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Cytotrophoblast cells from the placenta invade the maternal spiral arteries during normal pregnancy. This results in a striking increase in luminal diameter and causes the vessels to lose their smooth muscle enabling the expansion of vascular capacity necessary to support fetal growth. Preeclampsia, growth restriction, recurrent abortion, and preterm birth in many cases are caused by abnormal implantation with failure of this process. Of these implantation abnormalities, preeclampsia is well known to be associated with later life cardiovascular disease.^{1,2} Furthermore, several persistent metabolic and cardiovascular differences are present in women with preeclamptic compared with normal pregnancies. The data relating the other implantation disorders to later life cardiovascular diseases are less compelling. It is possible, however, in large population studies, to document increased cardiovascular mortality in women with pregnancies complicated by these disorders.^{1,3}

In this issue of *Hypertension*, Germain et al⁴ clearly demonstrate that similar abnormalities of endothelial function are present 11 to 27 months postpartum in women who had previous pregnancies complicated not only by preeclampsia but also by recurrent abortion. There is reduced flow-induced endothelial-mediated vasodilatation, reduced circulating NO, and higher cholesterol in both groups. They present the reasonable conclusion that endothelial dysfunction may predispose to abnormal implantation and incomplete placental bed vascular remodeling.

This is counter to an idea that I have previously advanced, including in a recent review in this journal.⁵ The concept of a 2-stage model of preeclampsia with the first stage being abnormal implantation and placental bed vascular remodeling and the second the maternal syndrome was presented. In it, it was posited that abnormal implantation was insufficient to explain the linkage of the 2 stages and that it was the "maternal constitution" interacting with the reduced placental perfusion that resulted in preeclampsia. Although the figure presenting the model (Figure) included a connection between the maternal constitution and abnormal implantation, this was largely to explain the impact of thrombophilias on placenta-

tion. It is clear in the presentation that the metabolic and vascular changes of the mother were proposed to have their impact exclusively by rendering the mother sensitive to the effects of reduced perfusion with resulting preeclampsia. Given the data from Germain et al,⁴ the model advanced previously may be both incorrect and correct.

The demonstration of abnormal endothelial function in women with recurrent abortion, as well as the previously recognized association of growth restriction, preterm birth, and abortion with an excess of cardiovascular disease in later life supports the concept that whatever increases the risk of later life cardiovascular disease also increases the risk of implantation abnormalities. Germain et al⁴ suggest that this abnormality is endothelial dysfunction leading to failed vascular remodeling. Although the causality of endothelial dysfunction is a reasonable suggestion, there are a plethora of metabolic differences that have been demonstrated in formerly preeclamptic women, including increased insulin resistance, elevated triglycerides, increased apolipoprotein B, and small dense low-density lipoprotein⁶ that were not tested in the women with recurrent abortion in this study. As devil's advocate it is also important to point out that there is no guarantee that the recurrent abortion or preeclampsia did not cause the resultant endothelial dysfunction rather than the converse. The authors of the article make the point that they were testing the relationship of the abnormal endothelial function to recurrent abortion to avoid the possibility that the vascular changes of preeclampsia would cause residual endothelial damage. They felt that this would not happen with recurrent abortion. This is reasonable, but again there is no evidence that it is true. It is also possible that a normal pregnancy improves cardiovascular function as indicated by increased stroke volume that persists after normal pregnancy and is further increased (and persists) with a subsequent pregnancy.⁷ Nonetheless, the suggestion that abnormal implantation is associated with cardiovascular and perhaps metabolic antecedents is well supported by the findings of the group. From that perspective, the model presented in this article was incorrect. However, there are differences found in the study by Germain et al⁴ between the women with former preeclampsia and those with previous recurrent abortion that support the contention that there are maternal characteristics that predispose the abnormal implantation to lead to the maternal syndrome of preeclampsia. The women with previous preeclampsia persisted with higher (but normal) blood pressure than either women with previous normal pregnancies or with recurrent abortion. Likewise, there was an excess of cardiovascular disease in the fathers of women with a history of preeclampsia. Thus, it does appear that the translation of reduced placental perfusion to the preeclampsia

