OBSTETRICS

Pregnancy induces persistent changes in vascular compliance in primiparous women

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OBJECTIVE: Pregnancy induces rapid, progressive, and substantial changes to the cardiovascular system. The low recurrence risk of preeclampsia, despite familial predisposition, suggests an adaptation associated with pregnancy that attenuates the risk for subsequent preeclampsia. We aimed to evaluate the persistent effect of pregnancy on maternal cardiovascular physiology.

STUDY DESIGN: Forty-five healthy nulliparous women underwent baseline cardiovascular assessment before conception and repeated an average of 30 months later. After baseline evaluation, 17 women conceived singleton pregnancies and all delivered at term. The remaining 28 women comprised the nonpregnant control group. We measured mean arterial blood pressure, cardiac output, plasma volume, pulse wave velocity, uterine blood flow, and flow-mediated vasodilation at each visit.

RESULTS: There was a significant decrease in mean arterial pressure from the prepregnancy visit to postpartum in women with an interval pregnancy (prepregnancy, 85.3 ± 1.8; postpartum, 80.5 ± 1.8 mm Hg), with no change in nonpregnant control subjects (visit 1, 80.3 ± 1.4; visit 2, 82.8 ± 1.4 mm Hg) ($P = .002$). Pulse wave velocity was significantly decreased in women with an interval pregnancy (prepregnancy, 2.73 ± 0.05; postpartum, 2.49 ± 0.05 m/s), as compared with those without an interval pregnancy (visit 1, 2.56 ± 0.04; visit 2, 2.50 ± 0.04 m/s) ($P = .005$). We did not observe a residual effect of pregnancy on cardiac output, plasma volume, uterine blood flow, or flow-mediated vasodilation.

CONCLUSION: Our observations of decreased mean arterial pressure and reduced arterial stiffness following pregnancy suggest a significant favorable effect of pregnancy on maternal cardiovascular remodeling. These findings may represent a mechanism by which preeclampsia risk is reduced in subsequent pregnancies.

Key words: cardiovascular remodeling, hypertension, preeclampsia, pregnancy, vascular stiffness

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Pregnancy is known to induce rapid, progressive, and substantial changes to the cardiovascular system, ultimately facilitating successful pregnancy outcome. Women who develop hypertensive disorders during pregnancy are considered to have failed the cardiovascular stress test of pregnancy and likely represent a subpopulation in whom cardiovascular accommodation was inadequate.[1-4]

Risk for preeclampsia, a failure of the pregnancy stress test, is highest for first pregnancies and decreases with subsequent pregnancies, with the length of the interpregnancy interval being an important determinant of subsequent pregnancy-associated hypertension.[5-8] This phenomenon suggests that there may be an adaptation associated with prior pregnancy that attenuates the risk for preeclampsia in subsequent pregnancies and whose influence is time-limited.

Evaluation of the persistence of pregnancy-induced cardiovascular remodeling is limited. Few studies describe changes caused by pregnancy with reference to prepregnancy values. Clapp and Capeless[9] reported a persistent increase in cardiac output as well as decreased peripheral vascular resistance at 1 year postpartum, with greater changes from prepregnancy values in parous women. Our laboratory has evaluated the pattern of changes in blood pressure that accompany a first pregnancy compared with a subsequent pregnancy and found reduced mean arterial pressure prior to and throughout subsequent pregnancies compared with first pregnancies.[10] In those observations, the interval of time between

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pregnancies was inversely related to the difference in mean arterial pressure between pregnancies, such that as time between pregnancies increased, the decrease in mean arterial pressure became smaller.

This phenomenon was confirmed in a larger cohort in which mean arterial pressure was found to be reduced in second pregnancies in a time-dependent fashion.[11] These observations are consistent with reports that longer interpregnancy intervals are associated with an increased risk for the recurrence of preeclampsia.[12-15]

The current report examines broad cardiovascular indices, including measures of uterine blood flow (UBF) and flow-mediated vasodilation (FMD) in nulliparous women prior to pregnancy and approximately 1 year postpartum compared with nulliparous women without an interval pregnancy, with matched elapsed time points. We aimed to evaluate the effect of pregnancy on postpartum cardiovascular physiology. We hypothesized that pregnancy would be associated with a reduction in arterial stiffness that would persist postpartum.

