Published in final edited form as:

Semin Perinatol. 2009 February ; 33(1): 12–19. doi:10.1053/j.semperi.2008.10.005.

Disorders of the Feto-Maternal Unit: Hematologic Manifestations in the Fetus and Neonate

L. Vandy Black, MD and

Instructor in Pediatric Hematology-Oncology, University of Alabama at Birmingham, Birmingham, AL

Akhil Maheshwari, MD* [Assistant Professor of Pediatrics and Cell Biology]

Divisions of Neonatology and Pediatric Gastroenterology, University of Alabama at Birmingham, 619 19th Street South, Ste NHB 525, Birmingham, AL 35233

Abstract

Histoarchitectural characteristics of the human placenta place the fetus at a high risk of growth restriction, abnormal fetomaternal cell traffic, and vertical transmission of pathogens. These abnormalities of the fetomaternal unit are frequently associated with hematological abnormalities in the fetus/neonate, and may be the first, most common, or the only clinical manifestations of these conditions. This article reviews the pathophysiology and characteristic hematological manifestations of these conditions in the fetus and the neonate.

The villus trophoblastic layers in the placenta form an effective barrier against the passage of potentially toxic chemicals and pathogens from the maternal circulation into the fetus, regulate the transfer of respiratory gases, nutrients, and various immune factors, and, as is being increasingly recognized, regulate bidirectional cellular trafficking between the mother and the fetus throughout the pregnancy.^{1,2} Considering the complexity and importance of the fetomaternal interface, it is not surprising that placental insufficiency and disruptions of the placental barrier are common events and can adversely affect the fetus and the neonate.

Hematological abnormalities are, perhaps due to ease of recognition, some of the most frequently encountered and best-described consequences of abnormal placental function during pregnancy. This review is focused on the hematological abnormalities seen in the neonate in three common clinical situations that are associated with abnormalities of the fetomaternal unit: infants born to mothers with pregnancy-induced hypertension (PIH), immune-mediated neonatal cytopenias, and intrauterine fetal infections.

Human placenta

The development of the human placenta starts on day 6–7 after conception, when the blastocyst adheres to and invades the uterine endometrium through its trophoblast layer. The trophoblast progenitor cells fuse to form the multinucleated syncytiotrophoblast and are organized to form trabeculae, which are villus-like primitive outgrowths, and the lacunae,

*Corresponding Author: Phone: (205) 934-4680; Fax: (205) 212-2014, akhil@peds.uab.edu.

the vacuolar spaces that separate the trabeculae.³ The invasion of these trabeculae by an actively proliferating cytotrophoblast layer leads to the formation of placental villi, which protrude into the lacunae or the inter-villus space. Fetal capillaries develop in the villus core by the 5th week after conception and are separated from maternal blood in the lacunar/inter-villus system only by the trophoblast layer. This 'hemochorial' organization is a characteristic feature of human and primate placentae.²

The unique histoarchitecture of the hemochorial placenta places the human fetus at risk of growth restriction due to abnormalities of uteroplacental perfusion, villus development, and/or vascularization.⁴ The limited anatomic separation between maternal and fetal circulations in a hemochorial placenta also increases the risk of disruption of the placental barrier, exposing the fetus to abnormal maternal immune responses and vertically-transmitted pathogens (Table 1).^{1,2}

Placental insufficiency and its hematological consequences in the fetus/neonate

The most common causes of placental insufficiency and consequent fetal intrauterine growth restriction (IUGR) are the PIH-spectrum disorders, which include PIH, preeclampsia, eclampsia, and the HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count).⁴ In this review, we have focused on PIH-spectrum disorders as a representative 'model' of placental insufficiency and IUGR. The primary pathology in all these conditions is a defect in placentation due to the inability of the trophoblast to invade the decidua and its arterial walls effectively, thereby leading to an inadequate blood supply to fetal tissues.⁵ The condition is further exacerbated by multifocal vascular obstruction due to microthrombi and vasospasm, and later, by abnormal development of the placental vascular tree.^{5,6} The severity of placental vasculopathy determines the severity of fetal growth restriction, tissue hypoxia, and the dysfunction of various organ systems in the fetus.⁷

Hematological abnormalities are frequently recorded in growth-restricted fetuses, and the severity of the hematopoietic dysfunction appears to be proportional to the degree of placental insufficiency and fetal growth restriction.⁸ Whereas mild placental dysfunction and consequent tissue hypoxia are associated with increased erythropoietin levels and polycythemia, more severe placental vasculopathy often leads to erythropoietin resistance and anemia.^{9,10} The mechanisms of fetal anemia in severe IUGR may include decreased erythropoiesis from abnormal erythroblast function as well as RBC destruction from microangiopathic injury in the placenta.⁸

Placental insufficiency and fetal stress are associated with the presence of nucleated RBCs (nRBCs) in neonatal blood.^{11–13} The magnitude of the nRBC count elevation has been directly correlated with the severity and chronicity of the hypoxic insult and is believed to reflect increased erythropoiesis as a compensatory response.¹⁴ The normal nRBC count is variable but rarely exceeds 8 nRBC/100 white blood cells (WBC) in healthy term neonates.^{15,16} Elevated nRBC counts in growth-restricted neonates may predict poor perinatal outcome.¹³ However, the specificity of elevated nRBC counts is low and can also be seen in other forms of fetal/neonatal stress including Rh isoimmunization, fetal

hemorrhage, maternal diabetes mellitus, respiratory distress syndrome, and intraventricular hemorrhage.^{15,16}

