Screening for Intrauterine Growth Restriction in Uncomplicated Pregnancies: Time for Action

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Abstract

A randomized clinical trial (RCT) noted that sonographic examination in the third trimester, in conjunction with delivery at term for abnormalities of fetal growth, significantly decreased the likelihood of small-for-gestational-age (SGA) neonates in uncomplicated pregnancies. We identified 15 characteristics of screening tests and attempted to determine if there is evidence to routinely obtain sonographic estimates of fetal weight in the third trimester and decrease rates of SGA. Of the 15 suggested characteristics, currently 10 (67%) are fulfilled, two are uncertain (sonographic examination is cost-effective or reliable), and one (the test must do its job) is possibly valid. Due to the lack of RCTs demonstrating reduction in morbidity, there is potential for lead-time and length bias. To observe a 36% decrease (from 4.1 to 2.6%) decrease in composite perinatal morbidity, 6000 women need to be randomized to at least two sonographic examinations in the third trimester versus routine prenatal care. Such an RCT is warranted and justified.

Keywords
- IUGR
- perinatal outcomes
- third-trimester sonography
- SGA

According to the American Congress of Obstetricians and Gynecologists (ACOG) practice bulletin,[1] estimated fetal growth below the 10th percentile for gestational age (GA) is intrauterine growth restriction (IUGR), and standards based on birth weight refer to small for gestational age (SGA). IUGR is "one of the most common and complex problems in modern obstetrics."[1] It is linked with low Apgar scores and umbilical arterial pH <7.00; admission to a neonatal intensive care unit and sepsis; increased stillbirth and neonatal mortality risks; learning difficulties and adult-onset cardiovascular disease.[1] There is an imperative to prenatally identify growth restricted fetuses because, according to the practice bulletin, the neonatal mortality among detected newborns with birth weight <10th percentile for GA is 8/1000 births compared with 21/1000 births for undetected newborns. The current recommendations for identification of growth-restricted fetuses are to obtain third-trimester sonographic estimates of fetal weight (SEFWs) in high-risk pregnancies and to perform serial fundal height measurement in low-risk pregnancies at each clinic visit. Among low-risk pregnancies, SEFWs should be reserved if there is lagging fundal height or no change in fundal height between examinations.[1]

In 2003, McKenna et al[2] published a randomized clinical trial (RCT) that assessed the utility of two sonographic examinations in low-risk women. They reported that women who had an SEFW at 30 to 32 weeks and at 36 to 37 weeks were significantly less likely to have SGA newborns (10.4%

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versus 6.9%, respectively; relative risk 0.67; 95% confidence intervals 0.50, 0.89) compared with those followed with fundal height measurements alone. The investigators concluded that although the two sonographic examinations and inductions for abnormalities noted with them increased interventions, they significantly reduced the risk of suboptimal growth. Currently the ACOG practice bulletins on IUGR[1] and on ultrasonography in pregnancy[3] do not recommend screening uncomplicated women with additional sonograms to assess fetal growth after 30 weeks.

One explanation for the lack of a recommendation in the bulletins for SEFW in low-risk women is that it does not meet the criteria for screening. As noted by Rouse et al,[4] as well as Grimes and Schulz,[5] inappropriate screening can lead to unnecessary obstetric intervention and harm. The purpose of this commentary is to determine whether sonographic examinations in the third trimester meet the criteria for screening tests.

Criteria for Screening Tests

We identified 15 characteristics for a useful screening test (►**Table 1**).[4,5] First, the disease should be medically important. Undeniably IUGR is important because it is associated with obstetric (stillbirth, oligohydramnios, cesarean delivery for nonreassuring fetal heart) and neonatal (hypothermia, sepsis, seizure) complications, as well as an increased risk of neonatal and infant mortality.[6] Second, the disease should be clearly defined. Though there are several definitions of IUGR (birth weight below 3%, 5%, 10%, or 15% for GA) both ACOG and Royal College of Obstetricians and Gynaecologists (RCOG) acknowledge that birth weight <10th percentile is growth restriction.[1,7,8] IUGR is diagnosed when, during sonographic examination, abdominal circumference (AC) or estimated fetal weight is <10% for GA.[1] Third, the prevalence should be known.[1] By strict definition, the prevalence of suboptimal growth is 10%.

