinopathies including sickle cell disease and b-thalassemia, hereditary persistence of fetal hemoglobin (HPFH), acute stress erythropoiesis and pregnancy)
- Subjectivity in picking up the maternal cells (*"ghost" outlines)

B. Underestimation
- ABO/Rh incompatibility, not adjusted for larger maternal circulating volume (>70kg). Incomplete staining of fetal cells (~90% stain), failure to correct for differences in fetal and maternal RBC volume (fetal cells = 30% larger then maternal cells.)

One important issue is that the KB test doesn't give any clue to etiology or timing of the suspected FMH. To avoid some of the problems with KB test, flow cytometry is being used at certain centers (only 4% in US) but is affected by some similar problems as KB test as it also counts the F-cells in the maternal blood. Other non-specific not widely used ways to diagnose FMH are 1) Elevated Maternal Hemoglobin prior to delivery can be a soft sign of FMH, 2) Elevated MSAFP levels (non-specific), 3) Maternal serum IgG placental alkaline phosphate levels are increased with fetal hydrops commonly with FMH and 4) Sequential measurement of cell-free DNA may provide insight to timing. FMH is also suspected when MCA Doppler, shows increased velocity due to preferential increased cerebral flow with fetal anemia.

Management: Obstetric (antenatal) management of FMH includes its diagnosis with KB test (>20% of fetal blood volume considered significant), further supported with MCA Doppler ultrasound (> 1.5 MOM) and finally depends on presence or absence of fetal compromise. All patients should be admitted for inpatient observation and in non - resolving cases should be managed as per gestational age 1) GA <32 weeks - intrauterine transfusion can be done in selected centers (can have complications such as acute progress to labor, stillbirth and unclear long term neurodevelopmental impairment); 2) GA >32 weeks delivery should be considered.

Neonatal (postnatal) management depends on the presence (likely acute blood loss or non-compensated anemia) or absence (chronic blood loss or compensated anemia) of signs of cardiac and circulatory failure. In severe acute cases the therapeutic goal is to administer adequate volume to restore tissue perfusion. Initial volume replacement should occur rapidly in infants with acute blood loss, or slower possibly necessitating an exchange transfusion in a compensated situation where transfusion could cause overload. Meanwhile simultaneous multisystem assessment and management is of paramount importance acutely and until discharge from the NICU.

Prognosis: FMH leading to neonatal anemia apart from the clinical severity and risk of short term morbidities and mortality (including neonatal death) has also been associated with very poor long term morbidity more specifically neurological impairment. As per recent review in 2013 by Christensen, R. D., et al outcomes were poorer in those with the lowest initial Hgb. The adverse outcomes of death, IVH, Periventricular leukomalacia (PVL), BPD or HIE were common; occurring in 71% of the studied patients, including all with an initial Hgb <5g/dl and born at <35 wks GA. In 2014 Maruyama et.al showed that when they follow the FMH cases for 12 months or more, 50% exhibited one of the following; cerebral palsy, mental retardation, attention deficit/hyperactivity disorder, and epilepsy. The base deficit in neonatal arterial blood increased significantly with decreasing neonatal Hb and also shows initial neonatal Hb independently can be a predictor of poor outcome. These studies stress the importance of correctly diagnosing FMH and parental education on its possible poor long term outcome depending on the severity.

Conclusion: True incidence and clinical significance of FMH is likely under-reported. There is a need for clinician education, better systems of reporting and a national registry due to low frequency but high clinical significance of this condition. Lack of fetal movements, non-reassuring fetal heart tracings should cause high index of suspicion for FMH. Hospital efforts should be directed towards increasing provider awareness and diagnosis, efficient use of the KB test and rapid and consistent communication between clinical specialties and labs. In this way, we can insure timely interventions along with parent education about long term significance.

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References:
Neonatal Hemochromatosis: Potentially Lethal but Possibly Preventable Disease

Neonatal hemochromatosis (NH) is one of the common causes of acute liver failure in neonates. It is characterized by severe hepatic injury and iron overload and associated with high perinatal morbidity and mortality. Antenatal findings are nonspecific and include oligohydramnios and intraterine growth restriction. Stillbirth and prematurity are not uncommon. Management and outcome have changed in recent years due to new understanding of the etiology of the disorder.

Etiology: NH was originally classified in the category of hereditary hemochromatosis (HH) disorders due to its occurrence in siblings. Pan X and Whitington PF showed complement-mediated hepatocyte injury triggered by IgG antibodies against fetal hepatocytes. These findings support that gestational alloimmune liver disease (GALD) is the cause of fetal liver injury leading to nearly all cases of NH. In GALD, maternal exposure to fetal liver antigen, not recognized as “self” triggers production of anti-hepatocyte IgG antibodies which cross the placenta and activate the terminal complement classical cascade. This results in formation of membrane attack complex (MAC) C5b-9 leading to hepatocyte injury. GALD can cause congenital cirrhosis or acute liver failure with or without iron overload and extrahepatic siderosis. It remains unclear how fetal liver antigen enters maternal circulation.

