infants published during the period 1990 through 1999. The clinically relevant end points were a reduction in the number and volume of RBC transfusions. The investigators found that treatment with EPO reduced RBC transfusions by an average of 11ml/kg, a value that was statistically significant ($p < 0.001$). However, there was extreme variation among trials. The variability in the studies included birth weight of study subjects, postnatal age at study entry, frequency and dose of EPO, use of iron supplementation, and triggers for RBC transfusion. Unfortunately, even among studies in which these variables were similar there were differences in results.

In another meta-analysis by Garcia and associates (63) the authors analyzed 8 randomized placebo-controlled studies that administered EPO or placebo after the first week of life and focused on erythrocyte transfusion needs after the third week of life ("late" transfusions). In this specific group of patients they found that neonates in the EPO group received significantly fewer transfusions proportional to the dose of EPO administered. Based on these two analyses, it remains unclear whether EPO treatment should be universally recommended for all premature babies as a means to prevent clinically significant anemia that will require RBC transfusion. It is also unclear whether the cost of the RBC transfusions that are avoided by treatment with EPO is higher than the cost of EPO. Furthermore, although no adverse effects of EPO could be demonstrated by 1 year of age (53) the long term side effects of EPO in premature infants is unknown. Recently development of neutralizing antierythropoietin antibodies was demonstrated in patients with chronic renal failure who developed pure red cell aplasia following treatment with EPO. These patients were adults who received EPO treatment for 3 to 67 months. The condition resolved several months after cessation of EPO treatment during which time the patients required multiple RBC transfusions. Whether neonates who are treated with EPO for less than 3 months can develop neutralizing antibodies remains to be determined (64), and this potential complication of EPO therapy should be taken into consideration when assessing the risk:benefit of EPO therapy in newborn infants (65).

In summary, the overall incremental benefit of EPO therapy in neonates in the setting of rigorous transfusion guidelines and effective strategies to minimize iatrogenic (phlebotomy) blood losses, plus appropriate iron and protein supplementation is not clear and requires further study in carefully designed prospective clinical trials. Alternative transfusion strategies, discussed in detail later in this chapter, may be equally effective in preventing multiple donor exposure and may be more cost-effective. Currently, the most prudent approach is for individual neonatal units to assess the impact of newer transfusion strategies in their population before implementing routine EPO therapy (66).

If a decision is made to administer recombinant EPO to decrease RBC transfusions to ill extremely low birth weight infants (birth weight <1,000 g) Calhoun and colleagues have recommended that a dose of 200 U/kg/day of EPO plus iron supplementation be given for two weeks; if the goal is to decrease or possibly eliminate the need for late transfusions to very low birth weight infants (birth weight <1,500 g) with the anemia of prematurity or the late anemia of Rhesus hemolytic disease the investigators recommend giving 400 U/kg of EPO three times per week subcutaneously for 2 weeks with added iron (67).

Anemia Caused by Blood Loss

Blood loss resulting in anemia may occur prenatally, at the time of delivery, or postnatally. Blood loss may be the result of occult hemorrhage before birth, obstetric accidents, internal hemorrhages, or excessive blood sampling for diagnostic studies (Table 46-2). Faxelius and colleagues (68) associated a low erythrocyte volume with a maternal history of bleeding in the late third trimester, placenta previa, abruptio placentae, nonelective cesarean section, deliveries associated with cord compression, Apgar scores less than 6, an early central venous hematocrit less than 45%, and a mean arterial pressure less than 30 mm Hg.

Occult Hemorrhage Before Birth

Occult hemorrhage before birth may be caused by bleeding of the fetus into the maternal circulation or by the bleeding of one fetus into another in multiple pregnancies. In approximately 50% of all pregnancies, some fetal cells can

TABLE 46-2
TYPES OF HEMORRHAGE IN THE NEONATE

Occult hemorrhage before birth
Fetomaternal
Traumatic amniocentesis
Spontaneous
After external cephalic version
Twin-to-twin
Obstetric accidents, malformations of the placenta and cord
Nuchal cord with placental blood trapping
Rupture of a normal umbilical cord
Precipitous delivery
Entanglement
Hematoma of the cord or placenta
Rupture of an abnormal umbilical cord
Varices
Aneurysm
Rupture of anomalous vessels
Aberrant vessel
Velamentous insertion
Communicating vessels in multilobed placenta
Incision of placenta during cesarean section
Placenta previa
Abruptio placentae
Internal hemorrhage
Intracranial
Giant cephalhematoma
Subgaleal
Retroperitoneal
Laceration of the liver
Ruptured spleen
Pulmonary