Materials and Methods

Thirty-four nulligravid women interested in conception were enrolled in this research study through an open advertisement. Women were provided with ovulation detection kits (Quidel Corp, San Diego, CA) to assist with achieving a successful conception. Twenty-eight women, also nulligravid, not interested in conception, were recruited as the control/nonpregnant group. All subjects were young (18-40 years), healthy nonsmokers with regular menstrual cycles at the time of enrollment. None of the women had a history of hypertension, autoimmune disease, diabetes, or other disorders known to affect blood pressure.

Subjects provided a list of current medications and supplements at each study visit. Subjects taking antihypertensive agents or other medications known to affect blood pressure were not eligible for study participation. A questionnaire completed at the time of the initial visit evaluated for a family history of hypertension, stroke, myocardial infarction, clotting disorder, and type 2 diabetes.

Of the pregnancy group, 30 women subsequently conceived. Eight subjects conceived before baseline prepregnancy studies were performed; 1 subject had a first-trimester miscarriage; 1 subject was lost to follow-up and 3 subjects did not return for their postpartum visit. The remaining 17 subjects, all of whom conceived singleton pregnancies, had complete prepregnancy assessments, term pregnancy outcomes, and a postpartum visit, comprise the current report.

One woman developed complicated hypertension during the third trimester with new-onset hypertension (>140/90 mmHg), elevated liver enzymes, elevated uric acid concentration (>5 mg/dL), and fetal growth restriction and had iatrogenic delivery at 37 weeks.

Women were enrolled consecutively over a 33 month period, from May 2004 through February 2007. Prior to each study visit, subjects were provided with a 3500 mg sodium-balanced diet for 72 hours. Each subject was asked to abstain from alcohol and caffeine, beginning at least 24 hours before the study, and to avoid the use of decongestants and nonsteroidal medications, beginning at least 48 hours before the study.

All study visits in nonpregnant women were performed during the follicular phase. The research protocols were approved by the University of Vermont Human Investigational Committees. All women studied provided written informed consent.

Each periodic assessment was conducted between 8:00 AM and 10:00 AM. Subjects were admitted to the University of Vermont Clinical Research Center on the day of the study after an overnight fast. For subjects' prepregnancy visit, first-void urine was obtained to confirm nonpregnant state. Following height and weight determination, subjects rested in the supine position for the remainder of the study and for a minimum of 30 minutes before physiological assessment.

Blood pressure

Pulse pressure and mean arterial pressure (MAP) were measured by continuous noninvasive tonometric radial artery blood pressure monitoring, using the Colin Pilot 9200 device (San Antonio, TX), with autostandardization to brachial artery measurements.

Cardiac output

Cardiac output was determined by Doppler echocardiographic examination. Doppler-derived forward stroke volume across the aortic valve was calculated as the product of the left ventricular outflow tract area and the outflow tract velocity time integral as assessed by pulsed Doppler using previously described methods.[9] Five complete spectral envelopes with the largest Doppler shift were recorded and averaged for each patient. The Doppler stroke volume was calculated as the product of the outflow tract area and the velocity time integral. Cardiac output is expressed as milliliters per minute after integration of stroke volume with pulse rate.

Plasma volume

Plasma volume (PV) was calculated using the Evans Blue Dye method, as previously described.[16] An 18 gauge intravenous saline lock was placed in the antecubital vein for baseline blood draw, administration of Evans blue dye, and subsequent blood draws. The PV was reported in total milliliters, and corrected for body mass index (BMI).

Pulse wave velocity

Brachial pulse wave forms were obtained by Doppler ultrasound using a 10 MHz transducer. Time from electrocardiogram R wave to peak systolic flow in the brachial artery was used to determine pulse wave velocity (PWV), relative to the distance from the heart to brachial artery. (The distance from the heart to brachial artery was calculated post hoc as height*0.33.)

Uterine blood flow

Uterine blood flow was assessed using color Doppler ultrasound with an 8.0 MHz transvaginal transducer using a Vivid 7 General Electric ultrasound unit (Milwaukee, WI). Uterine artery measurements were obtained lateral to the

cervix at the level of the internal os. Vessel diameter was measured between the inner surfaces of the vessel walls during real time power color Doppler imaging.

Five estimates of vessel diameter were made for each uterine artery. For the determination of average mean velocity, angle correction was used and all angles of sonoincidence were 60 degrees or less. Five velocity measurements were taken of each vessel, and the average mean velocity was calculated over an observation window of 1-3 minutes. Mean vessel diameter was used to calculate volumetric blood flow after integration with average mean velocity to express flow in milliliters per minute: (time averaged mean velocity) × cross-sectional area × 60. Right and left uterine artery blood flow calculations were added to obtain total uterine blood flow.

