Delivery May Affect Arterial Elasticity in Women

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Background: Estrogen is considered to be cardioprotective, but estrogen replacement therapy for postmenopausal women has not shown results for either primary or secondary cardiovascular event prevention. During normal pregnancy, women have significantly higher levels of estrogen and it may be endogenous estrogen that helps prevent atherosclerosis.

Methods and Results: The present cross-sectional study examined the association between pregnancy followed by delivery and clinical atherosclerosis using the brachial–ankle pulse wave velocity (PWV). A total of 2,560 women undergoing annual health screening at the Institute of Hyogo Prefecture Health Promotion Association in Japan were recruited. Pregnancy history (the age of menarche/ menopause and the number of gravida/para), conventional coronary risk factors, and brachial–ankle PWV were recorded. Multivariate linear regression by stepwise selection analysis demonstrated that women who had 1 or more deliveries had a significantly lower PWV, independent of age and other conventional coronary risk factors.

Conclusions: Pregnancy followed by delivery may decrease arterial stiffness and prevent the progress of atherosclerosis in women. The contribution of such a pregnancy followed by delivery-related decrease in arterial stiffness to the reduction of cardiovascular disease in women should be further evaluated. (Circ J 2009; 73: 750–754)

Key Words: Atherosclerosis; Estrogen; Delivery; Pregnancy; Pulse-wave velocity

The lower incidence of atherosclerosis in premenopausal women than in men is an established epidemiological observation. Menopause is also a well-known coronary risk factor, but estrogen replacement therapy for postmenopausal women has not shown the hoped-for results in either primary (WHI: Women’s Health Initiative) or secondary (HERS: Heart and Estrogen/Progesterin Replacement Study) cardiovascular event prevention. Even though large clinical studies such as HERS and WHI showed no additional benefit from exogenous estrogen to prevent atherosclerosis, we believe endogenous estrogen may help to prevent atherosclerosis. During normal menstrual cycles, women show high levels of estrogen just before ovulation and during the luteal phase. Previously we and other researchers reported that endothelium-dependent vasodilatation is increased in young women during the phases of their menstrual cycles when endogenous estrogen levels are high, and pregnant women show significantly high levels of estrogen. Therefore, we hypothesized that if women have been exposed for a longer time and/or at a higher level to endogenous estrogen, they may obtain estrogen’s beneficial “cardioprotective” or “anti-atherosclerosis” effect. To examine this hypothesis, we enrolled a substantial number of women and used a fairly simple measurement to evaluate clinical atherosclerosis. Increased arterial stiffness, as reflected by an increased pulse wave velocity (PWV), is a risk factor for atherosclerotic cardiovascular disease. PWV is a non-invasive technique widely used in the clinical setting, so we measured the brachial–ankle PWV (baPWV) as an indicator of arteriosclerosis. Although the baPWV reflects central and peripheral arterial stiffness, it is closely correlated with aortic arterial stiffness and the severity of atherosclerosis, so we considered it might be useful as both a marker of cardiovascular risk and an indicator of clinical arteriosclerosis.

In this cross-sectional study, we examined the association between pregnancy followed by delivery (number of both gravida and para) and the baPWV.

Methods

A total of 2,560 women undergoing an annual health screening examination at the institute of Hyogo Prefecture Health Promotion Association were recruited for the study (age range 22–83 years). Subjects with an ankle–brachial pressure index of less than 0.9 and with a significant arrhythmia such as atrial fibrillation, which may affect the results of PWV, were excluded from the study. Informed consent was obtained from all of the women who were enrolled and the study protocol was approved by the Ethics Committee of Hyogo Prefecture Health Promotion Association. The age at menarche, pregnancy history (number of both gravida and para), menopausal status and the use of estrogen replacement therapy were obtained by a self-reporting questionnaire, which was confirmed by medical staff at the Institute. Conventional coronary risk factors,
including hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM) and smoking, were also investigated by the same questionnaire. Women who had not menstruated in 12 months were considered to be menopausal, those who were pregnant at the time of the examination, those who could not precisely recall the date of their last menstrual period, and those who did not answer the questionnaire were excluded from the study.

