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Risk of Ischemic Placental Disease in Relation to Family History of Preeclampsia: Familial history of preeclampsia and ischemic placental disease

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Abstract

Objective: To assess the risk of ischemic placental disease (IPD) including preeclampsia, small for gestational age (SGA) and abruption, in relation to preeclampsia in maternal grandmother, mother, and sister(s).

Study design: We performed a secondary analysis of data from a randomized trial of vitamin C-E for preeclampsia prevention. Data on family history of preeclampsia was based on recall by the proband. The associations between family history of preeclampsia and the odds of IPD were evaluated from alternating logistic regressions.

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Results: Of the 9,686 women that delivered non-malformed, singleton live births, 17.1% had IPD. Probands provided data on preeclampsia in 55.5% (n=5,374) on all 3 family members, 26.5% (n=2,562) in mother and sister(s) only, and 11.6% (n=1,125) in sister(s) only. The pairwise odds ratio of IPD was 1.16 (95% confidence interval [CI] 1.00–1.36) if one or more of the female relatives had preeclampsia. The pairwise odds ratios of preeclampsia were 1.54 (95% CI 1.12–2.13) and 1.35 (95% CI 1.03–1.77) if the proband's mother or sister(s) had a preeclamptic pregnancy, respectively, but no associations were seen for SGA infant or abruption.

Conclusion: This study suggests that ischemic placental disease may share a predisposition with preeclampsia, suggesting a familial inheritance.

Keywords

Ischemic placental disease; preeclampsia; placental abruption; small for gestational age infant; family history; inheritance

Introduction

Vascular disorders in pregnancy, including preeclampsia, fetal growth restriction, and placental abruption, have a common pathophysiologic mechanism — uteroplacental ischemia.¹ Epidemiologic studies have reported increased risks of placental abruption not only among women with previous abruption,^{2–5} but also among gravida with preeclampsia in the preceding pregnancy.⁶ Similar increased cross-recurrence amongst the three obstetrical complications³ has led investigators to conclude that these conditions may share a common etiologic mechanism.

Preeclampsia tends to aggregate within families.^{7,8} The increased risk of preeclampsia in probands born of preeclamptic pregnancies or among sisters and, to a lesser extent, among sisters-in-law, suggests that genes that aggregate within families may shape the risk of preeclampsia.^{9,10} Similar patterns of familial inheritance to placental abruption have also been reported in Norway¹¹ and Finland,¹² as well as for small for gestational age births.^{13,14} Because the majority of these studies come from the Nordic or Scandinavian populations, the profile of women diagnosed with preeclampsia, placental abruption and small for gestational age may be different in comparison to those in the US.¹⁵ Whether similar increased familial aggregations for these ischemic conditions persist in a contemporary cohort in the US remains unknown.

The objective of this study was to evaluate the association between ischemic placental disease including preeclampsia, small for gestational age (SGA) infant, and placental abruption and family history of preeclampsia in maternal grandmother, mother, and sister(s). We hypothesized that the frequency of ischemic placental disease will be higher among women with a family history of preeclampsia.

Methods

We carried out a secondary analysis of data from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network

randomized controlled trial of prophylactic vitamins C and E supplementation for preeclampsia prevention (CAPPS).¹⁶ This multicenter, double blind RCT was implemented across 14 academic centers in the US between July 2003 and February 2008. Nulliparous women with singleton gestations were randomized to begin treatment (daily 1000 mg of vitamin C and 400 IU of vitamin E) or a matching placebo between the 9th and 16th week of gestation. The trial concluded that there was no benefit of the vitamin C and E supplementation on both severe pregnancy-associated hypertension and preeclampsia. Further details of the study can be found elsewhere.¹⁶ All data were collected by certified research personnel and uploaded to a database managed by an independent data coordinating center. The study was approved by the institutional review board at each clinical site and the data-coordinating center.

