Fetal blood sampling

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OBJECTIVE: We sought to review indications, technical aspects, risks, and recommendations for fetal blood sampling (FBS).

METHODS: A systematic review was performed using MEDLINE, PubMed, EMBASE, and Cochrane Library using the terms "fetal blood sampling," "percutaneous umbilical blood sampling," and "cordocentesis." The search was restricted to English-language articles published from 1966 through July 2012. Priority was given to articles reporting original research, in particular randomized controlled trials, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Evidence reports and guidelines published by organizations or institutions such as the National Institutes of Health, Agency for Health Research and Quality, American Congress of Obstetricians and Gynecologists, and Society for Maternal-Fetal Medicine were also reviewed, and additional studies were located by reviewing bibliographies of identified articles. Grade (Grading of Recommendations Assessment, Development, and Evaluation) methodology was employed for defining strength of recommendations and rating quality of evidence. Consistent with US Preventive Task Force guidelines, references were evaluated for quality based on the highest level of evidence.

RESULTS AND RECOMMENDATIONS: Ultrasound-guided FBS is the only procedure that provides direct access to the fetal circulation. When invasive testing is planned for suspected severe fetal anemia or thrombocytopenia, we recommend FBS as the procedure of choice, with availability of immediate transfusion if confirmed. We recommend against the use of FBS for indications in which other less invasive, and therefore lower risk, alternatives are available. The overall success rate of FBS is high, and blood samples can be obtained in >98% of patients. We suggest that counseling for FBS include discussion about the potential risk of FBS that may include, but may not be limited to: bleeding from puncture site (20-30%); fetal bradycardia (5-10%); pregnancy loss (≥1.3%, depending on indication, gestational age, and placental penetration); and vertical transmission of hepatitis or human immunodeficiency virus. We recommend that FBS be performed by experienced operators at centers with expertise in invasive fetal procedures when feasible.

Key words: cordocentesis, fetal blood sampling, indications, percutaneous umbilical cord blood sampling, risks, technical aspects

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Ultrasound-guided fetal blood sampling (FBS), also known as cordocentesis, or percutaneous umbilical cord blood sampling, was first described in the early 1980s.[1,2] In 1963, Liley[3] was the first to treat fetal anemia by intraperitoneal transfusion of blood. In 1979, Rodeck and Campbell[4] described the ability to perform FBS utilizing a fetoscopic approach, while 4 years later, Daffos et al[2] introduced the technique of ultrasound-guided FBS.

Inserting a needle to gain access into the fetal circulation allows the operator to sample or transfuse blood, or other blood products such as platelets. FBS also allows medication[5,6] or other substances, such as contrast media,[7] to be injected directly into the fetal circulation. Fetal blood can also be collected and specimens analyzed for laboratory markers of fetal health or disease. These include, but are not limited to, red cell indices, white blood cell and differential counts, lymphocyte subset counts,[8] microproteins,[9,10] blood gas analysis, and thyroid hormone levels.[11] It is important to assure that values obtained are compared with appropriate gestational age—matched normal values, as these may differ significantly from newborn levels.[12] In addition, use of fetal blood can allow rapid karyotyping when indicated for prenatal genetic diagnosis.[13]

Since its introduction into clinical practice in the mid-1980s, the indications for FBS have evolved. The emergence of newer, less invasive testing modalities and development of molecular genetic techniques have greatly decreased the need for FBS, although there is a paucity of national data published on changing rates and indications for FBS. From 2006 through 2011, the 21 member centers of the North American Fetal Therapy Network performed an average of 13 FBS procedures per center per year (unpublished data, courtesy of Francois I. Luks, MD, PhD, North American Fetal Therapy Network; written communication, Nov. 30, 2012).

The purpose of this guideline is to review the indications, technical aspects, risks, and current recommended clinical use for FBS.

What are the current possible indications for FBS?

FBS has been described for a large number of indications (Table 1), although many are now obsolete or represent isolated case reports. For many indications, FBS has been replaced by technologic advances such as molecular testing for genetic disorders or polymerase chain reaction (PCR) for viral infections that allow testing of chorionic villi or amniotic fluid samples, resulting in earlier, more accurate, and safer access to the same, and in some cases superior, diagnostic results.

