Intrauterine Transfusion With Red Cells and Platelets

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Having direct access to the fetoplacental circulation by ultrasound-directed needle puncture has led to therapeutic interventions for fetal anemia and thrombocytopenia. Most cases of red cell alloimmunization associated with fetal anemia are caused by the antibody to the D red cell antigen. The intravascular transfusion of red cells to a hydropic fetus in such cases has notably improved survival. Nonimmune hydrops fetalis due to maternal parvovirus infection has also been treated successfully with the intravascular transfusion of red cells, whereas fetomaternal hemorrhage has not proved amenable to such therapy. Sensitization to the PLA-1 platelet antigen is the most common cause of fetal thrombocytopenia in maternal platelet alloimmunization. Fetal platelet transfusions have not proved to be a practical therapeutic modality for this disorder owing to the short half-life of the platelets. Platelet transfusions to the fetus just before delivery may avert the need for cesarean section in cases of severe thrombocytopenia.

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Twenty years ago, the fetus was merely a passenger in a concealed environment that could be pierced only by radiographic studies. With the development of real-time ultrasonography, the fetus was elevated to the status of a patient. Despite improvements in imaging technology in the late 1970s, the fetal hematologic status could be assessed only indirectly through the measurement of bilirubin levels in the amniotic fluid.[1] In 1973 Valenti described the use of a 27-gauge needle introduced through an 18-F "laparoamnioscope" to puncture the chorionic plate blood vessels under direct visualization.[2] This procedure came to be known as fetoscopy.[3] Unfortunately, a fetal mortality rate of 5% complicated the procedure, severely restricting the number of applications.

In 1983 Daffos and co-workers described the exciting new technique of percutaneous umbilical blood sampling, whereby a 20-gauge needle was directed into the umbilical vessels under real-time ultrasonographic guidance.[4] The technique gained widespread acceptance with an acceptable fetal loss rate of approximately 1%.[5] The number of applications increased until as many as 23 have been described recently.[6] As more pregnant women underwent diagnostic procedures, the likelihood of finding a series of unaffected fetuses increased. Normal hematologic values for gestational age were thereby established, and the field of fetal hematology was born. The fetal hematocrit and leukocyte count increase with advancing gestational age, and erythroblast and reticulocyte counts decline.[7-9] The fetal platelet count remains fairly stable throughout gestation.[7]

The direct treatment of fetal anemia in such disorders as red cell alloimmunization, fetomaternal hemorrhage, and parvovirus infection has become possible. Therapy for fetal thrombocytopenia due to platelet alloimmunization has also been undertaken.

Intrauterine Transfusion of Red Cells

Red Cell Alloimmunization

Etiology. Although the human maternal and fetal circulatory systems are anatomically separate, flow cytometry studies have shown that small fetomaternal hemorrhages occur in virtually all pregnancies.[10] When fetal erythrocytes containing red cell antigens foreign to the mother gain access to the maternal circulation, antibodies form in a condition known as red cell alloimmunization. Because the placenta actively transports immunoglobulin (Ig) G antibodies into the fetal circulation, antibody-antigen interactions occur on the fetal red cells. Although most of these antibodies do not fix complement, cell-mediated destruction of antibody-opsonized erythrocytes is thought to take place in the fetal spleen, resulting in fetal anemia. Although the Rh or D antigen is the most common cause of red cell alloimmunization, more than 43 other red cell antigens have been implicated in hemolytic disease of the newborn.[11] Antibodies to c, Kell, Duffy (Fy^a), and Kidd (Jk^a and Jk^b) antigens constitute the

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ABBREVIATIONS USED IN TEXT

CMV = cytomegalovirus
Ig = immunoglobulin

other major causes of red cell alloimmunization in pregnancy.

