Fetal Anemia

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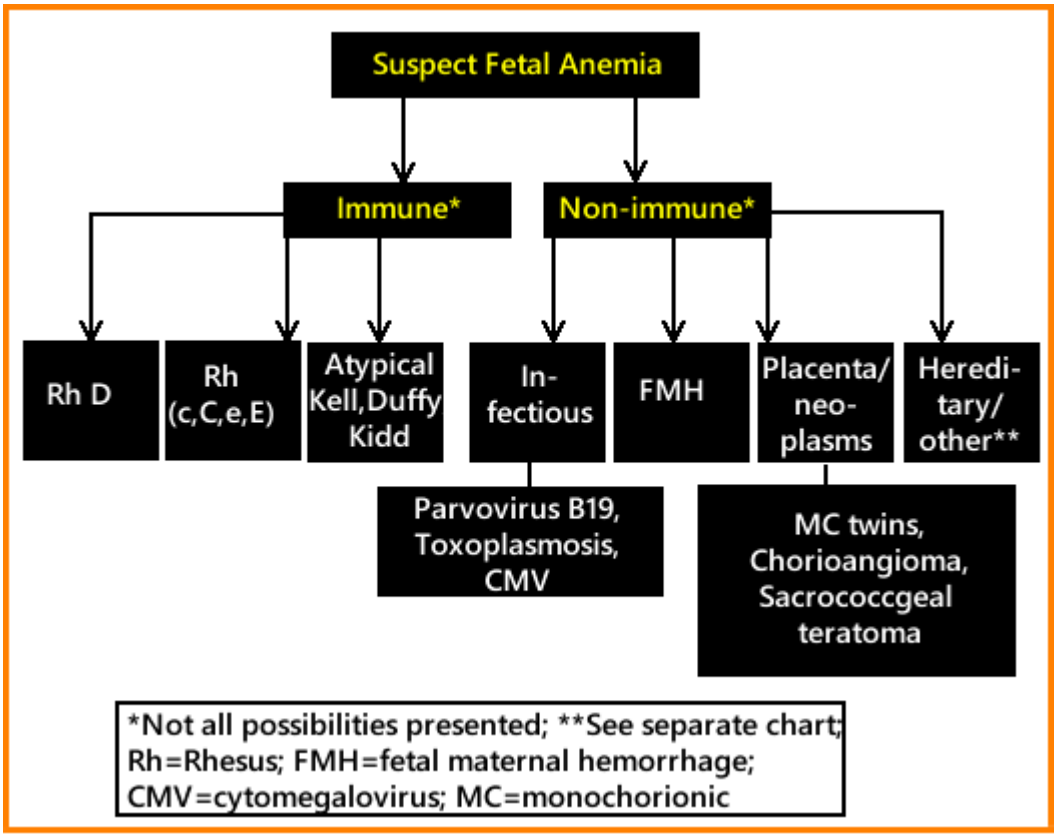
Introduction

Anemia is a major contributor to fetal morbidity and mortality. The etiology remains diverse and is sometimes difficult to detect by ordinary clinical means. Recently, the middle cerebral artery Doppler peak systolic velocity (MCA-PSV) has been recommended as the methodology of choice to detect and assess suspected fetal anemia. [1] This section covers causes of fetal anemia.