Suspected severe fetal anemia is the most common current indication for FBS in the United States. Direct measurement of fetal hemoglobin, and therefore accurate diagnosis of fetal anemia, can only be made by FBS. Anemia may be suspected due to the presence of maternal alloantibodies, maternal parvovirus exposure or infection, other viral infections, or due to ultrasound findings such as fetal hydrops or elevated peak systolic velocity (PSV) of the fetal middle cerebral artery (MCA) by Doppler studies.[14] Maternal anti-D alloimmunization remains the most common cause of fetal anemia, although this incidence has significantly decreased since the development and routine use of maternal anti-D prophylaxis with Rh immune globulin.[15,16] Most cases of anti-D alloimmunization in current practice result from failure of the mother to receive antenatal or postnatal prophylaxis, or to sensitization despite prophylaxis due to a high volume of fetomaternal red cell transfusion.[17] Given the decrease in cases of anti-D alloimmunization, fetal anemia due to sensitization from other red cell antigens (C, c, E, e, or Kell) or from infectious causes (usually parvovirus) has increased in relative proportion. In a study from one tertiary referral center in the United Kingdom, 45 women underwent FBS due to fetal anemia from 2003 through 2010. The causes were anti-D in 21 (47%), anti-Kell in 7 (16%), anti-C or E alloimmunization in 6 (13%), parvovirus infection in 6 (13%), Down syndrome (with red cell dysplasia) in 1 (2%), and unknown etiology of anemia in 4 (9%).[18]

Current management of the pregnancy at risk for fetal anemia typically involves assessment with Doppler velocimetry of the fetal MCA, which has widely supplanted amniocentesis as the primary means of assessment for fetal anemia in pregnancies complicated by red cell alloimmunization. Based on the principle that worsening anemia is associated with increases in blood flow velocity, fetal anemia can be predicted by Doppler MCA in most cases.[14] MCA Doppler measurements of PSV vary by gestational age, and values are converted to multiples of the median. A MCA PSV of $\geq$1.5 multiples of the median is generally considered indicative of moderate or severe fetal anemia,[14] and FBS is warranted to directly measure fetal hemoglobin (or hematocrit) levels and determine the need for intrauterine transfusion (IUT). IUT is generally performed if fetal anemia is confirmed. The degree of anemia that causes hydrops, and therefore increases the risk of fetal death, is unpredictable, but hydrops most commonly occurs when the fetal hemoglobin is $<$7 g/dL (equivalent to hematocrit of about $<$20%).[19]

Neonatal alloimmune thrombocytopenia (NAIT) is a disorder in which transplacental passage of maternal antiplatelet antibodies causes fetal (and neonatal) thrombocytopenia, at times severe and with devastating consequences such as intracranial hemorrhage. The diagnosis of fetal thrombocytopenia caused by NAIT in the current pregnancy can only be made with FBS. Historically, at-risk pregnancies have been managed with FBS to detect fetal thrombocytopenia, with platelets immediately available for fetal IUT. Currently, maternal intravenous immunoglobulin, sometimes in conjunction with corticosteroids, is administered to increase the fetal platelet count. While FBS is used in some circumstances to assess the response to this treatment, some experts believe that FBS may be unnecessary if maternal therapy is

TABLE 1
Indications for fetal blood sampling

Indications	Comment
Current common indications	
Diagnose and treat fetal severe anemia	Most common indication for FBS
Diagnose and evaluate therapeutic response in NAIT	
Evaluate nonimmune fetal hydrops	Only in selected cases[a]
Historical and less common indications	
Fetal aneuploidy for karyotyping	Rarely used in current practice; largely replaced by CVS or amniocentesis with FISH, or by NIPT
Determine fetal blood type and platelet antigen status	Largely replaced by other tests, eg, NIPT, CVS, or amniocentesis, and molecular testing
Diagnose genetic disorders (eg, hemophilia, thalassemia)	Largely replaced by CVS or amniocentesis for molecular genetic diagnosis
Measurement of biochemical or other serum markers for fetal disease (eg, fetal infection, thyroid function)	Largely replaced by amniocentesis and PCR (eg, infection); rarely needed (eg, thyroid function)
Direct intravascular therapy	Reported rarely, most commonly for failed maternal systemic treatment of fetal supraventricular tachycardia
Others	

CVS, chorionic villus sampling; *FBS*, fetal blood sampling; *FISH*, fluorescence in-situ hybridization; *NAIT*, neonatal alloimmune thrombocytopenia; *NIPT*, noninvasive prenatal testing; *PCR*, polymerase chain reaction.

[a] Especially if middle-cerebral artery peak systolic velocity is elevated; See text for details.