Incidence. Before the use of Rh immune globulin, 0.5% to 1.0% of all pregnant women were Rh-immunized.[12] Current recommendations for the routine administration of Rh immune globulin at 28 weeks' gestation and following delivery have dramatically reduced the incidence of Rh alloimmunization.[13] Data from the Centers for Disease Control noted that the incidence of Rh hemolytic disease of the newborn in the United States in 1984 was 10.6 cases per 10,000 total births.[14] Solola and associates reviewed seven previous series of Rh-positive pregnant women screened for irregular red cell antibodies.[15] In all, 400 cases of irregular antibodies were noted in the 131,898 patients, for an overall incidence of 1:330. Of the 400 infants in the series, 30 required exchange transfusions for hemolytic disease of the newborn. In their own population, Caine and Mueller-Heubach found 127 cases of Kell alloimmunization in 127,076 pregnancies (0.1%), 13 of which resulted in an affected fetus or newborn.[16] Two intrauterine deaths and one neonatal death occurred.

Diagnosis. Figure 1 depicts a typical plan of management for a pregnant woman with red cell alloimmunization.[17] An indirect Coombs' test should be performed in all women at their first prenatal visit. If an antibody is identified that has been associated with hemolytic disease of the fetus or newborn, a titer should be obtained. Paternal blood type and genotype should be determined. If the paternal blood type does not match the involved red cell antigen, the fetus will be unaffected, and further testing is unwarranted if paternity is certain. In cases of a paternal blood type that matches the involved red cell antigen or when the paternal status is unknown, maternal titers should be repeated at monthly intervals until a titer is obtained that indicates the fetus is at serious risk for the development of hydrops fetalis. If a heterozygous paternal genotype for the involved antigen is noted, percutaneous umbilical blood sampling can be offered to determine the fetal blood type. In half of such cases, the specific antigen will be absent from the fetal red cells and the fetus will be unaffected. Care should be taken to avoid puncturing the placenta with the sampling needle because a disruption of chorionic villi with leakage of fetal cells into the maternal circulation may increase the maternal antibody level, with subsequent worsening of the fetal anemia.[18,19]

In cases of a homozygous paternal genotype or when the fetus is found at the initial umbilical blood sampling to have the red cell antigen, serial samplings to determine the fetal hematocrit or serial amniocentesis to determine the Δ-OD450 values can be undertaken. Amniocentesis should be repeated every ten days to two weeks until a Δ-OD450 value at the 80th percentile of zone 2 of the Liley curve is noted. Intrauterine transfusion is then undertaken. Because analysis of amniotic fluid Δ-OD450

