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Abstract—Normal pregnancy is associated with profound alterations in the maternal cardiovascular system. The aim of the present study was to assess noninvasively, using applanation tonometry, the maternal central aortic blood pressures (BP), effects of wave reflection and arterial stiffness (aortic and brachial pulse wave velocity) in normal pregnancy. This was a cross sectional study including 193 women with normal singleton pregnancies at 11 to 41 weeks of gestation and 23 nonpregnant controls, matched for age and height. Compared to nonpregnant controls, pregnant women had lower mean arterial pressure (85±8.9 mm Hg versus 81.1±7.2 mm Hg; $P=0.01$), central systolic BP (103±11 mm Hg versus 96±8 mm Hg, $P=0.001$), central diastolic BP (71±9 mm Hg versus 67±7 mm Hg, $P=0.008$), and augmentation index (AIx) (19±11% versus 4±12%, $P<0.001$). The AIx changed significantly with gestation reaching its nadir at midpregnancy ($R^2=0.05$, $P=0.007$). This change was present even after adjusting for maternal age ($P<0.001$), heart rate ($P<0.001$), and mean arterial BP ($P<0.001$); known determinants of AIx. The pulse wave velocity (carotid-radial and carotid-femoral) did not change significantly with gestation and was marginally different between pregnant and nonpregnant women ($P=0.03$ and $P=0.05$ for carotid-radial and carotid-femoral respectively). However, adjustments for maternal age and mean arterial pressure rendered these differences nonsignificant ($P=0.2$ for carotid-radial, $P=0.5$ for carotid-femoral). In summary, we found that normal pregnancy is associated with a reduction in central BP and wave reflection. **(*Hypertension*. 2008;51:1047-1051.)**

Key Words: pregnancy ■ applanation tonometry ■ arterial stiffness ■ augmentation index ■ pulse wave velocity

Normal pregnancy is associated with increased intravascular volume, cardiac output, and heart rate, a marked decrease in vascular resistance and a tendency toward decreased mean blood pressure (BP).[1–4] The decrease in peripheral vascular resistance and generalized vasodilation is associated with increased aortic distensibility.[5,6] However, there is scanty information regarding maternal central hemodynamics and arterial stiffness. Noninvasive assessment of arterial stiffness is possible by the simple, validated, and reproducible technique of applanation tonometry.[7,8] Using this technique pulse wave analysis (PWA) and pulse wave velocity (PWV) can be carried out. With PWA of the radial artery waveform, it is possible to assess central pressures and augmentation index (AIx), a measure of arterial wave reflection whereas with PWV it is possible to measure the stiffness in the carotid-radial (muscular) and carotid-femoral (elastic) part of the arterial tree. Several studies in nonpregnant populations have shown that arterial stiffness is increased in patients with risk factors for cardiovascular disease such as hypertension, hypercholesterolemia, and diabetes mellitus.[9–11] Additionally, 3 studies in pregnancy suggested that preeclampsia is characterized by increased maternal arterial stiffness.[12,13,14] The aim of the present study was to assess the influence of normal pregnancy on maternal central pressures, arterial wave reflection, and stiffness using applanation tonometry.

Methods

Subjects

This was a cross sectional study involving 193 pregnant women with singleton pregnancies at 11 to 41 weeks of gestation and 23 healthy nonpregnant controls. The subjects were recruited from the routine antenatal clinic and hospital staff, respectively. They were all healthy, free of medication, and did not have a family history of premature heart disease. All pregnant women had uncomplicated pregnancies. None of the controls were taking hormonal contraception, and they were all studied in the follicular phase of the menstrual cycle. Maternal age, ethnic group, smoking status, parity, body mass index (BMI), and BP were recorded. The study was approved by the Institutional Review Committee, and all women gave written informed consent.

Arterial Stiffness and Wave Reflection Measurements

Peripheral BP was measured in the right arm using an ambulatory blood pressure monitor (Microlife Medical 90207), which has been validated in pregnancy.[15] Two measurements (systolic and diastolic

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From the Harris Birthright Research Centre for Fetal Medicine (M.L.M., D.L., M.D.S., K.H.N.), King's College Hospital, London, UK; and the Clinical Pharmacology Unit (C.M.M.), University of Cambridge, Addenbrooke's Hospital, Cambridge, UK.