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already being administered and vaginal delivery is not being considered, because FBS may not add enough additional information to justify the risks associated with the procedure.[20,21]

Fetal hydrops can also be evaluated by FBS. The differential diagnosis of fetal hydrops is extensive,[22,23] but fetal anemia, aneuploidy, and infection are relatively common causes. Much of the evaluation for hydrops can be first accomplished with maternal serum analyses, detailed ultrasound evaluation, and amniocentesis. However, it is reasonable to offer FBS in the setting of nonimmune hydrops, especially if the rest of the workup is negative and the fetal MCA PSV is elevated. Otherwise, amniocentesis carries fewer risks than FBS, and can rapidly identify parvovirus and exclude causes of hydrops, such as aneuploidy, for which IUT would not alter the prognosis. Nonetheless, because fetal anemia is one of the most common causes of hydrops, FBS with the availability of blood for possible IUT is often part of the management of fetal hydrops.

What are some historical or less common indications for FBS?

Several past indications for FBS have now been replaced by safer or more sophisticated tests, often available through noninvasive prenatal diagnosis, amniocentesis, or chorionic villus sampling (CVS) procedures.

Rapid karyotyping to diagnose aneuploidy is no longer an indication for FBS. Because of the widespread availability of fluorescence in-situ hybridization for chromosomes 21, 18, 13, X, and Y, many couples now elect CVS or amniocentesis with fluorescence in-situ hybridization, followed by karyotyping or chromosomal microarray analysis, when rapid testing for aneuploidy is indicated. In this way, they can avoid the increased risks associated with FBS, detect the majority of fetuses with common aneuploidies within 24-48 hours, and obtain a complete karyotype or chromosomal microarray analysis result in 7-10 days. Noninvasive prenatal testing can also provide karyotype results for chromosomes 21, 18, 13, X, and Y in 7-10 days. Mosaicism—the presence of >1 cell line—on a karyotype from an amniocentesis or CVS can represent a laboratory artifact, an abnormality confined to the placenta or membranes, or a true fetal chromosomal abnormality. Historically, FBS was recommended in many cases in which mosaicism was identified by amniocentesis or CVS, but the limited prognostic utility of this approach has led to a decrease in procedures done for this indication.[24]

Determination of fetal blood type and platelet antigen status is no longer an indication for FBS. Since the 1990s, fetal Rh status can be determined reliably by PCR analysis performed on amniocytes obtained from amniocentesis.[25] PCR analysis of amniocytes can also determine platelet antigen type,[26] and this has been shown to be very useful in the clinical management of pregnancies at risk for NAIT. PCR performed using amniocyte-derived DNA can be done earlier in gestation than FBS, has been proven to be highly accurate, and is more widely available, easier, and safer than FBS. Since its introduction for Rh genotyping, this technology can now determine fetal red cell genotype for virtually all antigens capable of causing fetal hemolytic disease. Recently, cell-free DNA isolated from maternal plasma has also been used as a substrate for PCR testing to determine fetal Rh status. This noninvasive modality has been shown to be highly sensitive and specific.[27] Noninvasive fetal Rh typing with cell-free DNA is commonly used in many European countries as the procedure of choice for fetal blood type and platelet antigen status determination.[28-30]

Inherited anemias or hemoglobinopathies have historically been a relatively common indication for FBS, with a sample of fetal blood traditionally required for hemoglobin electrophoresis to make a diagnosis of thalassemia. With the advent of modern molecular genetic techniques, fetal diagnosis can reliably be made using DNA obtained via CVS or amniocentesis.[31] Cases of FBS and intrauterine exchange transfusions have been reported in the management of fetuses affected with alpha-thalassemia, a disorder that typically results in hydrops and fetal demise in utero. While such treatment has been successful in a handful of cases, it is dependent on availability of effective postnatal treatments, and long-term outcomes are unclear.[32] In some parts of the world, sophisticated molecular techniques may be unavailable and hemoglobinopathies relatively common, so FBS continues to be routinely used in the diagnosis of alpha- and beta-thalassemia. In 1 recent study reported from Thailand, for example, >2000 cordocenteses were performed from 1989 through 2010; >75% of these were done due to a risk of fetal thalassemia.[33]

Other past indications for FBS include measurement of biochemical or other serum markers for fetal infections and diseases (eg, thyroid, renal).[34-37] FBS has been used to determine the presence and extent of fetal infection (eg, cytomegalovirus, toxoplasmosis, parvovirus), but amniotic fluid culture and/or PCR are currently the primary diagnostic modalities. In settings in which PCR is not readily available, FBS has been used for diagnosis, for example in rare cases of fetal varicella with measurement of varicella-zoster virus-specific IgM and viral culture.[38]