Ischemic placental disease

We examined ischemic placental disease as the primary outcome. Ischemic placental disease was defined to include one or more of the following conditions: preeclampsia, SGA infant or placental abruption. *Mild preeclampsia* was defined as systolic blood pressure between 140 and 159 mmHg or a diastolic pressure between 90 mm and 109 mmHg on two occasions 2 to 240 hours apart, with documentation of proteinuria within 72 hours before or after an elevated blood pressure measurement. Proteinuria was defined as total protein excretion of 300 mg or more in a 24-hour urine sample, or if a 24-hour urine sample was not available, 2+ or higher on urine dipstick, or a protein-to-creatinine ratio of 0.35 or more. After rupture of membranes, only catheterized urine samples were considered in the diagnostic criteria. *Severe preeclampsia* defined as systolic blood pressure of 160 mmHg or greater, or diastolic blood pressure 110 mmHg or greater on two occasions 2–240 hours apart on or after 20 weeks 0 days of gestation or protein excretion of 5 g or more in a 24-hour urine sample or as mild pregnancy-associated hypertension with oliguria (<500 ml in a 24-hour urine sample), pulmonary edema (confirmed by chest radiography), or thrombocytopenia (platelet count of <100,000 per cubic millimeter). All identified cases of preeclampsia were reviewed and confirmed by a deidentified medical chart review. The reviews were undertaken by at least three reviewers who were unaware of the treatment assignments in the original CAPPS trial.¹⁶

Among live births, small for gestational age infant was defined as birthweight below the 10th percentile adjusted for sex and race/ethnicity.¹⁷ Placental abruption was based on a clinical diagnosis, and defined using standard clinical criteria.¹⁸ The exposure was preeclampsia in female relatives (mother, maternal grandmother or sister(s)) of the probands in the CAPPS trial.

Cohort selection

For this secondary analysis, of the 10,152 women included in the CAPPS trial, we sequentially excluded a total of 404 women. These exclusions were because of missing data on pregnancy outcome (n=183), miscarriage (n=92), elective abortion (n=34), or if the newborn had any major anomaly present (n=95) or stillbirth with a malformation (n=5). After these exclusions, 9,748 (96%) women that delivered a singleton live birth (n=9,692) or stillbirth (n=56) remained in the analysis.

Statistical analysis

The primary analysis was based on women that delivered a non-malformed singleton live birth. Descriptive statistics for baseline characteristics were computed. Continuous variables were tested for the normal distribution and the median and the 25th and 75th quartiles (interquartile range) are reported for skewed distributions. We used logistic regression models to test the association between baseline characteristics and ischemic placental disease as the outcome. Odds ratios and 95% confidence intervals are reported.

Data on the exposure variable, family history of preeclampsia, was ascertained based upon the participant's recollection to the following three questions: "Sister(s) diagnosed/treated for preeclampsia?", "Mother diagnosed/treated for preeclampsia?" and "Maternal grandmother diagnosed/treated for preeclampsia?". Responses to each of the three questions were recorded as either "yes" or "no". An observation for each participant and each of her relatives was created and analyzed as a cluster. Subjects with no information about all 3 relatives were excluded. In other words, probands with information about 1 or 2 family members were not excluded. Therefore, the cluster size ranged between 2 (proband plus any one female relative with preeclampsia) and 4 (proband plus all three female relatives with preeclampsia). We used alternating logistic regression with full parameterized clusters for the log odds ratio structure.¹⁹ This model takes into account within-family clustering. The common log odds and the common log odds ratios for the cluster comparisons (for example, proband versus the mother) are reported. The odds ratio, hereto referred to as the pairwise odds ratio (pOR), was used as a measure of effect. The pOR is interpreted as the ratio of the odds of preeclampsia in the mother given that the proband had ischemic placental disease to the odds of the mother being normotensive when the proband did not have ischemic placental disease. A pOR above one indicates the increased aggregation of ischemic placental disease in the proband when a family member had preeclampsia in her pregnancy.

An important requirement of the alternating logistic regressions is that the specification model for the marginal means is correct. We therefore included risk factors that were significant in the baseline analysis (maternal age, race, pre-pregnancy body-mass index, and educational level) for the marginal mean model. In addition, we also adjusted the model for the pairwise odds ratios for maternal age, education, maternal race, pre-randomized maternal body-mass index.

Sensitivity analyses

We undertook two sets of sensitivity analysis. First, we examined the presence of familial aggregation of ischemic placental disease in relation to familial preeclampsia, with SGA infant defined as <5th and <3rd percentiles. Second, we examined if the exclusion of 49 antepartum and 7 intrapartum non-malformed stillbirths may have biased the associations. To test this, we included the 56 stillbirths in the analysis, but since birthweight was missing for all cases of stillbirths, ischemic placental disease was defined to only include preeclampsia and placental abruption.