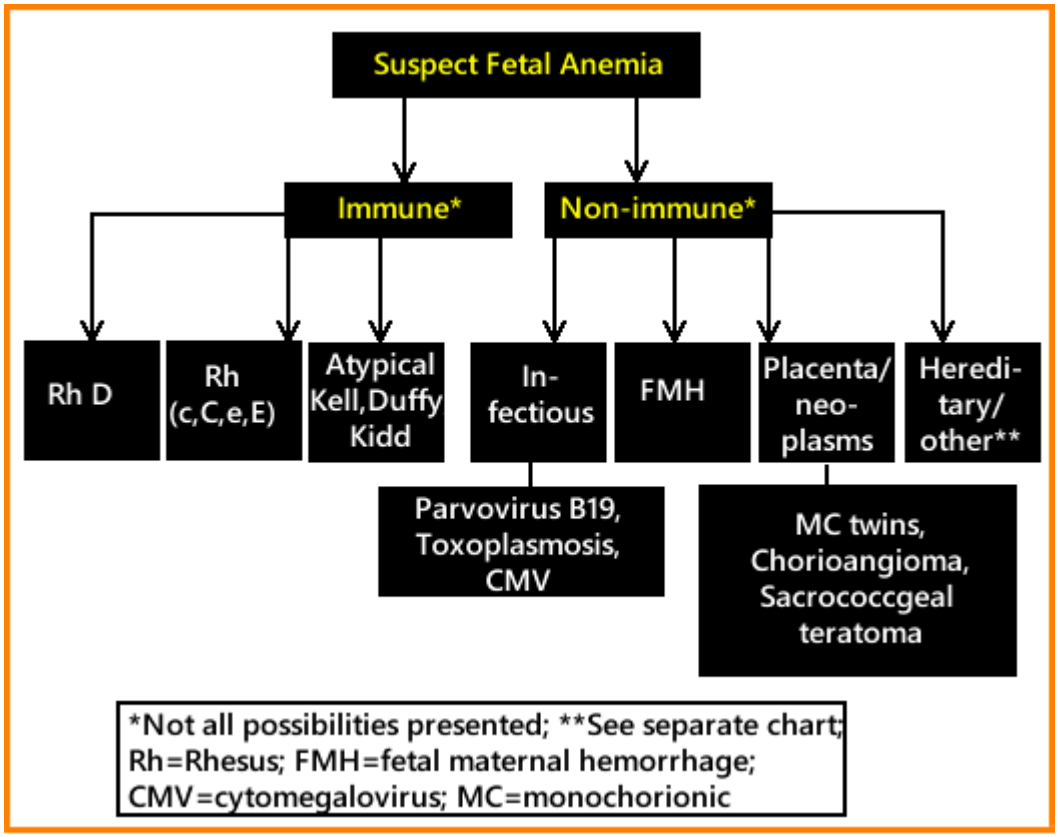
Etiology of Fetal Anemia

The etiology for fetal anemia can be divided into immune and non-immune



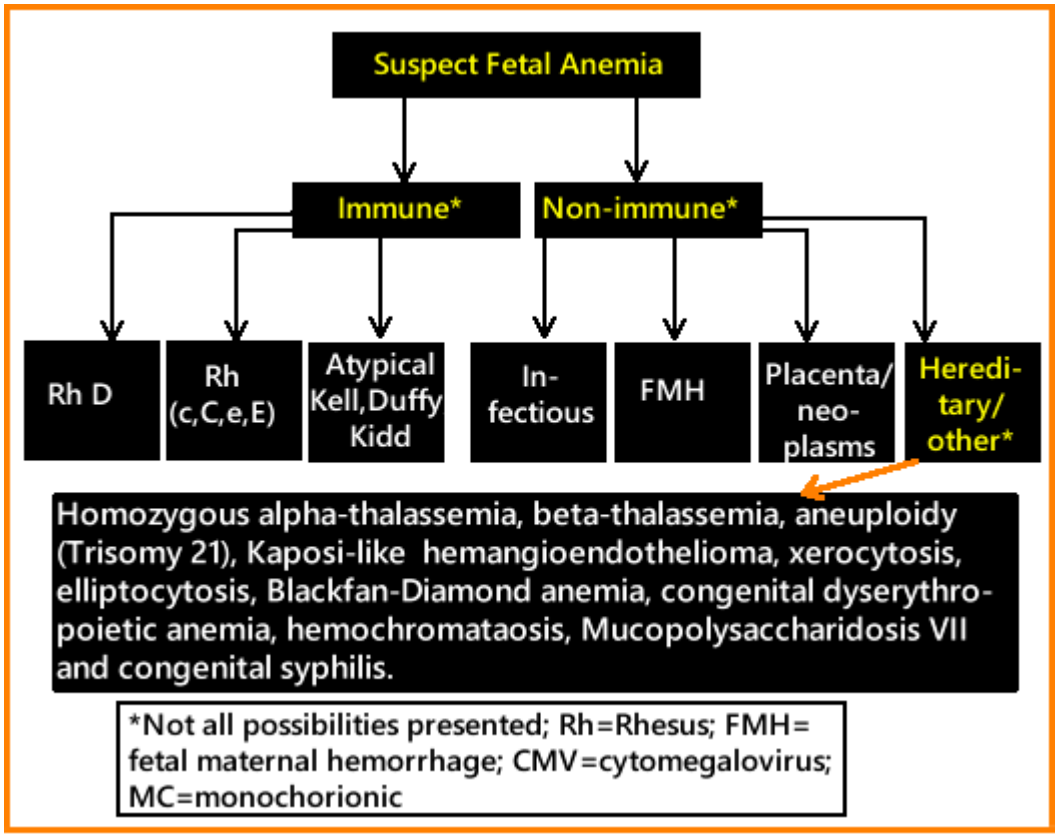
categories. Above. The most common immune cause remains Rh (rhesus) D sensitization in which an Rh negative mother is sensitized by her Rh positive fetus, initiating the transplacental passage of antibodies to bind antigens on fetal red blood cells causing their hemolysis, and, thus, anemia. Other Rh antigens (c, C, e, E) can result in red blood cell isoimmunization similar to Rh D. In addition, atypical antibodies such as Kell, Duffy and Kidd can result in fetal RBC anemia . Kell induced anemia is due to suppression of red blood cell formation and the Kell group of antigens are known to be associated with severe anemia and hydrops. [2]