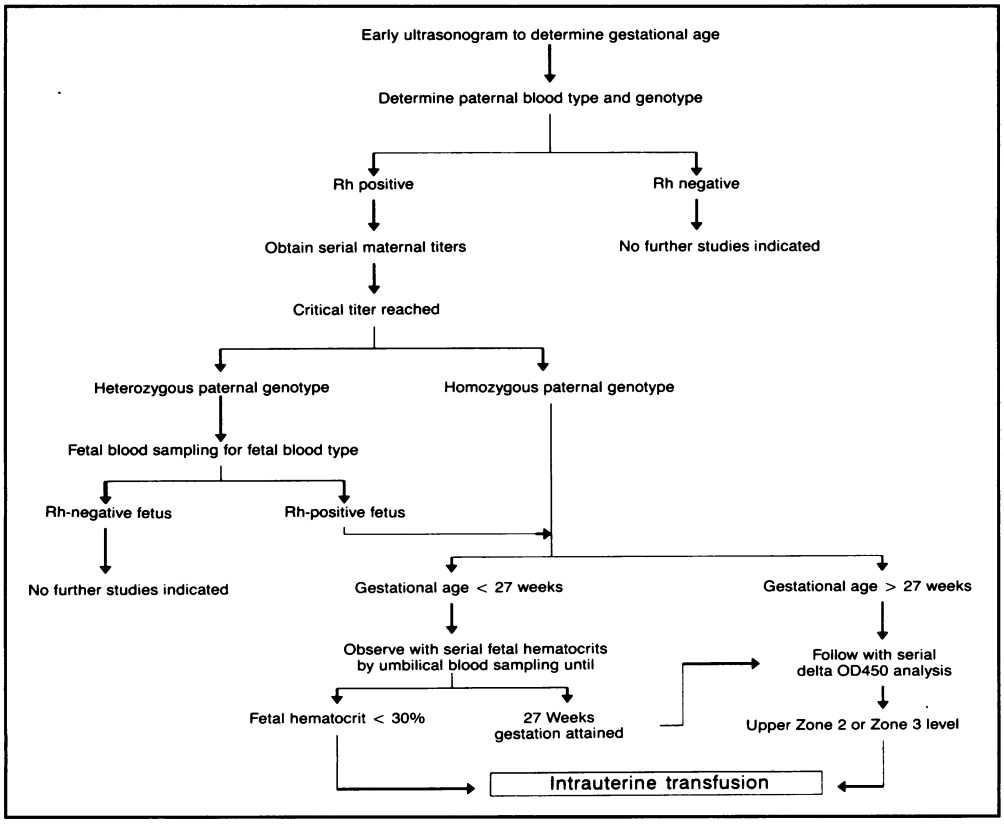

Figure 1.—The schematic shows the evaluation and treatment of red cell alloimmunization (modified from Moise et al[17]).

TABLE 1.—*University of Iowa Management Scheme for Red Cell Alloimmunization**

Hematocrit	Reticulocyte Count	Direct Coombs' Test	Interval for PUBS, wk	Interval for Ultrasonogram, wk	Comments
Normal	Normal	Negative to trace	--	4	If initial titer <128, repeat titer in 4 wk; if titer doubles, repeat PUBS
Normal	Normal or decreased	1+-2+	5-6	2	Do not repeat PUBS after 32 wk; deliver at term
Normal	Elevated	3+-4+	2	1	Repeat PUBS through 34 wk if stable; deliver after pulmonary maturity
Abnormal†	Any	Any	1-2	1	Repeat PUBS if hematocrit remains >0.30; deliver after pulmonary maturity
<0.30	Any	Any	--	--	Intrauterine transfusion

PUBS = percutaneous umbilical blood sampling

*Modified from Weiner et al.[21]
†A hematocrit that is >2 standard deviations below the mean value but above 0.30.

values has been found inaccurate using "modified" Liley curves before 28 weeks' gestation, serial umbilical blood sampling is the preferred method to assess fetal status if invasive testing is indicated at this point in gestation.[20] Weiner and co-workers have published guidelines regarding the frequency of serial samplings based on the initial values obtained for fetal hematocrit, direct Coombs' test, and reticulocyte count.[21] When a fetal hematocrit of less than 0.30 (30%) is noted, intrauterine transfusion is undertaken (Table 1).[21]

Technique. The first successful treatment of hemolytic disease of the fetus was described by Liley in 1963 when he introduced the technique of intraperitoneal transfusion.[22] No further modifications in technique occurred until 1981, when Rodeck and associates described the intravascular transfusion of a fetus by directing a needle into chorionic plate vessels under visualization through a fetoscope.[23] The following year, a group in Denmark reported the intravascular transfusion of a fetus by umbilical venous puncture under ultrasonographic guidance.[24]

By 1986, two schools of thought had emerged regarding the optimal method for intravascular transfusion. Investigators at Yale proposed an exchange intravascular technique similar to that used to treat hemolytic disease of the newborn in neonates.[25] Researchers at Mount Sinai School of Medicine of the City University of New York advocated a direct transfusion technique similar to that used by the Danish investigators.[26] As more experience was gained with the two techniques, the direct intravascular transfusion became more widely adopted by many centers because of its shorter procedure time. After the introduction of the intravascular transfusion, the intraperitoneal technique was virtually abandoned. The intravascular approach appeared to be a major technical advancement. An actual measure of fetal disease, the hematocrit, could be determined. In addition, red blood cells could be administered directly into the fetal circulation. In a comparative study between fetuses treated intravascularly and matched historical controls treated intraperitoneally, Harman and associates demonstrated a notable improvement in the survival of hydropic fetuses treated with the intravascular technique.[27] Survival in nonhydropic fetuses was not clearly improved by the procedure.