FBS allows direct intravascular therapy when indicated, although this has been reported relatively rarely. There are limited conditions for which a single dose of a medication is useful, and serial or chronic intravascular fetal therapy is impractical. In a number of cases and small series, direct intravascular administration of amiodarone or adenosine through the umbilical vein has been reported for treatment of fetal arrhythmias resistant to standard maternal systemic administration.[39] This has been most commonly reported in fetal hydrops due to supraventricular tachycardia, where transplacental therapy is less effective and a single injection may resolve the arrhythmia.[5,6,40] While a single case of chronic fetal umbilical vein cannulation followed by daily infusion of nutrients has been reported for a fetus with severe intrauterine growth restriction,[41] evidence regarding the risks and benefits of this intervention are lacking and this approach is not recommended. In another report, 16 fetuses were treated with intravenous fentanyl in an attempt to ameliorate the fetal stress response to intrahepatic fetal

TABLE 2
Summary of studies regarding fetal blood sampling technique

Study	No. of procedures	Maternal sedation	Local anesthesia	Ultrasound technique	Puncture site	Confirmation of fetal blood
Tangshewinsirikul et al,[43] 2011	2214	No	Yes	Freehand	PCI or free loop	n/a
Tongsong et al,[44] 2000	1320	No	Yes	Freehand	PCI or free loop	Yes
Aina-Mumuney et al,[45] 2008	210	Yes	Yes	n/a	IHV, PCI, or both	MCV
Nicolini et al,[46] 1990	214	Only 1 y, not last 2 y	n/a	Freehand	IHV	n/a
Somerset et al,[47] 2006	221	n/a	n/a	n/a	IHV, PCI, or intracardiac	n/a
Sikovanyecz et al,[48] 2001	268	n/a	No	Freehand	PCI or free loop	n/a
Liao et al,[49] 2006	2010	n/a	No	Fixed needle guide	97% free loop, 3% PCI	KHB
Boulot et al,[50] 1990	322	No	Yes	n/a	PCI (majority) or free loop	KHB or MCV
Johnstone-Ayliffe et al,[18] 2012	114	n/a	n/a	Freehand	PCI, IHV, or free loop	n/a

IHV, intrahepatic vein; *KHB*, Kleihauer-Betke test; *MCV*, mean corpuscular volume; *n/a*, not available; *PCI*, placental cord insertion.

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transfusion.[42] Again, no evidence of fetal benefit from this treatment was demonstrated. In general, FBS has rarely been used for medical therapies other than transfusions or refractory arrhythmias, and evidence for benefits from these other therapies is lacking.

What are the technical aspects of FBS?

Techniques to obtain samples of fetal blood for prenatal diagnosis, and to access the fetal circulation for the purpose of IUT have evolved over the last 50 years[1,2,4] (Table 2).[18,43-50] Currently, there are several ways to accomplish ultrasound-guided placement of a needle into the fetal circulation: directly into the umbilical cord (either at the placental cord insertion [PCI] or abdominal cord insertion [ACI] or into a free loop); into the intrahepatic portion of the umbilical vein (also called the intrahepatic vein [IHV]); or into the fetal heart (cardiocentesis). Besides differences in sampling sites, there are variations in other technical aspects of the procedure, such as use of prophylactic antibiotics, anesthesia, paralytic agents, ultrasound techniques, placental penetration, and other considerations. Table 2 summarizes technical aspects as reported by some of the largest series, while Table 3 provides a summary of suggestions.

Prophylactic antibiotics

There are no randomized trials on the efficacy of prophylactic antibiotic for FBS. Boulot et al[50] based their recommendation to use prophylactic antibiotics on the fact that 2 of the 6 fetal deaths in their series were attributed to amnionitis. However, most large series of FBS do not report use of prophylactic antibiotics for this sterile procedure.[18,43-50] In the American Congress of Obstetricians and Gynecologists Practice Bulletin on invasive testing for aneuploidy, there is no recommendation for the use of antibiotics to prevent intrauterine infection prior to invasive procedures.[51]

TABLE 3
Technical aspects of fetal blood sampling?[a]

Technical aspect	Comments
Prophylactic antibiotics	Insufficient evidence to recommend
Maternal sedation	Used infrequently
Local anesthesia	Used by some centers
Skin preparation	Preprocedural antibacterial skin preparation and aseptic technique are recommended
Needle guidance	Both needle guide instrument and freehand techniques have been reported and are acceptable; direct needle into target (eg, umbilical vein) under continuous ultrasound guidance; avoid umbilical arteries if feasible
Needle gauge and length	20- or 22-gauge; gauge and length depend on indication, suspicion of thrombocytopenia, gestational age, maternal body habitus, and distance from skin to target
Sampling site	• Umbilical vein usually preferred, either at PCI or ACI, or into free loop; • IHV • Fetal heart (cardiocentesis)
Paralytic agent for transfusion	Pancuronium, atracurium, or vecuronium

ACI, abdominal cord insertion; *IHV*, intrahepatic vein; *PCI*, placental cord insertion.