About 40–50% of growth-restricted neonates, particularly those born to mothers with PIH-spectrum disorders are neutropenic.^{17,18} This variety of neutropenia can be severe (neutrophil counts below 500/mm³), but it is usually transient, lasting only a few days.¹⁸ There is some conflicting data,¹⁹ but most reports indicate that the transient neutropenia in neonates born to mothers with PIH is unlikely to carry a significant risk of infection.^{17,20,21} The mechanism of neutropenia in these infants is decreased neutrophil production due to a placental inhibitor present in cord blood.²² Increased erythropoietin levels in some of these infants may have a contributory role through ‘progenitor steal.’¹⁴ PIH-related neonatal neutropenia generally resolves in less than 72 hours and almost invariably by the fifth day of life.¹⁸ If neutropenia in a neonate born to a mother with PIH persists for more than five days, we begin to consider alternative etiologies.

Growth-restricted neonates born to mothers with PIH can also have thrombocytopenia, especially if the mother has severe hypertension, evidence of severe placental dysfunction and IUGR, or HELLP syndrome.^{21,23}

Thrombocytopenia seems to be more likely in preterm infants but has been reported in term infants as well. The mechanism is related to decreased platelet production.²⁴ Platelet counts may transiently rise after birth in many neonates with PIH-related thrombocytopenia, indicating a pathophysiological contribution from microangiopathic sequestration and destruction of platelets in the placenta.⁸

Abnormal fetomaternal cell traffic and its hematological consequences in the fetus/neonate

A large body of evidence now indicates that the placenta is a site for bidirectional trafficking of blood cells throughout the pregnancy.^{1,5,25} The direct clinical significance of fetomaternal cell trafficking across an intact placental barrier, from a fetal standpoint, remains unclear.¹ This fetomaternal cell traffic is abnormally increased in abnormal placentation and PIH-spectrum disorders.⁵ Intriguingly, fetal hematopoietic progenitor cells can persist in maternal blood for several decades after the pregnancy.¹

Clinically important fetomaternal transfusions occur in up to 50% of all pregnancies, often in association with abnormal placentation and disruptions of the placental barrier.⁵ The most obvious fetal manifestations of larger fetomaternal transfusions are those of acute/chronic blood loss.²⁶ Whereas chronic fetomaternal transfusions may remain hemodynamically well-compensated and present as neonatal anemia, acute fetomaternal transfusions during obstetric procedures such as cephalic versions may cause fetal hypotension and intra-uterine demise.²⁷

Fetomaternal transfusions can also result in alloimmunization of the mother against paternal antigens present on fetal blood cells.²⁸ The transplacental transfer of these maternal antibodies into the fetus can cause destruction of the fetal blood cells carrying the cognate

antigen (Fig. 1). The pathogenesis of these disorders is not completely understood. Even though a majority of maternal-fetal pairs are incompatible for one/more blood cell antigens, alloimmunization is seen only in a minority.²⁹ This disparity between the numbers of incompatible vs. allo-immunized maternal-fetal pairs may be due to a number of plausible reasons: (1) threshold effect in fetomaternal transfusions, where a certain amount of the immunizing blood cell antigen is required to activate the maternal immune system;³⁰ (2) type of antibody response- IgG antibodies are more efficiently transferred across the placenta to the fetus;³¹ (3) differential immunogenicity of blood group antigens: most blood cell antigens arise in allelic polymorphisms of cell surface proteins, and the steric location of the involved amino acid residues (in exofacial vs. hidden molecular domains) can partially explain the differential immunogenicity for various blood cell antigens;³² and (4) differences in maternal immune response: even for the antigens that are frequently associated with alloimmunization, the number of women who develop an antibody response is significantly smaller than the number who would be predicted to have a significant fetomaternal transfusion. This discrepancy between the expected and actual incidence of alloimmune cytopenias is considered to be due to differences in the efficiency of antigen presentation by various major histocompatibility (MHC) loci. The role of MHC is best-known in the context of alloimmune thrombocytopenia, where maternal immune response to the human platelet antigen (HPA)-1a antigen is linked to the supertypic HLA DRB3*0101 allele.³³ The HLA DRB3*0101 locus has a binding affinity for the Leu33 substitution on HPA-1a but not for the Pro33 substitution on HPA-1b, demonstrating the importance of binding between fetal peptides expressed on the β_3 integrin and the maternal MHC locus.³⁴ Similarly, antibody response to the HPA-1a antigen is also associated with specific maternal HLA types.³³ Such genetic restriction on the maternal immune response to foreign fetal antigens may account, in large part, for the lack of alloantibody formation in most cases of maternal-fetal incompatibility for blood cell antigens.

Hemolytic disease of the newborn (HDN, *erythroblastosis fetalis*)

HDN is classically seen in a setting of blood group incompatibility between the mother and her fetus for markers of the Rh system, which include five antigens: C, D, E, c, and e (the *d* type is not antigenic).³⁵ Rh-mediated HDN affects about 1 in 1200 pregnancies.³⁶ In the majority of Rh-sensitized cases, the D antigen of the fetus sensitizes the Rh-negative mother (who carries the allele '*d*'), resulting in IgG antibody production during the first pregnancy. Most Rh negative women have no anti-Rh antibodies prior to pregnancy sensitization, and therefore, Rh-related HDN is usually a disease of the 2nd and subsequent pregnancies.³⁶