Non-immune: Infectious, Fetal Maternal Hemorrhage, Placental or Fetal Neoplasms



Above. Non-immune etiologies for fetal anemia include infectious ones, parvovirus B-19 infection (common), toxoplasmosis, and CMV (less common). [3] Other relatively common causes of anemia include fetal-maternal hemorrhage (FMH), fetal and placental etiologies such as sacrococcgeal teratoma, chorioangioma. [4] and monochoronic twins.

Non-immune: Hereditary

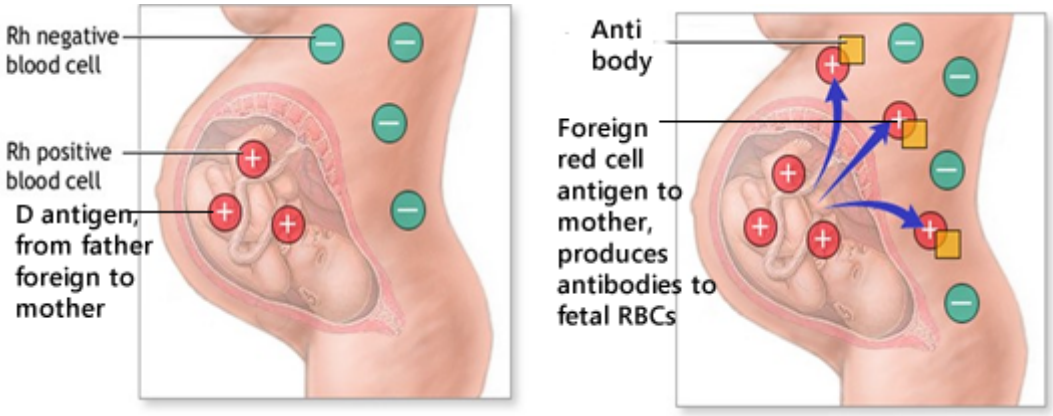


Above. Hereditary etiologies such as homozygous alpha-thalassemia and beta-thalassemia are reported. In addition, a miscellaneous group of rare etiologies are reported such as aneuploidy (Trisomy 21 with a myleoproliferative disorder). [5] Other causes for fetal anemia with low prevalence include Kaposi-like hemangioendothelioma, xerocytosis, elliptocytosis, Blackfan-Diamond anemia, congenital dyserythropoietic anemia, hemochromataosis, Mucopolysaccharidosis VII, and congenital syphilis. [6]

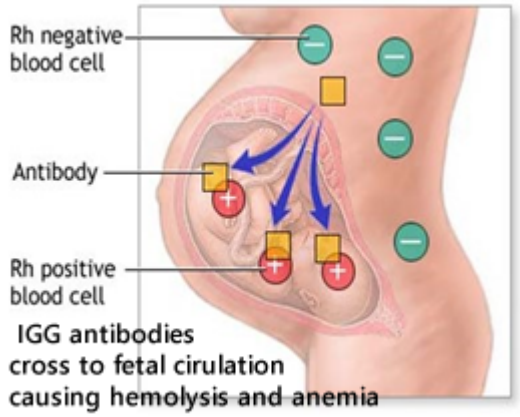
Alloimmunization

Rh sensitization, despite the introduction of Rh (D) immune globulin, affected 6.8 per 1000 live births in the United States or 26,933 women of all ages and all races in 2001. [7] When other red blood cell causes of anemia are included, an estimated 30,000 cases per year are possible. [8]