[a] See text for details.

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Maternal sedation

Use of maternal sedation is variable, although many centers no longer administer intravenous sedation (Table 2).

Local anesthesia

Use of local anesthesia varies depending on the preference of the operator, as well as type of procedure (diagnostic sampling or IUT). Of 9 studies cited, 4 of them[43-45,50] reported use of local anesthesia, although not all studies reported on this aspect (Table 2). While some centers use regional anesthesia after a viable gestational age and depending on the clinical circumstances, there are no data or clinical reports to support this practice.

Skin preparation

The majority of studies endorse using an aseptic technique, including a preprocedural antibacterial skin preparation to reduce the risk of infection.[18,43-50]

Needle guidance

The insertion of the needle into the fetal circulation can be accomplished either with a needle guide instrument that attaches to the end of the ultrasound transducer, or by using an ultrasound-guided freehand technique. With either method, the operator can control the transducer with one hand and the needle with the other, or an assistant can control the transducer and find the appropriate place for a needle insertion attempt. The majority of studies seemed to describe the freehand technique, which may allow for greater flexibility (Table 2), although no trials exist comparing the 2 methods. With either technique, the operator follows the tip of the needle under continuous ultrasound guidance from soon after percutaneous entry point to placement into the fetal circulation. When the fetal umbilical cord is accessed, effort is made to insert the needle into the umbilical vein without puncturing one of the arteries as these may vasoconstrict when punctured, leading to fetal bradycardia and a subsequent emergency delivery.

Needle gauge and length

Most centers use a 20- or 22-gauge spinal needle, depending on the indication for procedure (diagnostic vs therapeutic IUT), and suspicion for thrombocytopenia.[52] Other important considerations when choosing the appropriate needle are gestational age, maternal body habitus, and distance from skin to target. For example, at an earlier gestational age (eg, <24 weeks), it might be preferable to use a 22- (instead of 20-) gauge needle given the smaller umbilical cord vessels. In women with a thick panniculus, a larger-bore 20-gauge needle may be useful to prevent bending of the needle and to improve visualization. The distance from skin to target is also important to measure to determine if the standard 9-cm spinal needle length is appropriate, or if a longer needle is needed. Finally, some operators prefer to run heparin through the needle prior to sampling to prevent the formation of a blood clot within the needle.

Sampling site

FBS is most commonly performed via the umbilical vein close to the PCI. It is less commonly performed at the fetal ACI, through penetration of a free loop of cord, via cannulation of the IHV, and is rarely performed by fetal cardiocentesis. There are currently no published randomized control trials comparing the efficacy and safety of these techniques.[53] Advantages of sampling at the PCI are the relative stability of the cord for easier insertion and shorter procedure time.[43] A disadvantage is the possibility of contamination by maternal blood, and need to confirm that the sample obtained is indeed of fetal origin. FBS performed from a free loop of cord may result in more bleeding and longer bleeding time due to piercing of the wall of the vessel, although it has the advantage of avoiding placental penetration, and avoiding the need for confirmation of fetal origin.[48] Indeed in one large study comparing outcomes for PCI (n = 559) vs free loop (n = 1655), the mean duration of the procedure was significantly shorter in the PCI group (4.5 vs 6.7 minutes, $P = .001$), while the rate of maternal blood contamination was significantly lower in the free loop group (0.6% vs 2.3%, $P = .001$). There were no differences in success rates, fetal bradycardia, or fetal loss rates between groups.[43]

