Association of Parity With Carotid Diameter and Distensibility
Multi-Ethnic Study of Atherosclerosis

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Abstract—Pregnancy and childbirth are associated with hemodynamic changes and vascular remodeling. It is not known whether parity is associated with later adverse vascular properties such as larger arterial diameter, wall thickness, and lower distensibility. We used baseline data from 3283 women free of cardiovascular disease aged 45 to 84 years enrolled in the population-based Multi-Ethnic Study of Atherosclerosis. Participants self-reported parity status. Ultrasound-derived carotid artery lumen diameters and brachial artery blood pressures were measured at peak-systole and end-diastole. Common carotid intima-media thickness was also measured. Regression models to determine the association of carotid distensibility coefficient, lumen diameter, and carotid intima-media thickness with parity were adjusted for age, race, height, weight, diabetes mellitus, current smoking, blood pressure medication use, and total and high-density lipoprotein cholesterol levels. The prevalence of nulliparity was 18%. In adjusted models, carotid distensibility coefficient was $0.09 \times 10^{-5}$ Pa$^{-1}$ lower ($P=0.009$) in parous versus nulliparous women. Among parous women, there was a nonlinear association with the greatest carotid distensibility coefficient seen in women with 2 live births and significantly lower distensibility seen in primiparas ($P=0.04$) or with higher parity >2 ($P=0.005$). No such pattern of association with parity was found for lumen diameter or carotid intima-media thickness. Parity is associated with lower carotid artery distensibility, suggesting arterial remodeling that lasts beyond childbirth. These long-term effects on the vasculature may explain the association of parity with cardiovascular events later in life. (Hypertension. 2014;64:253-258.) ● Online Data Supplement

Key Words: carotid artery, common ■ carotid intima-media thickness ■ pregnancy ■ women

Parity has a nonlinear association with cardiovascular events,$^{1,2}$ with the minimum incidence in women with 2 births, a slightly higher incidence in nulliparas and primiparas, and a sharply higher incidence for women with higher parity. Parity is also associated with greater left ventricular mass.$^{3}$ Thus, childbearing may have long-lasting effects on the cardiovascular system, but the mechanism is unknown. There is a 40% increase in blood volume in pregnancy but no increase in systolic blood pressure because of a simultaneous reduction in peripheral vascular resistance.$^{4}$ Pregnancy is also associated with systemic arterial remodeling, presumably mediated by the peptide hormone relaxin.$^{5}$ Because remodeled arteries may have thicker walls especially in hypertension,$^{6}$ be stiffer, and stiffer arteries are associated with cardiovascular disease events,$^{7}$ we hypothesized that pregnancies in the past would be associated with remodeled systemic arteries that had larger lumens, relatively thicker walls, and lower distensibility. In this study, we investigated whether the parity and gravidity were associated with carotid artery diameter, intima-media thickness, and distensibility in middle-aged and older women.

Methods

Study Population

Multi-Ethnic Study of Atherosclerosis (MESA) is a multicenter multiethnic population-based study consisting of white, Chinese-American, black, and Hispanic-American race/ethnicities, aged 45 to 84 years, and free of clinical cardiovascular disease at baseline (2000–2002). The study was approved by the institutional review boards of all participating centers, and participants gave written informed consent. Of 3601 enrolled women, we excluded 300 because of unavailable imaging data and 18 because of missing parity data, resulting in a sample of 3283 women for this cross-sectional analysis.

Assessment of Gravidity and Parity

Gravidity and parity were self-reported. Gravidity, defined as the total number of pregnancies, and parity, defined as the total number of live births, were treated as ordinal variables (0, 1, 2, 3, 4, and 5+). If women reported a higher number of live births than pregnancies (n=30), the parity was assumed to be the number of pregnancies rather than the number of live births, presuming that this difference was because of multiple births. The validity of self-report for parity versus chart review is high ($k=0.93–0.98$) in prior studies.$^9$
Clinical Examination for Covariates
Participants answered questionnaires including self-reported age, race/ethnicity, educational attainment, current antihypertensive medication use, present or past use of birth control pills or hormone replacement therapy, and smoking. Height and weight were measured. Seated blood pressure was measured as the average of the second and third readings taken using Dinamap automated blood pressure device (Dinamap Monitor Pro 100) using appropriate Critikon cuff sizes as per the Critikon sizing chart. Total cholesterol categories (<200, 200–239, and ≥240) and high-density lipoprotein cholesterol categories (<40, 40–59, and ≥60) were defined from fasting lipid profiles. Diabetes mellitus was defined as fasting blood glucose ≥7 mmol/L or antidiabetic medication use.