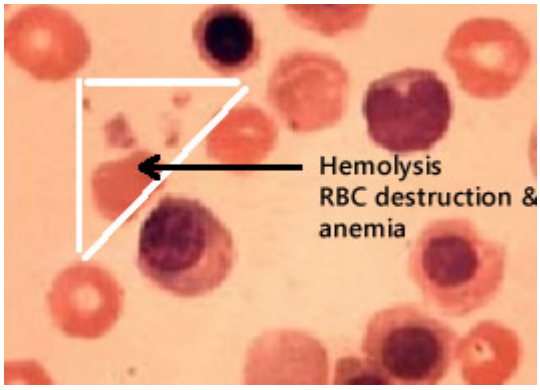
Schematic of Rh Sensitization



Above left. Schematic of Rh negative mother and Rh positive fetus. Above right. Formation of antibodies to fetal red blood cells (RBCs).



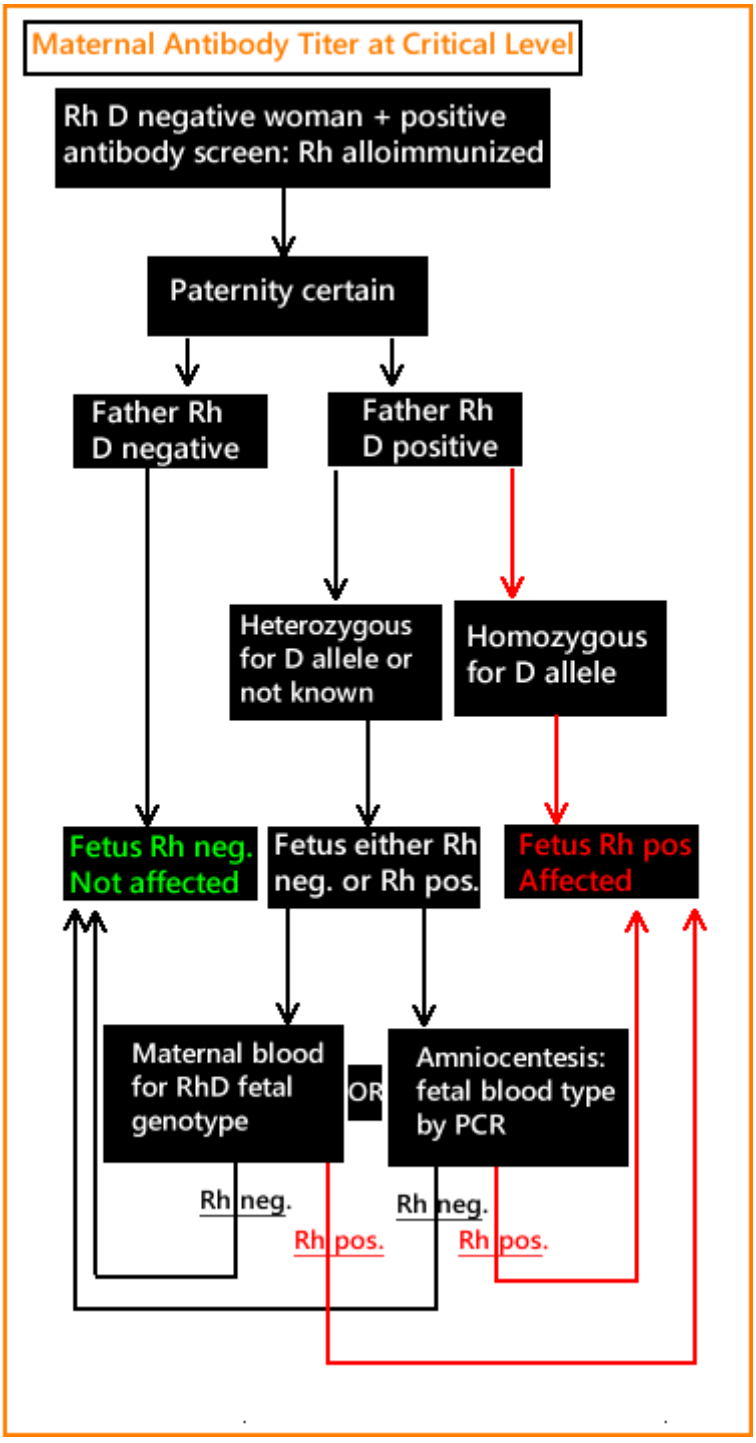
Above. Maternal IGG antibodies cross to the fetal circulation causing hemolysis (destruction of RBCs) and fetal anemia.