The manifestations of HDN in the first affected newborn are usually mild, often limited to anemia and indirect hyperbilirubinemia. However, subsequent pregnancies are at risk for the development of a more severe phenotype characterized by fetal anemia, heart failure, elevated venous pressure, portal vein obstruction, and hypoalbuminemia, which may manifest as edema, ascites, pleural and pericardial effusions, or all of these as fetal hydrops.³⁷ Improvements in fetal monitoring and intrauterine transfusions have reduced mortality in Rh-related HDN to less than 10%. However, fetal transfusions are considered safe only after 20 weeks of gestation and continue to carry a 1–3% risk of fetal demise from the procedure.^{37,38} Maternal treatment with high dose intravenous immunoglobulins (IVIG)

alone or in combination with plasma exchange may also be effective in reducing the severity of HDN.^{37,39} Newer experimental approaches include maternal administration of a synthetic anti-D antibody that lacks hemolytic activity and is designed to cross the placenta and block the action of maternal anti-D.⁴⁰ After birth, treatment of the affected neonate may include exchange transfusions to correct severe anemia, IVIG to reduce ongoing hemolysis, and aggressive treatment of hyperbilirubinemia with phototherapy and/or exchange transfusions.⁴¹

ABO Incompatibility—ABO hemolytic disease occurs almost exclusively in the offspring of women with blood group O, although occasional cases in group A mothers with high-titer anti-blood group B IgG have been reported.⁴² About 15–25% of all maternal/fetal pairs are ABO-incompatible and ABO HDN occurs in about 1% of these pairs that have pre-existing high-titer IgG antibodies. Hemolysis due to anti-A is more common (1 in 150 births) than due to anti-B antibodies.⁴³

The severity of hemolysis in ABO HDN is generally milder than in Rh alloimmunization. RBCs have fewer binding sites for anti-ABO antibodies than for Rh antibodies, which allows the antibody-coated RBCs in ABO HDN to survive longer than in Rh HDN.^{44,45} As a reflection of the longer circulating half-life of antibody-coated RBCs, peripheral blood films in ABO HDN show a large number of microspherocytes and few nucleated RBCs.⁴³ Neonates affected by ABO HDN usually have only minimal to mild anemia, though more severe phenotypes, including hydrops, have been reported.⁴⁵ In contrast to Rh HDN, ABO incompatibility and alloimmunization can cause hemolysis in the first-born infant, and the severity of disease in the first and subsequent pregnancies is generally similar.⁴³ The primary clinical manifestation of ABO alloimmunization is neonatal hyperbilirubinemia appearing within the first 24 hours of life.

Minor blood groups—The so-called minor blood groups account for a considerable number of cases of HDN. The principal allo-antibodies leading to these forms of HDN include anti-Kell, anti-Kidd (J^k), anti-Duffy (F^y), and antibodies of the MNS blood group system, including anti-U. Anti-Kell antibodies may account for up to 10% of all cases of HDN.⁴⁶ Most cases of Kell alloimmunization involve a K1-positive fetus and K1- negative mother; a small minority is due to incompatibility at the K2 locus (also called k). The Kell antigens are expressed on erythroid progenitors and mature RBCs, which implies that anemia in these infants is due to both hemolysis as well as suppression of erythropoiesis. Kell-alloimmunized fetuses have inappropriately low numbers of circulating reticulocytes and also have lower serum/amniotic fluid bilirubin levels than in Rh HDN.^{46,47} The titer of anti-Kell antibodies in maternal serum correlates poorly with fetal anemia.⁴⁶ The clinical features of HDN due to Rh, ABO, and Kell alloimmunization are summarized in Table 2.

Alloimmune Neonatal Neutropenia

Alloimmune neonatal neutropenia (ANN) is the neutrophil counterpart of HDN. Maternal antibodies against a paternal antigen present on fetal neutrophils cross the placenta and cause neutropenia in the fetus.⁴⁸ Anti-neutrophil antibodies are detectable in up to 20% of pregnant and postpartum women, but ANN occurs in only 0.2–2% of sampled newborns. A

wide variety of antigenic targets have been identified in ANN, including the HNA-1, HNA-2, and HNA-3 antigen groups as well as NC1, SH, SAR, LAN, LEA, and CN1.⁴⁹ The role of anti-HLA antibodies is controversial. In the United States, 50% of all cases of ANN are mediated by antibodies that bind to HNA-1a, HNA-1b, or HNA-2a antigens. The causative antigen remains unidentified in a large majority of the remaining cases.²⁹

Common clinical presentations of ANN include delayed separation of the umbilical cord, mild skin infections, fever, or pneumonia within the first two weeks after birth.²⁹ Omphalitis and subcutaneous abscesses have also been reported. Although most infections reported in patients with ANN are mild, overwhelming sepsis can occur with an overall mortality of about 5%.⁵⁰ Neutropenia in ANN lasts for a median of 7 weeks, ranging from 2 weeks to 6 months.⁴⁹

When prolonged (>7 days), severe (absolute neutrophil count <500/mm³), or associated with serious infections, ANN can be treated with subcutaneous recombinant human granulocyte colony stimulating factor (rhG-CSF).⁵⁰ We usually administer rhG-CSF at a dose of 10 mcg/kg/day in one or two divisions until the ANC rises above 1000/mm³. Higher doses of rhG-CSF may be required in ANN due to anti-HNA-2a antibodies, which is associated with decreased neutrophil production in addition to peripheral destruction of neutrophils.⁵¹ rhG-CSF is usually well-tolerated without adverse effects at the doses and duration of treatment needed for ANN. The mechanisms of action of rhG-CSF in ANN include increased neutrophil production, release of neutrophils from the post-mitotic storage pools in the marrow, and increased neutrophil survival. G-CSF may also downregulate the surface expression of the neutrophil antigens commonly incriminated in ANN.²⁹ Besides rhG-CSF, other treatments such as IVIG, exchange transfusions, and leukocyte transfusions have also been used in ANN associated with serious bacterial infections with varying success.⁵⁰ IVIG may cause remission of neutropenia is about 50% infants but the effects are often transient. Corticosteroids are generally not effective.

