Screening for fetal growth restriction using fetal biometry combined with maternal biomarkers

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Fetal growth restriction is a major determinant of perinatal morbidity and mortality. Screening for fetal growth restriction is a key element of prenatal care but it is recognized to be problematic. Screening using clinical risk assessment and targeting ultrasound to high-risk women is the standard of care in the United States and United Kingdom, but the approach is known to have low sensitivity. Systematic reviews of randomized controlled trials do not demonstrate any benefit from universal ultrasound screening for fetal growth restriction in the third trimester, but the evidence base is not strong. Implementation of universal ultrasound screening in low-risk women in France failed to reduce the risk of complications among small-for-gestational-age infants but did appear to cause iatrogenic harm to false positives. One strategy to making progress is to improve screening by developing more sensitive and specific tests with the key goal of differentiating between healthy small fetuses and those that are small through fetal growth restriction. As abnormal placentation is thought to be the major cause of fetal growth restriction, one approach is to combine fetal biometry with an indicator of placental dysfunction. In the past, these indicators were generally ultrasonic measurements, such as Doppler flow velocimetry of the uteroplacental circulation. However, another promising approach is to combine ultrasonic suspicion of small-for-gestational-age infant with a blood test indicating placental dysfunction. Thus far, much of the research on maternal serum biomarkers for fetal growth restriction has involved the secondary analysis of tests performed for other indications, such as fetal aneuploidies. An exemplar of this is pregnancy-associated plasma protein A. This blood test is performed primarily to assess the risk of Down syndrome, but women with low first-trimester levels are now serially scanned in later pregnancy due to associations with placental causes of stillbirth, including fetal growth restriction. The development of "omic" technologies presents a huge opportunity to identify novel biomarkers for fetal growth restriction. The hope is that when such markers are measured alongside ultrasonic fetal biometry, the combination would have strong predictive power for fetal growth restriction and its related complications. However, a series of important methodological considerations in assessing the diagnostic effectiveness of new tests will have to be addressed. The challenge thereafter will be to identify novel disease-modifying interventions, which are the essential partner to an effective screening test to achieve clinically effective population-based screening.

Key words: A-disintegrin and metalloprotease 12, alpha fetoprotein, biomarker, fetal biometry, fetal death, human chorionic gonadotropin, human placental lactogen, inhibin, models, placenta, placental growth factor, placental protein 13, prediction, pregnancy-associated plasma protein-A, randomized controlled trial, review, screening, small for gestational age, soluble endoglin, soluble fms-like tyrosine kinase-1, stillbirth, study design, ultrasound

"Fetal growth restriction" and "small for gestational age": differences between 2 commonly used terms and clinical implications

"Fetal growth restriction" (FGR) is defined as the failure of the fetus to reach its genetically determined growth potential. FGR is a major determinant of perinatal and childhood morbidity and mortality, and is associated with the risk of chronic diseases in later life.[1-3] An obstacle to the study of FGR is that there are no gold standard definition and diagnostic criteria for this condition. The size of the fetus or newborn is quantified with reference to the normal range for gestational age (GA) and those with birthweight (BW) <10th percentile are called "small for gestational age" (SGA). Inaccurately, the small size of the baby often becomes synonymous with FGR, and different thresholds for these measurements are used to define a FGR infant (eg, <2500 g, <10th percentile, or <3rd percentile).

Although SGA and FGR are sometimes used interchangeably, the 2 terms are distinct, as many SGA infants are constitutionally small and healthy. Hence, clinical research on screening for FGR has to address 2 main issues: (1) the sensitive and specific detection of SGA fetuses, and (2) the ability to discriminate between FGR and healthy SGA. The causes of FGR can be broadly categorized into maternal (eg, pregnancy-associated hypertensive diseases, autoimmune disease, poor nutrition, substance abuse, and teratogen exposure),[4-6] fetal (eg, multiple gestations, infections, genetic and structural disorders),[7,8] or placental.

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Received Sept. 1, 2017; revised Nov. 24, 2017; accepted Dec. 1, 2017.

This work was supported by the Medical Research Council (G1100221).

Disclosure: Dr Smith has received research support from Roche (supply of equipment and reagents for biomarker studies) and been paid to attend an advisory board by Roche.