Above. Peripheral blood smear showing RBC destruction.

Algorithm: Rh Alloimmunized Pregnancies

A number of algorithms have been reported to evaluate Rh alloimmunized

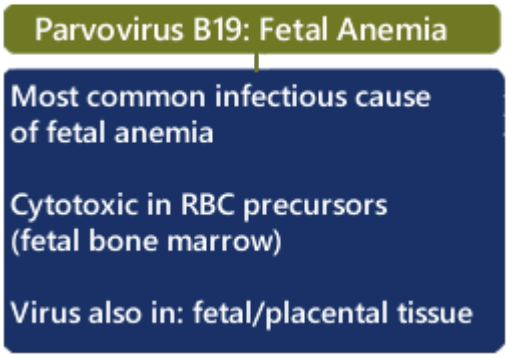


pregnancies. [9]

Above. For Rh D isoimmunization, the critical antibody titer for fetal anemia is usually reported at ≥ 1:16. If the paternity is uncertain or not available, it is now possible to determine the fetal blood Rh genotype through cell-free DNA

determination derived from maternal blood. [10] Alternatively, amniocentesis can be performed and the Rh genotype determined by PCR (polymerase chain reaction). Above legend: Antibody screen: indirect Coombs test; RH D=Rhesus D; neg.=negative; pos.=positive. Titers tend to correlate with the first affected Rh alloimmunized compared to subsequent sensitized pregnancies. [11] and titers may not be accurate in defining the severity of disease, especially among Kell sensitized pregnancies.