Carotid Artery Imaging for Measurement of Distensibility
A 20-second B-mode ultrasound recording of a longitudinal section of the right distal common carotid artery was made using a Logiq 700 machine (General Electric Medical Systems). The brachial blood pressure was simultaneously measured during the recording (DINAMAPP System, General Electric Medical Systems). The Pearson correlations of this blood pressure measurement with average seated blood pressure were 0.78, 0.74, and 0.78 for systolic, diastolic, and pulse pressure, respectively. The pulse rate was also measured in the recording. Image analysis was performed centrally at Tufts Medical Center, Boston, MA. Automated edge detection software was used to determine the interadventitial carotid artery diameter during systole and diastole. For 2 blinded replicate images taken on the same day (n=89), the correlations between systolic and diastolic diameters and diameter change were 0.93, 0.94, and 0.66, respectively.

Common carotid intima-media thickness (cIMT) was measured as mean of the site-specific maximum measurements of all scans and near and far walls of the left and right common carotid arteries.10

Supplementary Imaging Data
Because a study of the uterine artery11 has found that pregnancy affects outward remodeling, we also examined data for carotid wall-to-lumen (W/L) ratio measured using MRI,12 briefly described in the online-only Data Supplement.

Access of Protocols and Data
The full protocols and data access procedures for the MESA study can be found at http://www.mesa-nhlbi.org.

Statistical Methods
We tabulated the distribution of demographic and cardiovascular risk factors by nulliparity versus parity. Group differences were assessed using χ² tests for categorical variables and ANOVA for continuous variables. Arterial distensibility coefficient (DC) is defined as follows:

\[
\frac{\Delta A}{A \Delta P} = \frac{\Delta (\log A)}{\Delta P} = (\text{slope of } \log A \text{ vs. } P)
\]

where A is the arterial cross-sectional area, P is the arterial pressure, and \( \Delta \) represents the change in diameter and pressure from diastole to systole.13 The slope \( \Delta (\log A)/\Delta P \) was calculated directly within regression models adjusting for the confounders of both A and P in a single step.14 The excursions from the mean of the systolic and diastolic pressures, together constituting pulse pressure as separate observations for each individual, were added to the mixed regression model, whereas the mean of systolic and diastolic pressures was added as a covariate. Individual-level pulse-cycle mean log(area) and the individual-level slope of log(area) versus pressure between systole and diastole were estimated as random effects, and group-level differences in diameter and slopes are estimated as fixed effects. An illustrative example of this mixed model is shown in Figure S1 in the online-only Data Supplement.

Models were fit to estimate the association of parity and gravidity with carotid diameter and DC. Additional covariates included hemodynamic and physical characteristics (height, weight, and heart rate measured from the ultrasound recording), demographic characteristics (age and race/ethnicity), and cardiovascular risk factors (total cholesterol categories, high-density lipoprotein cholesterol categories, current smoking, diabetes mellitus, and blood pressure medication use).

We examined the association of carotid DC with the number of live births and pregnancies in different models. First, we analyzed these variables dichotomously (gravidas versus nulligravidas and parous versus nulliparous, respectively). Then, we categorized as 0, 1, 2, 3, 4, and 5+. We tested whether any of the groups 1 to 5+ differed from each other using an omnibus χ² test. If the omnibus test was positive, we also fit a spline model with a different linear association of carotid diameter DC with nulliparity, 1 to 2 live births, and with 3+ live births.

Similar analyses were performed secondarily to determine the association of parity with cIMT and W/L ratio.

Sensitivity Analysis
We examined whether the association of carotid DC with parity or gravidity was robust to the addition of further covariates, parity redefinition, exclusion of 68 women with self-reported kidney disease, and age stratification, as described in the online-only Data Supplement.

Results
The Table shows the sample characteristics by parity groups. At baseline, 13% of women were nulliparous and 30% of nulliparous women reported one or more past pregnancies. Nulliparous women had a lower mean age, were more likely to be white, and had a more favorable cardiovascular risk profile than parous women. In these unadjusted tabulations, there were statistically significant trends for higher cIMT and larger lumen diameters with higher parity. DC was also statistically significantly different by parity, but the differences were not monotonic—higher parity was associated with lower DC with the exception of parity 2, which did not follow the trend. A slightly higher level W/L ratio is with higher parity (Table S3).

The cross tabulation of the number of live births versus the number of pregnancies is shown in Table S1.

