Intergenerational Factors
A Missing Link for Preeclampsia, Fetal Growth Restriction, and Cardiovascular Disease?

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Preeclampsia and fetal growth restriction (FGR) are 2 obstetric syndromes that are generally associated with increased perinatal and maternal morbidities. Preeclampsia is defined as the onset of hypertension and proteinuria after 20 weeks gestation, and it complicates $\approx$3% to 5% of all pregnancies. FGR is defined as a birth weight below the fifth or 10th percentile for gestational age, and it can develop alone or in association with preeclampsia. Preeclampsia and FGR share similar pathophysiologic abnormalities, such as reduced uteroplacental blood flow, exaggerated inflammatory response, endothelial cell dysfunction, and a state of imbalance between proangiogenic and antiangiogenic factors. These pathophysiologic abnormalities are presumed to be the result of a cascade of events secondary to shallow trophoblast invasion and defective remodeling of the uterine spiral arteries. However, the etiologies of preeclampsia and FGR are multifactorial, and only FGR and preeclampsia related to placental insufficiency probably share abnormal placentation as a common pathway.

Pregnancies complicated by preeclampsia are associated with increased rates of FGR. Women with a history of preeclampsia in a previous pregnancy are also at increased risk for preeclampsia and/or FGR in subsequent pregnancies. The magnitude of the above risks depends on gestational age at onset of preeclampsia in the index pregnancy (the earlier in gestation the onset of preeclampsia, the higher are the rates of FGR and recurrent preeclampsia). In addition, women who are born fetal growth restricted are at increased risk of severe preeclampsia and FGR when they get pregnant, and they are at increased risk for cardiovascular disease later in life (fetal origin of adult disease).

During the past decade, several epidemiologic and case-control studies evaluated the association between preeclampsia and the development of cardiovascular disease in later life. These studies were the subject of a recent systemic review and meta-analysis that revealed a relative risk for chronic hypertension of 3.70 after 14.10 years average follow-up, a relative risk of 2.16 for ischemic heart disease after 11.70 years of follow-up, and a relative risk of 1.81 for ischemic stroke after 10.4 years of follow-up. In addition, the overall mortality after preeclampsia was increased by a relative risk of 1.49 after 14.5 years of follow-up. In a related study, Ray et al assessed cardiovascular health after maternal placental syndromes among 75 380 women whose pregnancies were complicated by preeclampsia, abruptio, or placental infarction, as evidenced by FGR. The outcome in these women was compared with that of women whose pregnancy was not complicated by these syndromes. The authors found that the risk of premature cardiovascular disease (median duration of follow-up: 8.7 years) is increased after maternal placental syndrome, particularly in the presence of poor fetal growth or in the presence of preexisting features of the metabolic syndrome before the index pregnancy. Recently, Magnussen et al examined the effect of cardiovascular risk factors before pregnancy on the risk of preeclampsia in 3494 women, of whom 133 (8.8%) developed preeclampsia. After adjustment for several confounding variables, the authors found positive associations between prepregnancy serum levels of triglycerides, cholesterol, low-density lipoprotein cholesterol, baseline systolic blood pressure, and subsequent development of preeclampsia. They concluded that women with prepregnancy risk factors for cardiovascular disease are predisposed to preeclampsia.

The mechanisms accounting for the relationship among preeclampsia, FGR, and the increased risk of subsequent cardiovascular disease and ischemic stroke in women having these complications are unclear. Suggested mechanisms have included the possibility that the development of these obstetric complications cause permanent metabolic or vascular disturbances in the mother that will ultimately result in cardiovascular complications. Alternatively, these women could have preexisting risk factors or genetic/environmental factors that predispose them to develop preeclampsia or FGR during pregnancy, and the same factors may also predispose these women to develop cardiovascular disease later in life.