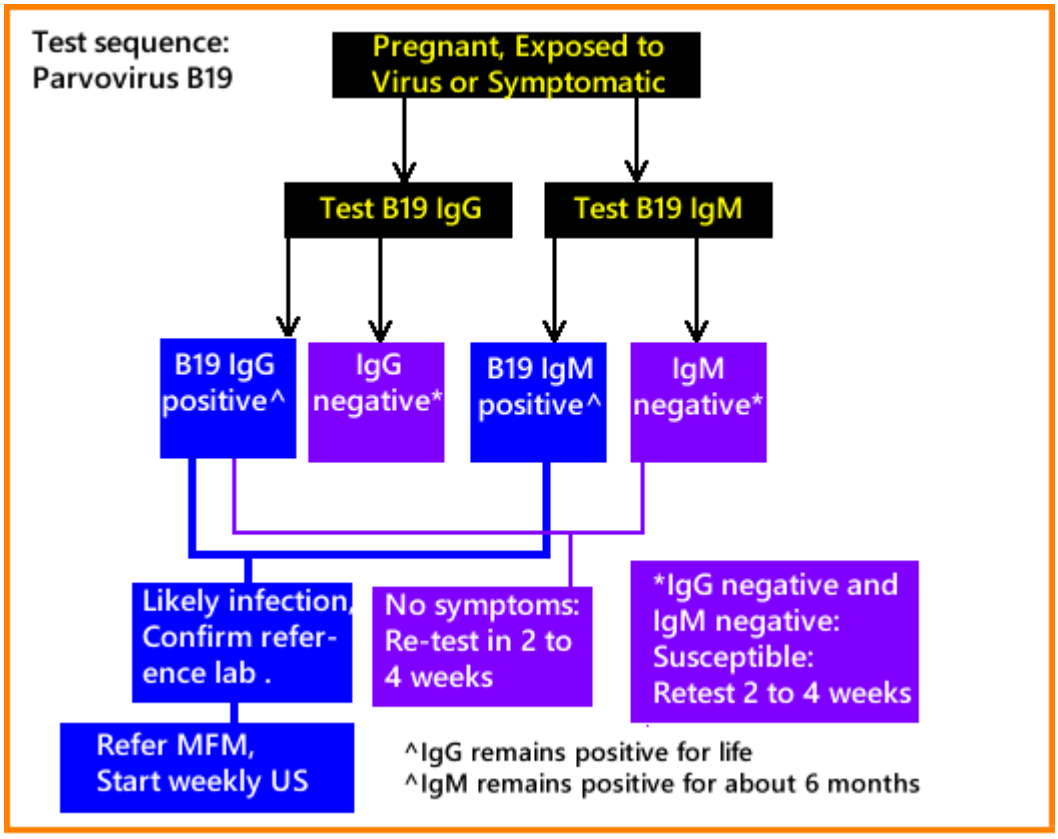
Parvovirus B19



Above. Maternal parvovirus B19 is the most common infectious cause of fetal anemia. [12] The virus is cytotoxic to the red blood cell precursors in the fetal bone marrow [13], and has been detected in other fetal and placental tissue sources causing a wide range of adverse fetal effects. [14]

Above. A recent comprehensive review suggests the following [15]: 1. 30 to 50% of pregnant women are not immune. 2. Seroconversion in susceptible women is from 1 to 1.5% but rising to 13 to 13.5% during epidemics. 3. Fetal death may occur with or without fetal hydrops in 5 to 10% and is more prevalent early in gestation compared to later in gestation. 4. The virus accounts for 8 to 20% of cases of non-immune hydrops. 5. The peak risk for hydrops is 4 to 6 weeks after maternal infection.

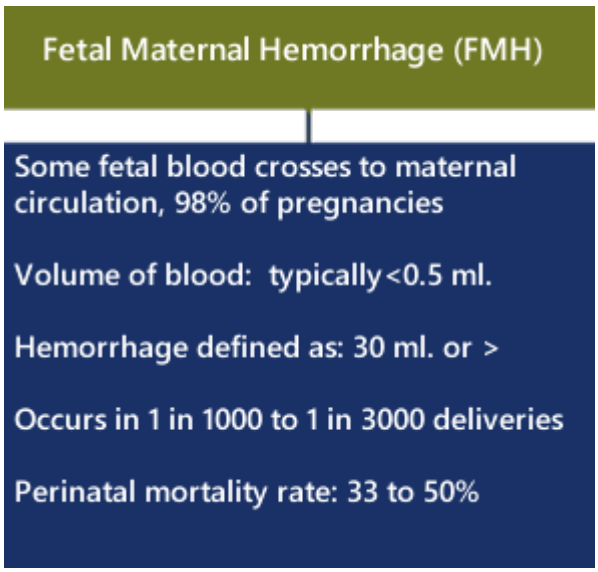
Diagnosis: Parvovirus B19



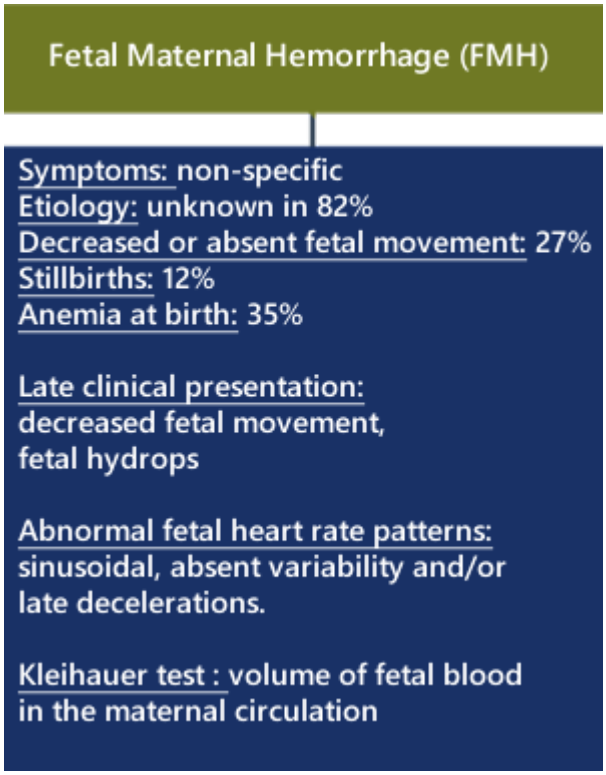
Above legend. Test sequence for suspected Parvovirus B19: IgG=B19 immunoglobin; IgM=B19 immunoglobin; lab.=laboratory; MFM=maternal fetal medicine; US=ultrasound Pregnant women exposed to the virus or who are symptomatic can be screened by determining their B19 immunoglobin G (IgG) and immunoglobin M (IgM) status. Parvovirus B19 IgM is present in blood within 2 to 3 days after an infection and remains for up to 6 months, while parvovirus B19 IgG appears several days after IgM and remains persistent for life. [16] Women who are IgG positive and IgM negative and who do not presently suggest evidence for infection should be re-tested in 2 to 4 weeks. In the woman who is both B19 IgG and B19 IgM negative and the incubation period has passed, she is susceptible but has not developed the infection. [17] In this instance, follow-up serum testing should be performed 2 to 4 weeks after maternal exposure. [18], [19] If IgM is present, irrespective of IgG status, the mother should be marked as likely infected, and maternal blood should be sent to a reference lab for confirmation. **Follow up:** If diagnosis of maternal infection is made, referral to a maternal fetal medicine center is suggested and serial ultrasounds (perform MCA-PSV and assess for