The first large series published on FBS via the IHV reported a 91% success rate for obtaining a sample, and a successful IUT in 90% of those attempted.[46] In this series, a 20-gauge needle was introduced into the fetal abdominal wall and advanced through the liver parenchyma into the umbilical vein or left portal vein. The needle was left unheld, allowing it to move freely with fetal movement and to minimize dislodgment. The dislodgment rate was 8.7%, and all of the 2.3% of cases of intraperitoneal bleeding resolved.[46] Potential advantages of the IHV approach are the lack of need to confirm fetal origin of the sample, less fetomaternal hemorrhage due to avoidance of the placenta, and less streaming.[45] In a retrospective study of outcomes of IHV sampling compared with cordocentesis, a total of 210 procedures were performed in 139 pregnancies. One hundred were by IHV only, 80 by cordocentesis only, 19 by IHV following failed cordocentesis, and 11 by cordocentesis following failed IHV. Success rates for IHV only, cordocentesis only, conversion of IHV to cordocentesis, and cordocentesis to IHV were 95%, 83%, 91%, and 84%, respectively. Postprocedure streaming was significantly less common with IHV (1% vs 31%); although there were no differences in nonreassuring fetal heart rate patterns, need for urgent delivery, or fetal/neonatal deaths.[45] In another series of 382 procedures, IHV sampling was performed in 76%, cordocentesis in 18%, and cardiocentesis in 5%.[54] Multivariable analysis demonstrated a statistically significant increased risk of fetal loss for the cardiocentesis group only. In general, success rates are high with all methods, and the particular sampling site should be individualized based on experience of operator, as well as placental, umbilical cord, and fetal position.

Placental penetration

Concerns for placental penetration during FBS involve the potential increased risk for fetomaternal hemorrhage, and potential for higher fetal death rates.

Few data exist, although a recent study compared 615 cases of cordocentesis with placental penetration to 1560 cases without penetration.[33] Not surprisingly, almost all cases with placental penetration had an anterior placenta. Cordocentesis with placental penetration was associated with a significantly higher rate of fetal loss (3.6% vs 1.3%, $P = .01$), low birthweight (14.5% vs 11.0%, $P < .05$), umbilical cord bleeding (32.0% vs 28.4%, $P < .05$), and lower gestational age at delivery. There were no differences in duration of procedure, success rate, or rates of fetal bradycardia. Significant placental bleeding was observed in a third of cases with placental penetration, and no cases without penetration.

Fetal blood specimen

Once the needle has been successfully placed, blood is aspirated into a previously heparinized syringe. Many centers send an initial sample to determine if the blood obtained is fetal in origin.[44,49,50] Techniques such as measuring mean corpuscular volume (MCV) and the Kleihauer-Betke test have been successful in determining fetal origin. Additionally some centers draw and evaluate a maternal sample drawn prior to the procedure, for comparison of MCV and hemoglobin/hematocrit, since the fetal MCV is usually larger, and fetal hemoglobin/hematocrit values are typically different than corresponding maternal values. When the IHV, a free umbilical cord loop, or ACI are accessed, or if fetal cardiocentesis is performed, there is no need for verification of fetal blood since these sites assure a lack of maternal blood contamination.[45] In the case of suspected fetal anemia, the blood is sent for immediate analysis of hemoglobin/hematocrit to determine the amount of blood needed for IUT. Once IUT or sampling is complete, the needle is withdrawn. There is insufficient evidence to assess if monitoring the puncture site for bleeding ("streaming") is necessary. During IUT, the fetal heart can be intermittently observed directly by ultrasound, and/or (with same view focused on umbilical insertion site) by using Doppler color flow or blood velocity waveforms by pulse Doppler.[55]

Use of paralytic agents

In 1988, Copel et al[56] first reported the intravenous injection of a muscle relaxant, pancuronium bromide, to reduce fetal movement during intravascular IUT. Since then, many centers routinely use agents such as pancuronium, atracurium, or vecuronium.[57-59] These agents differ in several respects. Pancuronium is a long-acting agent, while atracurium and vecuronium are both short-acting. Atracurium may be beneficial in fetuses with hydrops because it is not eliminated by the liver, and has the added benefit that the breakdown products do not have significant cardiovascular and neuromuscular effects.[58,60,61] In one study that compared the effects of pancuronium (0.1 mg/kg) or atracurium (0.4 mg/kg) on the onset and duration of fetal paralysis, fetal movements, and fetal heart rate parameters, no differences were found in the median time needed to complete the procedure or differences in transfusion volume, although pancuronium produced a major reduction in fetal heart rate variability and fetal movements after the procedure. The authors concluded that, when the need for use of fetal paralysis during IUT is thought to be necessary, atracurium may be a better choice.[60] Paralytic agents may be particularly useful when large transfusion volumes (and therefore longer operating times) are anticipated, or when vigorous fetal movements make the procedure more challenging. They are not usually necessary when FBS is performed for indications other than potential IUT, or when an anterior placenta and cord insertion are present.

Other

Several technical aspects of FBS are important, but not studied or well documented in the literature. For example, there is no reliable information about the efficacy or prevalence of regional anesthesia for FBS. Similarly, little information exists about the choice of physical location (eg, operating room, ultrasound suite, office) for the procedure. Once viability is reached, it is prudent to perform the procedure in close proximity to or within an available operating room should the need for emergency cesarean delivery arise. The decision to use prophylactic steroids for fetal lung maturity prior to FBS is also not well documented, but should be considered when FBS is performed around 23 0/7 to 33 6/7 weeks, given the increased risk of preterm birth.