Berends et al conducted an intergenerational case-control study comparing cardiovascular risk profiles among 3 groups of women and their parents at a median follow-up of 7.1 years after pregnancy. The study groups were white Dutch women whose pregnancies were complicated by preeclampsia or FGR (n=106), as well as their fathers (n=43) and mothers (n=64), and a control group of women who had normal, term pregnancies (n=106), as well as their fathers (n=51) and their mothers (n=68). Study participants and their parents underwent measurements of fasting lipids, glucose levels, body mass index (all subjects), anthropometrics, blood pressure, and intima-media thickness measurements, as well as prevalence of metabolic syndrome (women and their mothers only).
The Dutch study revealed that the prevalence of chronic hypertension was significantly higher among formerly pre-eclamptic women (46.7%) and in women with FGR pregnancies (26.9%) as compared with control women (8.9%). Women with pre-eclampsia and FGR who had chronic hypertension on follow-up also had an increased intima-media thickness, suggesting a link to atherosclerosis. Similar findings were found in mothers of women whose index pregnancies were complicated by preeclampsia or FGR; however, the results were not different because of limited sample size. In addition, they found that women with previous pre-eclampsia had significantly higher body mass index, waist circumference, fasting glucose levels, and higher prevalence of metabolic syndrome compared with control women. In contrast, women with FGR pregnancies had only elevated fasting glucose levels compared with control women. Moreover, fasting glucose levels, waist circumference, and prevalence of metabolic syndrome were significantly higher among mothers of formerly pre-eclamptic women as compared with the control group. No such differences were found for mothers of women with FGR pregnancies. Finally, only fasting glucose levels were significantly higher in fathers of both study women as compared with fathers of control women.

The findings of this study are remarkably similar to previous reports on this topic and provide further support for the increased risk of cardiovascular complications later in life in women whose pregnancies are complicated by preeclampsia and/or FGR. In addition, it is the first to assess maternal intergenerational risk profiles to explain the association among preeclampsia, FGR, and predisposition to subsequent cardiovascular disease. A major weakness of the study relates to the lack of information about thrombophilia, because this risk factor predisposes these women to preeclampsia, FGR, and cardiovascular disease. In addition, they did not collect information regarding birth weight status of the study women (whether they had FGR), parity (whether the index is a first pregnancy), and the presence of a previous preeclampsia or FGR before the index pregnancy. In addition, their case-control design does not allow us to control for the substantial loss to follow-up among the women and their parents, and it does not allow for adjustment to environmental exposures after the index pregnancy that might adversely affect the development of the metabolic syndrome and hypertension among the women and their parents. Failure to adjust for the above factors could have overestimated the strength of the association among preexisting genetic predisposition, pre-eclampsia, FGR, and cardiovascular complications. Finally, the population studied is fairly racially (white) and socioeconomically homogenous, with access to free health care, which might not be applicable to populations with diverse race or ethnicity without universal access to health care, similar to these seen in other countries.

Based on this study and recent reports, it is now clear that several genetic, environmental, and socioeconomic risk factors have already been established before conception that will ultimately play a central role in the development of certain obstetric complications (preeclampsia, FGR, or abruptio), as well as in the development of cardiovascular disease later in life. However, several questions remain unanswered by this and previous studies. Should all women of reproductive age be screened for cardiovascular risk factors before conception? If the results are positive, what should the clinician do with this information? It is unknown whether attenuation or elimination of these risk factors with treatment before conception will reduce the risks of preeclampsia or FGR. Some authors suggest that women with preeclampsia and FGR should be screened for risks of cardiovascular disease at 3 to 6 months postpartum, and, if positive, they should be enrolled in early intervention and treatment programs to prevent cardiovascular complications. However, there are no published studies that tested these recommendations. Thus, future research is needed to identify which patients may benefit from routine screening and what screening methods to use. Finally, there is an urgent need to conduct randomized trials to evaluate the benefits of various interventions before conception and/or 6 months postpartum.

Disclosures
None.

References