Flow-mediated vasodilation

These studies are functional in vivo assessments of endothelial health as reflected by the ability of the endothelium to generate a shear stress-mediated vasodilatory signal in response to an acute increase in volumetric flow. Studies were conducted by establishing baseline brachial artery vessel diameter under direct visualization with a 10 MHz linear transducer using a Vivid 7 General Electric ultrasound unit. A mean of 3 measurements was accepted as the best estimate of diameter. Visualization of vessels was made 2 finger breadths above the antecubital fossa of the arm. A blood pressure cuff was then placed across the distal extremity and inflated to 50 mm Hg above systolic pressure for a period of 5 minutes. Following deflation, vessel diameter (3 estimates at each time point) was measured at 50, 60, and 70 seconds, and the mean of these measurements was accepted as the postrestriction maximal diameter. The vasodilatory response was calculated as the difference in diameters, before and after restriction, divided by the baseline diameter, resulting in flow-mediated dilation percentage (FMD%) and expressed as a function of directly measured shear stress as described in the following text.

Shear stress measurements

Blood samples were collected in 8 mL ethylenediaminetetraaceticacid tubes and sent to the laboratory of R.R.M. at the University of Wisconsin—Madison for analysis. Blood viscosities were determined using a cylindrical spindle digital Torque viscometer (Brookfield Engineering Labs, Inc, Middleboro, MA). Shear stress (SS) was calculated by the following formula: 4 * UBF * viscosity/π * r3. FMD percentage was divided by SS to determine FMD/SS.

Statistical methods

Baseline characteristics were compared between subjects with and without an interval pregnancy using 2-sample Student *t* tests. Repeated-measures analyses of variance were used to compare physiological measures across groups and over time. SAS statistical software (SAS Institute, Cary, NC) was used for all data analysis. Data are presented as means ± SEM.

RESULTS

All interval pregnancies were singletons, and the majority of the subjects in both groups were white, 82% (37 of 45). Demographic characteristics are presented in Table 1. There were no significant differences between groups in age, BMI, cycle day studied, or interval of time between visits.

Women in the pregnancy group (Preg) were examined an average of 14.4 ± 1.2 months' postpartum. Family histories were similar between the 2 groups; 64.7% of Preg (11 of 17) and 50% of nonpregnant control group (NP) subjects (14 of 28, $P = .41$) reported a family history of hypertension in a first-degree relative. None of the women reported taking antihypertensive medications or other medications known to affect blood pressure at the time of their evaluations.

There was a significant decrease in MAP from the prepregnancy visit to postpartum in women with an interval pregnancy ($P = .013$; Figure 1). There was no significant change in MAP over time in the nonpregnant group (group*time interaction, $P = .002$; Table 2). PWV decreased in both groups over time (time effect, $P < .0001$; Table 2). PWV was, however, significantly decreased in those women with an interval pregnancy as compared with those without an interval pregnancy (group*time interaction, $P = .005$; Figure 2). Pulse pressure decreased from prepregnancy to postpartum in women with an interval pregnancy, and this trend was not seen in the NP group, but the group*time interaction did not reach statistical significance ($P = .17$; Table 2).

UBF significantly increased over time in both groups ($P < .0001$), and there was no significant difference in UBF between groups. Both PV/BMI and FMD/SS significantly decreased in both groups over time ($P = .04$ and $P = .02$, respectively), and there was no evidence of a group or group*time interaction (Table 2).

COMMENT

In this study of women examined prior to first pregnancy in addition to

TABLE 1
Demographic characteristics of study volunteers[a]

Characteristic	Nonpregnant (n = 28) Mean ± SE	Pregnant (n = 17) Mean ± SE	*P* value
Age, y	29.3 ± 1.1	29.9 ± 0.6	.63
Body mass index, kg/m^2	22.4 ± 0.6	23.2 ± 0.8	.46
Visit 1/prepregnancy cycle day	9.4 ± 0.7	8.1 ± 1.1	.36
Visit 2/postpartum cycle day	12.5 ± 1.1	11.8 ± 1.7[b]	.73
Interval between visits, mo	30.4 ± 1.3	29.3 ± 1.6	.59
Interval since delivery, mo		14.4 ± 1.2	

[a] Significance determined by Student *t* test; [b] One woman had not resumed cycling at her postpartum visit; thus, mean cycle day is based on n = 16.