Operator experience

A current dilemma with respect to the FBS procedure is the ongoing continuing need for FBS in certain clinical situations (Table 1), concomitant with a decrease in number of procedures performed annually in the United States, which affects the training of future physicians. Given the current paucity of widely accepted clinical indications for the procedure, the capability to train physicians to perform FBS and to maintain a reasonable level of skill in doing the procedure poses challenges. Several authors have described simulation models[62,63] that appear to be effective for teaching, and aid in the maintenance of the skills needed to competently perform FBS.

What are the procedure-related risks of FBS?

The risks of FBS often vary depending on the condition of the fetus, but there are common features (Table 4). The most common procedure-related risk is bleeding from the umbilical cord puncture site. The incidence has been reported to be 20-30% and is usually self-limiting, unless thrombocytopenia is present. An abnormal fetal heart rate can also occur after the procedure. Bradycardia is more common than tachycardia, with a reported incidence of 5-10%.[64] The majority of fetal bradycardias resolves within 5 minutes and usually requires no further intervention.

FBS does carry risk of procedure-related pregnancy loss, usually defined as the risk of pregnancy loss/fetal demise within 2 weeks of the procedure.[53] For a fetus without structural abnormalities, the procedure-related loss rate is estimated to be about 1%.[65,66] Higher loss rates have been reported for fetuses with structural malformations, severe growth restriction, or hydrops (7%, 14%, and

TABLE 4
Risks of fetal blood sampling[a]

Risk	Comments
Bleeding from puncture site (eg, umbilical cord)	20-30%; usually self-limited
Abnormal fetal heart rate	5-10% bradycardia; majority resolve within 5 min
Pregnancy loss	1.3% if no structural anomalies or hydrops and no placental penetration
Vertical transmission of maternal infection (eg, hepatitis B, hepatitis C, or HIV)	Insufficient information to estimate risk

HIV, human immunodeficiency virus.

[a] See text for details.

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25%, respectively) indicating that the procedure-related loss is dependent on the indication for the procedure.[65] Besides the procedure indication, placental penetration affects the procedure-related loss risk, as mentioned above.[33] Early gestational age (eg, <24 weeks) at the time of the procedure may also be associated with increased loss rates.[49]

Invasive prenatal diagnostic tests performed in women chronically infected with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) carry a theoretical risk of vertical transmission. Very limited information is available about the risk of vertical transmission during FBS. From small studies of amniocentesis, the procedure-related risks of vertical transmission of HIV, hepatitis B, and hepatitis C appear to be exceedingly low, and related to maternal viral load.[67-71] The risk of vertical HIV transmission is higher in women who are not taking antiretroviral therapy, compared with women who are being treated and have undetectable viral loads.[72] In patients for whom no alternative exists to FBS, eg, severe fetal hemolytic disease requiring IUT, the potential risks of FBS related to vertical transmission should be discussed prior to the procedure. Treatment aimed at decreasing the viral load for both HIV and hepatitis B virus in patients with these infections should be considered. When performing FBS in a patient with one of these infections, efforts should be made to avoid traversing the placenta with the needle, if possible.

TABLE 5
Society for Maternal-Fetal Medicine recommendations for fetal blood sampling

	Recommendations	Grade of recommendations (Table 6)
1	When invasive testing is planned for suspected severe fetal anemia or thrombocytopenia, we recommend FBS as procedure of choice, with availability of immediate transfusion if confirmed	1 C Strong recommendation, low-quality evidence
2	We recommend against use of FBS for indications in which other less invasive, and therefore lower risk, alternatives are available	1 C Strong recommendation, low-quality evidence
3	We recommend counseling patients about potential risk of FBS that may include, but may not be limited to: bleeding from puncture site; fetal bradycardia; pregnancy loss; and potential vertical transmission of hepatitis or HIV	Best practice
4	We recommend that FBS be performed by experienced operators at centers with expertise in invasive fetal procedures when feasible	Best practice

FBS, fetal blood sampling; *HIV*, human immunodeficiency virus.

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RECOMMENDATIONS

Ultrasound-guided FBS is the only procedure that provides direct access to the fetal circulation. While the number of indications for FBS is decreasing because of newly available less invasive and accurate techniques, FBS can be both beneficial and lifesaving in some cases of fetal anemia, NAIT, and hydrops (Table 1). The overall success rate of FBS is high, and blood samples can be obtained in >98% of patients.[49] This access comes at the price of at least a 1% incidence of fetal loss (Table 4). Proper technique should be adhered to, in order to minimize complications (Table 3).

