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