Association of Mean Carotid Artery Diameter and DC With Parity and Gravidity
In adjusted models, mean carotid artery diameter (geometric mean of systolic and diastolic diameters) was not different comparing parous versus nulliparous women (0.26% larger in parous women; 95% confidence interval [CI], −0.73% to 0.61%), nor gravid versus nulligravid women (0.63% larger in gravidas; 95% CI, −0.50% to 1.25%; P=0.61), nor gravid versus nulligravid women (0.63% larger in gravidas; 95% CI, −0.50% to 1.25%; P=0.61), nor gravid versus nulligravid women (0.63% larger in gravidas; 95% CI, −0.50% to 1.25%; P=0.61), nor gravid versus nulligravid women (0.63% larger in gravidas; 95% CI, −0.50% to 1.25%; P=0.61). However, carotid DC was 0.09×10⁻⁵ Pa⁻¹ lower (95% CI, −0.16 to −0.02×10⁻⁵ Pa⁻¹; P=0.009) in parous versus nulliparous women and was 0.12×10⁻⁵ Pa⁻¹ lower (95% CI, −0.19 to −0.04×10⁻⁵ Pa⁻¹; P=0.003) in gravid versus nulligravid women. In analyses restricted to 588 nulliparous women, gravidity was associated with a similar magnitude of lower carotid DC (0.09×10⁻⁵ Pa⁻¹); however, this difference did not reach statistical significance (95% CI, −0.25 to 0.06×10⁻⁵ Pa⁻¹; P=0.23).

Neither the degree of parity nor gravidity had any association with carotid artery diameter in adjusted models (Table S2). Figure 1 shows the association of carotid DC with parity. Nonlinearity is seen in this association: In spline models, primiparous women have lower DC than nulliparous women (P=0.014), women with 2 live births have higher DC than primiparous women (P=0.050), and women with >2 births
Table. Demographic, Cardiovascular Risk Factor, and Carotid Measurement Distributions by Parity in the Multi-Ethnic Study of Atherosclerosis (MESA) Baseline Examination

<table>
<thead>
<tr>
<th>Sample Characteristic</th>
<th>Nulliparous</th>
<th>1 Birth</th>
<th>2 Births</th>
<th>3 Births</th>
<th>4 Births</th>
<th>5+ Births</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>588</td>
<td>492</td>
<td>801</td>
<td>606</td>
<td>564</td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>Number of live births, median [IQR]</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>7 [6–8]</td>
<td></td>
</tr>
<tr>
<td>Any history of pregnancy</td>
<td>177 (30%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>60.7±11.0</td>
<td>60.6±10.1</td>
<td>61.2±9.9</td>
<td>62.7±9.7</td>
<td>65.9±9.8</td>
<td>68.4±8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race (column adds to 100%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>290 (49%)</td>
<td>162 (33%)</td>
<td>347 (43%)</td>
<td>220 (36%)</td>
<td>172 (30%)</td>
<td>43 (19%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chinese-American</td>
<td>35 (6%)</td>
<td>54 (11%)</td>
<td>112 (14%)</td>
<td>82 (14%)</td>
<td>80 (14%)</td>
<td>19 (8%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>186 (32%)</td>
<td>192 (39%)</td>
<td>212 (26%)</td>
<td>160 (26%)</td>
<td>154 (27%)</td>
<td>46 (20%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic-American</td>
<td>77 (13%)</td>
<td>84 (17%)</td>
<td>130 (16%)</td>
<td>144 (24%)</td>
<td>158 (28%)</td>
<td>124 (53%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td>43 (7%)</td>
<td>60 (12%)</td>
<td>82 (10%)</td>
<td>71 (12%)</td>
<td>70 (12%)</td>
<td>45 (19%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoking</td>
<td>74 (13%)</td>
<td>83 (17%)</td>
<td>91 (11%)</td>
<td>68 (11%)</td>
<td>48 (9%)</td>
<td>21 (9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>231 (39%)</td>
<td>212 (43%)</td>
<td>348 (43%)</td>
<td>298 (49%)</td>
<td>288 (51%)</td>
<td>135 (58%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of blood pressure medication</td>
<td>169 (29%)</td>
<td>165 (34%)</td>
<td>263 (33%)</td>
<td>223 (37%)</td>
<td>210 (37%)</td>
<td>108 (47%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past or present birth control pill use</td>
<td>292 (50%)</td>
<td>256 (52%)</td>
<td>432 (54%)</td>
<td>315 (52%)</td>
<td>234 (41%)</td>
<td>67 (29%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Past or present hormone replacement therapy</td>
<td>257 (44%)</td>
<td>230 (47%)</td>
<td>404 (50%)</td>
<td>293 (48%)</td>
<td>246 (44%)</td>
<td>84 (36%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.2±6.3</td>
<td>28.7±6.6</td>
<td>28.1±6.0</td>
<td>28.9±6.1</td>
<td>29.0±6.1</td>
<td>29.4±4.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.2 (0.9)</td>
<td>5.1 (0.9)</td>
<td>5.2 (0.9)</td>
<td>5.2 (0.9)</td>
<td>5.2 (0.9)</td>
<td>5.1 (1.0)</td>
<td>0.46</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.4)</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seated systolic blood pressure, mm Hg</td>
<td>124.3±23.1</td>
<td>125.1±23.2</td>
<td>125.0±22.9</td>
<td>127.2±22.7</td>
<td>130.5±22.3</td>
<td>135.0±25.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seated diastolic blood pressure, mm Hg</td>
<td>69.1±10.0</td>
<td>69.5±10.4</td>
<td>68.7±10.2</td>
<td>69.6±10.4</td>
<td>68.8±9.8</td>
<td>69.6±10.8</td>
<td>0.55</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64.9±10.3</td>
<td>66.0±10.1</td>
<td>64.4±10.0</td>
<td>64.2±10.0</td>
<td>65.0±10.2</td>
<td>64.4±9.3</td>
<td>0.050</td>
</tr>
<tr>
<td>Common carotid IMT, mm</td>
<td>0.82±0.17</td>
<td>0.83±0.20</td>
<td>0.83±0.17</td>
<td>0.85±0.17</td>
<td>0.89±0.20</td>
<td>0.90±0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumen diastolic diameter, mm</td>
<td>5.7±0.7</td>
<td>5.8±0.7</td>
<td>5.8±0.7</td>
<td>5.8±0.7</td>
<td>6.0±0.7</td>
<td>6.0±0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid distensibility coefficient, ×10⁻⁵ Pa⁻¹</td>
<td>2.13±1.10</td>
<td>1.97±0.81</td>
<td>2.05±0.94</td>
<td>1.90±0.80</td>
<td>1.72±0.80</td>
<td>1.57±0.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Distributions shown as median [interquartile range], number (%), or mean±SD. Differences in distributions by parity were tested using χ² tests for categorical variables and ANOVA for continuous variables. BMI indicates body mass index; HDL, high-density lipoprotein; IMT, intima media thickness; and IQR, interquartile range.