Neonatal Alloimmune Thrombocytopenia

Neonatal alloimmune thrombocytopenia (NAIT) occurs in approximately 1 in 2,000 live births and is characterized by a marked thrombocytopenia in the fetus and neonate.²⁸ Maternal antibodies directed against fetal platelet antigens lead to increased platelet destruction. Sixteen human platelet antigens have been identified, but fetomaternal incompatibility for three of these antigens (HPA-1a, HPA-5b, and HPA-15b), singly or in combination, accounts for 95% of the cases. The antigen system HPA-1a accounts for approximately 75% of the cases.⁵² A detailed description of NAIT can be found elsewhere within this issue of the *Seminars*.

Transplacental transfer of maternal autoantibodies directed against hematopoietic cell lineages

Transplacentally-transmitted maternal autoantibodies against RBC, neutrophil, and platelet antigens can cause the destruction of one or more of these cell lineages in the fetus. Beginning at about 17 weeks of gestation, maternal immunoglobulins are actively

transported across the placenta and this transfer increases with gestation. IgG1 and IgG3 subclasses are transferred with the highest efficiency. Serum IgG concentrations in the fetus are comparable to maternal levels at 33 weeks of gestation and exceed maternal levels by 40 weeks.⁵³ Whereas disruptions of the placental barrier increase the transmission of maternal antibodies, placental abnormalities and high total IgG concentrations in maternal blood may actually reduce antibody transfer to the fetus. Autoantibodies against hematopoietic lineages are frequently of the IgG1 subclass, which are transmitted to the fetus with high efficiency.^{50,54}

Neonatal autoimmune hemolytic anemia (AHA) is seen in infants born to mothers with anti-RBC antibodies due to autoimmune hemolytic anemia, systemic lupus erythematosus (SLE), or rheumatoid arthritis. Disease in the neonate is usually self-limited and resolves within a few weeks to months. In some cases, the maternal antibodies may also cross-react with other blood cells to cause concomitant neutropenia, thrombocytopenia, or both. The diagnosis is suggested by a positive direct Coombs' test in both the mother and the baby. Antenatal treatment with glucocorticoids may reduce the severity of the condition in the fetus.

Neonatal autoimmune neutropenia is analogous to AHA and is caused by the transplacental transmission of maternal anti-neutrophil autoantibodies. Most often, both the mother and the neonate are neutropenic. Most of these neonates remain asymptomatic, although severe cases may develop infections similar to ANN. If treatment is required, such as in the presence of a serious infection, high dose IVIG and/or rhG-CSF can increase neutrophil counts.

Neonatal autoimmune thrombocytopenia is generally milder than NAIT and is less often complicated by intracranial hemorrhage (<1%) or bleeding at other sites.⁵⁵ Thrombocytopenia is seen in about 10% of the infants born to mothers with autoimmune thrombocytopenia due to immune thrombocytopenia purpura (ITP), SLE, or other conditions. Most of these mothers, except for a small minority who are well-compensated due to marrow hyperactivity, are thrombocytopenic and may have increased mean platelet volume or obviously large platelets on peripheral blood smear. Symptomatic infants can be effectively treated with IVIG.⁵⁶

The aforementioned hematological abnormalities due to transplacentally-transmitted maternal autoantibodies may need clinical differentiation from true autoimmune sensitization in young infants.^{57,58} Autoimmune cytopenias can occur in infants and are usually seen beyond the neonatal period, although sensitization can rarely occur even *in utero*.⁵⁹

Hematological abnormalities in neonates with transplacental infections

The hemochorial organization of the human placenta renders the fetus somewhat susceptible to transplacental infections.⁶⁰ The risk of maternal-fetal transfer of pathogens is related to the number of cellular layers, their type, and the thickness of the layers separating maternal and fetal circulations in the placenta. In the hemochorial placenta, maternal blood vessels are destroyed by the fetal trophoblast, which is in direct contact with maternal blood across the huge surface area of the arboreally-organized villi.² In the hyporesponsive immune

environment of the pregnant uterus, vertically-transmitted pathogens often target the cytotrophoblast and the decidua and impair placental development.² Hematological manifestations are common in congenital infections and frequently provide the first clue that leads the clinician towards the diagnosis.