Correspondence to Dr M.D. Savvidou, Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, Denmark Hill, London SE5 8RS, UK. E-mail msavvidou@dsla.ndo.co.uk

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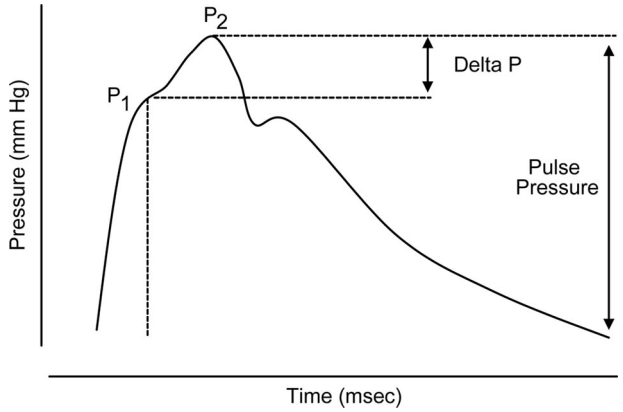

Figure 1. Typical ascending aortic waveform, showing 2 systolic peaks (P1 and P2). Augmentation index is calculated as the difference between P2 and P1, expressed as percentage of pulse pressure.

BP; SBP, DBP) were taken and averaged. Radial artery waveforms were obtained with a high-fidelity micromanometer (SPC-301; Millar Instruments) from the wrist, and a corresponding central waveform was generated with a validated transfer function (Sphygmocor; AtCor Medical)[16,17] as previously described in detail (Figure 1).[8] Augmentation index (AIx), a composite measure of systemic arterial stiffness and wave-reflection amplitude, mean arterial blood pressure (MAP), and central systolic, diastolic blood pressure, and pulse pressure (CSBP, CDBP, and CPP) were determined with the integrated software. Aortic (carotid to femoral) and brachial (carotid to radial) PWV and relevant transient times were measured as previously described.[8] For each subject the distance traveled by the pulse wave between the carotid-radial and the carotid-femoral artery was measured in a straight line using a pair of compasses to reduce the influence of altered body contour in pregnancy. All measurements were performed after a period of rest of at least 10 min in a left lateral position to avoid vena cava compression by the uterus. All measurements were made in duplicate and mean values used in the subsequent analysis.

Variability

To evaluate the interobserver variability, 2 observers performed PWA and PWV (carotid-femoral) on 15 pregnant women (5 women in each trimester of pregnancy), and the intraclass correlation coefficient was 0.95 and 0.9 for AIx and PWV, respectively. To assess the intraobserver variability, the same observer performed PWA and PWV on 2 occasions on 13 pregnant women (4, 5, 4 women in the 1st, 2nd, and 3rd trimester, respectively) and the intraclass correlation coefficient was 0.97 for AIx and 0.9 for PWV, which indicates very good variability. Additionally, the SphygmoCor quality control, which is incorporated within the software, was respected for each measurement.

Statistical Analysis

Normality of the distribution of the data were examined with the Kolmogorov-Smirnov test. For those parameters that were not normally distributed logarithmic transformation was performed. Data were expressed as mean±SD or as median (interquartile range) for normally and nonnormally distributed data, respectively. Comparisons between pregnant and nonpregnant women were performed using Student *t* test, χ^2 or multiple regression analysis, when adjustment for potential confounders thought to be necessary. The effect of gestational age on heart rate (HR), peripheral and central BP (SBP, DBP, pulse pressure), heart cycle, ejection duration, diastole time, Aix, and PWV (carotid-radial and carotid-femoral) was examined using regression analysis for continuous variables to look for linear, quadratic, or other relationships. The effect of gestational age on all the above parameters after adjusting for maternal age, ethnic group, parity, smoking, BMI, peripheral BP, and HR was examined using multiple regression analysis. The statistical analyses were performed using the Statistical Package for Social Sciences (Version 12.0).

Table 1. Demographic Characteristics of the Study Population

Parameter	Nonpregnant Controls (n=23)	Pregnant (n=193)	*P* Value
Maternal age, y	33.6±5.1	31.2±5.9	0.06
Ethnic group			
White, %	12 (52.2)	85 (56)	0.73
Black, %	7 (30.4)	69 (36)	0.6
Others, %	4 (17.4)	39 (8)	0.15
Smoking, %	0 (0)	38 (19.7)	0.02
Maternal height, m	1.6±0.07	1.63±0.06	0.9
Maternal weight, kg	65.8±13	72.7±13.7	0.02
Body mass index, kg/m^2	24.6±4.3	27.1±4.7	0.02
Nulliparity, %	13 (56.5)	110 (57)	0.09

Results

Recordings were successfully obtained from all women, and they all tolerated the studies well. The demographic characteristics of the women participating in the study are given in Table 1.

