Published in final edited form as:

Hypertens Pregnancy. 2018 November ; 37(4): 204–211. doi:10.1080/10641955.2018.1524479.

Brachial Artery Stiffening in Healthy Primigravidas is Associated with Weight Gain and Increased Cardiac Output

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Abstract

Objective: To assess brachial artery distensibility and associated factors in healthy primigravidas.

Methods: We assessed brachial artery distensibility using the DynaPulse 5000A in 37 women each trimester, and 6–8 weeks and 1–5 years postpartum. Associations with physical and cardiometabolic measures were considered.

Results: Mean (SE) brachial artery distensibility (% /mmHg) decreased (stiffened) from 7.50 (0.20) 12–14 weeks to 6.93 (0.22) 36–38 weeks ($p < .01$) and returned to baseline 7.52 (0.44) at 2.7 years postpartum. Weight gain and greater cardiac output were significantly related to greater stiffness.

Conclusion: Increased weight and cardiac output of pregnancy were associated with brachial artery stiffening.

Keywords

Arterial stiffness; pregnancy

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DISCLOSURES: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Declaration of Interests: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

INTRODUCTION

A recent systematic review and meta-analysis has demonstrated that women with pregnancies complicated by preeclampsia have greater arterial stiffness during and after pregnancies than do women with normotensive pregnancies.¹ The higher stiffness is likely due to different trajectories of change of stiffness throughout pregnancy as opposed to baseline differences.^{1, 2} But the normal changes in arterial stiffness during pregnancy are complex and not well understood. It has long been thought that pregnancy's acute effects on the vasculature are positive; both systemic vascular resistance and global (combined central and peripheral) arterial stiffness decrease during pregnancy.^{3, 4} Recent studies, however, suggest that the effects of pregnancy on the vasculature are more mixed. They have found that the carotid artery actually stiffens during the course of pregnancy,^{5, 6} is stiffer in pregnant women at greater gestational ages,⁷ and is stiffer in mid-life and older women of higher parity.⁸ In another study, common carotid artery intima-media thickness increased throughout pregnancy and remained increased at 2 years postpartum.⁹ Carotid-to-radial pulse wave velocity, a measure of peripheral arterial stiffness, shows an initial decrease, then a steady increase from the early second trimester through the end of pregnancy.¹⁰ But studies are limited by lack of prospective data collection throughout pregnancy,^{7, 8} small sample size,^{5, 6} and lack of collection of data on hemodynamic and metabolic changes during pregnancy.^{5-8, 10} that might illuminate reasons for the changes.

One measure of peripheral arterial stiffness, distensibility of the brachial artery, can be measured easily, reliably, and non-invasively in the outpatient setting using the DynaPulse system (Pulse Metric, Inc., San Diego, CA).¹¹ The DynaPulse has the advantage of simultaneously measuring several hemodynamic parameters known to change during pregnancy, including cardiac output, and thus can gather prospective information on both changes in arterial stiffness during pregnancy and factors associated with those changes. Understanding factors associated with changes in stiffness of the brachial artery during healthy pregnancy may illuminate processes that go awry in the development of hypertensive disorders of pregnancy.

An objective of the *Maternal Vascular Adaption to Healthy Pregnancy* (MVP) Study was to evaluate prospectively the normal changes in brachial artery distensibility that occur during uncomplicated first pregnancy. A secondary objective was to explore the relationship between pre-conception and pregnancy-related factors and brachial artery distensibility. We hypothesized that despite increases in fluid volume and weight, factors associated with higher arterial stiffness,¹² the brachial artery would not stiffen during pregnancy.

METHODS

MVP Study Design and Population

The MVP study prospectively assessed brachial artery distensibility in a cohort of healthy women experiencing their first pregnancies. Participants were healthy non-smoking women, age 21–39 years, at less than 38 weeks gestational age in their first pregnancies. Exclusion criteria were: 1) vasoactive medication use; 2) infertility history, defined as ever having had a period of at least 12 months of inability to achieve pregnancy, or using fertility medications

to achieve pregnancy; 3) family history of premature coronary artery disease; and 4) multiple gestation. Participants were recruited from the community (Pittsburgh, PA). All participants signed an informed consent document approved by the University of Pittsburgh, Human Research Protection Office.

