OBSTETRICS

Early and late preeclampsia are characterized by high cardiac output, but in the presence of fetal growth restriction, cardiac output is low: insights from a prospective study

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BACKGROUND: Preeclampsia and fetal growth restriction are considered to be placentally mediated disorders. The clinical manifestations are widely held to relate to gestation age at onset with early- and late-onset preeclampsia considered to be phenotypically distinct. Recent studies have reported conflicting findings in relation to cardiovascular function, and in particular cardiac output, in preeclampsia and fetal growth restriction.

OBJECTIVE: We conducted this study to examine the possible relation between cardiac output and peripheral vascular resistance in preeclampsia and fetal growth restriction.

STUDY DESIGN: We investigated maternal cardiovascular function in relation to clinical subtype in 45 pathological pregnancies (14 preeclampsia only, 16 fetal growth restriction only, 15 preeclampsia and fetal growth restriction) and compared these with 107 healthy person observations. Cardiac output was the primary outcome measure and was assessed using an inert gas-rebreathing method (Innocor), from which peripheral vascular resistance was derived; arterial function was assessed by Vicorder, a cuff-based oscillometric device. Cardiovascular parameters were normalized for gestational age in relation to healthy pregnancies using Z scores, thus allowing for comparison across the gestational range of 24—40 weeks.

RESULTS: Compared with healthy control pregnancies, women with preeclampsia had higher cardiac output Z scores (1.87 ± 1.35; P = .0001) and lower peripheral vascular resistance Z scores (−0.76 ± 0.89; P = .025); those with fetal growth restriction had higher peripheral vascular resistance Z scores (0.57 ± 1.18; P = .04) and those with both preeclampsia and fetal growth restriction had lower cardiac output Z scores (−0.80 ± 1.3 P = .007) and higher peripheral vascular resistance Z scores (2.16 ± 1.96; P = .0001). These changes were not related to gestational age of onset. All those affected by preeclampsia and/or fetal growth restriction had abnormally raised augmentation index and pulse wave velocity. Furthermore, in preeclampsia, low cardiac output was associated with low birthweight and high cardiac output with high birthweight (r = 0.42, P = .03).

CONCLUSION: Preeclampsia is associated with high cardiac output, but if preeclampsia presents with fetal growth restriction, the opposite is true; both conditions are nevertheless defined by hypertension. Fetal growth restriction without preeclampsia is associated with high peripheral vascular resistance. Although early and late gestation preeclampsias are considered to be different diseases, we show that the hemodynamic characteristics of preeclampsia were unrelated to gestational age at onset but were strongly associated with the presence or absence of fetal growth restriction. Fetal growth restriction more commonly coexists with preeclampsia at early gestation, thus explaining the conflicting results of previous studies. Furthermore, antihypertensive agents act by reducing cardiac output or peripheral vascular resistance and are administered without reference to cardiovascular function in preeclampsia. The underlying pathology (preeclampsia, fetal growth restriction, preeclampsia and fetal growth restriction) defines cardiovascular phenotype, providing a rational basis for choice of therapy in which high or low cardiac output or peripheral vascular resistance is the predominant feature.

Key words: arterial function, cardiac output, hypertension, pregnancy, vascular resistance

Preeclampsia (PE) is not simply a pregnancy-specific syndrome: its implications on later life cardiovascular[1] and cognitive function[2] and health care cost[3] are only now being understood. Fetal growth restriction (FGR) has a close but poorly understood relationship with PE. Although PE and FGR frequently present in isolation, they may occur together, particularly at early gestation.[4]

The underlying pathophysiology of PE has never been fully understood, but the cause has often been attributed to the placenta because PE resolves completely after delivery. Inadequate trophoblast invasion leading to uteroplacental malperfusion is thought to underlie both PE and FGR.[5,6] However, this placental theory does not explain why women who had PE in their pregnancies have a higher cardiovascular risk in later life[7-9] or why women with prepregnancy cardiovascular risk factors have a higher risk of PE and FGR in pregnancy.[10]

Emerging data suggest that maternal cardiovascular function is impaired after delivery in women with PE,[11,12] and high blood pressure prior to pregnancy increases the risk of PE developing.[10] Nevertheless, PE and FGR are commonly referred to as placenta-mediated disorders, suggested to arise through defective placentation.

Studies of cardiovascular function in pregnancy have shown inconsistent and, in some cases, contradictory results. The classic studies of Easterling et al[13] suggested that PE was associated

Cite this article as: Tay J, Foo L; Masini G, et al. Cardiac output in preeclampsia is associated with the presence of fetal growth restriction, not gestation at onset: a prospective cohort study. Am J Obstet Gynecol 2017;xxx:xx-xx.