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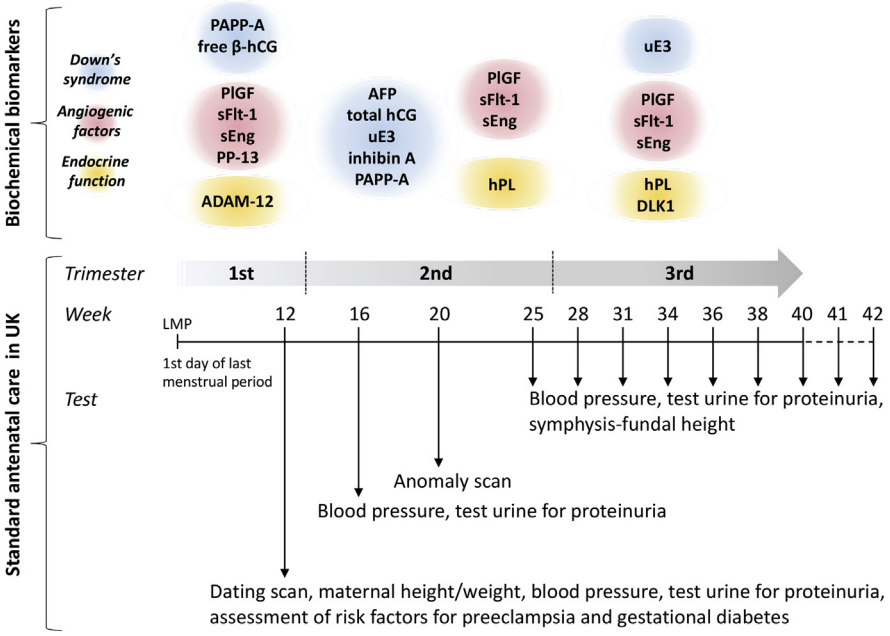
0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2017.12.002

FIGURE 1
Standard antenatal care in United Kingdom (UK) and biochemical markers measured throughout pregnancy



Measurement of pregnancy biomarkers in relation to UK antenatal care schedule. Biomarkers measured in clinical and research settings during pregnancy are plotted on a time scale representing standard antenatal care for nulliparous women in UK, which includes 10 routine midwife visits and additional visits for women delivering >40 weeks of gestation.

ADAM12, A-disintegrin and metalloprotease 12; *AFP*, alpha fetoprotein; *DLK1*, delta-like 1 homolog; *hCG*, human chorionic gonadotropin; *hPL*, human placental lactogen; *PAPP-A*, pregnancy-associated plasma protein A; *PlGF*, placental growth factor; *PP*, placental protein; *sENG*, soluble endoglin; *sFLT1*, soluble fms-like tyrosine kinase-1; *uE3*, unconjugated estriol

Gaccioli. Screening for fetal growth disorders. Am J Obstet Gynecol 2017.

It is thought that placental dysfunction accounts for the majority of FGR cases.[9] Hence, one of the most promising approaches to screening for FGR is to combine ultrasonic fetal biometry with measurement of biomarkers of abnormal placentation in the mother's blood.

Current status of screening with fetal biometry

In many countries, including the United Kingdom and United States, ultrasound scanning after the 20-week anomaly scan is only performed on the basis of clinical indications as universal ultrasound is not supported by the most recent Cochrane review.[10] It is worth noting that the evidence base can be described as an absence of evidence rather than compelling high-quality evidence of the absence of clinical effectiveness of screening. This is due to a number of problems with the 13 studies analyzed in the systematic review, including limited statistical power and lack of an effective interventional strategy.[11] Nevertheless, the current approach to screening for FGR is to assess the women for preexisting risk factors, acquired complications of pregnancy, and clinical examination (eg, symphysis-fundal height measurements) (Figure 1). Women identified as high risk using these methods are then selected for ultrasonographic assessment. Screening for FGR is just one element of the universal ultrasound.[12] Other elements include macrosomia, late presentation of fetal anomalies, abnormalities of amniotic fluid volume, and diagnosis of undetected malpresentation.

Ultrasonic markers of FGR

Fetal biometry and Doppler flow velocimetry are the primary methods used currently to diagnose FGR. The use of ultrasound markers of FGR is discussed in detail elsewhere in this issue, and will be only briefly summarized here. An estimated fetal weight (EFW) is derived from ultrasonic measurements of head size, abdominal circumference, and femur length, and an EFW centile is calculated using a reference standard.[13,14] While a single measurement of fetal size and the EFW <10th centile cutoff appears to be insufficient to discriminate growth-restricted and healthy small fetuses, serial fetal biometry reveals the growth trajectory of the fetus, and this helps differentiate between healthy SGA and FGR.[15,16] Doppler flow velocimetry provides information on the resistance to blood flow in the fetoplacental unit and it features in several proposed FGR definitions.[17] High-resistance patterns of flow in the uterine and umbilical arteries in early and mid pregnancy have been associated with an increased risk of preeclampsia, FGR, and stillbirth.[18-22] Other measurements associated with adverse pregnancy outcomes are middle cerebral artery and ductus venosus flow resistance, and cerebroplacental ratio (reviewed elsewhere).[17,18,23]

Biochemical biomarkers for FGR

Abnormal placentation leads to inadequate remodeling of maternal spiral arteries, altered uteroplacental blood perfusion, and impaired materno-fetal exchange of nutrients, gases, and waste products. These defects, collectively referred to as placental insufficiency, are thought to be underlying mechanisms of placentally-related complications including FGR, preeclampsia, and stillbirth. Hence, biochemical markers reflective of placental insufficiency become attractive tools to identify women at risk of these adverse pregnancy outcomes (Figure 1 and Table 1).

First-trimester screening

It is increasingly recognized that placental dysfunction leading to disease in the second half of pregnancy has its origins in the first trimester of pregnancy.[24] Studies of associations have been facilitated by the secondary analysis