All statistical analyses were performed in SAS (version 9.4; SAS Institute, Cary, NC).

Results

Ischemic placental disease was diagnosed in 17.1% of the cohort (n=1,659), of which preeclampsia, SGA, and abruption were recorded in 41.0%, 64.4%, and 3.1%, respectively (with overlap amongst the three conditions). The distribution of proband characteristics in relation to ischemic placental disease status is shown in Table 1. Probands provided data at their study enrollment visit (9–16 weeks' gestation) on preeclampsia in 55.5% (n=5,374) on all 3 members of the family, 26.5% (n=2,562) in mother and sister(s) only, and 11.6% (n=1,125) in sister(s) only. Many of the maternal characteristics were associated with ischemic placental disease. In comparison to women aged <20 years, the odds of ischemic placental disease declined with increasing maternal age. Although the CAPPS trial included only nulliparous women, 22.7% (n=2,202) women in the total cohort with a previous pregnancy were those that had an abortion or a miscarriage. Compared to women with education <8 years, those with higher years of schooling were at decreased odds of ischemic placental disease. Women that smoked during their pregnancy, were at increased odds of ischemic placental disease.

The association between preeclampsia in the female relatives and odds of ischemic placental disease in the proband are shown in Table 2. Women were at increased odds of ischemic placental disease if one or more of the female relatives had preeclampsia in their pregnancy (pOR 1.16, 95% CI 1.00–1.36). When this association was examined separately for the type of the family member, the increased odds were confined to mother or sister(s), although the association was of marginal strength. We then examined the pairwise association between preeclampsia and SGA infant and family history of preeclampsia. These analyses indicate that if the mother had a diagnosis of preeclampsia, then her daughter was at 54% increased odds of preeclampsia (pOR 1.54, 95% CI 1.12–2.13). Similar increased association was also evident when the sister(s) had preeclampsia (pOR 1.35, 95% CI 1.03–1.77). No associations were seen for SGA infant. The number of cases of placental abruption was too few for stable analysis.

Sensitivity analysis

First, when we examined the presence of familial aggregation of ischemic placental disease in relation to familial preeclampsia, with SGA infant defined as <5th and <3rd percentiles, the findings were similar to the overall analysis (Table 3). Second, we included the 56 non-malformed stillbirths in the analysis and with ischemic placental disease defined to only include preeclampsia and placental abruption (Table 4). These analyses showed that the overall associations between preeclampsia in female relatives and ischemic placental disease among probands were similar to the analysis based only on live births. However, pairwise associations were reversed and stronger when the sister(s) had preeclampsia (pOR 1.53, 95% CI 1.11, 2.11) than the mother (pOR 1.34, 95% CI 1.02, 1.76).

Discussion

Principal findings

Epidemiologic studies have documented a familial predisposition to increased risks of both preeclampsia^{10,20–23} and placental abruption.^{11,12} However, familial associations insofar as SGA infant is concerned remain unknown. Equally, whether such associations exist in the US, and if so, the strength of familial aggregation of preeclampsia, SGA infant and placental abruption – conditions that constitute the syndrome of ischemic placental disease²⁴ – also remain poorly understood. We show increased odds of ischemic placental disease in probands with first-degree female relatives of probands with preeclampsia. In particular, this increased familial aggregation was confined to probands with preeclampsia, and especially among mother and sister(s) of preeclampsia probands. Inclusion of stillbirths in the probands strengthened the associations.

Interpretation of findings

Epidemiologic studies have provided support to the presence of familial tendency for ischemic placental disease. Using population based data from the Medical Birth Registry of Norway covering all births since 1967 (about 1.7 million), Lie and colleagues²⁵ reported an odds ratio of 2.2 (95% CI 1.9, 2.5) for preeclampsia when the probands sister(s) had preeclampsia. In a case-control study of preeclampsia among low-income women in Peru, Sanchez and colleagues²⁶ reported no association between preeclampsia in women with family history of chronic hypertension (OR 1.0, 95% CI 0.5, 1.9), but a strong association between preeclampsia and family history of diabetes (OR 3.5, 95% CI 1.1, 10.7) and chronic hypertension and diabetes combined (OR 4.6, 95% CI 0.9, 23.0).