The baPWV was measured using a volume-plethysmographic apparatus (Form PWV/ABI, OMRON COLIN Co Ltd, Tokyo, Japan). The methodology has been described and validated. The women rested supine while ECG electrodes were placed on both wrists, and cuffs were wrapped around both arms and ankles. The cuffs were connected to plethysmographic sensors to determine the brachial and post-tibial arterial pressure waveforms and volume pulse forms, and to oscilloscopic sensors to measure the blood pressure (BP). Data were recorded for 10 s to obtain a sufficient amount of waveform data. The waveform characteristics were determined automatically according to the phase velocity theory. Components over 5 Hz were stored using a pass filter, and the wave front was determined. The time interval between the wave front of the brachial waveform and that of the ankle waveform was defined as the time interval between the brachium and the ankle (ATba). The distance between the baPWV sampling points was calculated automatically according to the height of the woman.

The path length from the suprasternal notch to the brachium (Lb) was obtained from superficial measurements: 

\[ L_b = 0.2195 \times \text{height (cm)} - 2.0734 \]

The path length from the suprasternal notch to the ankle (La) was also obtained from superficial measurements:

\[ L_a = 0.8129 \times \text{height (cm)} + 12.328 \]

Finally, the baPWV was measured after the subject had rested for at least 5 min: 

\[ \text{baPWV} = \frac{(L_a - L_b)}{\Delta \text{Tba}} \]

### Statistical Analysis

Data were expressed as the mean±standard deviation. We performed all analyses with STATA ver.8.2 (StataCorp, College Station, TX, USA). The mean of the right and left baPWV values for each subject was used for the statistical analysis. The relationship between pregnancy followed by delivery and the baPWV was evaluated by univariate and multivariate linear regression analyses adjusted for age and systolic BP. Multivariate linear regression analysis was also conducted to determine whether the number of pregnancies, number of deliveries or number of abortions were independent variables for baPWV, independent of age and other coronary risk factors (HT, HL, DM, obesity, and smoking). We created a model that included all significant covariates and selected the best prediction model by stepwise selection method (Inclusion criteria; P=0.10). We conducted a likelihood ratio test to select the final model in this analysis.

### Results

A total of 2,560 women were examined: 45 did not provide information regarding pregnancies; 572 had never been pregnant (G0) and 620 have never experienced delivery (P0). A total of 1,895 women had experienced at least 1 delivery (P≥1). The mean number of pregnancies and the mean number of deliveries was 2.02 and 1.65, respectively. Other factors potentially related to PWV are shown in Table 1.

Univariate analyses showed that the baPWV was significantly associated with pregnancy, delivery and abortion (P=0.005, 0.003 and 0.001, respectively). All the coefficients of the univariate analyses were positive. To adjust for the effect of aging and increased BP, we included age and mean BP in a linear regression model. Here, the right baPWV can be predicted by the following equations:

\[ \text{PWV} = -12.9 \times \text{Parous (n)} + 10.45 \times \text{mean BP (mmHg)} + 10.2 \]

\[ \text{Age (years)} + \text{Constant} \]

\[ \text{PWV} = -7.16 \times \text{Gestation(n)} + 10.46 \times \text{mean BP (mmHg)} + 10.1 \]

\[ \text{Age (years)} + \text{Constant} \]

The adjusted model showed that pregnancy and delivery were negatively correlated with the baPWV (both P-values <0.0001) (Table 2). The positive correlation of abortion and the baPWV was not significant after adjustment for age and mean BP.

Other significant variables in the univariate analysis for this cohort were age, body mass index (BMI), HT, DH, HL, gout, total cigarettes per day by year (Brinkman index) and mean BP. Because pregnancy and delivery were highly correlated (r=0.948), we modeled for parity only in the multivariate models.

We developed multivariate linear regression models to predict PWV for this cohort based on age and other known risk factors: Parous, having given birth to 1 or more viable children; mean BP (mmHg); age (years); BMI; gout (1 = Yes, 0 = No); HL (1 = Yes, 0 = No); DM (1 = Yes, 0 = No); HT (1 = Yes, 0 = No); Brinkman index: (cigarette/day)×smoking.