*Diabetes mellitus was defined as fasting blood glucose ≥7 mmol/L or the use of antidiabetic medications.
†Hypertension was defined as blood pressure ≥140/90 or antihypertensive medication use. 1 Pa⁻¹ = 133.32 mm Hg⁻¹ (conventional units).

have a linear decline in DC compared with women with 2 live births (P=0.018).

Figure 2 shows a similar analysis by increasing gravidity. However, only nulligravidas differ significantly from women with any pregnancy history; there is no difference in the DC by number of pregnancies among gravidas (P=0.17).

Secondary analyses showed that there was no overall adjusted association between parity groups and either W/L ratio (Figure S2, P=0.50) or for cIMT (Figure S3, P=0.32). Their associations are also tabulated for adjacent comparison in Table S4.

Sensitivity analyses showed that the association of carotid artery DC with parity and gravidity was robust to further adjustment for birth control pill use, hormone replacement therapy, serum creatinine as a proxy for renal function, and education, the use of as-reported number of live births not harmonized with number of pregnancies, exclusion of women with self-reported kidney disease and age-stratified analysis as detailed in the online-only Data Supplement.

Discussion

We have shown a strong association of the history of parity and gravidity with carotid artery distensibility, but not to lumen diameter of intima-media thickness, in women from a diverse multietnic population with a wide age range. To our knowledge, this is the first demonstration of this association. We have shown a nonlinear and nonmonotonic association of parity with DC, with relatively protected carotid artery diameters in women with 2 live births. However, this nonmonotonic association is not apparent in the analysis of gravidity. This suggests that live births, possibly leading to a lifetime of exposure to child rearing, may have different implications for this risk factor compared with the hemodynamic and metabolic consequences of pregnancy per se. Because lower arterial distensibility, that is, greater arterial stiffness is associated with cardiovascular events,7,8 our results suggest that the vascular effects of pregnancy and childbirth may contribute to cardiovascular risk in women. Our results after demographic, cardiovascular risk factor, and blood pressure adjustment show that the parity-related changes are not primarily due to thicker wall (cIMT), or external remodeling leading to changes in W/L ratio, but rather, they are attributable to the hemodynamics of distensibility.

Two studies have shown a J-shaped relationship of parity with cardiovascular events.1,2 Parikh et al1 showed in a Swedish population that the nadir of cardiovascular disease risk was...
metalloproteinases (TIMP-1 and TIMP-2) are also raised. Thus, a raised, but the circulating levels of tissue inhibitors of metal-

proteinase-9 levels are higher in normal pregnancy compared with nonpregnant women. In women with pregnancy-

-induced hypertension, matrix metalloproteinase-9 levels are statistically significant. Overall significance of the association of DC with parity (P=0.002). Asterisks mark significant differences from the nulliparous group (P<0.05). In pairwise comparisons, parity level 2 differs from parity levels 1, 4, and 5+ (P<0.05); all other pairwise differences do not reach statistical significance.

found in women with 2 children, whereas women with fewer or a larger number of children had a greater cardiovascular disease risk. Parikh et al adjusted for the effects of pregnancy-related complications including gestational diabetes mellitus and pregnancy-induced hypertension, which may be in the causal pathway for cardiovascular risk; information about these complications is not available in our population. Lawlor et al also showed a similar J-shaped relationship with coronary heart disease in a British population. However, this study also showed that men with 2 children had a nadir of coronary heart disease risk, suggesting that child rearing, rather than pregnancy and birth, may be partially responsible for this relative protection that extends to both men and women. Parikh et al showed an increase in left ventricular mass with larger left ventricular volume in parous versus nulliparous women from MESA.

