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Uterine and umbilical artery Doppler combined with PlGF assay for placental function

expertise in the assessment of fetal growth restriction: a response

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On behalf of all of our co-authors, we thank Dr’s Carbillon, Benbara, and Fermaut for their keen interest in our work (1). Currently, clinicians working in high-risk pregnancy care have very limited tools with which to infer a specific placental diagnosis for severe preeclampsia or fetal growth restriction (FGR) in the antenatal period. It is well-established that both clinical disorders are strongly associated with abnormal uteroplacental perfusion; our own observations showed bilateral abnormal uterine artery Doppler waveforms in 58% of a cohort of 196 patients with FGR and abnormal umbilical artery Doppler studies. (2) Convincing evidence that these circumstances result in hypoxia-mediated injury to the placental villous trees was elegantly demonstrated in a magnetic resonance oximetry publication from London UK. (3). Case-control studies, such as that cited by Herraiz et al. (4) illustrate the distribution of abnormal secretion patterns of placenta growth factor (PIGF) and soluble fms-like tyrosine kinase (sFLT1) in maternal blood when either preeclampsia or FGR is established, in this publication at a mean gestational age of 27 weeks. Readers should not that Herraiz et al. however did not obtain uterine artery Doppler waveforms in their study, nor did they obtain placental pathology. Therefore, they can only speculate as to the underlying pathologic basis for their findings and for their observed derangements in circulating angiogenic growth factors. They merely describe their subjects as having “early-onset placental dysfunction”. By contrast, the cited publication by Li et al (5) describes the association between uterine artery Doppler waveforms obtained at 23-24 weeks in “high-risk” pregnancies, and again no attempt was made to study placental pathology. Their findings support the sonographic practice of obtaining uterine artery Doppler waveforms, as an adjunct tool to stratify the risk of disease progress and need for iatrogenic preterm birth. Finally, the authors cite the elegant and classic work of Voigt
and Becker (6), who conducted a case-control study of placental biopsies in affected pregnancies and controls, and related their findings to uterine artery Doppler waveforms prior to delivery. Their findings showed a striking association between abnormal uterine artery Doppler and diseased uteroplacental spiral arteries sampled from the mid-portion of the placental bed. One limitation of the study is that they too did not report the gross and histologic findings in the delivered placenta. The University of Milan, Italy group, led by Dr. Enrico Ferrazzi has however contributed significantly to our understanding between abnormal uterine artery Doppler, uteroplacental vascular bed pathology, and the multiple gross and histologic abnormalities that result in the delivered villous placenta. (7) These changes are by consensus now termed maternal-vascular malperfusion (MVM) and they are very strongly associated with both suppressed PlGF and exponentially-elevated sFLT1 as reported by Herraiz et al. (4)

But what is missing from all of these studies, and was the overall goal of our publication, is to fully-integrate angiogenic growth factor testing, uterine artery Doppler and placental pathology, in a longitudinal manner from early pregnancy, in an attempt to provide some insights into the evolution of placenta-disease-specific pathologies. Our original publication on this subject (2) followed by 2 more recent prospective studies (8,9), each demonstrated that MVM is not the sole placental basis for early-onset preeclampsia or FGR – and that two specific pathologies with high recurrence risks, namely chronic histiocytic intervillositis (CHI) and massive perivillous fibrinoid deposition (MPVFD) are associated with normal uterine artery Doppler waveforms. This is the key learning point from our study, as we provide some of the
first evidence that specific placental diseases can be inferred early in pregnancy, in a gestational age window when pathology-specific intervention studies – beyond mere aspirin – could potentially be designed and evaluated. We disagree that our approach, beginning at 16 weeks has no diagnostic/prognostic value. In our study, women being followed for a prior diagnosis of either CHI or MPVFD, with serial very suppressed PlGF levels at < 20 week’s gestation, developed disease recurrence – with normal (i.e., non-predictive) uterine artery Doppler waveforms. Note also that pregnancies ending with two other placental diseases causing normotensive FGR that are also not characterized by placental bed vascular pathology, namely fetal vascular malperfusion and T-cell villitis of unknown etiology (VUE), likewise showed normal uterine artery Doppler waveforms.

In everyday discussions in tertiary care maternal-fetal medicine settings, a majority of high-risk clinicians are not aware of these key concepts in placental disease-specific progression. I encourage the group led by Dr. Carbillon, and others, to study high risk pregnancies in a similar fashion and to always capture placental pathology, to therefore plan clinical care are future research in a pathology-specific manner. Together we can advance the concept of placenta disease-specific clinical care, to the benefit of our patients.
REFERENCES