### Table 1. Population Characteristics (n=2,560)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right baPWV (cm/s)</td>
<td>1,368.57 (±244.58)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.23 (±8.95)</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td>13.14 (±1.47)</td>
</tr>
<tr>
<td>Gravida (n)</td>
<td>2.02 (±1.49)</td>
</tr>
<tr>
<td>Para (n)</td>
<td>1.65 (±1.15)</td>
</tr>
<tr>
<td>Abortion (n)</td>
<td>0.37 (±0.75)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.97 (±5.41)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.46 (±8.31)</td>
</tr>
<tr>
<td>BMI</td>
<td>22.38 (±3.22)</td>
</tr>
<tr>
<td>Smoking status (Brinkman index)</td>
<td>26.69 (±110.06)</td>
</tr>
<tr>
<td>Right mean BP (mmHg)</td>
<td>90.91 (±12.82)</td>
</tr>
<tr>
<td>HRT (%)</td>
<td>2.76</td>
</tr>
<tr>
<td>HT (%)</td>
<td>11.21</td>
</tr>
<tr>
<td>DM (%)</td>
<td>2.07</td>
</tr>
<tr>
<td>HL (%)</td>
<td>17.57</td>
</tr>
<tr>
<td>Gout (%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Family history of atherosclerosis (%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

SD, standard deviation; baPWV, brachial–ankle pulse wave velocity; BMI, body mass index; BP, blood pressure; HRT, hormone replacement therapy; HT, hypertension; DM, diabetes mellitus; HL, hyperlipidemia.

### Table 2. Multiple Linear Regression Analysis for Right baPWV in Pregnancy Adjusted for Age and Mean BP

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SE (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parous (n)</td>
<td>-12.9</td>
<td>2.93 (-18.7, -7.17)</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>10.45</td>
<td>0.27 (9.92, 10.99)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.2</td>
<td>0.40 (9.40, 10.99)</td>
</tr>
<tr>
<td>Gestations (n)</td>
<td>-7.16</td>
<td>2.28 (-11.6, -2.68)</td>
</tr>
<tr>
<td>Mean BP (mmHg)</td>
<td>10.46</td>
<td>0.27 (9.93, 11.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>10.10</td>
<td>0.41 (9.30, 10.89)</td>
</tr>
</tbody>
</table>

SE, standard error; CI, confidence interval; Parous, given birth to 1 or more viable children; Gestations, no. of previous pregnancies. Other abbreviations see in Table 1.
year. Here, the right baPWV can be predicted by the following equation:

\[
PWV = -12.35 \text{ Parous} + 9.81 \text{ Age} + 9.84 \text{ mean BP} - 1.64 \text{ BMI} + 40.31 \text{ DM} + 55.81 \text{ HT} + 64.7 \text{ Gout} + 15.23 \text{ HL} + 0.035 \text{ Brinkman index} + \text{Constant (Table 3).}
\]

The best predictors selected by stepwise regression analysis were:

\[
PWV = -12.72 \text{ Parous} + 9.82 \text{ Age} + 9.77 \text{ mean BP} + 21.5 \text{ HL} + 51.9 \text{ HT} + \text{Constant (Table 4).}
\]

The multivariate linear regression model including all other significant covariates (Table 3) and the model chosen by stepwise selection (Table 4) showed that pregnancy was negatively correlated with the baPWV. All P-values for deliveries in the 2 models were less than 0.001 with negative coefficients. Likelihood ratio test showed no statistically significant difference in terms of predicting the increasing PWV (P=0.16). We selected the stepwise selection model as our final model.

To overcome the hormonal effect on the PWV, we examined the 1,524 postmenopausal women and achieved the same results. Furthermore, when we excluded women with conventional coronary risk factors (HT, HL, DM, smoking), we also obtained the same results (n=890).

**Discussion**

This study confirmed that women who had had at least 1 pregnancy followed by delivery showed a decreased level of arteriosclerosis compared with those who had never experienced delivery. As far as we know, this is the first study to examine the relationship between pregnancy history and clinical arteriosclerosis measured non-invasively by baPWV. PWV is suggested to be significantly affected by BP\(^2\)\(^1\)\(^2\)\(^1\)\(^3\), hyperlipidemia, hypertension and Brinkman index: (cigarette/day)×smoking year.

**Figure.** Age and brachial–ankle pulse wave velocity (baPWV) according to the predicted values of multivariate stepwise linear regression in parous and nulliparous women. The predicted values of baPWV for the population having given birth to 1 or more viable children is less than that of the population having given no birth for all ages (P<0.01). Predicted baPWV adjusted for mean blood pressure (mmHg), hyperlipidemia, hypertension and Brinkman index: (cigarette/day)×smoking year.
for PWV by predicted values of multivariate stepwise linear regression analysis.