hydrops) should be performed every 1 to 2 weeks up to 12 weeks [20] or up to 30 weeks gestation. [21]

Fetal Maternal Hemorrhage (FMH)

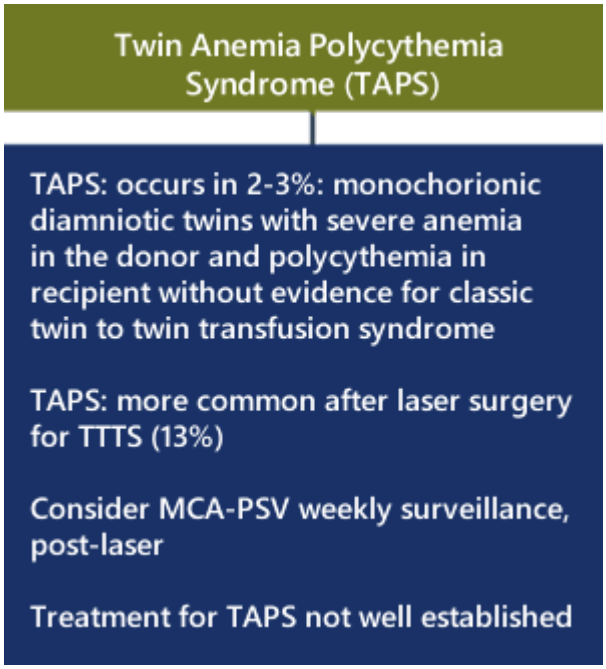


Some fetal cells cross to the maternal circulation in most pregnancies but in 98% of the cases, the volume of blood is < 0.5 ml or less. [22] Massive hemorrhage is defined as 30 ml or greater by some. [23] FMH in one form or another occurs in 1 in 1000 to 1 in 3000 deliveries with a perinatal mortality rate of 33 to 50%. [24] A clinically relevant fetal maternal bleed depends not only upon the volume of blood transferred to the maternal circulation but upon the rate and chronicity of the blood loss. [25]



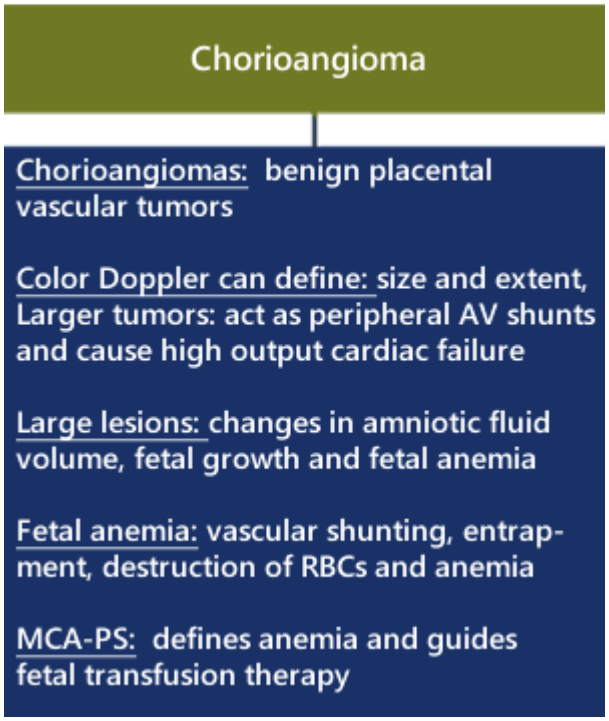
Above. The maternal symptoms of FMH are often non-specific. The etiology of FMB is unknown in 82% of cases while decreased or absent fetal movement and stillbirths may be seen in 27% and 12% of the cases respectively, and anemia at birth in 35% of cases. [26] A relatively late clinical presentation is decreased fetal movement, fetal hydrops, and abnormal fetal heart rate patterns such as sinusoidal, absent variability, and/or late decelerations. [27] Under these conditions, clinical means of assessment should be followed and immediate emergency delivery may be appropriate. The Kleihauer test is often used to estimate the volume of blood in the maternal circulation and MCA-PSV may help to detect fetal anemia in non-emergent cases. [28]

