Maternal and Uteroplacental Hemodynamics for the Classification and Prediction of Preeclampsia

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Preeclampsia is a major cause of maternal and perinatal mortality and morbidities worldwide, and its etiology remains unknown. The reported incidence of preeclampsia in healthy nulliparous women is approximately 6%, with 93% of cases developing at \( \pm 34 \) weeks gestation.¹

Knowledge about the pathogenesis of preeclampsia has changed significantly over the past decade by virtue of increased recognition of the heterogenous nature of this syndrome. Patients with preeclampsia can present with a wide spectrum of clinical manifestations in the mother and fetus. The degree of maternal hypertension, the amount of proteinuria, and the presence or absence of laboratory abnormalities are highly variable (ranging from mild to severe), with a variable time of onset.² The manifestations of preeclampsia can develop at <34 weeks (early onset), at \( \pm 34 \) weeks (late onset), during labor, or postpartum. Recently, it has been suggested that early and late onset preeclampsia may have different pathophysiology. Early onset preeclampsia is usually associated with fetal growth restriction (FGR) and evidence of ischemic lesions on placental examination, whereas late onset preeclampsia is not usually associated with FGR or ischemic placental lesions.³

Pregnancy is characterized by certain structural and functional changes in the cardiovascular systems that are necessary to accommodate the growing demands of the fetus and placenta. Adequate cardiovascular adaptation during early pregnancy leads to a state of high blood flow and low vascular resistance, which is a prerequisite to successful pregnancy outcome. In contrast, inadequate or excessive cardiovascular adaptation before 20 weeks gestation is associated with pregnancies complicated by gestational hypertension preeclampsia, FGR, or a combination of these.⁴ ⁵ In addition, numerous studies reported the hemodynamic findings in patients with established preeclampsia, however the results were inconsistent. Some studies found a hypodynamic state characterized by high cardiac output (CO) and low systemic vascular resistance (SVR) whereas others found a hypodynamic state characterized by low CO and elevated SVR, and one study reported 7 different hypodynamic models.⁶ ⁷ ⁸ These conflicting results among the various studies are probably related to definition criteria, disease severity, gestational age at onset, presence or absence of FGR, and maternal demographics.⁶ ⁷ ⁸

In this issue of Hypertension, Valensise et al⁹ present novel and important timely data indicating that early and late onset preeclampsia develop from two distinct hemodynamic states. The authors report data from 1688 high-risk nulliparous women who were referred because of the finding of unilateral or bilateral notching of uterine arteries (UA) between 20 to 22 weeks gestation. The patients subsequently underwent UA Doppler and maternal echocardiography evaluation with calculation of total vascular resistance (TVR) and left ventricular geometry at 24 weeks gestation. On follow-up, 1119 (83.2%) had normal pregnancy outcome, 107 (7.95%) had preeclampsia (75 early onset and 32 late onset), and 119 (8.85%) had other maternal or fetal complications (severe gestational hypertension, HELLP syndrome or coagulation abnormalities, abruptio placentae, or FGR). Patients with early onset preeclampsia had significantly higher rates of advanced maternal age and bilateral UA notching and lower gestational age at delivery and lower neonatal weight centile compared to both control and late preeclampsia groups. In contrast, patients with late onset preeclampsia had higher body mass index compared to the other two groups. In addition, patients with early preeclampsia had significantly high TVR and lower CO compared to those with late preeclampsia. Using receiver operator curve analysis, the authors found that a TVR value of \( \pm 1359 \) dyne s cm⁻¹ had a sensitivity of 89.3% and a specificity of 97% for predicting early PE, whereas a value of \( \pm 770 \) had a sensitivity of 87.5% and specificity of 93.4% for predicting late preeclampsia. Moreover, TVR was found superior to BMI in predicting late preeclampsia. Based on these findings, the authors suggested that early preeclampsia is related to abnormal placentation, whereas late preeclampsia is related to maternal factors.

The findings of this study provide important data regarding the clinical value of noninvasive measurements of maternal hemodynamics in predicting early and late onset preeclampsia; however, the results should be interpreted with caution. A major limitation of the study relates to exclusion of 20% of patients after enrollment, and the authors did not provide hemodynamic data on those with other adverse outcome (n=149). This will limit the predictive value of their TVR analysis. In addition, the study subjects were preselected based on the presence of abnormal UA Doppler studies at 20 to 22 weeks gestation, and thus may not apply to all healthy nulliparous women. This could explain the high rates of preeclampsia, particularly early onset (5.6%), which is substantially higher than the 1% rate reported in healthy nulliparous women.
Uterine artery Doppler and maternal hemodynamics at <20 weeks

Normal Doppler
- Normal CO
- Normal SVR
- Normal outcome
- Late preeclampsia
- Late GH
- Early preeclampsia
- Complicated GH
- FGR

Abnormal Doppler
- ↑ CO
- Low or Normal SVR
- Low CO
- ↑ SVR

Figure. Uteroplacental and maternal cardiovascular hemodynamics at <20 weeks and subsequent pregnancy outcome. During normal pregnancy there is systemic vasodilation with increase in CO compared to nonpregnant values. In women destined to develop late onset preeclampsia or GH, there is an exuberant increase in CO. On the other hand, in women destined to develop early preeclampsia, complicated GH, or FGR, there is impaired placentation that results in the release of certain factors leading to vasoconstriction and reduced CO. These changes are dynamic in nature and could change with advanced gestation.

On the other hand, the overall rate of FGR (with and without preeclampsia) in this study was only 3.7%, which is considerably lower than expected for a normal population (10%) and more so for patients with abnormal UA Doppler at 20 to 22 weeks, which casts doubt about the reliability of such a diagnosis.

The studies by Valensise9,10 and others4–7,11 provide valuable data about the dynamic nature of uteroplacental vascular remodeling and maternal cardiovascular adaptations early in pregnancy, and about the pathogenesis of gestational hypertension, preeclampsia, and FGR (Figure). Based on this study and recent reports, it is now evident that evaluation of utero-placental and maternal hemodynamics early in pregnancy may be useful for the prediction of gestational hypertension, preeclampsia (early or late onset), and FGR. In addition, measurements of maternal hemodynamics in patients with established gestational hypertension at 28 to 31 weeks may be useful to predict those who will ultimately progress to preeclampsia and severe hypertension resulting in early preterm delivery.10

The findings of this study9 and those of recent reports4–9 have important clinical implications concerning routine assessment of uteroplacental and maternal hemodynamics very early in pregnancy as a screening tool for the prediction and classification of the various hypertensive disorders of pregnancy and for prediction of FGR. In addition, they provide insight toward future design of targeted preventive therapy based on these hemodynamic results. However, more data are needed to determine the optimal gestational age as well as the best tool for screening. In addition, it is unknown whether ameliorization of altered hemodynamics with various intervention strategies will cause benefit or harm regarding the risks of preeclampsia, FGR, and other adverse pregnancy outcomes. Until then, the use of these tools for screening should remain experimental.

Disclosures
B.M.S. serves as a consultant for Ortho Clinical Diagnostics and Becton Coulter Inc regarding development of markers of preeclampsia.

References
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