The mean heart rate (HR) was higher in pregnancy compared to the nonpregnant controls (Table 2), increased linearly with gestation (Table 3), and this increase was associated with a reduction in both systole and diastole time of the heart cycle (Table 2).

Table 2. Vascular Characteristics of the Study Population

Parameter	Nonpregnant Controls (n=23)	Pregnant (n=193)	*P* Value
Heart rate, bpm	64±8	77±11.5	0.0001
Ejection duration, ms	337.8±17	320.9±26.6	0.003
Diastole time, ms	617.7±116.2	457.8±105.1	<0.0001
Peripheral systolic blood pressure, mm Hg	114±10.5	112±9.8	0.4
Peripheral diastolic blood pressure, mm Hg	70.5±9	65.5±7.2	0.002
Mean arterial pressure, mm Hg	85±8.9	81.1±7.2	0.01
Central systolic blood pressure, mm Hg	103±11	96±8	0.001
Central diastolic blood pressure, mm Hg	71±9	67±7	0.008
Central pulse pressure, mm Hg	31.9±6.1	29.3±5.5	0.03
Pulse wave velocity (carotid-radial), m/s	8±0.9	7.5±1.2	0.03
Pulse wave velocity (carotid-femoral), m/s	5.9±0.8	5.5±0.8	0.05
Transient time (carotid-radial), ms	72.8±9.3	79.8±13.3	0.01
Transient time (carotid-femoral), ms	67.9±8.7	75.5±10.1	0.001

Table 3. Results of the Multiple Regression Analysis in Pregnant Women

Parameter	Regression Equation	R^2	*P* Value
Heart rate (HR)	HR=67.226+0.406×GA	0.09	<0.001
Peripheral diastolic blood pressure (PDBP)	PDBP=63.923−0.095×GA+0.006×GA^2	0.06	0.002
Mean arterial blood pressure (MAP)	MAP=81.941−0.274×GA+0.009×GA^2	0.05	0.009
Central systolic blood pressure (CSBP)	CSBP=103.390−0.794×GA+0.018×GA^2	0.04	0.02
Central diastolic blood pressure (CDBP)	CDBP=64.4−0.048×GA+0.006×GA^2	0.07	0.001
Central pulse pressure (CPP)	CPP=38.954−0.747×GA+0.013×GA^2	0.05	0.004
Augmentation index (AIx)	AIx=27.039−1.976×GA+0.039×GA^2	0.05	0.007

GA indicates gestational age (wk).

The peripheral SBP was not significantly different between nonpregnant controls and pregnant women (Table 2) and did not change with gestation ($P=0.2$). In contrast, peripheral DBP, MAP, CSBP, CDBP, and CPP were lower in pregnant compared to nonpregnant controls, reached their nadir around midpregnancy, and increased to prepregnancy levels toward term (Tables 2 and 3; Figure 2).

The AIx was significantly lower in pregnant than nonpregnant women (4±12% versus 19±11%, $P<0.001$) even after adjusting for maternal age, HR, and MAP ($P<0.001$ for each factor). Within pregnancy, AIx decreased with gestation reaching its nadir at midpregnancy (Table 3; Figure 3), and this change was present even after adjusting for maternal age, HR, and MAP ($P<0.001$ for each factor).

Carotid-radial and carotid-femoral PWV were marginally different between pregnant and nonpregnant women (Table 2) but not ($P=0.2$ for carotid-radial, $P=0.5$ for carotid-femoral) after adjusting for maternal age and MAP, which were found to be significant predictors of PWV ($P<0.001$ and $P<0.01$, respectively). Similarly, PWV did not change significantly with gestation ($P=0.8$ for carotid-radial, $P=0.9$ for carotid-femoral) even after adjusting for maternal age ($P<0.001$) and MAP ($P=0.03$). Conversely, transient times for carotid-radial and carotid-femoral were significantly increased in pregnant women compared to controls (Table 2).

Discussion

The study has demonstrated that normal pregnancy is associated with a decrease in central systolic and diastolic BP and AIx, an indicator of wave reflection within the arterial tree. These changes were obvious from the first trimester, reached their nadir at midpregnancy, and rose thereafter to approximately prepregnancy levels by term.

