OBJECTIVE: Migraine affects 28% of women in their pregnancy-capable years and is associated with systemic inflammation, endothelial dysfunction, and increased risk of pregnancy-associated thromboembolic events. A history of migraine has also been associated with adverse pregnancy outcomes (APO) of placental origin, including hypertensive disorders of pregnancy (HDP) and preterm birth (PTB). We tested the hypothesis that self-reported migraine in nulliparous individuals is associated with higher odds of APO.

STUDY DESIGN: The multicenter Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) enrolled 10,038 nulliparous US participants with singleton gestation in early pregnancy, following them prospectively through delivery. The medical histories were collected from the study participants by standardized interview: the participants were asked, “Have you ever had any of the following medical conditions or diagnoses?” followed by a list of diagnoses, which included “migraine headaches.” We considered participants who responded “yes” to this question at the first-trimester study visit to have a migraine history. We defined “APO” as ≥1 of the following outcomes, defined according to the standardized definitions and adjudicated by maternal-fetal medicine specialists after delivery: gestational hypertension, preeclampsia or eclampsia, PTB (medically indicated or spontaneous), small gestations, and stillbirth.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Migraine (N=1752)</th>
<th>No migraine (N=7698)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any APO</td>
<td>700 (40.0)</td>
<td>2658 (34.5)</td>
<td>1.26 (1.13–1.40)</td>
<td>1.26 (1.12–1.41)</td>
</tr>
<tr>
<td>Any hypertensive disorder of pregnancy</td>
<td></td>
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<tr>
<td>- Gestational hypertension</td>
<td>451 (25.7)</td>
<td>1738 (22.6)</td>
<td>1.19 (1.06–1.34)</td>
<td>1.18 (1.04–1.33)</td>
</tr>
<tr>
<td>- Preeclampsia or eclampsia (including superimposed preeclampsia)</td>
<td>273 (15.6)</td>
<td>1082 (14.1)</td>
<td>1.13 (0.98–1.30)</td>
<td>1.12 (0.96–1.30)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>12 (0.7)</td>
<td>45 (0.6)</td>
<td>1.17 (0.59–2.15)</td>
<td>0.97 (0.42–1.99)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>186 (10.6)</td>
<td>599 (7.8)</td>
<td>1.41 (1.18–1.67)</td>
<td>1.44 (1.19–1.73)</td>
</tr>
<tr>
<td>- Medically indicated</td>
<td>77 (4.4)</td>
<td>232 (3.0)</td>
<td>1.48 (1.13–1.92)</td>
<td>1.44 (1.08–1.89)</td>
</tr>
<tr>
<td>- Spontaneous</td>
<td>109 (6.2)</td>
<td>367 (4.8)</td>
<td>1.33 (1.06–1.65)</td>
<td>1.40 (1.11–1.77)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>206 (11.8)</td>
<td>811 (10.5)</td>
<td>1.13 (0.96–1.33)</td>
<td>1.16 (0.97–1.38)</td>
</tr>
<tr>
<td>Sensitivity analysis 1c</td>
<td></td>
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<tr>
<td>Migraine with medication use, visit 1 (N=332)</td>
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<tr>
<td>n (%)</td>
<td></td>
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<tr>
<td>Any APO</td>
<td>146 (44.0)</td>
<td>2658 (34.5)</td>
<td>1.49 (1.19–1.86)</td>
<td>1.49 (1.18–1.88)</td>
</tr>
<tr>
<td>Sensitivity analysis 2d</td>
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<tr>
<td>Reported migraine all 4 visits (N=1011)</td>
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<tr>
<td>n (%)</td>
<td></td>
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</tr>
<tr>
<td>Any APO</td>
<td>413 (40.9)</td>
<td>2658 (34.5)</td>
<td>1.31 (1.14–1.50)</td>
<td>1.32 (1.15–1.52)</td>
</tr>
</tbody>
</table>

Models were adjusted for the following covariates that differed significantly between exposure groups (P<.1) in univariable analysis: race or ethnicity, chronic hypertension, renal disease, autoimmune disorders (systemic lupus erythematosus or antiphospholipid syndrome), smoking in the 3 months before pregnancy, and family history of preeclampsia in mother or sister.

APO, adverse pregnancy outcome; CI, confidence interval; nuMoM2b, Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be; OR, odds ratio.

ORs having P<.05; Chronic hypertension not included in adjusted model for outcome of gestational hypertension; Sensitivity analysis 1: exposure group defined as those who reported migraine headaches with medication use within the last 2 months at visit 1; Sensitivity analysis 2: exposure group defined as those who reported migraine headaches at all 4 study visits.

for gestational age at birth, or stillbirth. We compared characteristics between participants who did and did not report migraine, including demographics, family history of preeclampsia, and comorbidities such as obesity, recent smoking, chronic hypertension, chronic kidney disease, pregestational diabetes mellitus, and autoimmune disorders. We created logistic regression models to estimate the odds ratios (ORs) and 95% confidence intervals (95% CIs) for the association of migraine with APO, adjusting for characteristics that showed between-group differences (P<1) in univariable analysis. In secondary analyses, we estimated the associations between migraine and individual APOs and tested for interactions between migraine and chronic hypertension, obesity, and diabetes mellitus. We performed sensitivity analyses, restricting the exposed group to (1) those who reported using migraine medications within the last 2 months and (2) those who reported migraine headaches at all 4 study visits during the pregnancy.

RESULTS: Of 9450 participants with complete data included in the analysis, 1752 (19.1%) reported a diagnosis of migraine at visit 1. The cohort characteristics are presented in the Supplemental Data. Age, income level, and body mass index did not differ between the exposure groups. Participants with migraine had higher proportions of self-identified White race, recent smoking history, autoimmune disorders, and chronic kidney disease. Adjusting for all factors that differed to P<1 in univariable analysis, participants with migraine had increased odds of any APO (adjusted OR, 1.26; 95% CI, 1.12–1.41). For individual APO, participants with migraine had higher odds of any HDP and both medically indicated and spontaneous PTB but not small for gestational age or stillbirth (Table). There were no significant interactions between migraine and obesity, chronic hypertension, or diabetes mellitus. Sensitivity analyses showed a larger effect in participants who reported recent medication use (adjusted OR, 1.49; 95% CI, 1.18–1.88).

CONCLUSION: In a diverse, prospective cohort of 9450 nulliparous US participants, self-reported migraine headaches were associated with 26% higher odds of APO—an effect driven by HDP and both medically indicated and spontaneous PTB. Migraine may be an underrecognized risk factor for APO.

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