We show that even a single pregnancy without live birth may have the same magnitude of association with lower carotid DC, even though this association did not reach statistical significance because of the smaller sample size. The contrasting association of gravidity and parity with carotid DC in our study is consistent with the idea that the vascular consequences of pregnancies may not have a J-shaped relationship and may be superimposed on the consequences of child rearing, which may indeed have a J-shaped relationship.

The mechanism by which pregnancy may affect the long-term vasculature modeling and changes is not well understood. During pregnancy, relaxins secreted by the corpus luteum result in vasodilatation and a reduction in peripheral vascular resistance. The matrix metalloproteinase system has been a suggested mechanism for the remodeling of systemic arteries during pregnancy. Circulating matrix metalloproteinase-9 levels are higher in normal pregnancy compared with nonpregnant women. In women with pregnancy-induced hypertension, matrix metalloproteinase-9 levels are raised, but the circulating levels of tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2) are also raised. Thus, a balance between the metalloproteinases and their inhibitors is required for appropriate remodeling of the systemic vasculature. Although pregnancy-related hemodynamic changes are largely reversed postpartum, our findings suggest that some of the changes remain on the long term. In addition, although gestational insulin resistance is normal, its consequences may persist beyond repeated pregnancies resulting in long lasting vascular insult.

Our study shows that nulliparous women have better levels of cardiovascular risk factors including diabetes mellitus, hypertension, and lipid profile than parous women, as shown by others. Parous women tend to gain obesity that persists after pregnancy. Bennett et al showed worsening weight and weight-related health behaviors among women with and without gestational diabetes mellitus after their pregnancies. A persistence of these factors over a lifetime may result in vascular injury. Nicholson et al showed that grand multiparity (5+ births) was associated with a higher incidence of diabetes mellitus. The study of Nicholson et al pooled 1 to 2 live births into a single group; thus, we cannot distinguish whether women with 2 live births were relatively protected versus those with 1 live birth. We adjusted our analysis for lipid levels and diabetes mellitus as confounders. Another effect of parity, rather than gravidity, relates to the socioeconomic consequences of child rearing, especially for larger families. We have attempted to account for this by using educational attainment as a proxy for socioeconomic status in sensitivity analyses. In addition, our results were unaffected by exclusion of women with self-reported kidney disease or adjustment by serum creatinine as a proxy for impaired renal function, which may result in remodeling with thinner cIMT.

A strength of our study is the population-based multiethnic sample with a wide age range, enhancing the generalizability to multiple subgroups of women. The questionnaires and imaging measurement protocols were centrally standardized. We have also analyzed both gravidity and parity unlike prior studies. Our study also suffers from certain

Figure 1. Differences in carotid artery distensibility coefficient (DC; ×10−5 Pa−1) by parity compared with nulliparas. Regression coefficients and 95% confidence intervals adjusted for systolic and diastolic blood pressure, height, weight, pulse rate, age and race/ethnicity, total cholesterol categories, high-density lipoprotein cholesterol categories, current smoking, diabetes mellitus, and blood pressure medication use. Asterisks mark significant differences from the nulliparous group. In pairwise comparisons, parity level 2 differs from parity levels 1, 4, and 5+ (P<0.05); all other pairwise differences do not reach statistical significance.

Figure 2. Differences in carotid artery distensibility coefficient (DC; ×10−5 Pa−1) by gravidity compared with nulligravidas. Regression coefficients and 95% confidence intervals adjusted for systolic and diastolic blood pressure, height, weight, pulse rate, age and race/ethnicity, total cholesterol categories, high-density lipoprotein cholesterol categories, current smoking, diabetes mellitus, and blood pressure medication use. Asterisks mark significant differences from the nulliparous group. In pairwise comparisons, parity levels 2 and 3 differ from parity level 5+ (P<0.05); all other pairwise differences do not reach statistical significance.
limitations. All covariates are measured during a cross-sectional study in middle age or older women, although the mechanism we suggest is related to changes that occur during pregnancy and a lifetime of exposure. We did not have any information of pregnancy-related confounders, which may be risk factors for (or indicators of) cardiovascular disease, including gestational weight gain, gestational diabetes mellitus, preeclampsia, preterm birth, or small for gestational age infants.\textsuperscript{24} We have also estimated carotid DC from brachial blood pressure measurements, which may differ systematically from carotid blood pressure measurements, especially in younger people. However, we did not see significant qualitative differences in our findings in age-stratified analyses. We do not have information whether pregnancies that did not result in live births were as a result of miscarriages representing existing vascular disease or because of elective procedures. We also did not have information on health behaviors associated with child rearing. We were unable to discern the reasons why women had a pregnancy but no live birth (eg, elective abortion, miscarriage, or intrauterine fetal death), limiting our ability to characterize differential risks in the nulliparous population. Also, educational attainment, our proxy measure of socioeconomic status, may not appropriately represent the socioeconomic pressures related to child rearing. Nevertheless, the association we have found is robust correcting for the economic pressures related to child rearing. We do not have any information of pregnancy-related confounders, which may be risk factors for (or indicators of) cardiovascular disease, including gestational weight gain, gestational diabetes mellitus, preeclampsia, preterm birth, or small for gestational age infants.\textsuperscript{24} We have also estimated carotid DC from brachial blood pressure measurements, which may differ systematically from carotid blood pressure measurements, especially in younger people. However, we did not see significant qualitative differences in our findings in age-stratified analyses. We do not have information whether pregnancies that did not result in live births were as a result of miscarriages representing existing vascular disease or because of elective procedures. We also did not have information on health behaviors associated with child rearing. We were unable to discern the reasons why women had a pregnancy but no live birth (eg, elective abortion, miscarriage, or intrauterine fetal death), limiting our ability to characterize differential risks in the nulliparous population. Also, educational attainment, our proxy measure of socioeconomic status, may not appropriately represent the socioeconomic pressures related to child rearing. Nevertheless, the association we have found is robust correcting for the covariates that we do have and represents the situation in a population-based sample.