The Society for Maternal-Fetal Medicine Publications Committee has adopted the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach in the development of its clinical recommendations (www.gradeworkinggroup.org).[73] Recommendations regarding FBS are presented in Table 5. The grading scheme classifies recommendations as either strong (grade 1) or weak (grade 2), and classifies the quality of evidence as high (grade A), moderate (grade B), or low (grade C).[73,74] Thus, the recommendations can be 1 of the following 6 possibilities: 1A, 1B, 1C, 2A, 2B, 2C (Table 6).

TABLE 6
Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations[73,74]

Grade of recommendation	Clarity of risk/benefit	Quality of supporting evidence	Implications
1A Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form; further research is unlikely to change our confidence in estimate of benefit and risks	Strong recommendations, can apply to most patients in most circumstances without reservation; clinicians should follow strong recommendation unless clear and compelling rationale for alternative approach is present
1B Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens, or vice versa	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design; further research (if performed) is likely to have impact on our confidence in estimate of benefit and risks and may change estimate	Strong recommendation and applies to most patients; clinicians should follow strong recommendation unless clear and compelling rationale for alternative approach is present
1C Strong recommendation, low-quality evidence	Benefits appear to outweigh risks and burdens, or vice versa	Evidence from observational studies, unsystematic clinical experience, or randomized, controlled trials with serious flaws; any estimate of effect is uncertain	Strong recommendation, and applies to most patients; some of evidence base supporting recommendation is, however, of low quality
2A Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form; further research is unlikely to change our confidence in estimate of benefit and risks	Weak recommendation, best action may differ depending on circumstances or patients or societal values
2B Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens; some uncertainly in estimates of benefits, risks, and burdens	Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design; further research (if performed) is likely to have impact on our confidence in estimate of benefits and risks and may change estimate	Weak recommendation, alternative approaches likely to be better for some patients under some circumstances
2C Weak recommendation, low-quality evidence	Uncertainty in estimates of benefits, risks, and burdens; benefits may be closely balanced with risks and burdens	Evidence from observational studies, unsystematic clinical experience, or randomized, controlled trials with serious flaws; any estimate of effect is uncertain	Very weak recommendation; other alternatives may be equally reasonable
Best practice	Recommendation in which either: (i) there is enormous amount of indirect evidence that clearly justifies strong recommendation—direct evidence would be challenging, and inefficient use of time and resources, to bring together and carefully summarize; or (ii) recommendation to contrary would be unethical		

SMFM. Fetal blood sampling. Am J Obstet Gynecol 2013.

Quality of evidence

The quality of evidence for each article was evaluated according to the method outlined by the US Preventative Services Task Force:

I	Properly powered and conducted randomized controlled trial (RCT); well-conducted systematic review or metaanalysis of homogeneous RCTs.
II-1	Well-designed controlled trial without randomization.
II-2	Well-designed cohort or case-control analytic study.
II-3	Multiple time series with or without the intervention; dramatic results from uncontrolled experiment.
III	Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.

Recommendations were graded in the following categories:

Level A
The recommendation is based on good and consistent scientific evidence.

Level B
The recommendation is based on limited or inconsistent scientific evidence.

Level C
The recommendation is based on expert opinion or consensus.

This opinion was developed by the Publications Committee of the Society for Maternal–Fetal Medicine with the assistance of Stanley M. Berry, MD, Joanne Stone, MD, Mary Norton, MD, Donna Johnson, MD, and Vincenzo Berghella, MD, and was approved by the executive committee of the society on March 11, 2012. Dr Berghella and each member of the publications committee (Vincenzo Berghella, MD [chair], Sean Blackwell, MD [vice-chair], Brenna Anderson, MD, Suneet P. Chauhan, MD, Jodi Dashe, MD, Cynthia Gyamfi-Bannerman, MD, Donna Johnson, MD, Sarah Little, MD, Kate Menard, MD, Mary Norton, MD, George Saade, MD, Neil Silverman, MD, Hyagriv Simhan, MD, Joanne Stone, MD, Alan Tita, MD, Michael Varner, MD) have submitted a conflict of interest disclosure delineating personal, professional, and/or business interests that might be perceived as a real or potential conflict of interest in relation to this publication.

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The practice of medicine continues to evolve, and individual circumstances will vary. This opinion reflects information available at the time of its submission for publication and is neither designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal—Fetal Medicine.