Fourth, the natural history should be known. ACOG has identified 33 risk factors, which are categorized as 24 arising from maternal causes, six placental and three with fetal origins.[1] The understanding of IUGR due to uteroplacental insufficiency is that cytotrophoblast invasion is shallow and endovascular invasion is rudimentary in placental development leading to poor perfusion. Morphologic placental studies have noted that the mean surface area as well as the capillary surface area is reduced. Results of cordocentesis reveal that pregnancies complicated by IUGR have fetal hypoxemia, acidosis, hypoglycemia, α-amino nitrogen, and especially branched chain amino acids.[9] Reduced urinary output is associated with oligohydramnios, which in turn is linked with cord compressions and stillbirth.[1] Long-term adverse outcomes in these babies are purported to be due fetal programming to adapt to the intrauterine environment, which lead to maladaptation.[10]

Fifth, an effective intervention must exist. As noted by ACOG, the following interventions do not decrease the likelihood of suboptimal growth: nutrient treatment, zinc or calcium supplementation, plasma volume expansion, maternal oxygen therapy, antihypertensive medications, and heparin or aspirin therapy. Though IUGR is unpreventable, the associated morbidity and mortality can be ameliorated. Antepartum testing with appropriate interventions lowers mortality.[11] According to the ACOG practice bulletin,[1] the corrected perinatal mortality with IUGR is 21.3 per 1000 births if these fetuses are undiagnosed and do not have antenatal tests. However, if they are detected and have antenatal surveillance, the perinatal mortality rate decreases by 60% to 8.4 per 1000.[1] A meta-analysis of 18 trials with over 10,000 women concluded that use of Doppler ultrasound in high-risk pregnancies reduced the risk of perinatal death and resulted in less obstetric interventions like induction of labor and cesarean delivery.[12] The number needed to monitor to prevent one death is 203 (95% confidence interval of 103 to 4352). If fetal well-being is not assured and preterm delivery is indicated, then the effective interventions include administration of corticosteroids and transfer for delivery at a tertiary center, with a neonatal intensive care unit.[13]

The sixth criterion is that the screening test must be cost-effective. A PubMed search, using combinations of the terms "cost effective," "intrauterine growth restriction," "small for gestational age," and "estimate fetal weight," identified a paucity of publications on the cost-effectiveness of screening for growth restriction. Such an analysis seems daunting because growth restriction is associated with both stillbirth[1] and hypoxic ischemic injuries,[14] which are leading causes of obstetric litigation.[15] It is noteworthy that Gilbert and Danielsen[16] reported that with newborns delivered at 30 to 41 weeks, the hospital charges for growth-restricted newborns are significantly higher than for those with adequate growth. This does not assure that screening for suboptimal growth will be cost-effective but suggests it might be.

Seventh, facilities must be readily available to diagnose the disease. When the clinical estimate is <2500 g or if the GA is <37 weeks, then clinical estimate is not as reliable as SEFW.[17] Factors that make fundal height assessment difficult may include maternal obesity[18] as well as the inability to determine if AC is <10% for GA, a criteria for IUGR.[1] SEFW can identify IUGR and those measurements are most accurate when done by registered diagnostic medical sonographers, rather than residents, obstetricians, or maternal fetal medicine subspecialists.[19,20] Although detection of anomalies is optimum at tertiary centers,[21] there is no suggestion that SEFW should be done solely at these centers.[20] According to the national vital statistics reports, 67% of women with live births had sonographic examinations during their pregnancy.[22] Thus, it seems that there are facilities available to do sonographic examinations and diagnose the disease.