Despite its advantages, complications such as umbilical cord hematoma, fetal bradycardia, and porencephalic cysts not previously described in fetuses treated with intraperitoneal transfusions have been reported after intravascular therapy.[28-30] In addition, analysis of serial hematocrits from fetuses transfused with intravascular techniques reveals wide swings between transfusions. We evaluated a combined intraperitoneal-intravascular transfusion method and found it to result in a more stable hematocrit between procedures than either the exchange or direct intravascular transfusion.[31] A combined technique also allows for longer intervals between transfusions. Our technique involves administering enough packed red cells to achieve a final fetal hematocrit of 0.35 to 0.40. An intraperitoneal transfusion is then done (volume of blood to be transfused [ml] = [gestational age in weeks − 20] × 10). An intravenous dose of vecuronium (0.1 mg per kg of ultrasonogram-estimated fetal weight) is given at the start of the intravascular transfusion. This eliminates fetal movement for as long as two hours during the procedure, thereby preventing fetal injury. Transfusions are undertaken at two-week intervals for the first two transfusions, then the interval is lengthened to three to four weeks.

The end point of intrauterine transfusion is subject to debate among fetal therapists. Most centers use a target hematocrit to decide when a transfusion is complete. Advocates of direct intravascular therapy usually give transfusions to a final fetal hematocrit of 0.50 to 0.65, whereas advocates of the combined transfusion technique use 0.35 to 0.40 as a final value. Hydropic or severely anemic fetuses that are detected early in the second trimester do not tolerate intravascular transfusions as well as do older or less severely affected fetuses. A posttransfusion increase in fetal hematocrit by more than four times and an increase in the umbilical venous pressure of greater than 10 mm of mercury have both been associated with a pronounced increase in mortality in this subgroup.[32,33] For this reason, we administer transfusions to these fetuses to a final fetal hematocrit of 0.20 to 0.25 at the first treatment. A second transfusion is then done 48 hours later to achieve a final hematocrit of 0.35.

When to deliver a fetus undergoing intrauterine trans-

fusions is also a topic of considerable debate. When intraperitoneal transfusions were the sole means of in utero therapy, fetuses were routinely delivered at 32 weeks' gestation. Hyaline membrane disease and the need for neonatal exchange transfusions for the treatment of hyperbilirubinemia were common. As experience with intravascular transfusions became more widespread, fetuses were delivered at later gestational ages. Most physicians will now give the final transfusion at 35 weeks with delivery anticipated at 37 to 38 weeks. A recent (1992) cost analysis at our institution revealed that physician and hospital charges for the care of an Rh-positive fetus undergoing six intrauterine transfusions, an 11-day nursery course with 4 days of phototherapy, and readmission at 1 month of age for a final transfusion totaled more than $57,000.

In the past, O-negative, cytomegalovirus (CMV)-negative, heterologous red blood cells were used as the primary source of blood for intrauterine transfusion. Patient concern regarding the transmission of the human immunodeficiency virus has led several centers to use maternal blood for intrauterine transfusion. Advantages include the availability of fresh blood and the decreased chance for sensitization to new red cell antigens if some of the transfused blood escapes back into the maternal circulation. With folate and iron supplementation, these patients are easily able to maintain an adequate level of hemoglobin.[34]

Donor blood should be routinely screened for various infectious agents. The red cells are washed to remove the offending antibody and tightly packed to achieve a final hematocrit of 0.75 to 0.85. The unit is then filtered through a leukocyte-poor filter and irradiated with 25 Gy (2,500 rad) of external-beam radiation to prevent graft-versus-host reaction. Even if the pregnant woman has antibody to CMV, the blood may still be used because the dormant CMV virus is removed with the leukocytes in the filtering process. On some occasions an ABO incompatibility may be detected between a woman and her fetus after the initial umbilical blood sampling. In these cases, maternal blood should not be used due to the risk of sensitizing the fetus.

Outcome. Before the introduction of fetal or neonatal treatment, the perinatal mortality from hemolytic disease of the newborn was 40% to 50%.[35] The development in 1945 of the neonatal exchange transfusion was accompanied by a 50% reduction in perinatal mortality. Despite this innovative neonatal therapy, hydropic fetuses continued to die in utero. The introduction of the intraperitoneal fetal transfusion resulted in 50% survival of hydropic fetuses and 78% survival of nonhydropic fetuses.[35]

A survival rate after intravascular transfusion of as high as 96% has been reported by at least one center.[36] A more realistic statistic can be gleaned from a survey of 1,087 intravascular transfusions (389 fetuses) performed at 16 centers in the United States and Canada.[5] The survival rate for nonhydropic fetuses was 90% and of hydropic fetuses was 82%. Although previous studies regarding the developmental outcome of infants who had undergone intraperitoneal transfusions for severe anemia have shown no major deficits, long-term follow-up studies of infants after intravascular transfusions have not been reported to date.