Study visits were scheduled at 12–14 weeks, 24–26 and 36–38 weeks of pregnancy, and at 6–8 weeks postpartum, and occurred between June 2010 and March 2013. We originally intended to enroll all women at the 12–14 week visit; however, we changed the study design to allow women to begin at any pregnancy visit when recruitment proved to be slower than anticipated. After a telephone screening for eligibility, women began the study at the next scheduled pregnancy visit. The targeted sample size of 46 women was calculated to provide greater than 80% power to detect a 0.5 SD difference, given an assumed 0.5 correlation among the repeated observations, assuming that 20% of women would develop a pregnancy complication and that there would be 25% attrition from the study.

Women were later invited to return for an additional follow-up visit 1–5 years after their initial participation. Women were excluded if currently pregnant or if they had a pregnancy within the past 4 months (5 women). Fourteen women had moved out of the region. Seventeen women returned, of whom 14 had uncomplicated first pregnancies and are included in this analysis. These visits occurred between October 2014 and July 2015.

Brachial Artery Distensibility and Cardiac Output

Brachial artery distensibility and cardiac output were measured using the DynaPulse 5000A (Pulse Metric, Inc., San Diego, CA) by vascular sonographers from the University of Pittsburgh Ultrasound Research Laboratory. Participants rested in a seated position for 5 minutes and then a standard cuff sphygmomanometer was attached to the left arm. The cuff was automatically inflated for a calibration run; after calibration 3 runs were performed, and the mean of the 3 used for the analysis. The offline waveform analysis of arterial pressure signals performed by PulseMetric, Inc. uses validated models of the vascular system to calculate cardiovascular parameters.¹¹ The brachial artery distensibility coefficient is calculated as change in volume divided by change in pressure (% /mmHg), or as $4\pi/(dP/dt_{pp} * t_{pp})$, where dP/dt_{pp} is the amplitude from the peak positive pressure derivative to the peak negative pressure derivative of oscillometric pulsation signal and t_{pp} is the interval between the peak positive and peak negative pressure derivatives.¹³ Thus, lower values represent greater arterial stiffness. To calculate cardiac output, dP/dt_{pp} was used to approximate left ventricular dP/dt_{pp} , and a Gaussian transformation function was then used to calculate left ventricular contractility (LVC). Cardiac output was calculated as cardiac output = LVC * heart rate * body surface area. Body surface area was calculated as a function of weight and height.¹⁴ Validation studies of the methods have been published, with a linear regression correlation of $r = 0.83$ for compliance compared with measurements from intraarterial cannulation.¹¹

Demographic, Physical and Laboratory Measures

Women completed a self-administered demographic form with information on age, race/ethnicity, marital status, education, employment, income, insurance status and intended birth

site at their initial study visit. After the 6–8 week postpartum visit, staff reviewed pregnancy and birth records. At the 1–5 years postpartum visit participants completed updated history forms focused on subsequent reproductive history. Each visit included physical measures, vascular evaluation, and laboratory assays. Research staff measured height using a stadiometer with the participant not wearing shoes. The mean of 2 readings from the first study visit was used. Lightly clothed participants were weighed on a standard balance scale and the mean of 2 readings used. Pre-pregnancy weight was identified as the pre-pregnancy weight documented in the prenatal record or, if not available, as a documented weight in the health record in the three months prior to the last menstrual period. Pre-pregnancy body mass index (BMI) was calculated as pre-pregnancy weight in kilograms divided by height in meters squared. Weight change was calculated as the difference between weight at each study visit and pre-pregnancy weight.