Pathology: GALD-NH affected liver tissue display marked hepatic necrosis. Surviving hepatocytes show siderosis, gaint cell transformation and canicular bile plugs. Severe panlobular parenchymal fibrosis is a dominant feature as well. Immunohistochemical staining shows MAC in hepatocytes. Extrahepatic siderosis is seen in acinar epithelium of the exocrine pancreas, thyroid follicles, and salivary glands and the myocardium, but the reticuloendothelial system (spleen, lymph nodes) is spared. The fetal liver controls iron flux from placenta by producing hepcidin, a small peptide hormone that binds with a transmembrane iron transporter called ferroportin. In state of iron sufficiency the hepcidin suppresses the expression of ferroportin and thus decreases iron influx. In fetus with GALD, liver injury results in decreased production of hepcidin, as a result there is less negative feedback on ferroportin and thus excess iron is transported from placenta to fetus.

Neonatal Clinical Findings: GALD-NH can present any time in utero to a few hours or days after birth with liver failure. Common signs are hypoglycemia, coagulopathy, hypoalbinumemia, jaundice, hyperammonemia, edema, renal involvement with oliguria. In twins, the severity may differ with one twin more severely affected than the other. Patent Ductus Venosus has been observed.

Laboratory evaluation reveals marked conjugated and unconjugated hyperbilirubinemia (bilirubin exceeding 30 mg/dL), mildly elevated aminotransferases (rarely above 100 IU/L), high a-fetoprotein levels (>100,000 ng/ml with normal value in term neonate <80,000ng/ml). Serum ferritin levels are >800 ng/ml (normal value 40-775 ng/ml), transferrin is low and iron saturation is high. Serum ferritin levels are a sensitive indicator for NH but not specific.

Diagnosis of NH is based on liver disease and extrahepatic siderosis. Extrahepatic siderosis can be detected by tissue iron staining (Prussian blue, Perl's stain) or by magnetic resonance imaging (MRI), particularly of liver and pancreas (Fig.1). An adequate oral biopsy of submucosal glands or T2 weighted liver and pancreas MRI each demonstrate iron overload in 60% of cases in autopsy proven NH. Combined sensitivity approaches 80%. If extrahepatic siderosis cannot be demonstrated, liver biopsy for CSB-9 staining should be considered.

Treatment: Without intervention the prognosis of NH is extremely poor. Treatment with deferoxamine, Vitamin E, N acetylcysteine, selenium and other antioxidant aimed at reducing iron overload and the attendant oxidative injury had low survival rates (10-20%) and no reduction in the need for liver transplantation. Marked improvement in survival (75%) without need for liver transplantation has been demonstrated since the introduction of a new treatment regimen combining double-volume exchange transfusion, to remove circulating antibodies, and high-dose IVIG (1gm/kg, repeated 1-2 times if needed) to block antibody induced complement activation. Reversal of cirrhosis with this treatment has been observed suggesting that the neonatal liver is able to recover even from severe injury.

Liver transplantation may be considered when medical treatment is ineffective but can be extremely challenging given the severity of clinical presentation often complicated by prematurity and multiorgan failure. The overall survival of infants receiving liver transplant for NH is approximately 35%.

Prevention: The recurrence rate of GALD-NH with subsequent pregnancies is greater than 90%. However, the disease can be prevented in 99% of affected pregnancies. At risk women should be treated with IVIG (1gm/kg) at 14 weeks, 16 weeks, and then weekly from the 18th week of gestation until the end of pregnancy. The effectiveness of this intervention in affected pregnancies underscores the importance of rigorous investigation for the cause of stillbirths and spontaneous recurrent pregnancy loss. Microscopy showing siderosis and immunohistochemical staining demonstrating MAC confirms the diagnosis.

Conclusion: GALD-NH should be suspected in infants who manifest liver disease antenatally or in the immediate post birth period. It should also be suspected in cases of unexplained stillbirth, neonatal demise, or early infant death. GALD-NH is likely underdiagnosed. Global knowledge of the disorder and high level of suspicion is important to establish diagnosis and implement timely prevention and treatment to improve pregnancy and neonatal outcomes.

References:

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Fig1: MRI and histopathology of liver and pancreas in NH: liver (left arrow) and pancreas (right arrow) had a markedly reduced T2 signal intensity (dark area) relative to the spleen. (a) Severe liver injury with loss of hepatocytes, Perl’s Prussian blue stain showing abnormal iron deposition in the (b) liver, (c) pancreas.
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