Fetomaternal Hemorrhage

Substantial fetomaternal hemorrhage is the cause of fetal mortality in 1 of 1,000 births and of fetal morbidity in 1 of 800 deliveries.[37] The use of intrauterine transfusion to treat this problem has been described in five cases.[38-41] In four of these, the patient presented with a chief complaint of decreased fetal movement, and subsequent fetal monitoring revealed a sinusoidal heart rate pattern. In the fifth case, hydrops fetalis was noted as an incidental finding at the time of a routine ultrasonogram.[38] The results of a maternal Kleihauer-Betke stain were positive in all cases. A single intrauterine transfusion was done in three cases, and two were done in the remaining two. Despite this therapy, pregnancy was prolonged in only one case. In this case, an intraperitoneal transfusion at 21 weeks was successful in reversing hydrops fetalis with delivery of a normal infant at 38⅐ weeks' gestation.[38] In the other reported cases, fetal bradycardia or the return of decreased fetal movement necessitated delivery by cesarean section. Samplings in three of these fetuses revealed a falling hematocrit caused by continued fetomaternal hemorrhage. Thus, the use of intrauterine transfusion as a beneficial therapy in the treatment of fetomaternal hemorrhage should be questioned.

Parvovirus Infection

Human parvovirus B19 is the etiologic agent of fifth disease (erythema infectiosum, or "slapped cheek disease") in children. During outbreaks, household contacts or school teachers can be exposed. Approximately 50% of persons lack immunity, and 20% of these will become infected after exposure.[42,43] Although the infected pregnant woman will manifest a typical exanthema in about two thirds of cases, the remaining third will be asymptomatic.[44] Reported rates of fetal infection range from 2.5% to 38%.[45,46] Parvovirus inhibits fetal erythropoiesis with the subsequent development of aplastic anemia, nonimmune hydrops, and fetal death.

Maternal infection is usually confirmed by the finding of a specific IgM antibody that appears three to four days after the onset of clinical disease and persists for three to four months.[47] Fetal infection is thought to occur during a window of four to six weeks after maternal infection. Weekly ultrasonograms to evaluate the presence of hydrops fetalis should be done for this period. When hydrops is noted, donor red cells should be readied and percutaneous umbilical blood sampling performed. Studies of fetal blood typically show a negative direct Coombs' test, anemia, an inappropriately low reticulocyte count, normal serum bilirubin levels, elevated levels of total IgM, and elevated levels of hepatic enzymes.[48] Viral particles can be seen with electron microscopy in fetal ascitic fluid or blood.[49] In addition, viral DNA can be identified from fluids of fetal origin using specific probes.[47]