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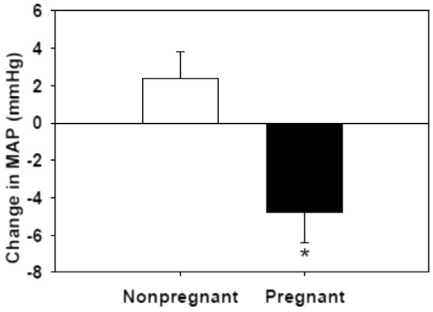
FIGURE 1
Changes in mean arterial pressure



Bar graph showing the changes in MAP from visit 1 to visit 2 in women with and without an interval pregnancy. Data presented are means ± SEM. *Asterisk* indicates significant change in MAP from visit 1 to visit 2 at $P < .05$.

MAP, mean arterial pressure.

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postpartum, we evaluated the effect of pregnancy on cardiovascular physiology and compared women with an interval pregnancy with a time-matched group of women who did not have an interval pregnancy. We found that women with an interval pregnancy had significantly decreased blood pressure and increased arterial compliance compared with their prepregnancy evaluation, when compared with those without an interval pregnancy. Our observations suggest a significant beneficial effect of pregnancy on cardiovascular remodeling that may contribute to the attenuation of preeclampsia risk in a subsequent pregnancy.

Few studies have evaluated postpartum cardiovascular measures relative to prepregnancy values. Clapp and Capeless[9] found at 1 year postpartum, as compared with prepregnancy values, women had significantly higher cardiac output because of both increased stroke volume and increased end-diastolic volume. Women in their study also demonstrated lower systemic vascular resistance at 1 year postpartum when combining primiparous with multiparous women but showed no significant change in mean arterial pressure. We did not observe increased cardiac output relative to prepregnancy values. However, our group of women were nulliparous at study entry, and subsequent pregnancies may amplify the increase in cardiac output because Clapp and Capeless[9] found a significantly greater increase in cardiac output in multiparous as compared with primiparous women.

Preeclampsia risk is generally highest for first pregnancies and decreases with subsequent pregnancies in the absence of a prior preeclamptic pregnancy.[5-8] Furthermore, a longer time interval between subsequent pregnancies is associated with an increasing risk of preeclampsia, suggesting a protective effect of pregnancy that diminishes over time.[11-15]

Our data showing a decrease in MAP after pregnancy strongly suggests positive cardiovascular adaptation that may favor future pregnancy outcome and suggests a mechanism by which preeclampsia risk is reduced in subsequent pregnancies. This is further supported by earlier studies from our laboratory showing a strong negative correlation between length of interpregnancy time interval and reduction in mean arterial pressure between first and second pregnancies.[10] These findings were reproduced in a larger cohort in which MAP was approximately 2 mm Hg lower in the second pregnancy with a very short interpregnancy interval, and the decrease in MAP was nonexistent after 2 years.[11]

PWV is considered the gold standard for measuring arterial stiffness and is correlated with future risk for cardiovascular disease and mortality.[17,18]

TABLE 2
Comparison of physiological variables between women with and without an interval pregnancy[a]

	Pregnant (Preg) (n = 17)		Nonpregnant controls (NP) (n = 28)		*P* value		
Variable	Prepregnancy	Postpartum	Visit 1	Visit 2	Group effect	Time effect	Group*time interaction
Physiological measures							
MAP, mm Hg	85.3 ± 1.8	80.5 ± 1.8	80.3 ± 1.4	82.8 ± 1.4	.53	.29	.002
PWV, m/s	2.73 ± 0.05	2.49 ± 0.05	2.56 ± 0.04	2.50 ± 0.04	.17	< .001	.005
PP, mm Hg	44.1 ± 2.2	39.6 ± 2.2	42.4 ± 1.7	42.9 ± 1.7	.71	.28	.170
CO, L/min	4.7 ± 0.2	4.7 ± 0.2	4.6 ± 0.2	4.4 ± 0.2	.35	.32	.460
UBF, mL/min	20.7 ± 4.0	38.5 ± 4.1	22.7 ± 3.1	34.7 ± 3.2	.84	< .001	.270
PV/BMI	124.9 ± 5.1	117.3 ± 5.1	132.5 ± 3.9	120.6 ± 3.9	.27	.02	.610
FMD/SS	0.33 ± .05	0.17 ± 0.06	0.22 ± .05	0.17 ± 0.05	.31	.04	.240

CO, cardiac output; *FMD/SS*, flow-mediated vasodilation/shear stress; *MAP*, mean arterial pressure; *PP*, pulse pressure; *PV/BMI*, plasma volume/body mass index; *PWV*, pulse wave velocity; *UBF*, uterine blood flow.