Perspectives

Nulliparas and nulligravidas have more distensible carotid arteries than parous women and gravidas. Gravidity is not further associated with carotid distensibility. However, women with a parity level of 2 are relatively protected from loss of carotid distensibility. This effect on the vasculature may partially explain the effects of gravidity and parity on cardiovascular disease events. Longitudinal vascular and biochemical studies performed through pregnancy and postpartum will be necessary to determine the mechanism through which gravidity and parity affect arterial distensibility.

In conclusion, we have shown that gravidity and parity are associated with lower carotid artery distensibility, suggesting arterial remodeling that lasts beyond childbirth.

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Disclosures

D. Vaidya is a consultant for MBC Inc. The other authors report no conflicts.

References


**Novelty and Significance**

**What Is New?**
- We show the association between pregnancy and live birth history with arterial distensibility in later life.

**What Is Relevant?**
- The association of gravidity and parity with lower carotid artery distensibility suggests arterial remodeling that lasts beyond childbirth.

**Summary**
Our article examines a large multiethnic US population sample and shows that pregnancy and childbearing have long-term implications on vascular properties. Our study provides a possible explanation of the previously reported association of parity with cardiovascular events.
Association of Parity With Carotid Diameter and Distensibility: Multi-Ethnic Study of Atherosclerosis
Dhananjay Vaidya, Wendy L. Bennett, Christopher T. Sibley, Joseph F. Polak, David M. Herrington and Pamela Ouyang

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Supplemental Material

This supplemental Material has been provided to give additional methods and data about the work.

Supplement to:

Association of Parity with Carotid Diameter and Distensibility: MultiEthnic Study of Atherosclerosis

Dhananjay Vaidya, Wendy L. Bennett, Christopher T. Sibley, Joseph F. Polak, David M. Herrington, Pamela Ouyang
Illustrative explanation of the regression model to determine group differences in carotid artery distensibility coefficient

Arterial distensibility coefficient (DC) is defined as:

\[
\frac{\Delta A}{\Delta P} \approx \frac{\Delta (\log A)}{\Delta P} = \text{slope}(\log(A) \text{ vs. } P)
\]

where \( A \) is the arterial cross sectional area, \( P \) is the arterial pressure and \( \Delta \) represents the change in diameter and pressure from diastole to systole. Because \( A \) and \( P \) have multiple confounders, we did not use this definition to calculate the DC within each person, but rather the slope of \( \log A \) vs. \( P \) was calculated within a regression model that adjusts for the confounders of arterial pressure.

Figure S1: As an illustration, we graph the data from 6 nulligravid women (closed circles, solid lines) and 6 age, race and height matched gravidas (women with the past history of pregnancies, open circles, dashed lines).

For each woman, the diameter of the right common carotid artery during systole and diastole on the logarithmic scale is plotted against the excursion of the pressure during systole and diastole from the mean of the systolic and diastolic pressures. The mixed model regression fits an intercept, i.e., the \( \log \) of (diameter) at the mean of systolic and diastolic pressures, and a slope of \( \log \) (diameter) vs. pressure to each individual as random effects. The overall fit for the two groups (thick black line for nulligravidas and thick grey line for gravidas) is estimated as the fixed effect of the regression. The group mean of distensibility is \( 2 \times \) (fixed effect slope), as defined above. The mean of the systolic and diastolic blood pressures, and other confounders of blood pressure, e.g., age, race, etc., are included as covariates in this regression. Because blood pressures and diameters enter separately as independent and dependent variables in this regression, the estimates for group mean distensibility are fully and appropriately adjusted for the confounders.