Blood pressure was measured according to a standardized protocol. After participants rested for 5 minutes in a quiet room, research staff palpated the right radial pulse for 30 seconds and then measured blood pressure in that arm using a mercury sphygmomanometer, with auscultation of the 5th Korotkoff sound indicating diastolic pressure. The mean of the last 2 of 3 measurements was used for the analysis. Data on demographic and physical measures and from records reviews were collected and managed using REDCap electronic data capture tools hosted at the University of Pittsburgh.¹⁵

Laboratory assays were performed on fasting serum samples at the Heinz Nutrition Laboratory at the University of Pittsburgh, Graduate School of Public Health (Pittsburgh, PA). Total cholesterol,¹⁶ high density lipoprotein (HDL-c),¹⁷ low density lipoprotein (LDL-c)¹⁸, triglycerides¹⁹ and glucose²⁰ were determined using standard laboratory procedures. Insulin was measured using standard radio-immune assay (Linco Research, St. Charles, MO). HOMA-IR, a measure of insulin resistance, was calculated as (glucose x insulin)/405.²¹ High-sensitivity C-reactive protein (hsCRP) was measured with an enzyme-linked immunoassay (Alpha Diagnostics International, Inc. San Antonio, TX).

Statistical Analysis

Distributions were assessed for all variables. Measures with approximately normal distributions are presented as means $\pm$ standard deviations (SD); measures not normally-distributed are presented as medians with interquartile range, and categorical variables are presented as percentages. HOMA-IR and hsCRP were skewed and were log-transformed to meet the linear assumptions of regression modeling. Linear mixed models were used to calculate 1) estimated mean brachial artery distensibility adjusted for maternal age and pre-pregnancy BMI, and indicators of each trimester and postpartum; 2) the overall effect of trimester or length of time postpartum on distensibility; and 3) which specific time points (trimester, postpartum) vary from each other.

To determine associations between cardiovascular risk factors and distensibility a hierarchical regression approach was used. Maternal age and pre-pregnancy BMI were a priori included in all models. Models were constructed including time-varying systolic blood pressure, weight, weight change, heart rate and cardiac output. Predictors significant at a two-sided P-value of <0.05 (systolic blood pressure, weight, weight change and cardiac

output) were included in the full models and, and statistically significant predictors were retained in a best model. Next, biomarkers were tested individually in the best model. Biomarkers with statistical significance (glucose, HDL, triglycerides and hsCRP) were then modeled together, and only statistically significant biomarkers were retained. Modeling was done using data from the first 4 visits, because of the smaller sample size for the fifth visit, and the fact that varying numbers of subsequent pregnancies, times from subsequent pregnancies, and breastfeeding status would make interpretation difficult. A sensitivity analysis was performed eliminating 3 outliers for hsCRP, and another was done including only the 15 women who completed all of the first 4 study visits. All analyses were performed using SAS statistical software versions 9.3 and 9.4 (SAS Institute, Cary, NC).

RESULTS

The study enrolled 44 women, of whom 43 had multiple visits and 6 developed pregnancy complications, leaving 37 women in the sample for this analysis. Participants' average age at baseline was 28.4 ± 4.6 years and average BMI was 24.3 ± 3.3 (kg/m²). A majority were white (91.9%), married or living as married (89.2%), well-educated (89.2% college graduate or greater) and employed (64.9% full time, 24.3% part time). **Mean birth weight was 3427.2 ± 224.5 g and mean gestational age at birth was 39.7 ± 1.3 weeks. Route of birth was vaginal for 91.2% of women, and no newborns had Apgar scores less than 7 at 1 or 5 minutes of life. At the 6–8-week postpartum visit, 88% of participants were exclusively breastfeeding their infants.**

The mean number of initial visits attended was 3.3 (range 2–4). Fifteen women enrolled at the 12–14 week visit and completed all 4 initial visits. Two women enrolled at the 12–14 week visit and completed the 3 pregnancy visits, but moved postpartum and did not attend a postpartum visit. Fifteen women enrolled at the 26–28 week visit and completed the subsequent pregnancy visit and postpartum visit. Five women enrolled at the 36–38 week visit and then completed the 6–8 week postpartum visit. Fourteen women attended the second postpartum visit, at a mean (SD) of 2.7 (0.8) years.

The brachial artery stiffened between the 12–14 week and 24–26 week visits, and remained stiffer at 6–8 weeks postpartum. The brachial artery distensibility coefficient decreased from mean (SE) 7.50 %/mm Hg (0.20) at 12–14 weeks of pregnancy to 7.01 %/mm HG (0.21) at 24–26 weeks of pregnancy, and then remained stable at 6–8 weeks postpartum (overall $P = .049$) (Table 1). After adjustment for maternal age and pre-pregnancy BMI, this pattern remained the same (Figure 1a). This stiffening resolved by 2.7 years postpartum with a mean of 7.52 %/mmHg (0.44) ($P = 0.66$ compared to 12–14 weeks value). Patterns were the same in the sensitivity analysis including only the 15 women who completed all 4 initial visits (Figure 1b).