Cytomegalovirus

CMV is the most common congenital infection in the United States.⁶¹ Hematological abnormalities including thrombocytopenia, anemia, and extramedullary hematopoiesis are common in symptomatic infants, although these abnormalities usually resolve during the first year of life. The mechanisms of thrombocytopenia and anemia include both decreased production due to progenitor infection and increased destruction secondary to hypersplenism. CMV infection of the cytotrophoblast may impair the remodeling of uteroplacental vessels and cause placental insufficiency and IUGR, thereby providing an additional mechanism for the observed hematological abnormalities.⁶²

Toxoplasmosis

Anemia occurs in up to 75% of all symptomatic patients and is often accompanied by a reticulocytosis and hyperbilirubinemia, suggesting a hemolytic etiology.⁶³ Thrombocytopenia, likely due to increased peripheral destruction, occurs in up to 10% of all patients.⁶⁴ Eosinophilia is seen in nearly 25% patients. Some patients may also have decreased CD4 lymphocyte counts and abnormal cell-mediated immunity.⁶⁵ Both neutropenia and neutrophilia have been described.⁶⁶

Syphilis

Anemia occurs in more than 60% of all patients, usually secondary to a Coombs' negative hemolytic process, but can also result from marrow hypoplasia or replacement of the marrow by granulation tissue.⁶⁷ Hydrops fetalis has been reported. Thrombocytopenia occurs in nearly half of all patients and is due to increased destruction. Lymphocytosis may occur in some patients.⁶⁸

Rubella

Thrombocytopenia may be seen in up to 80% infants with congenital rubella syndrome. It is usually transient but can last up to several months. In contrast to other congenital infections, thrombocytopenia in congenital rubella infections may be due to decreased megakaryocyte production.⁶⁹ Patients can also develop a hemolytic anemia which can persist for months and potentially progress to red cell aplasia. The leukocyte count is variable.⁷⁰

Parvovirus

Serious fetal complications may occur with parvovirus B19 infections during the first 12 weeks of gestation. The virus infects RBC progenitors, which may cause fetal anemia and hydrops due to fetal red cell aplasia.⁷¹ Intrauterine transfusions can be used in some patients, allowing for the eventual recovery of RBC precursors and restoration of normal hematopoiesis.⁷²

HIV

HIV infection may cause autoimmune thrombocytopenic purpura in the mother, resulting in secondary immune-mediated thrombocytopenia in the infant.⁷³ Thrombocytopenia has also been reported as an initial manifestation of symptomatic congenital HIV infection.⁷⁴

Other Infections

Maternal echovirus and coxsackie B infections may cause fetal thrombocytopenia.⁷⁵ Congenital malaria and tuberculosis are also associated with fetal anemia and thrombocytopenia.^{63,76,77}

Conclusions

Hematologic problems such as thrombocytopenia, anemia, and neutropenia are commonly encountered when caring for critically ill neonates. Although many diverse etiologies can contribute to these manifestations, disorders of the fetomaternal unit are a frequent cause and must be considered in the differential diagnosis.

References

1. Bianchi DW. Fetomaternal cell trafficking: A new cause of disease? *Am J Med Genet.* 2000; 91:22–28. [PubMed: 10751084]
2. Pereira L, Maidji E, McDonagh S, Tabata T. Insights into viral transmission at the uterine-placental interface. *Trends Microbiol.* 2005; 13:164–174. [PubMed: 15817386]
3. Moll W. Structure adaptation and blood flow control in the uterine arterial system after hemochorial placentation. *Eur J Obstet Gynecol Reprod Biol.* 2003; 110(Suppl 1):S19–27. [PubMed: 12965087]
4. Robertson WB, Brosens I, Landells WN. Abnormal placentation. *Obstet Gynecol Annu.* 1985; 14:411–426. [PubMed: 3885098]
5. Holzgreve W, Ghezzi F, Di Naro E, Ganshirt D, Maymon E, Hahn S. Disturbed feto-maternal cell traffic in preeclampsia. *Obstet Gynecol.* 1998; 91:669–672. [PubMed: 9572208]
6. Zhou Y, Damsky CH, Chiu K, Roberts JM, Fisher SJ. Preeclampsia is associated with abnormal expression of adhesion molecules by invasive cytotrophoblasts. *J Clin Invest.* 1993; 91:950–960. [PubMed: 7680671]
7. Davies N, Snijders R, Nicolaides KH. Intra-uterine starvation and fetal leucocyte count. *Fetal Diagn Ther.* 1991; 6:107–112. [PubMed: 1789915]
8. Kush ML, Gortner L, Harman CR, Baschat AA. Sustained hematological consequences in the first week of neonatal life secondary to placental dysfunction. *Early Hum Dev.* 2006; 82:67–72. [PubMed: 16198513]
9. Snijders RJ, Abbas A, Melby O, Ireland RM, Nicolaides KH. Fetal plasma erythropoietin concentration in severe growth retardation. *Am J Obstet Gynecol.* 1993; 168:615–619. [PubMed: 8438939]
10. Weiner CP, Williamson RA. Evaluation of severe growth retardation using cordocentesis—hematologic and metabolic alterations by etiology. *Obstet Gynecol.* 1989; 73:225–229. [PubMed: 2536145]
11. Philip AG, Tito AM. Increased nucleated red blood cell counts in small for gestational age infants with very low birth weight. *Am J Dis Child.* 1989; 143:164–169. [PubMed: 2916486]
12. Ferber A, Minior VK, Bornstein E, Divon MY. Fetal “Nonreassuring status” Is associated with elevation of nucleated red blood cell counts and interleukin-6. *Am J Obstet Gynecol.* 2005; 192:1427–1429. [PubMed: 15902127]