An alternate definition of DC using the arterial diameter \( D \) is as follows:

\[
\frac{2}{D} \times \frac{\Delta D}{\Delta P} \approx 2 \times \frac{\Delta (\log D)}{\Delta P} = 2 \times (\text{slope log}(D) \text{ vs. } P)
\]

This is mathematically identical with the expression the uses the arterial cross sectional area.

\( \text{slope log}(A) \text{ vs. } P = \text{slope log}(\frac{\pi D^2}{4}) \text{ vs. } P = \text{slope}\left(2 \times \log(D) + \log(\frac{\pi}{4})\right) \text{ vs. } P = 2 \times (\text{slope of logD vs. } P) \)

We thus note that using either \( \log \) (diameter) of \( \log \) (area) in the formula, rather than using non-logarithmic transformed values, results in the identical value for DC.

Supplementary Methods for Measurement of Wall-to-Lumen Ratio

The details of the high-resolution magnetic resonance imaging (MRI) used to determine carotid wall-to-lumen (W/L) ratio are described in detail by Wasserman et al. (Stroke. 2008
Briefly, imaging was done using 1.5T MRI scanners with bilateral carotid receive-only coils placed on the neck. Cross sectional images through the common carotid artery (T1 and T2-weighted images) were obtained as guided by proton-density weighted black blood longitudinal section of the carotid artery. Vessel wall and lumen areas were analyzed using the semiautomated Vesselmass software.

**Supplementary Methods for Sensitivity Analyses:**

We examined if the association of carotid DC with parity or gravidity was robust to the addition of the following covariates: history of the past or current use of birth control pills, history of the past or current use of hormone replacement therapy, serum creatinine as a proxy for renal function and educational achievement (less than high school, high school, bachelor’s degree, graduate degree) as a proxy for socioeconomic status. We also repeated the analyses using the number of live births as reported by the women (not reset lower to the number of pregnancies for 30 women). We also repeated the analysis in two age strata (ages 45-64, and ages 65-84) to examine the patterns of association, because the difference between brachial and carotid pressures may differ with age.

**Supplementary results for Sensitivity Analyses**

The association of carotid artery DC with parity and gravidity was robust to further adjustment for birth control pill use, hormone replacement therapy, serum creatinine as a proxy for renal function, and education level as a proxy for socioeconomic status. Results were unchanged when we used parity groups based on reported number of live births that exceeded the reported number of pregnancies in 30 women. The association of DC with parity in both age strata in the secondary analysis showed a pattern similar to the overall, i.e., parity 1 had lower DC than nulliparous, parity 2 had greater DC than parity 1, and parity 3, 4, and 5+ had incrementally lower DC than parity 2. The confidence intervals of the parity association beta coefficients overlapped each other substantially (interaction p-values for various parity groups range from 0.32 to 0.49).
Table S1: Cross tabulation of the number of pregnancies versus the number of live births in the baseline examination of the Multiethnic Study of Atherosclerosis (MESA)

<table>
<thead>
<tr>
<th>Number of Live Births</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>411</td>
<td>87</td>
<td>51</td>
<td>24</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>273</td>
<td>120</td>
<td>65</td>
<td>29</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>512</td>
<td>178</td>
<td>101</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>362</td>
<td>239</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>542</td>
<td>22</td>
</tr>
<tr>
<td>5+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>232</td>
</tr>
</tbody>
</table>
Table S2: Association of History of Parity and Gravidity with Carotid Artery Diameter in the Multiethnic Study of Atherosclerosis (MESA)

<table>
<thead>
<tr>
<th>Number of Live Births</th>
<th>Percent Difference in Geometric Mean of Systolic and Diastolic Carotid Diameter [95% CI] vs. Nulliparous</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>0.76% [-0.54% to 2.08%]</td>
<td>0.25</td>
</tr>
<tr>
<td>2</td>
<td>0.23% [-0.92% to 1.40%]</td>
<td>0.70</td>
</tr>
<tr>
<td>3</td>
<td>-0.48% [-1.70% to 0.76%]</td>
<td>0.44</td>
</tr>
<tr>
<td>4</td>
<td>0.65% [-0.64% to 1.95%]</td>
<td>0.33</td>
</tr>
<tr>
<td>5+</td>
<td>0.25% [-1.47 to 2.00%]</td>
<td>0.78</td>
</tr>
<tr>
<td>Omnibus p-value for groups</td>
<td></td>
<td>0.43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Pregnancies</th>
<th>Percent Difference in Geometric Mean of Systolic and Diastolic Carotid Diameter [95% CI] vs. Nulligravidas</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ref</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>0.95% [-0.59% to 2.51%]</td>
<td>0.23</td>
</tr>
<tr>
<td>2</td>
<td>0.72% [-0.61% to 2.06%]</td>
<td>0.29</td>
</tr>
<tr>
<td>3</td>
<td>-0.18% [-1.52% to 1.18%]</td>
<td>0.80</td>
</tr>
<tr>
<td>4</td>
<td>1.02% [-0.27% to 2.31%]</td>
<td>0.12</td>
</tr>
<tr>
<td>5+</td>
<td>0.72% [-0.99 to 2.47%]</td>
<td>0.41</td>
</tr>
<tr>
<td>Omnibus p-value for groups</td>
<td></td>
<td>0.28</td>
</tr>
</tbody>
</table>