Changes in weight, blood pressure, heart rate, cardiac output, and lipid, glucose and hsCRP concentrations followed expected patterns for healthy pregnancies (Table 1). When weight and hemodynamic factors were assessed, a lower brachial artery distensibility coefficient was associated with higher systolic blood pressure, higher weight, greater weight change, and greater cardiac output (Table 2). When weight and hemodynamic factors were modeled

together, greater weight gain and cardiac output remained significantly associated with lower brachial artery distensibility coefficient (Table 3).

When metabolic factors were considered individually, higher HDL-c concentrations were associated with a stiffer brachial artery and higher triglycerides, glucose, and hsCRP concentrations were associated with lower stiffness. Insulin and insulin resistance were not significantly associated with stiffness. After modeling the significant metabolic factors together, only hsCRP remained significantly associated with lower stiffness (Table 3). Including hsCRP substantially changed the beta coefficient for the postpartum period, from -0.735 (0.01) to -0.368 (.29). Results of all analyses were consistent with those from the sensitivity analysis including only the women who completed all initial 15 study visits (data not shown).

DISCUSSION

This first study to evaluate changes in brachial artery distensibility during the course of normal first pregnancies found that the brachial artery stiffened between the 12–14 weeks and 24–26 weeks visits, remained stiffer than 12–14 weeks values at 6 to 8 weeks postpartum, but appeared to return to baseline levels by 2.7 years postpartum. This postpartum value was higher than that reported for similarly-aged white women in the Bogalusa Heart Study (6.7 %/mmHg), and may reflect that ours was a healthier population.²² These changes were associated with greater weight gain and increase in cardiac output during pregnancy, suggesting these factors mediate the change. Brachial artery distensibility was not associated with blood pressure independent of changes in weight, and was associated with several markers of inflammation, including hsCRP, triglyceride, and glucose concentrations.

These findings support the observation that the pregnancy's effect on the vasculature differs by vascular bed. While overall systemic resistance decreases and the aorta becomes more compliant during pregnancy, mounting evidence shows that the carotid artery, and perhaps the brachial artery, stiffen.^{5–7, 10, 23} Our study, using a different measure, also found that the brachial artery stiffened during healthy pregnancy. The mechanism for the different effects on different arterial beds is unknown. It has been speculated that the carotid artery and aorta may express different proportions of receptors for estrogen and angiotensin II,⁶ and that this may explain the varied effects of pregnancy.

These findings are consistent with research showing that change in arterial stiffness is strongly related to weight change in young adults. Lower brachial artery distensibility has been associated with higher BMI in several studies in young people.^{24, 25} In an observational study, weight change over a 2 year period was significantly related to change in aortic stiffness in 20–40 year old adults, independent of aging and changes in blood pressure.¹² Our clinical trial examining a weight loss intervention coupled with a low sodium diet found that weight loss over a 6 month period was associated with decreased arterial stiffness, again independent of changes in blood pressure.²⁶ The mechanism of these changes is unknown, but researchers have speculated that weight gain is independently related to increased vascular stiffness.²⁷ Our study measured cardiac output, and strongly suggests that in

pregnancy weight gain and increased cardiac output were related to the increased arterial stiffness. Consistent with findings from the Cardiovascular Risk in Young Finns study,⁷ lipid concentrations were not independently related to arterial stiffness. Perhaps the hormonal milieu of pregnancy, which includes high levels of sex hormones and relaxin, may have a protective effect on the vasculature from what may normally be negative metabolic conditions.

This research may have implications for research into hypertensive disorders of pregnancy. Peripheral arterial stiffness in pregnancy has been found to be higher in pregnancies complicated by preeclampsia than in healthy pregnancies in some,^{28, 29} but not all studies,³⁰ and at 16 months postpartum.³¹ Our findings provide baseline data that can be used in future research examining patterns of arterial stiffness in healthy pregnancies compared to pregnancies complicated by preeclampsia. The DynaPulse device is easily used in the outpatient setting, and could be a useful clinical tool.

