A placenta clinic approach to the diagnosis and management of fetal growth restriction

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Effective detection and management of fetal growth restriction is relevant to all obstetric care providers. Models of best practice to care for these patients and their families continue to evolve. Since much of the disease burden in fetal growth restriction originates in the placenta, the concept of a multidisciplinary placenta clinic program, managed primarily within a maternal-fetal medicine division, has gained popularity. In this context, fetal growth restriction is merely one of many placenta-related disorders that can benefit from an interdisciplinary approach, incorporating expertise from specialist perinatal ultrasound and magnetic resonance imaging, reproductive genetics, neonatal pediatrics, internal medicine subspecialties, perinatal pathology, and nursing. The accurate diagnosis and prognosis for women with fetal growth restriction is established by comprehensive clinical review and detailed sonographic evaluation of the fetus, combined with uterine artery Doppler and morphologic assessment of the placenta. Diagnostic accuracy for placenta-mediated fetal growth restriction may be enhanced by quantification of maternal serum biomarkers including placenta growth factor alone or combined with soluble fms-like tyrosine kinase-1. Uterine artery Doppler is typically abnormal in most instances of early-onset fetal growth restriction and is associated with coexistent preeclampsia and underlying maternal vascular malperfusion pathology of the placenta. By contrast, rare but potentially more serious underlying placental diagnoses, such as massive perivillous fibrinoid deposition, chronic histiocytic intervillositis, or fetal thrombotic vasculopathy, may be associated with normal uterine artery Doppler waveforms. Despite minor variations in placental size, shape, and cord insertion, placental function remains, largely normal in the general population. Consequently, morphologic assessment of the placenta is not currently incorporated into current screening programs for placental complications. However, placental ultrasound can be diagnostic in the context of fetal growth restriction, for example in Breus' mole and triploidy, which in turn may enhance diagnosis and management. Several examples are illustrated in our figures and supplementary videos. Recent advances in the ability of multiparameter screening and intervention programs to reduce the risk of severe preeclampsia will likely increase efforts to deliver similar improvements for women at risk of fetal growth restriction. Placental pathology is important because the underlying pathologies associated with fetal growth restriction have a wide range of recurrence risks. Rare conditions such as massive perivillous fibrinoid deposition or chronic histolytic intervillositis may recur in >50% of subsequent pregnancies. Postpartum care in a placenta-focused program can provide effective counseling for modifiable maternal risk factors, and can assist in planning future pregnancy care based on the pathologic basis of fetal growth restriction.

Key words: angiogenic growth factors, Doppler, fetal growth restriction, pathology, placenta, small for gestational age, ultrasound

Introduction

The concept of a placenta clinic, providing comprehensive medical and surgical care for a wide spectrum of disorders, has developed in several academic centers worldwide over the past 20 years. Success is based on interdisciplinary management in a hospital-based tertiary care environment led by maternal-fetal medicine subspecialists working with nurse practitioners, internal medicine subspecialties and gynecologic surgeons with support from neonatal pediatrics, perinatal pathology, magnetic resonance imaging (MRI), reproductive genetics, obstetrical anesthesia, and perinatal psychiatry. These resources offer an enhanced model of care in the context of suspected fetal growth restriction (FGR), and are especially useful for women with preexisting hypertension, complex obstetrical backgrounds, or other medical comorbidities that place women at higher risk of placental pathology. By placing a focus on the prenatal diagnosis of placental diseases, this approach aids the distinction between a healthy small for gestational age (SGA) fetus and a fetus at risk of perinatal complications due to FGR. Comprehensive electronic medical records are a key component of care, ensuring accurate interpretation of gestational age-dependent ultrasound observations, integration of ambulatory care, and seamless transition into inpatient care, delivery, and postpartum follow-up. Integration of multiparameter screening for FGR is an emerging important component of available software.[1] Clinic-based website resources can also be used to enhance

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TABLE 1
Risk factors for impaired fetal growth

