Insulin Resistance in Preeclampsia

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In this issue of Hypertension, Parretti and her associates have tested the relationship of insulin resistance to preeclampsia.1 They make 2 exciting observations. First, insulin resistance is more common in women who are destined to develop preeclampsia months before clinically evident disease. Second, simple assessments of insulin resistance based on a single determination of fasting insulin and glucose can predict preeclampsia at least as well as the current gold standard for prediction of preeclampsia, uterine artery Doppler velocimetry.

Increased insulin resistance is well established to be associated with preeclampsia.2 Its relevance as either a risk for preeclampsia or as causally important to its pathophysiology can be questioned. Most studies have not taken into account obesity, which is associated both with increased insulin resistance and with preeclampsia. There is no guarantee that insulin resistance is the mechanism by which obesity increases the risk of preeclampsia. Other relevant pathophysiological consequences of obesity include elevated inflammatory activity,3 altered adipokines,4 and higher concentrations of circulating asymmetrical dimethylarginine (an endogenous inhibitor of NO synthase). In addition, several prior studies have identified insulin resistance only in women with manifest preeclampsia, questioning a cause and effect relationship. Parretti and colleagues avoid both pitfalls. Tests were done in early pregnancy before clinically evident preeclampsia and were limited to lean (body mass index \( \leq 25 \)) women. Thus, the study supports a direct association of insulin resistance and preeclampsia. Whether the insulin resistance is a component of the pathophysiology or whether it is a preexisting risk factor cannot be answered by the study. The latter would seem more likely based on the fact that insulin resistance is higher in women who have previously had preeclampsia6 and that increased cholesterol, another component of the metabolic syndrome, can be demonstrated to be increased before a preeclamptic pregnancy.7

How might insulin resistance increase the risk of preeclampsia? There is an extensive literature on insulin resistance and hypertension, and there are several suggestions to explain this relationship. Elevated insulin increases sympathetic tone and muscle blood flow and also in chronic settings (unlikely relevant to preeclampsia) increases vascular smooth muscle growth.8 The effect of insulin resistance on blood pressure has been suggested by the finding that drugs that reduce insulin resistance (eg, thiazolidinediones) also lower blood pressure.9 However, these drugs are also peroxisome proliferator activator receptor-\( \gamma \) agonists and may have other effects, including inhibition of Ca\(^{2+} \) channels, that reduce blood pressure.

Insulin resistance is only one of the components of the metabolic syndrome that is present in preeclamptic women. Whether other components are the important factors is an open question. Altered lipids, especially increased free fatty acids9 and perhaps even increased uric acid,10 may have relevant pathophysiological effects. The pathophysiology of preeclampsia extends beyond simply hypertension, and effects of insulin, insulin resistance, and other components of the metabolic syndrome on endothelial function or generalized inflammation may also be quite relevant. Which or how many of these physiological systems are affected by hyperinsulinemia and other components of the metabolic syndrome is a subject for future studies. The value of these studies to understand preeclampsia is supported by the evidence from the Parretti study that insulin resistance is likely to be involved in the pathogenesis of preeclampsia rather than being caused by preeclampsia. The dissection of the role of the metabolic syndrome and its component factors must nonetheless be established before modification of any single component is attempted as a means to improve outcome.

The possible predictive value found in this study for simple tests of insulin resistance also deserves further study. The results as presented would indicate these studies to be better than any currently available predictive test. The current “gold standard” is uterine artery Doppler done at about the same time in pregnancy as the initial determination of insulin sensitivity in the Parretti study. The positive predictive value of uterine artery Doppler in low risk populations is approximately 20% compared with 65% to 69% for the insulin sensitivity tests. It is, however, difficult to generalize from this homogeneous, lean white population. An example of this is the relatively high frequency of preeclampsia. The incidence of 6.6% is somewhat surprising in light of the exclusion of obese women in whom relative risk is more than twice that of the general population.11 Nonetheless, even in a setting with a frequency of preeclampsia of 1%, the predictive value would still be equivalent to the much more complex and costly assessment of risk by uterine artery Doppler.12 Furthermore, it will be of interest to determine whether the putative role of insulin resistance will be present in other women at high risk for preeclampsia (eg, prior preeclampsia, twins). If this were the case, it is possible that the predictive value of increased insulin resistance in these settings of increased preeclampsia prevalence would be sufficient to stratify risk to influence care delivery.
Insulin resistance is an important part of the metabolic syndrome and predicts cardiovascular disease in later life. The study by Parretti et al suggests a similar relationship to preeclampsia. These findings dictate further mechanistic studies of insulin resistance and the metabolic syndrome in the pathophysiology of preeclampsia and indicate confirmatory tests for the predictive value of insulin resistance in other populations.

References
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