13. Minior VK, Shatzkin E, Divon MY. Nucleated red blood cell count in the differentiation of fetuses with pathologic growth restriction from healthy small-for-gestational-age fetuses. *Am J Obstet Gynecol.* 2000; 182:1107–1109. [PubMed: 10819841]
14. Rollins MD, Maxwell AP, Afrasiabi M, Halliday HL, Lappin TR. Cord blood erythropoietin, ph, pao2 and haematocrit following caesarean section before labour. *Biol Neonate.* 1993; 63:147–152. [PubMed: 8324093]
15. Green DW, Hendon B, Mimouni FB. Nucleated erythrocytes and intraventricular hemorrhage in preterm neonates. *Pediatrics.* 1995; 96:475–478. [PubMed: 7651781]
16. Green DW, Mimouni F. Nucleated erythrocytes in healthy infants and in infants of diabetic mothers. *J Pediatr.* 1990; 116:129–131. [PubMed: 2248625]
17. Christensen RD, Henry E, Wiedmeier SE, Stoddard RA, Lambert DK. Low blood neutrophil concentrations among extremely low birth weight neonates: Data from a multihospital health-care system. *J Perinatol.* 2006; 26:682–687. [PubMed: 17036034]
18. Koenig JM, Christensen RD. Incidence, neutrophil kinetics, and natural history of neonatal neutropenia associated with maternal hypertension. *N Engl J Med.* 1989; 321:557–562. [PubMed: 2761599]
19. Doron MW, Makhoulf RA, Katz VL, Lawson EE, Stiles AD. Increased incidence of sepsis at birth in neutropenic infants of mothers with preeclampsia. *J Pediatr.* 1994; 125:452–458. [PubMed: 8071757]
20. Paul DA, Leef KH, Sciscione A, Tuttle DJ, Stefano JL. Preeclampsia does not increase the risk for culture proven sepsis in very low birth weight infants. *Am J Perinatol.* 1999; 16:365–372. [PubMed: 10614705]
21. Fraser SH, Tudehope DI. Neonatal neutropenia and thrombocytopenia following maternal hypertension. *J Paediatr Child Health.* 1996; 32:31–34. [PubMed: 8652209]
22. Koenig JM, Christensen RD. The mechanism responsible for diminished neutrophil production in neonates delivered of women with pregnancy-induced hypertension. *Am J Obstet Gynecol.* 1991; 165:467–473. [PubMed: 1714678]
23. Christensen RD, Henry E, Wiedmeier SE, et al. Thrombocytopenia among extremely low birth weight neonates: Data from a multihospital healthcare system. *J Perinatol.* 2006; 26:348–353. [PubMed: 16642027]
24. Saxonhouse MA, Rimsza LM, Stevens G, Jouei N, Christensen RD, Sola MC. Effects of hypoxia on megakaryocyte progenitors obtained from the umbilical cord blood of term and preterm neonates. *Biol Neonate.* 2006; 89:104–108. [PubMed: 16192692]
25. Lo YM, Lo ES, Watson N, et al. Two-way cell traffic between mother and fetus: Biologic and clinical implications. *Blood.* 1996; 88:4390–4395. [PubMed: 8943877]
26. Giacoia GP. Severe fetomaternal hemorrhage: A review. *Obstet Gynecol Surv.* 1997; 52:372–380. [PubMed: 9178311]
27. Samadi R, Greenspoon JS, Gviazda I, Settlege RH, Goodwin TM. Massive fetomaternal hemorrhage and fetal death: Are they predictable? *J Perinatol.* 1999; 19:227–229. [PubMed: 10685227]
28. Kaplan C. Neonatal alloimmune thrombocytopenia. *Haematologica.* 2008; 93:805–807. [PubMed: 18515877]
29. Maheshwari A, Christensen RD, Calhoun DA. Immune-mediated neutropenia in the neonate. *Acta Paediatr Suppl.* 2002; 91:98–103. [PubMed: 12477271]
30. Howarth DJ, Robinson FM, Williams M, Norfolk DR. A modified kleihauer technique for the quantification of foetomaternal haemorrhage. *Transfus Med.* 2002; 12:373–378. [PubMed: 12473154]
31. Rieben R, Buchs JP, Fluckiger E, Nydegger UE. Antibodies to histo-blood group substances a and b: Agglutination titers, ig class, and igg subclasses in healthy persons of different age categories. *Transfusion.* 1991; 31:607–615. [PubMed: 1891791]
32. Zimring JC, Spitalnik SL, Roback JD, Hillyer CD. Transfusion-induced autoantibodies and differential immunogenicity of blood group antigens: A novel hypothesis. *Transfusion.* 2007; 47:2189–2196. [PubMed: 17764514]