0002-9378/$36.00

https://doi.org/10.1016/j.ajog.2018.02.007

AJOG at a Glance

Research question: why was this study conducted?

To resolve the unanswered questions as to the precise hemodynamic changes in pregnancies complicated by preeclampsia, fetal growth restriction, and the combination of the 2 and whether gestation at onset determines these changes.

Key Findings

In preeclampsia, cardiac output is high and peripheral resistance low. In fetal growth restriction with preeclampsia, the opposite is true, and in growth restriction, there is increased peripheral resistance. Arterial function is abnormal in all cases.

What does this add to what is known?

Preeclampsia and fetal growth restriction are associated with distinctly different and opposing cardiovascular phenotypes that are not related to gestation of onset. These findings may be important in monitoring maternal and fetal condition and guiding therapy.

with a high cardiac output (CO) state, although this relationship was thought to be explained, at least in part, by the increased body surface area.[14] Other studies have suggested that PE should be subdivided into those in which low or high CO is predominant.[15]

FGR with and without PE have a different cardiovascular profile[16,17] although the relationship of these changes to a healthy pregnancy or PE without FGR has not been studied. A recent systematic review concluded that studies of cardiovascular function in gestational hypertension and PE show conflicting results. The authors concluded that "increased peripheral vascular resistance correlates with disease severity," but of note, the coexistence of FGR was not considered in a majority of the studies.[18]

Previous studies on cardiovascular function in PE have incompletely characterized FGR,[19] recruited only within a particular gestational range[16] and/or not compared findings with a healthy reference pregnant population.[20] Existing studies provide interesting insights to cardiovascular dysfunction in pathological pregnancies but leave important questions unanswered in relationship with gestational effects and pregnancies in which PE and FGR are combined.

Over the last 2 decades, it has become customary to subdivide PE into early and late variants with an arbitrary 34 week gestational age cutoff. This distinction arose not because of a pathophysiological difference between the conditions but because of the inability of screening by uterine artery Doppler to effectively identify cases of late-onset disease.[21-23] It is suggested that early and late variants have different underlying vascular characteristics, although in most studies, late PE is rarely or never associated with FGR.[20] Adding further complexity, recent studies have suggested that PE at term is associated with babies with larger birthweight.[14]

We sought to investigate the relationship between cardiovascular function and clinical phenotype of PE and FGR alone and in combination across a gestation range, with cardiac output being the primary outcome measure. Cardiovascular function changes with gestational age, therefore, to allow comparison, we transformed all data in relation to that obtained from women with healthy pregnancies using the statistical technique of Z scoring. This removed the need for a gestation-matched cohort design and allowed all data points to be considered.[19] In doing so, we performed comprehensive hemodynamic assessments from 24 weeks' gestation onward in women with healthy pregnancies, with PE in combination with FGR (PE and FGR), PE without FGR (PE only), and FGR without PE (FGR only), managed and monitored in a single maternity unit.

Materials and Methods

Study protocol

In this prospective cross-sectional study, women between weeks 24 and 40 of pregnancy were recruited from the antenatal clinic, labor ward, day assessment unit, and antenatal ward of a tertiary-level London teaching hospital between January 2015 and May 2017. The study protocol was approved by National Health Service National Research Ethics Committee, London Riverside, and all participants gave written informed consent. Gestation of pregnancy was determined by measurement of crown-rump length between 11 and 13 weeks in early pregnancy.

Women were recruited at presentation or diagnosis where it was feasible to conduct a detailed cardiovascular examination and were not included if they were already in labor, undergoing induction of labor, or imminent delivery was planned (Figure 1). We describe the diagnosis as those with PE alone (PE only), FGR alone (FGR only), and PE together with FGR (PE and FGR). Women's assessments are reported at the time of initial diagnosis of 1 of these conditions, and the diagnosis assigned at the time of study inclusion.

One hundred seven healthy person observations acted as control cases with no control subject assessed twice within the same epoch. PE was defined as blood pressure at diagnosis of >140/90 mm Hg and urine protein creatinine ratio of >30.

FGR was defined as fetal abdominal circumference or estimated fetal weight <10th centile[24] and umbilical Doppler PI >95th centile on ultrasound scan.[25] Those women with known underlying cardiovascular conditions, multiple pregnancies, and fetal anomalies were excluded from the study.

Participants underwent peripheral blood pressure measurement, comprehensive cardiovascular assessments, and fetal ultrasound scans as detailed in the following text.

Cardiovascular assessments

Participants were requested to abstain from caffeinated drinks for 4 hours before the visit. In brief, cardiovascular