Since the publicity of HERS, a secondary prevention trial, and the WHI, a large randomized primary prevention trial, questions have been raised about the cardioprotective effect of estrogen. The results of the WHI study may have been biased because of the subjects having a high incidence of obesity, a wide age range, and a relatively late start of hormone replacement therapy (HRT), which did not correspond to the conventional use of HRT. In contrast, the results of the Estrogen in the Prevention of Atherosclerosis Trial, a randomized, double-blind, placebo-controlled trial, suggest a cardioprotective effect of estrogen. Pregnancy followed by delivery differs from "exogenous" HRT; however, it may be that, even though it lasts less than the 40 weeks, during pregnancy women have an elevated level of "endogenous" estrogen in their bodies. Pregnancy may be natural endogenous estrogen augmentation or estrogen "pulse" therapy.

Human umbilical vein endothelial cells exposed to high concentration of 17-estradiol was used as an anti-atherosclerotic agent to demonstrate feasibility in an in-vitro vascular model. Cecic et al demonstrated that a high concentration of estrogen reduces the level of asymmetric dimethylarginine (ADMA), which is an endogenous competitive inhibitor of nitric oxide (NO) synthase. Estradiol, by reducing ADMA, may therefore facilitate NO synthesis in endothelial cells. Previously, we reported that endothelium-dependent vasodilatation is increased in young women during the phases of the menstrual cycle when endogenous estrogen is elevated. In the normal physiology of pregnancy, women have significantly higher levels of estrogen derived mainly from the placenta. Pregnant women demonstrate 100-fold higher blood levels of both estrone and estradiol, and 1,000-fold higher blood level of estril compared with non-pregnant women in the same age group. These high levels of estrogen derived from the placenta may be related to decreased arterial stiffness; a few clinical studies demonstrating improved endothelial function and decreased PWV during pregnancy support this.

We have also reported that even a reduced dose of estrogen after standard dosing of oral conjugated estrogen 0.625 mg and medroxyprogesterone acetate 2.5 mg per day for post-menopausal osteoporotic Japanese women for 3 years improved endothelial function in the brachial artery and prevented progression of the carotid intima–media thickness. Mares et al also reported that HRT with estradiol valerate and cyproterone acetate improved endothelium-dependent vasodilatation and arterial wall compliance in postmenopausal women.

The arterial PWV, measured as baPWV, is a marker of parietal elasticity. In addition to resting tone, this measurement can reflect sclerotic components of the artery. Hormone-related changes in vascular tone, such as endothelium-dependent vasodilatation, would be expected to evolve more rapidly than sclerotic components, and be more readily reversed by hormonal change such as HRT. Therefore, PWV rather than endothelium-dependent vasodilatation or intima–media thickness in the carotid artery might reflect long-term effects on the vessel by elevated endogenous estrogen levels. Initially, we hypothesized that if women were exposed for a longer time to endogenous estrogen, such as with multiple deliveries, then they may have a greater decrease in arterial stiffness. However, when we compared women with P1 and those with P2 or more, there was no difference between them. It seems that there is no additional reduction in PWV after women experience at least 1 delivery. Furthermore there are only 13 women who had more than 5 deliveries (25), so we are unable to conclude that multiple deliveries are cardioprotective in our study setting.

Because this study was clinical observation, we can not conclude that delivery alone is an influential factor. We can not fully exclude the following factors, which may be related to PWV reduction and influenced the results: human chorionic gonadotropin or other hormones that may increase or decrease during pregnancy. Socioeconomic factors or lifestyle changes after delivery may also be involved in this phenomenon; however, further studies are needed to evaluate these anti-atherosclerotic mechanisms. It is known that menopause or lack of endogenous estrogen is a risk factor for cardiovascular disease. We have confirmed that women who are regularly menstruating have a decreased PWV compared with post-menopausal women of the same age. We have also confirmed that a younger age at menarche correlates with PWV reduction. This finding may support the idea that as long as women are exposed to endogenous estrogen they have decreased arterial stiffness.

If we can differentiate the women’s gravida/para status in the Framingham study or other population-based studies we may gain new insights. We suspect that women with P≥1 compared with G0 or P0 have a lower incidence of cardiovascular events. Animal models in which we can control the number of pregnancies and environmental factors may clarify estrogen’s effects on atherosclerosis. For example, when we examine apolipoprotein E knockout mice based on the gravida/para status, there may be a difference in the development of atherosclerosis. At the same time, using molecular biology techniques, we can investigate molecular mechanisms such as changes in the estrogen receptor α or β. Further studies will clarify the mechanism underlying this phenomenon.

We conclude that pregnancy followed by delivery may delay the progress of arteriosclerosis in women.

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References