A total of eight fetuses have undergone treatment for

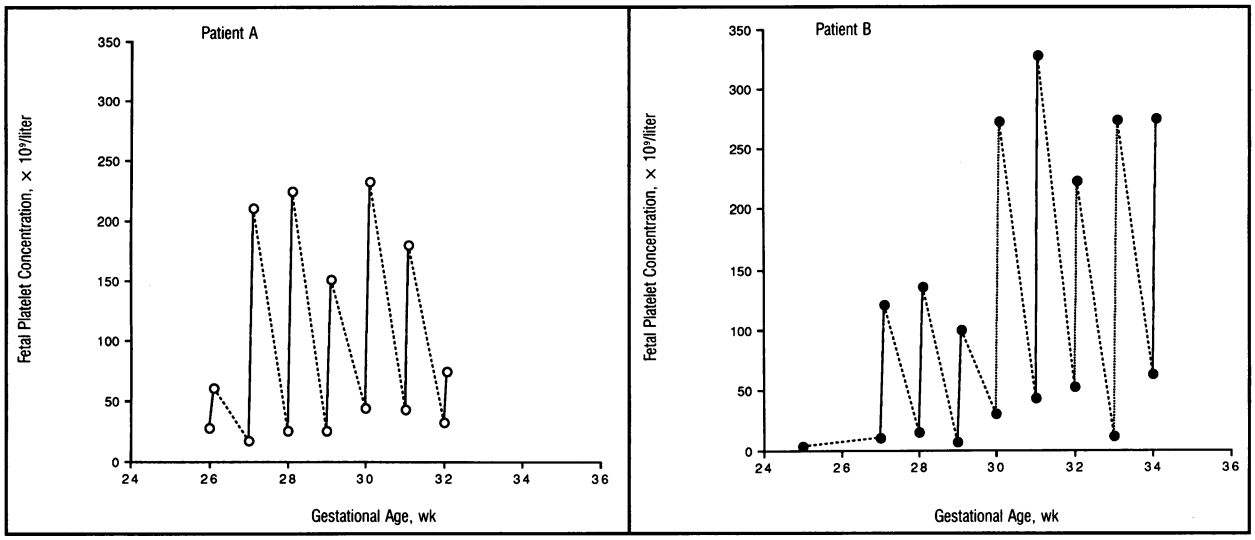

Figure 2.—Platelet counts are shown in fetuses affected by PLA-1 alloimmunization and being treated with serial intrauterine transfusions of maternal platelets: **Patient A,** 7 intrauterine transfusions were given between 26 and 32 weeks' gestation; **patient B,** 8 transfusions were given between 27 and 34 weeks' gestation. (Reprinted with permission from Nicolini et al.[61])

confirmed parvovirus infection.[44,48,50,51] All presented with hydrops and underwent intravascular transfusion. Five fetuses were transfused once, two fetuses twice, and one fetus three times. As is the case in a fetus with immune hydrops, severe fetal anemia should be corrected with serial transfusions at short intervals (one to seven days). An increase in the fetal reticulocyte count signals a recovery of the fetal bone marrow and eliminates the need for further transfusions. Experience with anemic Rh-positive fetuses undergoing intrauterine transfusions indicates that further transfusions may suppress fetal erythropoiesis and lead to fetal dependence on serial procedures to maintain the hematocrit. Nonimmune hydrops due to parvovirus infection may require several weeks to resolve after the fetal hematocrit has returned to normal. Follow-up of infants transfused for parvovirus infection has revealed normal neonatal outcomes. Based on these limited data, intravascular transfusion should be strongly considered as a therapeutic option in cases of fetal parvovirus infection and hydrops fetalis.

Intrauterine Transfusion of Platelets

Platelet Alloimmunization

Neonatal alloimmune thrombocytopenia, a disease process analogous to red cell alloimmunization, complicates 1 in 1,000 to 2,000 live births.[52] In this situation, the transplacental transfer of maternal antibodies to fetal platelet antigens of paternal origin results in severe fetal and neonatal thrombocytopenia. In utero intracranial hemorrhage occurs in 10% of cases and has been documented as early as the second trimester.[53,54] In about 75% of cases, the platelet antigen involved is the PLA-1 antigen (now called the HPA-1 antigen).[55] Unlike Rh alloimmunization, the first fetus may be severely affected, and maternal antibody titers are not predictive of the degree of fetal thrombocytopenia.[53,56] The clinician becomes aware of the disease only after an affected infant is born to the patient or her sister. Subsequent pregnancies are usually complicated by worsening fetal disease.[57]

The initial evaluation in the case of an affected neonate should include platelet antigen testing of the newborn, mother, and father. In a subsequent pregnancy, an initial cordocentesis at 20 weeks' gestation has been proposed to determine the fetal platelet count and antigen status. This approach is not without risk; 14 cases of fetal death caused by hemorrhage have occurred after fetal blood sampling in this disorder.[6] Maternal platelets for transfusion should be available at the time of the procedure in cases of excessive streaming of blood from the puncture site. Alternatively, if a rapid assessment of the platelet count can be done before the needle is removed, platelets should be infused in cases of a fetal platelet count of less than 50×10^9 per liter (50×10^3 per μl). Several authorities have proposed this threshold based on neonatal courses complicated by bleeding in infants born to women with autoimmune thrombocytopenia.[58] Because approximately 98% of the population has the PLA-1 platelet antigen, maternal platelets are usually used for fetal transfusion.[59] The platelets are obtained by apheresis 24 hours before their anticipated use, washed to remove any trace of plasma with its offending antibody, and resuspended in ABO-compatible plasma.