Risk factor	Population	Type of fetal growth impairment	Strength of association (95% CI)
Use of assisted reproductive techniques	Declercq et al,[3] 2015 Longitudinal cohort study N = 334,628 Pregnancies from unselected obstetric population	Low birthweight <2500 g SGA	aOR 1.26 (1.08–1.41) aOR 1.10 (0.96–1.27)
Loss of co-twin	Prömpeler et al,[4] 1994 Retrospective cohort study N = 43 Twin pregnancies with single fetal death	SGA	22% Incidence in surviving twin
Heavy first-trimester vaginal bleeding	Saraswat et al,[5] 2010 Systematic review N = 14 studies included	Low birthweight <2500 g SGA	OR 1.83 (1.48–2.28) OR 1.54 (1.18–2.00)
Increased nuchal translucency	Kumar et al,[6] 2017 Prospective cohort study N = 2168 Unselected singleton pregnancies	SGA	OR 1.72 (1.07–2.77)
Low PAPP-A: <1st percentile, <0.29 MoM Low PAPP-A: <5th percentile, <0.38 MoM Free ß-hCG: <1st percentile, <0.21 MoM	Krantz et al,[7] 2004 Prospective cohort study N = 8012 Pregnancies from unselected obstetric population	SGA	OR 5.4 (2.8–10.3), PPV 24.1% OR 2.7 (CI 1.9–3.9), PPV 14.1% OR 2.7 (1.3–5.9), PPV 14.3%
Low PAPP-A alone: <5% of values for gestational age, <0.4 MoM High AFP: >5% of values for gestational age [>1.7 MoM] and low PAPP-A	Smith et al,[8] 2006 Multicenter prospective cohort N = 8483 Unselected singleton pregnancies in early pregnancy ≤14 wk gestation	SGA	OR 2.8 (2.0–4.0) OR 8.5 (3.6–20.0)
Low PIGF: <5th percentile, <12 pg/mL	Crovetto et al,[1] 2016 Nested case-control study within prospective cohort study N = 9150 Unselected singleton pregnancies	Early-onset FGR <34 wk Late onset FGR ≥34 wk	AUC 0.925 (0.872–0.977) DR 86.4% (85.7–87.1) at FPR 10% AUC 0.761 (0.726–0.796) DR 65.8% (64.8–66.8)
Discrepancy between crown-rump length measurements and accurate menstrual history by 2–6 d	Smith et al,[9] 1998 Retrospective cohort study N = 4229 Healthy unselected singleton pregnancies	Low birthweight <2500 g SGA <5th percentile	RR 1.8 (1.3–2.4) RR 3.0 (2.0–4.4)

AFP, alpha-fetoprotein; *aOR*, adjusted odds ratio; *AUC*, area under curve; *CI*, confidence interval; *DR*, detection rate; *FGR*, fetal growth restriction (<10th percentile due to underlying pathology); *FPR*, false positive rate; *hCG*, human chorionic gonadotropin; *MoM*, multiples of median; *OR*, odds ratio; *PAPP*, pregnancy-associated plasma protein; *PIGF*, placenta growth factor; *PPV*, positive predictive value; *RR*, relative risk; *SGA*, small for gestational age (<10th percentile of birthweight unless range stated otherwise).

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patient understanding of placenta-related diseases.[2]

Diagnostic evaluation in suspected FGR

Review of pregnancy history and prior test results

Fetal growth assessment begins with assignment of gestational age, ideally using ultrasound measurements from the first or early second trimesters. Subsequent biometry data are then used to review the trajectory of growth. Several risk factors for SGA birth or FGR that include the use of assisted reproductive technologies, loss of a co-twin, heavy first-trimester vaginal bleeding, increased nuchal translucency, abnormal screening analyte data, and crown-rump length discrepancy are listed in Table 1.[1,3-9] Accurate dating is essential for establishing the subsequent diagnosis of either a healthy SGA fetus or a fetus with growth restriction.[10] Relevant maternal comorbidities should be noted and addressed, in particular chronic hypertension, diabetes, and elevated body mass index. Prior uterine surgeries are relevant in subsequent planning of mode of delivery. Obtaining a travel history (to Zika virus–affected areas) is also relevant to the evaluation of a suspected