Preeclampsia is a pregnancy-specific disorder that presents major health problems for mothers and their babies. It is a major cause of maternal mortality, especially in developing countries, where it may account for 80% of maternal deaths.1 Even in developed countries, perinatal mortality is increased 5-fold. The last figure is especially tragic. Many of these infant deaths are secondary to iatrogenic prematurity, because the management remains as it has for the last 100 years (early delivery to terminate the process). Understandably, preeclampsia has been a major target of research to improve pregnancy outcome, yet it remains an enigmatic “disease of theories.” Nonetheless, in the last 10 years, an approach to understanding the disorder that addresses features other than simply the accompanying hypertension has rapidly accelerated understanding.2 In this issue of Circulation, Dechend and colleagues3 present another in their fascinating series of observations demonstrating that preeclamptic women manifest agonistic antibodies to angiotensin-1 (AT1) receptors. They demonstrate that these antibodies have the capability to activate the production of tissue factor by vascular smooth muscle cells in vitro. How does this observation fit into emerging concepts of the pathogenesis of preeclampsia?

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Eclampsia was described nearly 2000 years ago as seizures occurring during pregnancy that abated with delivery. It was not until the turn of this century that it was recognized that increased blood pressure and proteinuria accompanied, and in most cases preceded, eclampsia, hence “preeclampsia.”4 With this recognition, it was rapidly evident that these signs, even unaccompanied by seizures, signaled a disorder that could rapidly progress to maternal and fetal morbidity and mortality. Despite the value of these signs in aiding in recognition of the syndrome, it is abundantly evident that preeclampsia is more than “pregnancy-induced hypertension.” The pregnant woman with preeclampsia manifests alterations in many organ systems. Vasospasm, activation of the coagulation cascade, and reduced intravascular volume secondary to increased endothelial permeability lead to reduced perfusion to virtually all maternal organs, including the uterus, intervillosus space, and placenta.1 A common denominator in these abnormalities appears to be altered endothelial function that can be demonstrated functionally and by blood-borne markers months before clinically evident preeclampsia.5

Pregnancy is required for preeclampsia, but what is the responsible feature of pregnancy? Preeclampsia could be secondary to the presence of a distended uterus, characteristic of pregnancy, but this does not seem likely. Preeclampsia can occur with abdominal ectopic pregnancy. In this setting, the uterus is not markedly distended, because the fetus develops outside of the uterus.6 The presence of a fetus is also not necessary. Preeclampsia can occur, and is actually more common, in the pregnancy disorder hydatidiform mole, in which there is virtually no fetal tissue. Thus, the important pregnancy component appears to be the placenta. However, all pregnancies have placentas, yet preeclampsia occurs in only 5%. What is unique about the placenta? Page,6 60 years ago, championed the idea that reduced placental perfusion was this unique feature. He pointed out that obstetric conditions with large placental mass, such as hydatidiform mole and multiple gestations, were associated with an increased risk for preeclampsia. He posited that this was secondary to a relative reduction in placental perfusion due to the inability of the maternal vascular system to adequately perfuse this large placental mass. Further evidence was the increased incidence of preeclampsia in women with underlying medical conditions with attendant microvascular disease, such as hypertension and collagen vascular disease.1 The most compelling evidence, however, was the abnormal placental implantation characteristic of preeclampsia. Normal pregnancy leads to a striking adaptive modification of the uterine vessels that supply the placenta. The uterine spiral arteries, typically small muscular arteries in nonpregnant women, are modified to flaccid nonmuscular tubes with a diameter 4 to 5 times that present before pregnancy. There is no vascular smooth muscle and no inner elastic lamina. The vessels are no longer lined by maternal endothelium but rather by fetal trophoblasts that express endothelial antigens.7 This remarkable physiological adaptation does not occur in preeclampsia, strikingly reducing the perfusion of the placenta.8 Investigations of this modification indicate anomalies of the invasive properties of fetal trophoblastic cells in women with preeclampsia.1,7 This failure of the admixture of fetal and maternal cells in preeclampsia suggests that immune mechanisms that ordinarily allow the intimate associations of 2 different genotypes (maternal and fetal) are not operative in preeclampsia.

Epidemiological features of preeclampsia suggest an interesting immunologic mechanism in which prior exposure to

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**Angiotensin-1 Receptor Autoantibodies**

**A Role in the Pathogenesis of Preeclampsia?**

James M. Roberts, MD

Epidemiological features of preeclampsia suggest an interesting immunologic mechanism in which prior exposure to
paternal antigen is protective. Preeclampsia is most common in first pregnancies; the relative risk of preeclampsia is reduced by >50% after first pregnancy.9 If a new individual fathers subsequent pregnancies, the risk is intermediate,9 whereas exposure to paternal antigen through intercourse, either by a longer time of sexual exposure with the father before pregnancy or the use of nonbarrier contraceptives, reduces risk.10,11 Current thinking favors the concept that this immunologic contribution to the pathogenesis of preeclampsia has its impact primarily on implantation. In this model, the increased frequency of preeclampsia in first pregnancy is secondary to immunologically mediated abnormal implantation resulting in reduced placental perfusion. This deficit is “cured” by paternal antigen exposure during the first pregnancy. The demonstration of function-perturbing autoantibodies in the blood of women with preeclampsia by Dechend and associates3 challenges this concept.