Cnattingius and colleagues²² showed that the liability of preeclampsia to aggregate within families was 35% due to a pure maternal genetic effect, 20% to a paternal effect, 13% to a shared couple effect, and 32% to an environmental effect. In a similar study Salonen Ros and colleagues²⁷ showed that, among twin gestations, a genetic and environmental factors contributed to 54% and 46%, respectively, to the total liability to preeclampsia.

Peltier and colleagues²⁸ examined the associations between family history of thromboembolic disease among first-degree male and female relatives and the odds of placental abruption among probands. Thromboembolic diseases in relatives were reported by the abruption proband and controls. The prevalence of thromboembolic disease was 7.5% in 852 relatives of 212 placental abruption cases and 4.8% in 792 relatives of 206 controls. This increased frequency of thromboembolic disease was driven by an association among sister(s) of abruption probands (OR 6.8, 95% CI 1.8, 26.0), and to a lesser extent, among mothers (OR 2.0, 95% CI 1.0, 4.2); no associations were evident among male relatives.

Collectively, these studies suggest that roughly half of the total liability to preeclampsia is genetically inherited. Unfortunately, similar data on SGA infants and placental abruption remains unknown and may be topics worthy of future investigation.

Limitations of the data

A few limitations of the study merit discussion. First, there is some degree of recall bias in the reporting of family history of preeclampsia in female relatives by the proband. This bias is, however, non-differential with respect to status since probands were asked about familial history of preeclampsia at their first enrollment visit (9–16 weeks of gestation) in the CAPPS trial,¹⁶ and well before a diagnosis was made for preeclampsia, SGA birth or placental abruption in the proband. Second, the prevalence estimates of preeclampsia in maternal grandmother, mother, and sister(s) as recalled by the proband, were 3.1%, 7.5%, and 4.6%, respectively. These are consistent with the expected risks. However, the proband's recall of preeclampsia in all three of the female relatives were missing in only 4%, but in up to 42.3% among maternal grandmother. It is likely that the proband's recall of preeclampsia was best amongst sister(s) and less so for her maternal grandmother. Therefore, the results pertaining to the maternal grandmother must be cautiously interpreted. Third, the possibility of confounding by unmeasured factors cannot be overlooked. Fourth, whether the probands that participated in the randomized trial were, or were not, first born children remains unknown. This has implications for the interpretation of the data since the frequency of preeclampsia for the daughters may be lower if preeclampsia in the mother occurred with another child and not with the proband.

Strengths of the study

Notwithstanding the limitations, we show increased predisposition to ischemic placental disease when female relatives of probands have had preeclampsia. The strengths are that the findings are generalizable given that the study was implemented across 14 centers in the US. Ascertainment of ischemic placental disease in the probands was based on medical chart review with every case confirmed by a research coordinator and a physician at every center. Adjustment for potential confounders was incorporated in the regression models to estimate the pairwise association measures in the framework of alternating logistic regression. This regression methodology provides an innovative approach to estimate the familial associations that are strongly influenced by family (cluster) size, and failure to account for this clustering will produce biased associations.

Conclusions

In conclusion, the frequency of ischemic placental disease in the proband is higher among women with a family history of preeclampsia in their pregnancy. In particular, this increased frequency appears confined to women when her mother or sisters had preeclampsia in their pregnancies. These observations highlight that ischemic placental disease may share a predisposition with preeclampsia, suggesting a familial inheritance.