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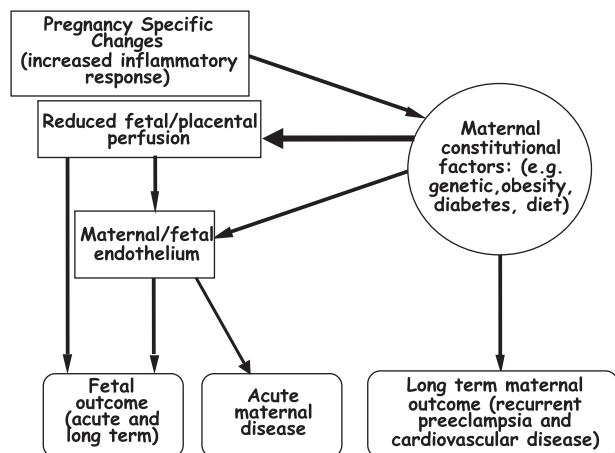
From the Magee-Womens Research Institute (J.M.R., F.V.V.-H.) and the Department of Obstetrics Gynecology and Reproductive Sciences (J.M.R., F.V.V.-H.) and Epidemiology (J.M.R.), University of Pittsburgh, Pa.

Correspondence to James M. Roberts, Magee-Womens Research Institute, 204 Craft Avenue, Pittsburgh, PA 15215. E-mail RSIJMR@mwri.magee.edu

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Maternal fetal/placental interactions in preeclampsia. Maternal constitutional factors, such as endothelial dysfunction, lead to abnormal remodeling of maternal vessels with subsequent reduced placental perfusion. The development of the maternal syndrome of preeclampsia requires that reduced placental perfusion interact with maternal factors. These constitutional factors are the maternal characteristics that increase the risk of cardiovascular disease in later life. They are modified by the physiological changes of pregnancy.

syndrome and the abnormal implantation may both be dictated by features of the maternal constitution but not necessarily the same factors.

This new interpretation of the role of the maternal constitution in implantation diseases raises 2 interesting questions. First, what are the differences between women with abnormal implantation that result or do not result in a maternal syndrome of preeclampsia? Second, how do maternal constitutional differences and, for the purposes of discussion of the article by Germain et al,⁴ endothelial dysfunction, result in abnormal implantation and failed vascular remodeling of the placental bed vessels?

Uterine artery Doppler velocimetry in the second trimester is useful to predict preeclampsia, intrauterine growth restriction, and preterm birth.⁸ The abnormal Doppler pattern is interpreted to indicate increased distal resistance secondary to failed placental bed vascular remodeling. It is interesting that not only are these implantation disorders predicted by the abnormal Doppler findings but that $\approx 50\%$ of the women with this finding go on to normal pregnancy outcome. Yet, even in women with abnormal Doppler findings and normal outcomes, there are measurable differences from women with normal uterine artery velocimetry. Women with abnormal Doppler velocimetry have an excess of low plasma ascorbate concentrations,⁹ increases in the concentration of the NO antagonist asymmetrical dimethylarginine,¹⁰ and increased frequency of an activating autoantibody for the angiotensin I receptor¹¹ that are present more frequently in women with preeclampsia. These are present regardless of outcome. Thus, not only does reduced placental perfusion not always result in preeclampsia, these data suggest that perfusion may be reduced and still be associated with normal pregnancy outcome. An interesting and important question is what determines the impact of reduced perfusion in a specific pregnancy? Also where do the physiological abnormalities

diverge to result in different outcomes? Perhaps studying women with Doppler evidence of reduced placental perfusion could help determine the sequence of the abnormalities present in preeclampsia: metabolic changes, inflammation, endothelial dysfunction, and so forth. Which of these are necessary and which are sufficient for the several implantation disorders? Relevant to the article by Germain et al,⁴ is reduced placental perfusion associated with later life cardiovascular disease even when associated with normal pregnancy outcome?

If abnormal endothelial function is the deficit resulting in failed remodeling, is there a logical mechanism? Endothelial progenitor cells are reduced in preeclampsia.¹² These cells are also reduced with increasing cardiovascular risk and are felt necessary for endothelial health. As advanced by Gammill et al,¹² it is possible that a deficiency of these cells could result in failed vascular remodeling.

Although more questions are presented than answers provided, the insights from this study and the questions raised by them direct us toward a new understanding of the relationship of adverse pregnancy outcome and cardiovascular disease.

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