[a] Data are presented as means ± SE.

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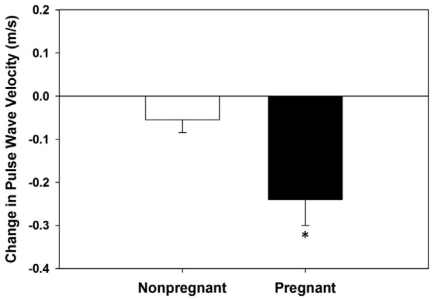
FIGURE 2
Changes in pulse wave velocity



Bar graph showing the changes in PWV from visit 1 to visit 2 in women with and without an interval pregnancy. Data presented are means ± SEM. *Asterisk* indicates significant change in PWV from visit 1 to visit 2 at $P < .05$.

PWV, pulse wave velocity.

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Several studies show increased PWV after the clinical onset of preeclampsia.[19-21] More recently women destined to develop preeclampsia have been shown to have increased PWV as compared with normal pregnancies as early as 11-13 weeks' gestation.[22,23]

Our laboratory has previously reported decreased arterial compliance prior to pregnancy, manifested by increased pulse pressure and PWV, in patients who later develop preeclampsia.[24] To our knowledge, the current study is the first to describe attenuation of PWV by pregnancy as compared with a nonpregnant control cohort and suggests that risk for preeclampsia as assessed by arterial compliance may be modified by pregnancy.

We did not observe a significant effect of pregnancy on UBF, although UBF increased significantly over time in both groups. UBF is known to fluctuate during the menstrual cycle, with the uterine arteries demonstrating a progressive increase in blood flow beginning after menstrual day 10 and continuing through the luteal phase.[25]

Although many studies have used Doppler ultrasound to evaluate uterine artery velocity waveforms in early and midpregnancy with the goal of predicting adverse pregnancy outcome, few have evaluated prepregnancy UBF. Hale et al[26] evaluated UBF and uterine artery resistance index before pregnancy and correlated this with early pregnancy values. They observed that prepregnancy UBF was positively correlated with UBF in early pregnancy, suggesting that uterine physiology and hemodynamics prior to pregnancy may be an important determinant of uterine physiology during pregnancy.

To our knowledge, this is the first longitudinal report to evaluate UBF before pregnancy and in the postpartum period, in comparison with a time-matched nulliparous control group. We suspect the increase in UBF seen between visit 1 and visit 2 in both groups was at least in part due to timing during the menstrual cycle because subjects on average were assessed later during their menstrual cycle at visit 2 (visit 1 cycle day, 8.9 ± 0.61; visit 2 cycle day, 12.2 ± 0.96).

Impaired endothelial function as assessed by ultrasound measurement of FMD of the brachial artery in response to SS has been shown to be an independent predictor of future cardiovascular events.[27,28] Existing reports of FMD in the third trimester of normotensive pregnancy show mixed results; however, impaired FMD in preeclamptic pregnancies is well described.[29,30] We did not see evidence of pregnancy-induced change in FMD, although FMD/SS decreased over time in both groups. Consistent with this observation, in prior studies from our laboratory, FMD/SS was not found to be associated with subsequent preeclampsia when assessed prior to first pregnancy.[31] Similarly, we did not see an effect of pregnancy on plasma volume when corrected for BMI (PV/BMI), although PV/BMI decreased in both groups over time.

In this study we evaluated the effect of pregnancy on cardiovascular physiology. Our observations of decreased MAP and increased arterial compliance following pregnancy suggest a significant favorable effect of pregnancy on cardiovascular remodeling. These findings may represent a mechanism by which preeclampsia risk is reduced in subsequent pregnancies. Additional longitudinal prospective studies would be useful to explore this phenomenon in women who were destined to develop preeclampsia to evaluate their specific postpartum cardiovascular phenotypic adaptation and their time course. ■

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