Genetic Variants in Pre-Eclampsia: A Meta-Analysis EDITORIAL COMMENT

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ABSTRACT

Preeclampsia affects 5% to 8% of pregnancies and contributes significantly to maternal and fetal morbidity and mortality. Preeclampsia is thought to result from complex interactions between genetic components and environmental factors. Which genes are involved and how individual genetic variants contribute to preeclampsia are unknown. This study was undertaken to review the genetic variants associated with preeclampsia and to perform a meta-analysis to assess the pooled effects of associated genetic variants.

PubMed, EMBASE, and Web of Science databases were searched for studies that evaluated genetic variants in preeclampsia. Case-control studies that compared genetic variants between patients with preeclampsia and healthy women with uncomplicated pregnancies were extracted. In genetic association studies, when a genetic variant was significantly associated with preeclampsia at the allelic or genotypic level in 2 or more studies, that variant was considered to be reproduced. For these reproduced genetic variants, all other genetic studies were identified to estimate the pooled effect of the variant on preeclampsia. The main outcome of the meta-analysis was the pooled odds ratio (OR, calculated at the allele level) for the association between reproduced genetic variants and preeclampsia. Data were pooled using a random-effects model to account for between-study heterogeneity. The analysis was performed only for genetic variants that were significantly associated with preeclampsia after the meta-analysis and for which the number of studies that investigated the genetic variant was more than 10.

Of the initial 2965 articles, 542 were genetic association studies regarding preeclampsia, from which 22 polymorphisms in 15 genes were identified as associated with preeclampsia and described in 163 articles, representing 283 studies published from 1993 through 2012. In a random-effects meta-analysis, 7 genetic variants in or near 6 genes were significantly associated with preeclampsia and maintained this association after the meta-analysis. Odds ratios of significant associations with preeclampsia ranged from 1.20 to 2.42. Two variants in coagulation factor V (*FV*) gene, rs6025 and rs6020, were associated with preeclampsia in the meta-analysis (pooled OR of 1.94 [95% confidence interval {CI}, 1.56–2.45] and 1.94 [95% CI, 1.05–3.60], respectively). The variant rs1799963 of coagulation factor II (*F2*) was associated with preeclampsia with an OR of 1.95 (95% CI, 1.43–2.66). The variant rs1799889 in *SERPINE1* had an OR of 1.17 (95% CI, 1.03–1.33). For the *ACE* variant, rs4646994, the pooled OR was 1.20 (95% CI, 1.08–1.34). The *CTLA4* variant, rs231775, had an association with preeclampsia (OR, 1.24; 95% CI, 1.01–1.52). The variants rs1800590 and rs268 in *LPL* were reproduced in preeclampsia, but only rs268 remained so after the meta-analysis (OR, 2.42; 95% CI, 1.25–4.68). The rs3025039 variant in *VEGF* was reproduced in preeclampsia, but not after the meta-analysis (OR, 1.36; 95% CI, 0.64–2.91).

In this meta-analysis, 7 genetic variants (*ACE*, *CTLA4*, *F2*, *FV* [2 variants], *LL*, and *SERPINE1* genes) were associated with preeclampsia. The results suggest that the renin-angiotensin system, coagulation and fibrinolysis, lipid metabolism, and inflammation may have a role in the pathogenesis of preeclampsia. These data may help clarify the pathogenesis of preeclampsia and reveal molecular pathways that can be targeted in the management of this condition. Further studies investigating the relative contribution of these variants and the mechanisms by which they affect the risk of developing preeclampsia are warranted.

EDITORIAL COMMENT

(Preeclampsia continues to plague the obstetrician, with frustratingly little progress having been made into better understanding the causes or to finding preventive measures or cures. In John Irving's book, "The Cider House Rules," about a home for unwed mothers at the turn of the last

century, young women with preeclampsia were treated with magnesium sulfate and delivered prematurely. It seems sometimes that we have made little progress over the past 100 years.

We have learned, however, that preeclampsia has a genetic component and is more common in women who have had first-degree relatives similarly affected. It is now recognized that preeclampsia is a complex disorder with genetic and environmental components that interact to cause the familiar symptoms. We have also learned that women who have been diagnosed with preeclampsia are more likely to have cardiovascular disease and adverse metabolic profiles later in life (*Am J Obstet Gynecol* 2009;200:58: e1–58.e8; *Obstet Gynecol* 2005;105:1373–1380). It has been suggested that similar genotypes may be present in individuals with preeclampsia and from cardiovascular disease, thus explaining some of the familial associations of these conditions.

In this abstracted article, the authors performed a meta-analysis of studies that have assessed the association between genetic variants and preeclampsia. They were careful in theirmethods and included only genetic variants that were found to be associated with preeclampsia in an initial study and independently reproduced in at least 1 additional study. Interestingly, the 7 genetic variants found to be consistently associated with preeclampsia included genes involved in the renin-angiotensin system, coagulation and fibrinolysis, lipid metabolism, and inflammation. Given prior studies on the pathophysiology of preeclampsia and of cardiovascular disease, this is not surprising, but quite interesting and certainly biologically plausible.

Preeclampsia is characterized by inadequate placentation, oxidative stress, inflammation, and widespread endothelial dysfunction. Furthermore, preeclampsia and cardiovascular disease share many risk factors, including obesity, hypertension, dyslipidemia, hypercoagulability, and insulin resistance. As mentioned previously, evidence suggests that genetic determinants associated with the metabolic syndrome, inflammation, and subsequent endothelial dysfunction are involved in both disorders.

One strength of this study is that the authors included only genetic variants that were associated with preeclampsia in more than 1 independent study. Publication bias, in which positive results are preferentially published, can lead to an increased likelihood of selective reporting of false-positive results. When meta-analyses are performed using multiple studies with false positive results, this can continue to perpetuate unreliable conclusions. As the cynics say, "garbage in, garbage out." However, the fairly stringent inclusion criteria of this study, as well as the biological plausibility and the epidemiologic consistency with cardiovascular disease, all support these findings.

Finding genetic associations such as those reported here is of some interest, but such associations are even more compelling if these ultimately lead to a useful prevention or treatment. Low-dose aspirin has been reported to be of benefit in decreasing, albeit slightly, both cardiovascular disease and preeclampsia in patients who are at high risk. It would be helpful and exciting if findings such as those reported in this article resulted in new biologic insights and targets for improved prevention. A deeper understanding of the relative contribution of these genetic variants, interaction of such with environmental factors, and the mechanisms involved will hopefully evolve over time; studies such as this are useful steps along the path to furthering our understanding.—MEN)