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Appendix

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Table 1

Maternal characteristics in relation to ischemic placental disease

Maternal characteristics	Total cohort No. (%)	Ischemic placental disease		
		Present No. (%)	Not Present No. (%)	Odds ratio (95% confidence interval)
Total number	9,686	1,659	8,027	
Vitamin C-E treatment arm	4,858 (50.2)	846 (17.4)	813 (16.8)	1.04 (0.94, 1.16)
Gestational age at randomization (weeks) [¶]	13.4 (11.9, 15.1)	13.4 (11.9, 15.3)	13.4 (11.9, 15.1)	
Preeclampsia	681 (7.0)	681 (41.1) *	—	—
Small for gestational age birth			—	—
<10 th percentile	1,067 (11.0)	1,067 (64.4) *	—	—
<5 th percentile	459 (4.8)	459 (27.7) *	—	—
<3 rd percentile	255 (2.6)	255 (15.4) *	—	—
Placental abruption	51 (0.5)	51 (3.1) *	—	—
Family history of preeclampsia				
Any female relative				
Yes	1,255 (13.0)	248 (19.8)	1,007 (13.0)	1.25 (1.08, 1.45)
No	8,042 (83.0)	1,324 (79.8)	6,718 (83.7)	1.00 (Reference)
Unknown	389 (4.0)	—	—	—
Maternal grandmother				
Yes	296 (3.1)	52 (3.1)	244 (3.0)	1.09 (0.80, 1.48)
No	5,297 (54.6)	867 (52.3)	4,427 (55.2)	1.00 (Reference)
Unknown	4,096 (42.3)	—	—	—
Mother				
Yes	725 (7.5)	145 (8.7)	580 (7.2)	1.29 (1.06, 1.56)
No	7,438 (76.8)	1,211 (73.0)	6,227 (77.6)	1.00 (Reference)
Unknown	1,523 (15.7)	—	—	—
Sister(s)				
Yes	449 (4.6)	91 (5.5)	358 (4.5)	1.26 (1.00, 1.60)
No	8,612 (88.9)	1,442 (86.9)	7,170 (89.3)	1.00 (Reference)
Unknown	625 (6.5)	—	—	—
Maternal age (years) [¶]	22 (19, 27)	22 (19, 26)	23 (20, 27)	—
<20	2,486 (25.7)	499 (30.1)	1,987 (24.8)	1.35 (1.16, 1.57)
20–24	3,691 (38.1)	629 (37.9)	3,062 (38.2)	1.10 (0.95, 1.27)
25–29	2,129 (22.0)	335 (20.2)	1,794 (22.4)	1.00 (Reference)
30–34	986 (10.2)	138 (8.3)	848 (10.6)	0.87 (0.70, 1.08)
35	394 (4.1)	58 (3.5)	336 (4.2)	0.92 (0.68, 1.25)
Educational level (years)				

Maternal characteristics	Total cohort No. (%)	Ischemic placental disease		
		Present No. (%)	Not Present No. (%)	Odds ratio (95% confidence interval)
<8	378 (3.9)	70 (4.2)	308 (3.84)	1.00 (Reference)
8–11	2,135 (22.0)	431 (26.0)	1,704 (21.2)	1.11 (0.84, 1.47)
12–15	4,469 (46.1)	810 (48.8)	3,659 (45.6)	0.97 (0.74, 1.28)
16	2,704 (27.9)	348 (21.0)	2,356 (29.4)	0.65 (0.49, 0.86)
Previous pregnancy	2,202 (22.7)	366 (22.1)	1,836 (22.9)	1.05 (0.92, 1.19)
Maternal race				
White	4,824 (49.8)	738 (44.5)	4,086 (50.9)	1.00 (Reference)
Black	2,460 (25.4)	506 (30.5)	1,954 (24.3)	1.43 (1.27, 1.63)
Other	2,402 (24.8)	415 (25.0)	1,987 (24.8)	1.16 (1.01, 1.32)
Prepregnancy BMI (kg/mg ²) [¶]	23.9 (21.2, 28.0)	24.1 (21.1, 29.2)	23.8 (21.2, 27.7)	—
<18.5	441 (4.6)	98 (5.9)	343 (4.3)	1.00 (Reference)
18.5–24.9	5,251 (54.2)	823 (49.6)	4,428 (55.2)	0.65 (0.51, 0.82)
25.0–29.9	2,271 (23.5)	379 (22.9)	1,892 (23.6)	0.70 (0.55, 0.90)
30.0	1,723 (17.8)	359 (21.6)	1,364 (17.0)	0.92 (0.72, 1.19)
Smoker	1,489 (15.4)	302 (18.2)	1,187 (14.8)	1.28 (1.12, 1.47)
Blood pressure (mmHg) – mean ± SD				
Systolic	109 ± 10	101 ± 11	109 ± 10	—
Diastolic	65 ± 8	66 ± 8	65 ± 8	—

* The proportions listed are among women diagnosed with ischemic placental disease only

[¶] Denotes median (25th, 75th percentiles)

Table 2

Associations between family history of preeclampsia in female relatives and ischemic placental disease in probands: Adjusted pairwise odds ratio (95% confidence interval)