One of the major considerations in deciphering the pathogenesis of preeclampsia is determining how reduced placental perfusion can result in the maternal systemic syndrome. Any explanation must also account for preeclampsia being largely a disease of first pregnancies. Furthermore, hypotheses must take cognizance of the fact that although reduced placental perfusion is believed to be necessary for preeclampsia, it is certainly not sufficient. Identical implantation abnormalities are present in the placental bed of women with growth-restricted infants (without the maternal syndrome) and in one third of pregnancies terminating with preterm birth.8,12 These facts have led to the concept that the “maternal constitution” (genetic, behavioral, or environmental) must interact with the facts have led to the concept that the “maternal constitution” (genetic, behavioral, or environmental) must interact with the reduced placental perfusion for the maternal syndrome to occur. Several investigators have suggested that this interaction could be explained by the maternal and fetal/placental factors converging to generate oxidative stress.13 This hypothesis posits that reduced placental perfusion, perhaps through hypoperfusion reperfusion mechanisms, generates reactive oxygen species. The consequences of the generation of these moieties are determined by the maternal antioxidant status and by the availability of target substrates (eg, small, dense LDL present in excess in women with preeclampsia.)14 There is abundant evidence of oxidative stress in women with preeclampsia, and in a recent small trial, antioxidant therapy from midpregnancy ameliorated signs of endothelial activation.13,15 Thus, this hypothesis proposes that the mother’s phenotype influences whether reduced placental perfusion leads to the maternal syndrome. The first-pregnancy predominance is related to immunologically mediated reduced perfusion that is associated with first pregnancies.

Do the agonistic angiotensin antibodies identified by Dechend and associates offer an alternative linkage between reduced placental perfusion and the maternal syndrome? In a prior presentation, they demonstrated the presence of autoantibodies to the AT1 receptor by bioassay and Western blotting.16 In the current presentation, they strengthen and extend this observation.3 They demonstrate reciprocal immunoprecipitation by commercial AT1 receptor antibodies and the putative autoantibodies from preeclamptic women. The finding that these antibodies can target vascular smooth muscle angiotensin receptors to activate tissue factor is consistent with the activation of the coagulation cascade that is characteristic of preeclampsia. The blockade of responses by AT1 receptor antagonists and the similarity of the signal-transduction pathway further support the agonistic nature of this IgG.

There are numerous other functions of AT1 receptors relevant to preeclampsia. AT1 receptor activation increases vasoconstriction, a prominent feature of preeclampsia. Furthermore, there is evidence of increased sympathetic activity in preeclampsia,1 and one of the predominate actions of angiotensin II in the central nervous system is to increase sympathetic outflow.17 Endothelin concentrations are increased in the blood of women with preeclampsia, and AT1 receptor activation can increase circulating endothelin.5,18 Recent information suggests activation of the inflammatory response in pregnancy that is further augmented in preeclampsia.19 Chronic administration of angiotensin activates inflammatory processes.18 Endothelial permeability is increased in preeclampsia.2 It has been found that serum from preeclamptic women increases endothelial permeability through a kinase-C–sensitive mechanism, consistent with activation of AT1 receptors on endothelium.20 Perhaps most intriguing is the finding that AT1 receptor activation can generate reactive oxygen species through long-term activation of endothelial and vascular smooth muscle of NADH/NADPH-oxidase.18 In addition, increased sensitivity to angiotensin is a well-recognized feature of preeclampsia that may antedate clinically evident disease.1 One of the mechanisms speculated on by Dechend et al is that the antibody may alter the conformation of the AT1 receptor to render it more sensitive to endogenous angiotensin. Thus, they convincingly demonstrate the presence of agonistic antibodies to the AT1 receptor in preeclampsia. Activation of the AT1 receptor by these antibodies could explain many of the pathophysiological features of preeclampsia.

There are, however, several pieces of evidence that must be provided and conceptual inconsistencies that must be resolved to establish the role of these antibodies in preeclampsia. The first, of course, is the relationship of these in vitro findings to the intact organism. Can the activities demonstrated in vitro occur at IgG concentrations present in vivo? How does the IgG in vivo have access to smooth muscle? And is it appropriate to extrapolate increased tissue factor production in coronary vascular smooth muscle to placental tissue factor production? There are numerous activities that can be demonstrated with the exposure of different cell types to serum or plasma from preeclamptic women.5 Attempts to characterize these have resulted in the identification of more than one activity, including an activity that resides in non-HDL lipoproteins, primarily LDL.21 Clearly, the autoantibodies are only one of several factors present in the blood of preeclamptic women that can alter cellular function in vitro. Dechend et al3 raise several other issues. What is the origin of these antibodies, and is their disappearance consistent with the time course of the resolution of preeclampsia? Why do these antibodies not persist after pregnancy? Are these antibodies present only during first pregnancies (and why), or is there an alternative explanation as to how this phenomenon is compatible with the first-pregnancy preponderance of
preeclampsia? Why do only some women develop these antibodies, and how does this development fit with known risk factors for preeclampsia such as obesity and race? The major question is whether these findings are pathophysiological or an epiphenomenon. The woman with preeclampsia manifests profoundly deranged pathophysiological function. Are these antibodies the cause or are they a result of vascular damage? Many of the pathophysiological changes of pre-eclampsia can be demonstrated before clinically evident disease.\(^2\) It would be strong evidence for a causal role if the antibodies were present before the woman became clinically ill.

The findings presented by Dechend and coworkers\(^3\) are intriguing. There are, however, currently more questions than answers as to their relevance. We will watch with interest as these talented investigators continue their characterization of the activities of these molecules and proceed to resolve the questions raised above.

References

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