This study was to our knowledge the first to prospectively follow a cohort of pregnant women into the postpartum period with a reliable measure of brachial artery distensibility and concurrent collection of various hemodynamic and metabolic measures. It benefited from high retention of participants in the original study. However, there were some limitations to the study. The first visit did not occur until 12–14 weeks of pregnancy. Substantial hemodynamic changes occur as early as 5 weeks of pregnancy,⁴ so it is likely that our first visit does not represent a true pre-pregnancy baseline. It is possible that an initial increase in brachial artery distensibility coefficient occurred before the 12–14 weeks pregnancy visit. Additionally, we were unable to meet our goal of enrolling all women at 12–14 weeks of pregnancy. This decreased the statistical power of the study, possibly leading to false negative results. Pre-pregnancy weights were largely self-reported; it has been shown that women tend to under-report pre-pregnant weight.³² Participants were overwhelmingly breastfeeding (94%) at the 6–8 weeks postpartum visit, and the results might not reflect those in women formula feeding their infants. The largely white, well-educated women in this cohort may not be representative of the general population of first time pregnant women, yet the study provides valuable baseline data against which arterial stiffness changes in other demographic groups can be assessed.

We found that the brachial artery stiffens between the 12–14 weeks and 24–26 weeks of a healthy first pregnancy, remains stiffer at 6–8 weeks postpartum, and appears to return to baseline at 2.7 years postpartum. The stiffening during pregnancy appears to be explained by the increased weight and cardiac output that occur during pregnancy, and is independent of changes in blood pressure. Several inflammatory markers are associated with greater stiffening, but after multivariable adjustment only hsCRP was independently associated. This stiffening is similar to stiffening demonstrated in the carotid artery, but different from the increased compliance seen in the aorta. Understanding normal arterial changes may allow for better understanding of the physiology of hypertensive disorders of pregnancy and identify women at risk for complications early in pregnancy.

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Figure 1a.
Changes in brachial artery distensibility over time.

Figure 1b. Changes in brachial artery distensibility over time; results of sensitivity analysis including only the 15 women who completed all 4 initial study visits.

Table 1
Unadjusted values for cardiovascular measures and biomarkers by trimester and postpartum

Measure	1 st Trimester n=17	2 nd Trimester n=32	3 rd Trimester n=37	1 st Postpartum n=35	Overall p Value
BrachD (%/mm Hg)	7.50 (.20)	7.01 (.21)	6.93 (.22)	6.95 (.17)	0.049
Weight (kg)	68.7 (2.2)	73.1 (1.6)	79.5 (1.8)	69.2 (1.5)	<0.0001
Weight change (kg)	0.55 (0.46)	7.27 (0.62)	14.4 (0.91)	4.3 (0.75)	0.0005
Systolic blood pressure (mm Hg)	103.7 (2.1)	106.0 (1.7)	110.4 (1.4)	106.2 (1.7)	<0.0001
Heart rate (bpm)	78.0 (2.4)	79.8 (1.6)	82.0 (1.5)	68.1 (1.5)	<0.0001
Cardiac Output (L/min)	5.24 (.25)	5.71 (.23)	6.23 (.23)	4.46 (.10)	<0.0001
Total cholesterol (mg/dl)	201.7 (8.9)	257.3 (7.0)	273.1 (7.2)	191.4 (5.5)	<0.0001
LDL-c (mg/dl)	111.2 (7.0)	148.0 (6.3)	155.5 (6.6)	114.7 (4.8)	<0.0001
Triglycerides (mg/dl)	108.3 (10.5)	176.5 (10.2)	250.7 (13.6)	77.3 (7.0)	<0.0001
HDL-c (mg/dl)	68.8 (2.2)	74.0 (3.1)	66.8 (2.3)	61.2 (1.8)	<0.0001
Glucose (mg/dl)	79.3 (1.5)	77.2 (1.1)	77.0 (1.2)	82.6 (1.2)	0.0007
Insulin (μU/ml)	8.84 (0.78)	11.25 (0.98)	11.95 (0.81)	8.59 (0.50)	0.0008
HOMA-IR	1.64 [1.32, 2.09]	2.16 [1.56, 2.56]	2.28 [1.67, 2.51]	1.72 [1.34, 2.13]	0.01
hsCRP (mg/L)	3.58 [2.16, 5.57]	3.36 [2.31, 5.49]	3.29 [2.24, 7.01]	1.20 [1.77, 2.44]	<0.0001

Normally distributed values presented as mean (SE) and p value from mixed models.