donor (anemic) twin is smaller, and there is associated oligohydramnios; the recipient (polycythemic, hypervolemic) twin is larger, and there is associated polyhydramnios. Intrauterine diagnosis is therefore dependent on identification of same sex, size difference, oligohydramnios/polyhydramnios, and a monochorionic placenta. When diagnosed in utero, twin-to-twin transfusion syndrome can be classified into five discreet stages (79). Stage I is defined by the finding of isolated discrepancy in amniotic fluid volumes between fetuses; absence of a urine filled bladder in the donor fetus defines Stage II, absent or reversed end-diastolic flow in the umbilical artery of the donor fetus or abnormal venous Doppler pattern in the recipient, such as reversed flow in the ductus venosus or pulsatile umbilical venous flow Stage III, hydrops fetalis Stage IV and demise of one or both fetuses Stage V. Perinatal outcomes correlate with disease severity as assessed by the stage at presentation and gestational age at delivery; overall the perinatal mortality rate for the twin-to-twin transfusion syndrome is 30% to 50% (80). Therapy has included repeated amniocentesis to reduce polyhydramnios, photocoagulation of placental vascular anastomoses, amniotic septostomy, and selected feticide by cord occlusion (78).

Obstetric Accidents and Complications

Obstetric accidents and malformations of the placenta and cord may be responsible for major blood loss at the time of delivery. These accidents may be unreported to the pediatrician and may result in diagnostic confusion about the cause of shock in the early hours of life or the presence of pallor and unexplained anemia during the second or third day of life.

The obstetric conditions that can produce neonatal hemorrhage are listed in Table 46-2. Severe and often fatal fetal hemorrhage may accompany placenta previa, abruptio placentae, or accidental incision of the placenta or umbilical cord during a cesarean section. A tight nuchal cord may cause venous obstruction leading to excessive blood trapping in the placenta and resulting in severe hypovolemia (81) and anemia (82). A prospective study of red cell mass suggested that babies born with a tight nuchal cord had a significantly lower red cell mass than controls (83).

In women with late-third-trimester bleeding, Clayton and associates (84) were able to anticipate the birth of a possible anemic infant by examining the vaginal blood for the presence of fetal erythrocytes, employing the acid elution technique of Kleihauer (75,84).

It is good pediatric practice to obtain a hemoglobin measurement routinely at the time of delivery of all babies born of women with late third-trimester bleeding. This determination should be repeated in 6 to 12 hours to observe the expected fall in hemoglobin resulting from the hemodilution that follows recent blood loss.

Severe bleeding as a result of an obstetric accident or complication of delivery often results in the birth of a pale, limp infant. Respirations, which usually commence spontaneously, are often irregular and gasping. They are not associated with retraction, as in conditions accompanied by primary pulmonary disease. Cyanosis is minimal, and the infant's pale color is not improved by oxygen administration. The peripheral pulses are weak or absent, and the blood pressure is reduced. The venous pressure measured after the insertion of an umbilical catheter is found to be extremely low.

Internal Hemorrhage

Anemia that appears in the first 24 to 72 hours of life and is not associated with significant jaundice is commonly caused by hemorrhage at the time of birth or by a postnatal internal hemorrhage. Traumatic deliveries may result in subdural or subarachnoid hemorrhages or cephalhematomas of sufficient magnitude to produce anemia. Subaponeurotic or subgaleal hemorrhages are relatively common after vacuum extraction and may lead to significant neonatal anemia.

Breech deliveries may be associated with hemorrhage into the adrenals, kidney, spleen, or retroperitoneal area. Rupture of the liver or subcapsular hemorrhage into the liver may occur more commonly than is clinically recognized (85–87). An infant with a ruptured liver may appear well for the first 24 to 48 hours of life and then suddenly go into shock. The abdomen may appear distended, and a mass contiguous with the liver is often palpable. Shifting dullness on abdominal percussion can often be demonstrated, and an elevation of the right hemidiaphragm may be seen on the radiograph. Splenic rupture may occur after a difficult delivery or as a result of the extreme distension of the spleen that is often seen in babies with severe erythroblastosis fetalis. The physician should always suspect a rupture of the spleen when an anemic, and often hydropic, infant with erythroblastosis is found to have a low initial venous pressure at the time of exchange transfusion. The diagnosis of intraabdominal hemorrhage is readily made with ultrasonography.

In infants with birth weights less than 1,500 g, bleeding into the cerebral ventricles, subarachnoid space, and parenchyma can also produce significant decreases in hemoglobin concentration.

Iatrogenic Anemia due to Blood Sampling

Anemia appearing during the first week of life is often caused by blood removal for diagnostic studies required for the frequent monitoring of critically ill infants. Removal of more than 20% of a subject's blood volume produces anemia. In an infant of 1,500 g, this represents a blood loss of only 25 mL. If frequent blood sampling is necessary, a flow sheet should be used to record the amount removed at any given time. This simple technique often converts a diagnosis of idiopathic anemia to one of iatrogenic anemia.

Despite the use of micromethods using small volumes of blood by most laboratories, cumulative blood losses through sampling for laboratory monitoring are often surprisingly large in small infants. Blanchette and Zipursky