The eighth criterion of a valuable screening test is that facilities for treatment should be available. When IUGR is detected then antepartum testing should be initiated.[1,11] According to ACOG, a nonstress test, a contraction stress test, or a modified or complete biophysical profile are reliable surveillance modalities to assess fetal well-being.[11] Because nonstress test and contraction stress test involve fetal heart rate monitoring, which is the predominant modality to assess fetal well-being during labor,[23] these treatment options are

Table 1 Screening for Intrauterine Growth Restriction among Uncomplicated Pregnancies

	Characteristics of Screening Test	Applicable	Comments
1	The disease should be medically important	Yes	Morbidity and mortality with suboptimal growth are well known[1,6]
2	The disease is clearly defined	Yes	Though there are several definitions of suboptimal growth (<1%, <3%, <10%, or <15%), both ACOG and RCOG define SGA as birth weight below 10% for gestational age[1,7,8]
3	The prevalence reasonably well known	Yes	Based on the criteria to define SGA (see 2 above), the prevalence is well known
4	The natural history should be known	Yes	Abnormal invasion of cytotrophoblasts, decreased capillary surface area; reduced fetal urinary flow rate[9] and oligohydramnios; cord compression and stillbirth[1]; long-term morbidity is due to fetal origin of disease[10]
5	An effective intervention must exist	Yes	Although there are no preventive measures to decrease the likelihood of growth restriction, there are interventions (antenatal testing, Doppler of umbilical artery, corticosteroids, inductions, transfer to hospital with neonatal intensive care unit and delivery) that improve the morbidity and mortality linked with aberrant growth[1,11–13]
6	Screening program must be cost effective	Unknown	PubMed search (December 2010) did not identify publication that ascertained if screening uncomplicated pregnancies for IUGR is cost-efficient
7	Facilities for diagnosis must be readily available	Yes	Over 65% of women giving live births have sonographic examinations during pregnancy[23]; thus, it is feasible for the majority to have sonographic estimate in birth weight in the third trimester
8	Facilities for treatment must be readily available	Yes	Though there are no treatment to prevent abnormal growth, antepartum testing (nonstress or contraction stress tests), administration of corticosteroids, induction or transfer to tertiary center if preterm delivery is indicated is available,[1,11,13] all of which improve associated morbidity and mortality
9	The test must do its job	Possibly	The likelihood ratio for the detection of IUGR is over 10, albeit in high-risk pregnancies[27]
10	The test must be safe	Yes	ACOG and AIUM attest to the safety of sonographic examinations during pregnancy[3,28]
11	Test must have a reasonable cutoff level defined	Yes	Both ACOG and RCOG consider abdominal circumference or estimated fetal weight <10% for gestational age as criteria for IUGR[1,13]
12	The test must be valid	Yes	About 80% of newborns have birth weight <10% for gestational age; when prenatal, they were suspected of being IUGR[35]
13	The test must be reliable	Uncertain	Although earlier studies indicated that the measurements of biometric parameters are not reliable,[36] the low interobserver variability in recent studies is reassuring[37,38]
14	Lead-time bias	Unknown	Need randomized clinical trial
15	Length bias	Unknown	Need randomized clinical trial

ACOG, American College of Obstetrician and Gynecologists; AIUM, American Institute of Ultrasound and Medicine; IUGR, intrauterine growth restriction; RCOG, Royal College of Obstetrician and Gynaecologists; SGA, small for gestational age.

readily available. Administration of corticosteroids and transfer to a tertiary care facility are accepted effective treatment for spontaneous preterm labor,[24] and they should be equally efficacious for indicated preterm delivery secondary to IUGR and comorbidities like absent or reverse end diastolic flow in the umbilical artery.[13]

The screening test must do its job is the ninth criterion. According to the guidelines established by the Evidence-Based

Medicine Working Group, a diagnostic test is useful if the likelihood ratio (LR) is at least 10 or less than 0.1.[25] Prior publications have reported that the LR for detection of IUGR has ranged from 2.3 to 11.[26,27] The reason for the variation in the LR includes that the sonographic examination were being done by physicians with varying years of experience. Consistent with a review article on the topic,[20] when EFW is done by registered diagnostic medical sonographers, the LR was 11. Thus, it seems sonographic estimates can detect suboptimal growth, but additional studies are needed to determine the factors that enhance the detection and whether it can be done in low-risk pregnancies.

