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A sister's risk: Family history as a predictor of preeclampsia

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Objective: The purpose of this study was to determine if women with preeclampsia are more likely to have a sister who also had preeclampsia.

Study design: This was a population-based case-control study using data from Washington (WA) state birth certificates linked to hospital discharge records. Cases were women with gestational hypertension (n = 1611) or preeclampsia (n = 1071); controls (n = 8041) had normotensive pregnancies. All women delivered their first child between 1987 to 2002 and had a sister with a previous delivery in WA.

Results: Women with preeclampsia were 2.3 times (95%CI 1.8-2.9) more likely to have a sister who had preeclampsia; those with gestational hypertension were 1.6 times (95%CI 1.3-2.0) more likely to have a sister with gestational hypertension. Similar results were obtained following stratification by age, race, smoking status, or body mass index.

Conclusion: The greater likelihood of preeclampsia among sisters of women with a previous preeclamptic pregnancy is consistent with a pathophysiologic role for genetic and/or behavioral factors that cluster in families.

Hypertensive disorders affect 5% to 10% of pregnancies worldwide[1] and constitute a leading cause of maternal mortality.[2] In the United States, approximately 7% of the 3,900,000 births that occur annually are complicated by hypertensive disorders of pregnancy.[3] Endothelial dysfunction is a central event in the pathogenesis of preeclampsia.[4] Mechanisms that have been suggested to contribute to this abnormality include genetic predisposition,[5-9] underlying maternal disorders,[10,11] immunologic maladaption,[12,13] and abnormal placentation.[14]

We hypothesized that preeclampsia would cluster in families, consistent with a genetic component in the pathophysiology of these diseases. To test this hypothesis, we conducted a population-based case-control study to determine whether a woman with preeclampsia/eclampsia or gestational hypertension during her first pregnancy had a greater risk of having a sister who also had one of these hypertensive complications during her past pregnancy. We also evaluated the potential influence of maternal age, race, body mass

Drs Carr, Epplein, and Johnson contributed equally to this work.

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index (BMI), cigarette smoking during pregnancy, and discordance of these characteristics between sister pairs, on this association.

Material and methods

A 'Sisters' database was constructed by linking birth certificates of girls born to the same mother in Washington state. A subset of sisters was then constructed from among sister pairs where each sister subsequently delivered at least 1 singleton infant in Washington state. The first 2 sisters in a family who delivered their first pregnancies between 1987 and 2002 were selected. For each sister pair, we designated the second sister to give birth as the 'index sister' and the sister who delivered before her sister as the 'exposure sister' (Figure). All index sisters were nulliparous; if the exposure sister had given birth more than once, her first pregnancy recorded in the database was chosen. Information for each sister was obtained from the birth certificate of her infant and the Comprehensive Hospital Abstract Recording System, which contains hospital discharge data for all hospitalizations in nonfederal institutions in Washington state. Median household income for each woman was estimated based on 1990 and 2000 Census data. Height was obtained from the Washington state driver's license database.

We conducted a population-based case-control study as follows. Among the index sisters, cases were defined as women diagnosed by ICD-9 codes as having preeclampsia (ICD-9 codes 642.4-642.5), eclampsia (ICD-9 code 642.6), or gestational hypertension (ICD-9 code 642.3) on the hospital discharge data, and/or eclampsia or gestational hypertension on the birth certificate during their first pregnancy. Controls were index sisters who were not diagnosed during their first pregnancy with preeclampsia/eclampsia or gestational hypertension. We excluded sisters who were diagnosed with chronic hypertension (ICD-9 codes 642.0, 642.1, 642.2, 642.7, and 642.9 or birth certificate checkbox), or multifetal gestation (ICD-9 codes 651.0, 651.1, 651.2, and 651.8), or fetal demise <24 weeks' gestation (ICD-9 code 632). The primary exposure of interest was the occurrence of a hypertensive disorder of pregnancy in the exposure sister, that is, the sister of the index sister (Figure). Preeclampsia/eclampsia or gestational hypertension in the exposure sister was defined in the same manner as for the index sister.

The odds of a woman having a sister who had a hypertensive pregnancy given that her own first delivery was affected by a hypertensive disorder, relative to women who did not have a hypertensive first pregnancy, was estimated using odds ratios (ORs) obtained by stratified Mantel-Haenszel procedures and test-based methods to obtain 95% CIs.

To measure the possible effects of risk factors for hypertensive disorders of pregnancy, estimates of the ORs were stratified by: age (<20, 20-34, ≥ 35 years); race/ethnicity (white, black, Asian/Pacific Islander, Native American); BMI, as calculated from prepregnancy weight on the birth certificate and height (underweight <18.5 kg/m^2; normal 18.5-24.9 kg/m^2; overweight 25.0-29.9 kg/m^2, obese ≥ 30 kg/m^2); smoking during pregnancy; and whether the sisters had the same father (full—same father, half—different father). These variables were also evaluated as potential confounders; only those that were considered biologically important or that changed the OR substantially were included in the final analysis.

Stratified analyses were performed to determine if the relationship between having a hypertensive first pregnancy and having a sister with a hypertensive pregnancy was altered by whether the sisters were concordant or discordant with respect to specific risk factors for hypertensive disorders. For this subanalysis, variables were dichotomized as follows: lower risk (20-34 years) versus higher risk age groups (<20 or >34 years); lower risk (underweight or normal) versus higher risk BMI (overweight or obese); and lower risk (smoking during pregnancy) versus higher risk smoking status (no smoking during pregnancy).

The Human Subjects Review Committee at the University of Washington reviewed and approved the study protocol.

Results

Among the index sisters, cases were generally similar to those of controls (Table I). Cases were more likely to be overweight or obese before conception, to have excessive weight gain during pregnancy, and to have gestational diabetes. Cases were less likely to smoke during pregnancy than controls. Among cases, women with preeclampsia/eclampsia were more likely to have pregestational diabetes than either women with gestational hypertension or controls, and more likely to have delivered <36 weeks' gestation.

Among the exposure sisters, sisters of cases compared with sisters of controls were generally similar in their reference pregnancy (Table II). Exposure sisters were slightly more likely to have delivered <36 weeks' gestation in their reference pregnancy if their index sister had preeclampsia/eclampsia than if the index sister was unaffected or had gestational hypertension.

Overall, 371 (13.8%) of 2682 index sisters with preeclampsia/eclampsia or gestational hypertension had a sister whose reference pregnancy was also affected by a hypertensive disorder compared with 686 (8.5%) of 8041 controls (OR 1.7, 95% CI 1.5-2.0). Furthermore, when using the exposure sisters' entire reproductive history (ie, a hypertensive disorder in any previous pregnancy), the association between a hypertensive disorder of pregnancy in the index sister's first pregnancy