The volume of platelet concentrate to be used can be calculated by the formula $V = VSF\,(C_3 - C_1)/C_2$, where V represents the volume of platelets to be infused, VSF is the estimated fetoplacental blood volume for the appropriate gestational age,[8] C_1 is the fetal platelet concentration before transfusion, C_2 is the concentration of the donor platelets, and C_3 is the fetal platelet concentration desired after transfusion.[60] The optimal posttransfusion platelet count to prevent bleeding complications has yet to be determined. For this reason, most physicians will empirically transfuse a quantity of platelets based on the formula described here. Although a final fetal platelet

count should be recorded at the conclusion of the procedure, it is not necessary to await this result before removing the needle.

The first description of fetal platelet transfusions in cases of platelet alloimmunization involved serial infusions of maternal platelets by cordocentesis. Four cases have been reported to date.[60-62] In two of these, the median decline in platelets per day was 23.6×10^9 per liter. Limited experience with this technique has shown that the short half-life (four to seven days) of the platelet requires weekly transfusions to maintain an adequate fetal platelet count (Figure 2).[61] Bussel and associates have argued that this approach is associated with undue fetal risk from multiple umbilical cord punctures.[63] In an alternative approach, Lynch and colleagues successfully combined the maternal administration of steroids and weekly intravenous pooled γ-globulin to increase the fetal platelet count at delivery to greater than 50×10^9 per liter in 11 of 18 cases.[64] More important, no case of intracranial hemorrhage occurred in the treatment group, compared with a 33% incidence in antecedent siblings.[64] Therefore, serial in utero platelet transfusions are not a reasonable primary approach to the management of affected fetuses with alloimmune thrombocytopenia.

An approach proposed by Daffos and co-workers is to do a cordocentesis at term in fetuses suspected of having thrombocytopenia due to maternal platelet alloimmunization.[60] The documentation of fetal lung maturity by amniotic fluid studies obtained by amniocentesis may be indicated in women with uncertain menstrual dating. If a fetal thrombocytopenia is detected, a transfusion with previously processed maternal platelets can then be undertaken. Inducing labor with vaginal delivery would then be a safe alternative to elective cesarean section for delivery of the fetus.

Fetal transfusion of platelets just before delivery has been reported in ten cases.[56,60,62,65] Early in their experience, investigators performed the fetal platelet transfusion and then proceeded with elective cesarean section, with the reasoning that delivery by cesarean section has not proved totally protective against intracranial hemorrhage in fetuses with alloimmune thrombocytopenia.[66] Later in the series, vaginal delivery was allowed after transfusion in four of the ten cases without evidence of adverse neonatal sequelae. Sia and associates suggested that this approach was permissible only when the posttransfusion fetal platelet count was greater than 100×10^9 per liter.[66] The intrauterine transfusion of maternal platelets in fetuses found to be thrombocytopenic ($<100 \times 10^9$ per liter) at percutaneous umbilical blood sampling just before delivery deserves further study before it gains widespread acceptance.

Other Indications

Pronounced fetal thrombocytopenia has been associated with severe hydrops fetalis caused by red cell alloimmunization or parvovirus infection.[48,67] In these cases, random-donor platelets should be available at the time of the intrauterine transfusion of red cells. If a fetal platelet count of less than 50×10^9 per liter is noted in the pretransfusion specimen, the administration of an appropriate volume of platelets may prevent fetal death due to prolonged bleeding from the umbilical vessel puncture site.

Conclusion

The intrauterine transfusion of red cells in cases of fetal anemia due to red cell alloimmunization or parvovirus infection has improved fetal survival substantially. Fetal platelet transfusions in cases of platelet alloimmunization appear to have a limited therapeutic role because of the short half-life of this blood component.

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