	No ischemic placental disease [*]	Ischemic placental disease in proband		
		Any ischemic placental disease	Preeclampsia	Small for gestational age <10 th percentile
Any female relative	1.00 (Reference)	1.16 (1.00, 1.36)	— [‡]	— [‡]
Maternal grandmother	1.00 (Reference)	0.97 (0.72, 1.31)	1.16 (0.77, 1.74)	0.94 (0.65, 1.35)
Mother	1.00 (Reference)	1.19 (0.93, 1.52)	1.54 (1.12, 2.13)	0.96 (0.70, 1.30)
Sister(s)	1.00 (Reference)	1.20 (0.99, 1.45)	1.35 (1.03, 1.77)	1.04 (0.82, 1.33)

Pairwise odds ratios were adjusted for maternal age, education, maternal race, pre-randomized maternal body-mass index through alternating logistic regressions. The model for the marginal means included maternal age, education, maternal race, and pre-randomized maternal body-mass index

^{*} The comparison group for an outcome includes women diagnosed with the other two conditions in the syndrome of ischemic placental disease. For example, with preeclampsia as the outcome, the comparison group would include women with SGA and/or placental abruption

[‡] Alternating logistic regressions for these outcomes did not converge

Table 3

Associations between family history of preeclampsia in female relatives and ischemic placental disease in probands: Adjusted pairwise odds ratio (95% confidence interval)

	Ischemic placental disease in proband			
	No ischemic placental disease [*]	Any ischemic placental disease	Preeclampsia	Small for gestational age infant <5 th percentile
Any female relative	1.00 (Reference)	1.29 (1.08, 1.54)	1.48 (1.19, 1.83)	1.02 (0.77, 1.34)
Maternal grandmother	1.00 (Reference)	1.09 (0.78, 1.52)	1.16 (0.77, 1.74)	1.07 (0.65, 1.76)
Mother	1.00 (Reference)	1.21 (0.97, 1.51)	1.35 (1.03, 1.77)	0.94 (0.66, 1.35)
Sister(s)	1.00 (Reference)	1.37 (1.05, 1.80)	1.54 (1.12, 2.13)	1.13 (0.74, 1.73)
	No ischemic placental disease [*]	Any ischemic placental disease	Preeclampsia	Small for gestational age infant <3 rd percentile
Any female relative	1.00 (Reference)	1.32 (1.10, 1.60)	1.48 (1.19, 1.83)	1.10 (0.77, 1.58)
Maternal grandmother	1.00 (Reference)	1.02 (0.71, 1.47)	1.16 (0.77, 1.74)	1.00 (0.51, 1.97)
Mother	1.00 (Reference)	1.25 (0.99, 1.58)	1.35 (1.03, 1.77)	1.04 (0.66, 1.64)
Sister(s)	1.00 (Reference)	1.40 (1.05, 1.86)	1.54 (1.12, 2.13)	1.18 (0.68, 2.05)

Pairwise odds ratios were adjusted for maternal age, education, maternal race, pre-randomized maternal body-mass index through alternating logistic regressions. The model for the marginal means included maternal age, education, maternal race, and pre-randomized maternal body-mass index

^{*} The comparison group for an outcome includes women diagnosed with the other two conditions in the syndrome of ischemic placental disease. For example, with preeclampsia as the outcome, the comparison group would include women with SGA and/or placental abruption

[‡] Alternating logistic regressions for these outcomes did not converge

Table 4

Associations between family history of preeclampsia in female relatives and ischemic placental disease (preeclampsia and placental abruption only) in probands: Adjusted pairwise odds ratio (95% confidence interval)

	Ischemic placental disease in proband		
	No ischemic placental disease*	Any ischemic placental disease	Preeclampsia
Any female relative	1.00 (Reference)	1.35 (1.10, 1.67)	1.47 (1.19, 1.82)
Maternal grandmother	1.00 (Reference)	1.06 (0.71, 1.58)	1.16 (0.77, 1.74)
Mother	1.00 (Reference)	1.23 (0.94, 1.60)	1.34 (1.02, 1.76)
Sister(s)	1.00 (Reference)	1.47 (1.08, 2.00)	1.53 (1.11, 2.11)

This analysis includes 49 antepartum and 6 intrapartum non-malformed stillbirths as a sensitivity analysis. Small for gestational age (SGA) birth status was unknown for stillbirths, so SGA births are excluded in this analysis

Pairwise odds ratios were adjusted for maternal age, education, maternal race, pre-randomized maternal body-mass index through alternating logistic regressions. The model for the marginal means included maternal age, education, maternal race, and pre-randomized maternal body-mass index