Skewed values presented as median [IQR] and p value from Wilcoxon rank-sum test.

BrachD is brachial artery distensibility. Weight change is change from pre-pregnancy weight.

Table 2

Associations¹ between brachial artery distensibility, age, BMI, weight, and hemodynamic predictors.

Predictor	Model 1 ²		Model 2		Model 3		Model 4		Model 5	
	β (SE)	p value	β (SE)	p value	β (SE)	p value	β (SE)	p value	β (SE)	p value
Trimester 1	Ref		Ref		Ref		Ref		Ref ³	
Trimester 2	−0.595 (.27)	0.03	−.587 (.26)	.03	−.315 (.29)	.28	−.047 (.32)	.88	−.211 (.25) ³	.40
Trimester 3	−0.732 (.26)	0.01	−.533 (.28)	.06	−.032 (.38) ³	.93	.491 (.47) ³	.30	−.080 (.25) ³	.75
Postpartum	−0.744 (.27)	0.01	−.707 (.28)	.01	−.626 (.28)	.03	−.462 (.29)	.12	−1.00 (.24)	<.0001
Baseline Age (years)	0.000 (.03)	0.997	−.011 (.03)	.75	−.031 (.04)	.38	−.029 (.03)	.38	−.057 (.03)	.08
Pre-pregnancy BMI (kg/m ²)	−0.086 (.05)	0.08	−.040 (.05)	.44	.046 (.07)	.51	−.087 (.05)	.06	.015 (.05)	.75
Systolic blood pressure (mm Hg)			−.030 (.01)	.02						
Weight (kg)					−.054 (.02)	.01				
Weight change (kg)							−.091 (.03)	.00		
Cardiac Output (L/min)									−.539 (.10)	<.0001

¹Linear mixed models.

²Model 1: Adjusted for age and pre-pregnancy BMI. Model 2: Model 1 systolic blood pressure. Model 3: Model 1 plus weight change. Model 4: Model 1 plus cardiac output.

³Different from postpartum at p <.05.

⁴Different from second trimester at p <.05.

BMI is body mass index. Weight change is from pre-pregnancy.

Table 3

Associations¹ between brachial artery distensibility, age, BMI and independent predictors.

Predictor	Model 1 ²		Model 2 ²		Model 3 ²	
	β (SE)	p value	β (SE)	p value	β (SE)	p value
Trimester 1	Ref		Ref		Ref	
Trimester 2	−0.595 (.27)	0.03	0.214 (.30) ³	0.48	.358 (.29)	.23
Trimester 3	−0.732 (.26)	0.01	0.846 (.42) ^{3,4}	0.05	.951 (.42) ^{3,4}	.03
Postpartum	−0.744 (.27)	0.01	−0.735 (.26)	0.01	−.320 (.26) ⁴	.23
Baseline Age (years)	0.000 (.03)	0.997	−0.076 (.03)	0.02	−.082 (.03)	.02
Pre-pregnancy BMI (kg/m ²)	−0.086 (.05)	0.08	0.002 (.05)	0.96	−.019 (.05)	.70
Weight change (kg)			−0.074 (.03)	0.01	−.075 (.03)	.01
Cardiac Output (L/min)			−0.486 (.10)	<0.0001	−.490 (.10)	<.0001
Log hsCRP					.289 (.10)	<0.01

¹Linear mixed models.

²Model 1: Adjusted for age and pre-pregnancy BMI. Model 2: Model 1 plus weight change and cardiac output. Model 3: Model 2 plus Log hsCRP.

³Different from postpartum at p <.05.

⁴Different from second trimester at p<.05. BMI is body mass index. Weight change is from pre-pregnancy.