The 10th criterion is the safety of the test. Ultrasound examination during pregnancy is considered safe as evidenced by the practice guideline published by American Institute of Ultrasound in Medicine[28] and the ACOG.[3] In 2009, ACOG confirmed that "ultrasonography is safe for the fetus when used appropriately and when medical information about pregnancy is needed."[3] There is, however, a potential for small risk. The practice bulletin does note that energy produced by ultrasound and delivered to the fetus cannot be assumed to be completely innocuous. Under laboratory conditions, ultrasonography can produce physical effects, such a mechanical vibration, referred to as "cavitation," or an increase in tissue temperature.[3]

Earlier reports have observed that with ultrasound examinations there were complications like IUGR,[29] delayed speech,[30] dyslexia[31] and left-handedness.[32] But a meta-analysis of nine RCTs comparing routine versus selective ultrasound in early pregnancy noted that there was no significant difference in the two groups with regards to low Apgar scores, low birth weight, admission to a neonatal intensive unit, corrected (excluding anomalies) perinatal mortality, and neurodevelopmental outcomes such as poor reading, dyslexia, or hearing defect.[33]

It is significant that the World Health Organization Ethics Review Board has approved a multicountry prospective study on fetal growth with seven serial ultrasound exams during pregnancy. This decision was based on a meta-analysis of 41 reports that concluded that sonographic examinations during pregnancy are not associated with adverse maternal or perinatal effects, impaired physical or neurological development, increased risk s of malignancies in childhood, or subnormal intellectual performance.[34]

The 11th criterion for a screening test is that it must have a reasonable and well-defined cutoff level. According to ACOG and RCOG, AC or estimated fetal weight <10% for GA[1,13] is consistent with IUGR. A recent report confirmed that these cutoffs do identify pregnancies that are at significant risk for oligohydramnios, cesarean delivery for nonreassuring fetal heart rate, admission to a neonatal intensive care unit, and newborns with an actual birth weight <10% for GA.[35] Due to a small sample size ($n = 410$), the investigators did not demonstrate that fetuses with sonographic suspicion of IUGR are at increased risk of composite morbidity like Apgar score <4 at 5 minutes, umbilical arterial pH <7.00, neonatal seizures within 24 hours, grade III or IV intraventricular hemorrhage, or proven sepsis or death within 28 hours. Additional studies are needed to link AC or EFW <10% with composite neonatal morbidity.

The screening test should be valid is the 12th criteria. As noted by Grimes and Schulz, validity is the ability of a test to measure what it sets out to measure, usually differentiating between those with and without the disease present.[5] According to Chauhan et al, when IUGR was suspected sonographically, 80% of the newborns actually weighed <10% for GA, as compared with 14%, when growth was considered normal.[35] Thus, it does seem that the SEFW below the 10% for GA is a valid screening test for IUGR.

The 13th criterion is whether the test is reliable. An initial report[36] suggested that the interobserver variability for measuring biometric parameters was excessive, rendering SEFW unreliable. Recent publications, however, note that the intra- and interobserver variability for paramedics in Bangladesh, with no prior sonographic experience, is reliable.[37] Similarly, Rijken et al[38] documented that local health workers in the Thailand-Myanmar border can obtain biometric measurements with an interclass coefficient >0.99, suggesting that the diagnostic test is reliable. We do acknowledge that retrospective multicenter studies have noted that detection of growth restriction is not reliable among women with hypertensive disease.[26] The difference between recent publications on interobserver variability and multicenter studies is the inherent bias and shortcoming of retrospective studies. Though we agree that at present there are insufficient or conflicting reports on the reliability of detecting IUGR, it is important that in the randomized trial by McKenna et al,[2] the midwives were able to lower the rate of SGA significantly with just 3 months of training in sonographic examinations.