33. Killie MK, Husebekk A, Kjeldsen-Kragh J, Skogen B. A prospective study of maternal anti-hpa 1a antibody level as a potential predictor of alloimmune thrombocytopenia in the newborn. *Haematologica*. 2008; 93:870–877. [PubMed: 18443267]
34. L'Abbe D, Tremblay L, Filion M, et al. Alloimmunization to platelet antigen hpa-1a (pia1) is strongly associated with both hla-drb3*0101 and hla-dqb1*0201. *Hum Immunol*. 1992; 34:107–114. [PubMed: 1358865]
35. Eder AF. Update on hdn: New information on long-standing controversies. *Immunohematology*. 2006; 22:188–195. [PubMed: 17430078]
36. Moise KJ Jr. Management of rhesus alloimmunization in pregnancy. *Obstet Gynecol*. 2008; 112:164–176. [PubMed: 18591322]
37. Moise KJ Jr. Management of rhesus alloimmunization in pregnancy. *Obstet Gynecol*. 2002; 100:600–611. [PubMed: 12220785]
38. Kumar S, Regan F. Management of pregnancies with rhd alloimmunisation. *BMJ*. 2005; 330:1255–1258. [PubMed: 15920129]
39. Urbaniak SJ. Noninvasive approaches to the management of rhd hemolytic disease of the fetus and newborn. *Transfusion*. 2008; 48:2–5. [PubMed: 18184231]
40. Nielsen LK, Green TH, Sandlie I, Michaelsen TE, Dziegiel MH. In vitro assessment of recombinant, mutant immunoglobulin g anti-d devoid of hemolytic activity for treatment of ongoing hemolytic disease of the fetus and newborn. *Transfusion*. 2008; 48:12–19. [PubMed: 17764508]
41. Urbaniak SJ, Greiss MA. Rhd haemolytic disease of the fetus and the newborn. *Blood Rev*. 2000; 14:44–61. [PubMed: 10805260]
42. Wang M, Hays T, Ambruso DR, Silliman CC, Dickey WC. Hemolytic disease of the newborn caused by a high titer anti-group b igg from a group a mother. *Pediatr Blood Cancer*. 2005; 45:861–862. [PubMed: 16007582]
43. Murray NA, Roberts IA. Haemolytic disease of the newborn. *Arch Dis Child Fetal Neonatal Ed*. 2007; 92:F83–88. [PubMed: 17337672]
44. Waldron P, de Alarcon P. Abo hemolytic disease of the newborn: A unique constellation of findings in siblings and review of protective mechanisms in the fetal-maternal system. *Am J Perinatol*. 1999; 16:391–398. [PubMed: 10772197]
45. Grundbacher FJ. The etiology of abo hemolytic disease of the newborn. *Transfusion*. 1980; 20:563–568. [PubMed: 7191589]
46. Vaughan JI, Manning M, Warwick RM, Letsky EA, Murray NA, Roberts IA. Inhibition of erythroid progenitor cells by anti-kell antibodies in fetal alloimmune anemia. *N Engl J Med*. 1998; 338:798–803. [PubMed: 9504940]
47. Weiner CP, Widness JA. Decreased fetal erythropoiesis and hemolysis in kell hemolytic anemia. *Am J Obstet Gynecol*. 1996; 174:547–551. [PubMed: 8623782]
48. Lalezari P. Alloimmune neonatal neutropenia and neutrophil-specific antigens. *Vox Sang*. 1984; 46:415–417. [PubMed: 6205508]
49. Bux J, Jung KD, Kauth T, Mueller-Eckhardt C. Serological and clinical aspects of granulocyte antibodies leading to alloimmune neonatal neutropenia. *Transfus Med*. 1992; 2:143–149. [PubMed: 1284978]
50. Maheshwari A, Christensen RD, Calhoun DA. Immune neutropenia in the neonate. *Adv Pediatr*. 2002; 49:317–339. [PubMed: 12214777]
51. Maheshwari A, Christensen RD, Calhoun DA. Resistance to recombinant human granulocyte colony-stimulating factor in neonatal alloimmune neutropenia associated with anti-human neutrophil antigen-2a (nb1) antibodies. *Pediatrics*. 2002; 109:e64. [PubMed: 11927737]
52. Barney CK, Sola MC, Christensen RD. An unusual case of severe neonatal thrombocytopenia. *Adv Neonatal Care*. 2007; 7:66–68. [PubMed: 17605445]
53. Englund JA. The influence of maternal immunization on infant immune responses. *J Comp Pathol*. 2007; 137(Suppl 1):S16–19. [PubMed: 17553516]
54. Chan H, Moore JC, Finch CN, Warkentin TE, Kelton JG. The igg subclasses of platelet-associated autoantibodies directed against platelet glycoproteins iib/iiia in patients with idiopathic thrombocytopenic purpura. *Br J Haematol*. 2003; 122:818–824. [PubMed: 12930395]