Twin Anemia Polycythemia Syndrome (TAPS)



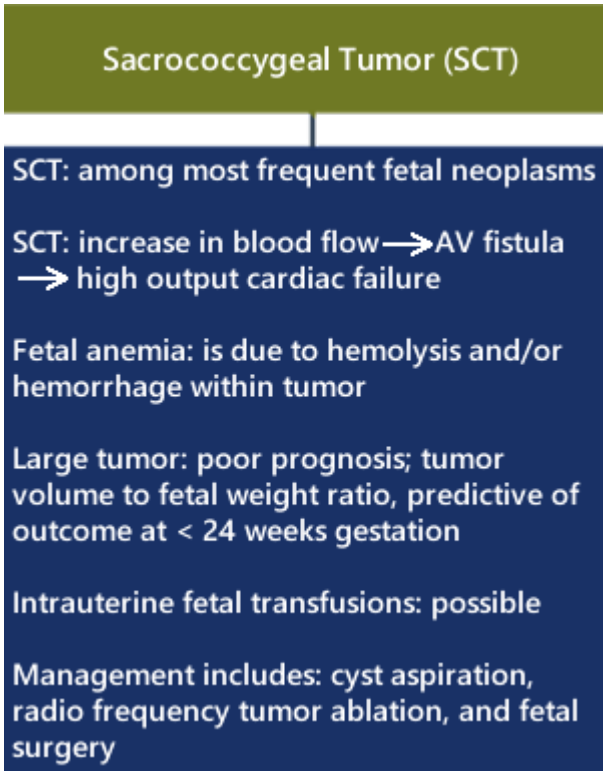
Above. In monochorionic diamniotic twins, severe anemia can exist in the donor twin and polycythemia in the recipient twin (TAPS) without evidence for classic twin oligohydramnios/polyhydramnios seen in twin to twin transfusion syndrome (TTTS). [29] This event occurs in 2 to 3% of monochorionic diamniotic pregnancies, but occurs more commonly after laser surgery for TTTS (13%). [30] While some recommend MCA-PSV weekly surveillance in post-laser patients, the application of intrauterine transfusions in the case of TAPS is not established at this time. [31]

Chorioangioma



Above. Chorioangiomas are benign vascular tumors of the placenta. Larger lesions can be seen on ultrasound, and color Doppler can define their size and extent. Larger tumors can be associated with fetal morbidity, as the tumors act as peripheral arteriovenous (AV) shunts and cause high output cardiac failure. Lesions can be clinically associated with changes in amniotic fluid volume, fetal growth, and fetal anemia. As a result of vascular shunting to the tumor, entrapment and destruction of red blood cells occurs and leads to hemolysis and anemia. MCA-PSV defines anemia and can guide fetal transfusion therapy. [32] Intrauterine fetal transfusions for this condition is reported. [33]

Fetal Sacrococcygeal Teratoma



Above. Sacrococcygeal tumors (SCT) are among the most frequent fetal neoplasms encountered. [34] The increase in blood flow through the SCT acts as an AV fistula causing high output cardiac failure [35], while fetal anemia is usually due to hemolysis and/or hemorrhage within the tumor. Larger tumors have a poor prognosis, and tumor volume to fetal weight ratio is predictive of outcome for SCT fetuses at less than 24 weeks gestation. [36] While intrauterine fetal transfusions have been reported [37], cyst aspiration, radio frequency tumor ablation, and fetal surgery are possible alternative management strategies.

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