The 14th and 15th criteria for a useful screening test are lead time and length bias. As noted by Grimes and Schulz,[5] lead-time bias is a spurious increase in longevity attributed to screening and length bias is improvement in longevity that is not related to the test. The way to rectify these biases is to do an RCT. Although the randomized trial by McKenna et al[2] did reduce the rate of SGA, it lacked sufficient sample size to show improvement in longevity, which the authors acknowledged. They calculated that 30,000 women would need to be randomized for a trial to have sufficient power to detect a 30% reduction in perinatal mortality rates between the two groups. Before such a large RCT is undertaken, we suggest a multicenter randomized trial with a composite morbidity as the primary outcome defined as, at least one of the following: admission to a neonatal intensive care unit for at least 48 hours, hypoglycemia, thrombocytopenia at term, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage (grades III or IV), sepsis, or perinatal death (stillbirth after randomization or death before newborn's discharge from the hospital).

The inclusion and exclusion criteria for the proposed randomized trial are listed in ►**Table 2**. As with the protocol utilized by McKenna et al,[2] the expectant management group will have sonographic examination in the third trimester if there is clinical suspicion for fetal growth or amniotic fluid abnormalities, decreased fetal movements, or other obstetric indications like preterm labor or hypertensive disease. The intervention group will have sonographic examinations,

Table 2 Enrollment Criteria for Proposed Randomized Trial

Inclusion Criteria	Exclusion Criteria
• Nonanomalous singleton • Fetal anatomy ultrasound by 22 weeks • Expected third-trimester care and delivery at the participating hospital	• Autoimmune disorders (antiphospholipid antibody, lupus, rheumatoid arthritis, scleroderma) • Cerclage in the index pregnancy • Diabetes mellitus—gestational or pregestational • Enrollment in another randomized clinical trial • Hematologic disorders (coagulation defects, sickle cell disease, thrombocytopenia, thrombophilia) • Hypertension (chronic or pregnancy induced) before randomization • HIV • Institutionalized individuals (prisoners) • Prior obstetric history of: (1) intrauterine growth restriction, (2) preterm birth before 34 weeks, (3) severe preeclampsia, eclampsia, HELLP syndrome, and (4) stillbirth after 24 weeks or neonatal death • Preterm labor or ruptured membranes before randomization • Psychiatric disorder (bipolar, depression) on medication • Placenta previa/third-trimester bleeding • Renal insufficiency (serum creatinine >1.5 mg/dL) • Restrictive lung disease • Fetal red blood cell isoimmunization • Seizure disorder on medication • Thyroid disease on medication

HELLP, hemolysis, elevated liver enzymes, and low platelet count.

evaluating fetal growth and amniotic fluid, at 30 to 32 weeks and at 36 to 37 weeks. In both groups, indications for delivery at 37 to 39 weeks will include abnormalities of amniotic fluid (oligohydramnios or hydramnios), or IUGR. Considering the vagaries of SEFW[20] and that all of the women in the trial are uncomplicated, it is possible that many of newborns suspected of being growth restricted will not be, leading to unnecessary induction and iatrogenic neonatal morbidity. These theoretical concerns are valid, but it is noteworthy that in the randomized trial by McKenna and colleagues,[2] the rate of SGA was decreased significantly, without concomitant increase in induction rate or admission to neonatal intensive care unit, a surrogate for neonatal morbidity.

A published report[39] points out that the likelihood of combined neonatal morbidity (hypoglycemia, respiratory distress syndrome, thrombocytopenia, sepsis, intraventricular hemorrhage, and intubation) was 22% with growth restriction with otherwise uncomplicated pregnancies versus 2% among those with normal growth. Accordingly, in a population with a 10% rate of growth restriction, the overall rate of the combined neonatal morbidity is 4.1%. To have 80% power to observe a 36% decrease (from 4.1 to 2.6%) in composite perinatal morbidity, we would need 2966 patients in each group ($\alpha = 0.05$). Assuming a loss rate of 10%, the RCT needs to recruit 6000 uncomplicated patients. To obtain this sample size, 12,000 women need to be screened, assuming ~50% of pregnancies are complicated or will decline participation.