Adjusted for systolic and diastolic blood pressure, height, weight, pulse rate, age and race/ethnicity, total cholesterol categories, HDL-cholesterol categories, current smoking, diabetes, BP medication use.
Table S3: Means and Standard deviations of %Wall thickness to Lumen Ratio by Parity in the Multiethnic Study of Atherosclerosis (MESA) Baseline Examination

<table>
<thead>
<tr>
<th>Parity</th>
<th>0 births</th>
<th>1 birth</th>
<th>2 births</th>
<th>3 births</th>
<th>4 births</th>
<th>5+ births</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36.7 ± 5.7</td>
<td>36.8 ± 6.9</td>
<td>36.8 ± 5.8</td>
<td>37.2 ± 6.3</td>
<td>37.8 ± 7.0</td>
<td>37.5 ± 6.5</td>
<td>0.027</td>
</tr>
</tbody>
</table>


Table S4: Adjacent presentation of the association of carotid vascular parameters with parity

<table>
<thead>
<tr>
<th>Number of Live Births</th>
<th>Percent Difference in Geometric Mean of Systolic and Diastolic Carotid Diameter [95% CI] vs. Nulliparous</th>
<th>Differences in Carotid Artery Distensibility Coefficient ($\times 10^{-5}$Pa$^{-1}$) [95% CI] vs. Nulliparous</th>
<th>Differences in Common Carotid Intima-Media Thickness (mm) [95% CI] vs. Nulliparous</th>
<th>Differences in Geometric Mean of W/L Ratio (dimensionless) [95% CI] vs. Nulliparous</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>1</td>
<td>0.76% [-0.54% to 2.08%]</td>
<td>-0.11 [-0.2 to -0.02]</td>
<td>-0.01 [0.03 to 0.02]</td>
<td>0.004 [-0.004 to 0.011]</td>
</tr>
<tr>
<td>2</td>
<td>0.23% [-0.92% to 1.40%]</td>
<td>-0.02 [-0.1 to 0.05]</td>
<td>-0.01 [0.03 to 0.02]</td>
<td>0.003 [-0.004 to 0.010]</td>
</tr>
<tr>
<td>3</td>
<td>-0.48% [-1.70% to 0.76%]</td>
<td>-0.08 [-0.17 to 0]</td>
<td>-0.01 [0.03 to 0.02]</td>
<td>0.004 [-0.003 to 0.012]</td>
</tr>
<tr>
<td>4</td>
<td>0.65% [-0.64% to 1.95%]</td>
<td>-0.14 [-0.23 to -0.06]</td>
<td>0 [0.04 to 0.02]</td>
<td>0.007 [-0.001 to 0.014]</td>
</tr>
<tr>
<td>5+</td>
<td>0.25% [-1.47 to 2.00%]</td>
<td>-0.16 [-0.27 to -0.05]</td>
<td>-0.01 [0.04 to 0.03]</td>
<td>0.000 [-0.010 to 0.010]</td>
</tr>
<tr>
<td>Omnibus p-value</td>
<td>0.43</td>
<td>0.002</td>
<td>0.32</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Adjusted for systolic and diastolic blood pressure, height, weight, pulse rate, age and race/ethnicity, total cholesterol categories, HDL-cholesterol categories, current smoking, diabetes, BP medication use.
Figure S1

Individual areas at mean BP (random effect)

Individual slopes (random effect)

Linear fit for groups (fixed effect)
intercept = average area; slope = average distensibility
adjusted for mean BP, and confounders of BP and area

Carotid Area (sq.mm)

Systolic-Diastolic Excursion of BP from Mean (mmHg)
Figure S2

Differences in W/L ratio by parity compared to nulliparas. Regression coefficients and 95% confidence intervals adjusted for systolic and diastolic blood pressure, height, weight, pulse rate, age and race/ethnicity, total cholesterol categories, HDL-cholesterol categories, current smoking, diabetes, BP medication use. P-value for any difference by parity group, p = 0.50
Differences in common carotid intima-media thickness by parity compared to nulliparas. Regression coefficients and 95% confidence intervals adjusted for systolic and diastolic blood pressure, height, weight, pulse rate, age and race/ethnicity, total cholesterol categories, HDL-cholesterol categories, current smoking, diabetes, BP medication use. Overall p-value for any difference by parity group, p = 0.32