55. Weibert KE, Mittal R, Sigouin C, Heddle NM, Kelton JG. A retrospective 11-year analysis of obstetric patients with idiopathic thrombocytopenic purpura. *Blood*. 2003; 102:4306–4311. [PubMed: 12947011]
56. Kaplan C. Immune thrombocytopenia in the foetus and the newborn: Diagnosis and therapy. *Transfus Clin Biol*. 2001; 8:311–314. [PubMed: 11499984]
57. Motta M, Cavazza A, Migliori C, Chirico G. Autoimmune haemolytic anaemia in a newborn infant. *Arch Dis Child Fetal Neonatal Ed*. 2003; 88:F341–342. [PubMed: 12819171]
58. Bux J, Kissel K, Nowak K, Spengel U, Mueller-Eckhardt C. Autoimmune neutropenia: Clinical and laboratory studies in 143 patients. *Ann Hematol*. 1991; 63:249–252. [PubMed: 1958748]
59. Calhoun DA, Rimsza LM, Burchfield DJ, et al. Congenital autoimmune neutropenia in two premature neonates. *Pediatrics*. 2001; 108:181–184. [PubMed: 11433074]
60. Koi H, Zhang J, Parry S. The mechanisms of placental viral infection. *Ann N Y Acad Sci*. 2001; 943:148–156. [PubMed: 11594535]
61. Ross SA, Boppana SB. Congenital cytomegalovirus infection: Outcome and diagnosis. *Semin Pediatr Infect Dis*. 2005; 16:44–49. [PubMed: 15685149]
62. Zhou Y, Fisher SJ, Janatpour M, et al. Human cytotrophoblasts adopt a vascular phenotype as they differentiate. A strategy for successful endovascular invasion? *J Clin Invest*. 1997; 99:2139–2151. [PubMed: 9151786]
63. Fleming AF. Haematological manifestations of malaria and other parasitic diseases. *Clin Haematol*. 1981; 10:983–1011. [PubMed: 7030561]
64. Couvreur J, Desmonts G, Tournier G, Szusterkac M. A homogeneous series of 210 cases of congenital toxoplasmosis in 0 to 11-month-old infants detected prospectively. *Ann Pediatr (Paris)*. 1984; 31:815–819. [PubMed: 6517457]
65. Hohlfeld P, Forestier F, Marion S, Thulliez P, Marcon P, Daffos F. *Toxoplasma gondii* infection during pregnancy: T lymphocyte subpopulations in mothers and fetuses. *Pediatr Infect Dis J*. 1990; 9:878–881. [PubMed: 1980540]
66. Guerina NG. Congenital infection with *Toxoplasma gondii*. *Pediatr Ann*. 1994; 23:138–142. 147–151. [PubMed: 8015862]
67. Sanchez PJ. Congenital syphilis. *Adv Pediatr Infect Dis*. 1992; 7:161–180. [PubMed: 1616684]
68. Hira SK, Bhat GJ, Patel JB, et al. Early congenital syphilis: Clinico-radiologic features in 202 patients. *Sex Transm Dis*. 1985; 12:177–183. [PubMed: 4081939]
69. Hohlfeld P, Forestier F, Kaplan C, Tissot JD, Daffos F. Fetal thrombocytopenia: A retrospective survey of 5,194 fetal blood samplings. *Blood*. 1994; 84:1851–1856. [PubMed: 8080991]
70. Franco SA, Riley HD Jr, Chitwood LA. The congenital rubella syndrome. *South Med J*. 1970; 63:825–830. [PubMed: 5427175]
71. de Jong EP, de Haan TR, Kroes AC, Beersma MF, Oepkes D, Walther FJ. Parvovirus b19 infection in pregnancy. *J Clin Virol*. 2006; 36:1–7. [PubMed: 16488187]
72. Kailasam C, Brennand J, Cameron AD. Congenital parvovirus b19 infection: Experience of a recent epidemic. *Fetal Diagn Ther*. 2001; 16:18–22. [PubMed: 11125246]
73. Glantz JC, Roberts DJ. Pregnancy complicated by thrombocytopenia secondary to human immunodeficiency virus infection. *Obstet Gynecol*. 1994; 83:825–827. [PubMed: 8159363]
74. Tighe P, Rimsza LM, Christensen RD, Lew J, Sola MC. Severe thrombocytopenia in a neonate with congenital hiv infection. *J Pediatr*. 2005; 146:408–413. [PubMed: 15756230]
75. Ouellet A, Sherlock R, Toye B, Fung KF. Antenatal diagnosis of intrauterine infection with coxsackievirus b3 associated with live birth. *Infect Dis Obstet Gynecol*. 2004; 12:23–26. [PubMed: 15460192]
76. Vottier G, Arsac M, Farnoux C, Mariani-Kurkdjian P, Baud O, Aujard Y. Congenital malaria in neonates: Two case reports and review of the literature. *Acta Paediatr*. 2008; 97:505–508. [PubMed: 18307546]
77. Sanchez PJ. Perinatal infections and brain injury: Current treatment options. *Clin Perinatol*. 2002; 29:799–826. [PubMed: 12516747]

Fig. 1. Maternal alloimmunization during pregnancy

Abnormal exposure of the maternal immune system to antigens present on fetal blood cells can result in antibody formation. Subsequent transmission of these maternal antibodies into the fetus can cause destruction of the fetal blood cells carrying the cognate antigen.

Table 1

Disorders of the Feto-maternal Unit Resulting in Hematological Manifestations in the Fetus/Neonate

Placental insufficiency

- PIH-spectrum disorders (preeclampsia, eclampsia, HELLP syndrome)
- Maternal diabetes
- Transplacentally-acquired infections (such as CMV)
- Systemic conditions (malignancies, cardiac disease, thyroid disease, SLE and other autoimmune disorders etc.)

Immune-Mediated Disorders

- Hemolytic disease of the newborn
- Alloimmune Neonatal Neutropenia
- Neonatal Alloimmune Thrombocytopenia
- Autoimmune Hemolytic Anemia
- Neonatal Autoimmune Neutropenia
- Neonatal Autoimmune Thrombocytopenia

Transplacentally-acquired Infections

- Toxoplasmosis
- Syphilis
- Cytomegalovirus (CMV), Rubella, Human Immunodeficiency Virus (HIV), Parvovirus B19 Echovirus, Coxsackie B Virus
- Tuberculosis
- Malaria

Table 2

Hemolytic disease of the newborn.

	<i>Rh</i>	<i>ABO</i>	<i>Kell</i>
Blood Groups			
Mother	Rh-negative	O (occasionally B)	Negative (K1)
Infant	Positive (D, sometimes C)	A (sometimes B)	Positive (K1)
Clinical features of hemolytic disease in the newborn			
Occurrence in first-born	5%	40–50%	Rare
Severity in subsequent pregnancies	Predictable	Difficult to predict	Somewhat predictable
Stillbirth/hydrops	Frequent	Rare	10%
Severe anemia	Frequent	Rare	Frequent
Jaundice	Prominent, severe	Mild-moderate	Mild
Laboratory tests			
Direct Coombs' test (Infant)	Positive	Positive or Negative	Positive or Negative
Reticulocyte count	High	High	May not be high
Maternal antibodies	Usually detectable	May not be detectable	Usually detectable
	Maternal antibody titers can help predict fetal disease	Titers may not correlate with fetal disease	Titers may not correlate with fetal disease; fetus affected at titers lower than for Rh-mediated hemolysis