Maternal Serum Analytes as Predictors of Fetal Growth Restriction with Different Degrees of Placental Vascular Dysfunction

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KEYWORDS

- Serum analytes • Doppler velocimetry • Placental vascular dysfunction
- Placental pathology • Fetal growth restriction
- Absent or reverse end-diastolic velocity

KEY POINTS

- Abnormal levels of maternal serum analytes have been associated with perinatal complications such as fetal growth restriction (FGR) and preeclampsia secondary to placental vascular dysfunction.
- Placental vascular dysfunction can be assessed by direct and indirect methods, which include abnormal Doppler velocimetry and abnormal placental pathology.
- The ability to accurately predict adverse perinatal outcomes due to placental dysfunction remains elusive.
- A combination of abnormal analytes and absent or reversed end-diastolic velocity of the umbilical artery may identify FGR fetuses at highest risk of adverse outcomes.

INTRODUCTION

Fetal growth restriction (FGR), also referred to as intrauterine growth restriction (IUGR), is a significant cause of fetal and neonatal morbidity and mortality. The term generally describes a fetus that has not reached its growth potential because of fetal, placental, or maternal factors. Accurately identifying the FGR fetuses at highest risk for

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adverse perinatal outcomes remains challenging and is of great importance in prenatal screening and antenatal fetal surveillance. The most common definition of FGR is an estimated fetal weight (EFW) less than the 10th percentile for gestational age. However, this description does not distinguish between fetuses that are constitutionally small and those that are pathologically small because of genetic or environmental factors.[1,2] Although multiple etiologic pathways may result in FGR, they often share a final common pathophysiologic mechanism: impaired uteroplacental blood flow.[3]

Invasion of extravillous trophoblasts into the maternal spiral arteries and decidual stroma is essential for successful placental development and function during pregnancy. Early placental development occurs in a hypoxic environment.[4] Endovascular plugs occlude the spiral arteries and prevent maternal blood flow from entering the intervillous space until 10 to 12 weeks of gestation.[5,6] At this time, the maternal intervillous circulation is established and the intraplacental oxygen concentration increases significantly.[7] Disruption and eventual replacement of the smooth muscle of the spiral arterioles with dilated, inelastic tubes devoid of maternal vasomotor control facilitates a high-flow, low-resistance vasculature.[8,9] In normal pregnancy, this corresponds to a decrease in uterine artery (UtA) resistance throughout gestation.[10]

Placental vascular dysfunction or maldevelopment results from deficient trophoblast invasion and spiral artery remodeling during early gestation. Placental vascular dysfunction leads to persistence of a high-resistance vasculature, impaired placental perfusion, oxidative stress, and ischemia-reperfusion injury.[11] The failure of transition of the UtA vascular bed from the normal high-resistance state to one of low resistance, which occurs in normal pregnancies, is associated with early-onset third-trimester complications of pregnancy and may be evaluated using UtA Doppler.

The degree of placental functional impairment can be described by various methods, including abnormal Doppler velocimetry and abnormal placental pathology. Abnormal umbilical artery (UmbA) Doppler, as indicated by absent or reversed end-diastolic velocity (A/REDV), can identify pathologically small fetuses with a severely compromised placental vasculature.[12,13] Placental pathology specimens from affected pregnancies demonstrate abundant fibrin deposition, dysregulated apoptosis, and sparsely branched, abnormally thin, and elongated vessels within the terminal villi representative of impaired angiogenesis.[14,15] Several pregnancy complications and adverse outcomes are associated with these findings, including FGR, preeclampsia, preterm birth, and pregnancy loss, including intrauterine fetal death (IUFD).[16]

Maternal serum biomarkers are widely used to screen for aneuploidy and open neural tube defects (NTD). Abnormal levels of these analytes have also been associated with placental dysfunction and its associated perinatal complications, as described above, in pregnancies with chromosomally normal fetuses.[17–20] However, no single biomarker or combination of biomarkers currently in use has yet been identified as adequate as a screening tool to predict adverse pregnancy outcomes in a low-risk or unselected population.[21,22] The predictive value of these analytes when used in a high-risk population, or in conjunction with other independent physiologic measures such as Doppler analysis, may prove to be higher. Maternal biochemical markers fundamentally reflect fetoplacental function, including endocrine as well as endothelial dysfunction. Reduced placental size and functional capacity may result in decreased production of pregnancy-associated plasma protein-A (PAPP-A) and unconjugated estriol (uE3). Leakage of other proteins, such as human chorionic gonadotropin (hCG), inhibin A, and α-fetoprotein (AFP), into the maternal circulation in increased quantities may occur secondary to placental hypoxia and apoptosis.