Discussion

Compared with those with appropriate growth, the increased perinatal morbidity and mortality with growth-restricted newborns is undeniable. At least 10 interventions (bed rest, aspirin, nutrient supplements with calcium or zinc, maternal oxygenation, heparin, plasma volume expansion, calcium channel blockers, hormonal therapy, and smoking cessation) have been tried, but all have proven unsuccessful without decreasing the rate of IUGR or its associated complications.[1] Now there is a CONSORT compliant RCT that unequivocally demonstrated a reduction in the rate of IUGR, with two additional sonographic examinations in the third trimester.[2] Despite the promising results, sonographic estimated fetal weight after 30 weeks is not being used as a screening test.[1] Thus, we reviewed the literature to determine what is present and lacking for it to be a successful screening test.

We described 15 important characteristics of an ideal screening test. SEFW to detect IUGR meets 66% (10/15) of these criteria (►**Table 1**), which is reassuring. The criteria it does not meet currently, however, are worth emphasizing. A cost-effective analysis is warranted and should be done. Additional studies of IUGR in low-risk populations are needed to determine that among uncomplicated women, if SEFW can reliably identify IUGR, as it can with high-risk pregnancies. Although there are interobserver variability reports on measurements of biometric parameters, investigators should ascertain if detection of IUGR is reliable. The most important finding, however, of this review is that a multicenter RCT is warranted with the primary objective of reducing the combined morbidity linked with IUGR. A formidable concerted multicenter study that screens 12,000 women and randomizes ~6000 is urgently needed. Such a study is justified, even at term. Neonatal charges to treat a growth-restricted newborn are about $16,000 more than those for a newborn with appropriate growth, and the likelihood of neonatal seizures, proven sepsis, grade III or IV intraventricular hemorrhage, and death within 28 days are significantly higher.[16]

Strategies aimed at screening growth-restricted fetuses should address the results of GRIT (Growth Restriction Intervention Trial) trial, which randomized women with "fetal compromise" to immediate versus delayed delivery.[40,41] Of the 548 women enrolled, the likelihood of death before discharge was similar in the two groups (10% in immediate versus 9% in delayed group; odds ratio 1.1; 95% confidence interval 0.6 to 1.8). Additionally at 2 years, the overall rate of death or disability was not significantly different between the groups (19% in immediate and 16% in delayed group; adjusted odds ratio of 1.1; 95% confidence interval 0.7 to 1.8). These reports[40,41] suggest that there may not be any benefit of screening for growth restriction, but we do not think the results are applicable to uncomplicated pregnancies. In GRIT trial, 7%[39] of women had multiple pregnancies, 36% (196) were randomized at 24 to 30 weeks, and 43% (234) had hypertension. Because the GRIT trial included preterm patients and had medical complications, we think our proposed randomized study should be undertaken.

There is evidence that impaired intrauterine growth is linked with several major diseases in adult life, like coronary heart disease, hypertension, and type 2 diabetes. The suggestion, referred to as "fetal programming," is that intrauterine environment provides stimulus or insult at a critical, sensitive period of early life, which has permanent effects on structure, physiology, and metabolism.[42,43] Screening with sonographic examinations in the third trimester and inducing if abnormalities were noted significantly decreased the rate of newborns with suboptimal growth.[2] Thus one could speculate that such program will decrease disease in adult life, but this would need long-term follow-up of newborns, which would be a Herculean task.

In summary, it may be feasible to reduce the rate of IUGR and its associated morbidity and mortality. At present, however, routine screening of uncomplicated women with sonographic estimated fetal weight in the third trimester is not recommended. An RCT and cost-effective analysis are needed before third-trimester sonographic estimate weight can be considered a successful screening test.

Note

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