In this issue of Hypertension, Rasmussen and Irgens provide strong support for the relationship of preeclampsia and intrauterine growth restriction (IUGR). They also provide data that support but also some that argue against the concept that the pregnancy complication, preeclampsia, may be more than one disease. In previous studies these authors demonstrated that women who had a growth-restricted infant without preeclampsia are more likely to have preeclampsia in a subsequent pregnancy.

Those data and similar findings in the current study support pathological findings indicating the similarity of IUGR and preeclampsia. In preeclampsia, IUGR and interestingly also in about one third of cases of preterm birth, the maternal myometrial and decidual vessels perfusing the placental site do not undergo the normal remodeling of pregnancy. In normal pregnancy trophoblastic invasion is associated with a greatly increased diameter and removal of vascular smooth muscle from the wall of these vessels. This results in large diameter, flaccid, unresponsive tubes that greatly increase placental perfusion. These changes are not present in pregnancies complicated by IUGR, preeclampsia, and some with preterm births. Implicit in the current study is the concept that preterm birth as well as IUGR is related to subsequent preeclampsia. Although preterm birth is not assessed directly, the effect of low birth weight (IUGR and preterm birth) was greater than the effect of IUGR alone. In a far smaller study our group was able to more directly support the relationship of preterm birth and preeclampsia, as women with early onset preeclampsia were more likely to have preterm birth in a subsequent nonpreeclamptic pregnancy.

The current study extends the prior observation of the relationship of IUGR and preeclampsia but also raises other interesting points. In this larger study the authors were able to determine a “dose response” for reduced growth, demonstrating that the smaller the baby the greater the odds ratio for a subsequent pregnancy with preeclampsia. Although this is what might be expected, what is not as straightforward was the fact that small babies increased the risk of early onset and severe preeclampsia more than they increased the risk for “mild” preeclampsia occurring at the end of pregnancy. This difference in the effect on different degrees of IUGR supports numerous observations suggesting that early onset preeclampsia may be a different disease than preeclampsia occurring at term. There are abundant epidemiological observations indicating differences in recurrence rates and relationship to later life cardiovascular disease. The authors of the current manuscript previously examined the database used in this study to test the relationship of preeclampsia to later-life cardiovascular mortality. A median of 14 years after a first pregnancy, women with preeclampsia before 37 weeks gestation had 8 times more cardiovascular deaths than women with normal pregnancy. For women with preeclampsia at term, the increase was only 1.7-fold. The likelihood that preeclampsia will recur is almost 60% for early onset preeclampsia, whereas it is 10% to 20% for preeclampsia near term.

Pathophysiological markers are also different. For example, antiangiogenic factors are much better predictors of early onset preeclampsia than late onset disease. Also, whereas early preeclampsia is associated with an excess of small babies, late onset does not share that relationship and there is actually an excess of larger babies. The data presented in the current Rasmussen study support a concept that early preeclampsia is associated with reduced placental perfusion and is a different disease than preeclampsia at term in which reduced perfusion may not be a major component (Figure, Panel 1). The authors suggest this may indicate a different genetic origin for the disorder that occurs early and late.

Their data, however, also support an alternative explanation. Several years ago we expanded on a concept introduced by the Oxford Group that preeclampsia was a 2-stage disorder. The first stage was proposed to be reduced placental perfusion, and the second the maternal response to this reduced perfusion. In this model reduced placental perfusion could result in IUGR or preterm birth (or both) but the maternal syndrome of preeclampsia would only occur in women in whom “constitutional factors” (genetics, behavior, environment, etc) rendered the mother sensitive to the effects of reduced placental perfusion. The findings in the Rasmussen study also provide support for this hypothesis. In this study it appears that such constitutional factors might evolve over time. At the time of the first pregnancy these constitutional factors were not sufficient to cause maternal disease in response to reduced placental perfusion, only IUGR or preterm birth resulted. However, by the time of the second pregnancy maternal constitutional factors were sufficient to result in preeclampsia. This progression of maternal sensitivity to reduced perfusion is supported by the finding that the relationship of IUGR to subsequent preeclampsia increased with lengthening interpregnancy interval. Further support for the role of maternal genes and constitution was the observation that it was only the mother and not the father who conferred the risk of preeclampsia to a second pregnancy.

This model of maternal fetal interaction provides an alternative explanation for the heterogeneous presentation of preeclampsia early and late other than 2 different diseases. The
Figure (panel 2) indicates preeclampsia as one disease with different manifestations depending on the relative contribution from maternal constitution and reduced fetal placental perfusion. Thus, profoundly reduced perfusion (A) results in preeclampsia in virtually any woman and would be accompanied by IUGR. Lesser degrees of reduced perfusion (B) might result in IUGR with or without preeclampsia depending on the maternal constitution whereas in the profoundly sensitive woman minimally reduced perfusion (or perhaps merely the results of normal perfusion) are sufficient to lead to preeclampsia (C).

Which is the appropriate model? We would suggest both. The genesis of reduced perfusion is very different than what might cause the posited increased response to reduced perfusion. From a genetic perspective, maternal and fetal (paternal) genes contributing to reduced placental perfusion are likely quite different than those rendering the woman sensitive to the putative results of reduced perfusion. Interestingly, many of these maternal constitutional factors or genetic factors that increase the risk of preeclampsia, eg, obesity, lipid abnormalities, black race, and metabolic syndrome are also risks for later life cardiovascular disease. The data in the current study indicate a further level of complexity. In this study early onset preeclampsia, the variety of preeclampsia most associated with later life cardiovascular disease, is the form best predicted by IUGR, the marker of reduced perfusion. It appears that not only are the constitutional factors associated with the maternal response but that they may also be associated with abnormal implantation, failed vascular remodeling, and reduced placental perfusion. Preterm birth without preeclampsia in work by the same group predicts cardiovascular disease better than term preeclampsia. In addition, habitual abortion associated with similar abnormalities of placental bed vascular remodeling but with no maternal syndrome of preeclampsia is also associated with abnormal endothelial function long after delivery. These data suggest that at least some of the constitutional factors leading to the maternal preeclampsia syndrome in response to reduced placental perfusion can also contribute to reduced perfusion.

Is the identification of subtypes of preeclampsia important? We would suggest it is vitally important. Whether the differences are qualitative or quantitative the finding in this and other studies suggest the same end point can be reached by different routes. This concept is supported by the consistent observation that whatever linkage between reduced perfusion and maternal disease is suggested, eg, oxidative stress, excess antiangiogenic factors, increased endogenous antagonists of nitric oxide, or autoantibodies that activate the angiotensin II receptor type 1, none of these is increased in all preeclamptic women. We would urge investigators to be cognizant of this (as are the authors of the Rasmussen article) and to look for and pay attention to differences in logical subsets of preeclamptic women. Analogous to diabetes, a disorder originally ascribed solely to one cause, insulinopenia, progress in understanding, preventing, and treating preeclampsia would be enormously aided by the identification of subsets of disease, which take a different pathway to a fairly nonspecific diagnosis of new onset hypertension in pregnancy.

Sources of Funding

Support for this work was funded by NIH P01 HD30367.

Disclosures

None.

References