Healthy pregnancy is associated with minimal changes in peripheral SBP and a fall in DBP, which reaches its lowest levels at midpregnancy, as confirmed in our study.[2] Hence, it seems that alterations in aortic central BP in pregnancy are more pronounced than peripheral BP. This phenomenon is likely to be attributable to a reduction in the impact of wave reflection on the central pressure waveform. Central and peripheral BP are not the same, and cardiovascular risk

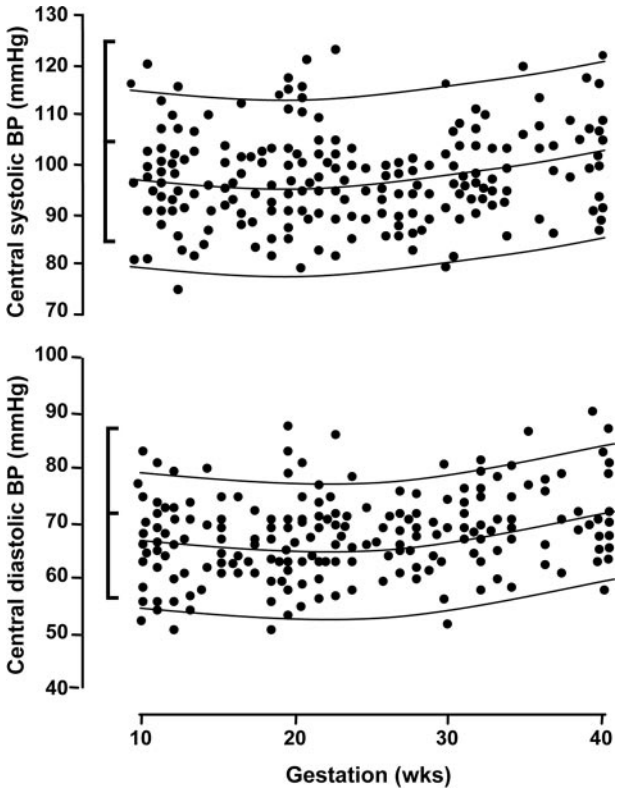

Figure 2. Central systolic blood pressure (CSBP) (top) and central diastolic blood pressure (CDBP) (bottom) with gestation, illustrating individual values and the regression lines of the mean, 95th and 5th centiles. The vertical line illustrates the mean, 95th and 5th centiles of the nonpregnant.

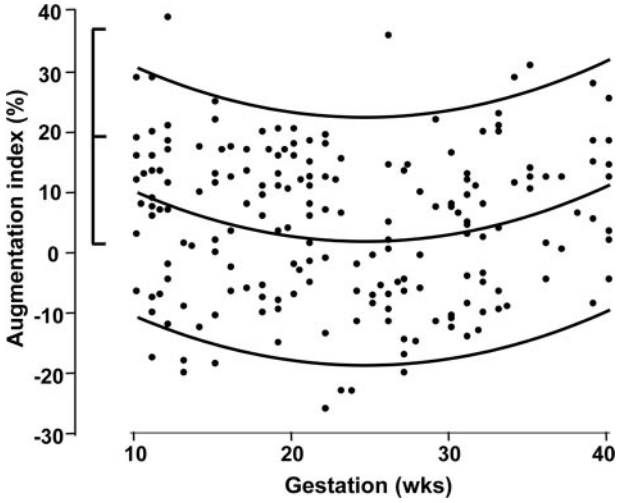

Figure 3. Augmentation index (AIx) with gestation, illustrating individual raw values and the regression lines of the mean, 95th and 5th centiles. The vertical line illustrates the mean, 95th and 5th centiles of the nonpregnant controls.

factors and antihypertensive agents can exert differential effects on them.[10,18] Furthermore, another study has demonstrated that noninvasively-determined central pulse pressure is more strongly related to vascular hypertrophy, extent of atherosclerosis, and cardiovascular events than is brachial blood pressure.[19] Therefore, assessing changes in central BP may be more useful in the early detection of pregnancies complicated by hypertensive disorders. This, however, needs further investigation.

We have also shown that normal pregnancy is associated with a decline in wave reflection within the arterial tree. A previous cross-sectional study of 53 pregnant women, from 17 to 36 weeks of gestation, reported that AIx was lower throughout these gestations compared to nonpregnant controls.[20] However, the investigators did not examine the relationship of AIx with gestation and did not adjust AIx for maternal age, HR, and MAP, all of which are known determinants of AIx.

It is possible that the decrease in wave reflection observed in our study is a consequence of the enhanced nitric oxide (NO) production associated with normal pregnancy.[21,22] Indeed, inhibition of NO by intravenous infusion of L-N^G-monomethyl arginine results in increased AIx.[23] Augmentation index has recently been shown to be positively associated with asymmetrical dimethyl-arginine (ADMA), an endogenous inhibitor of NO synthase[24] and inversely correlated with global endothelial function,[25] which is NO dependent. This is further supported by previous findings of reduced levels of ADMA and enhanced endothelial function, as assessed by flow-mediated dilatation and venous occlusion plethysmography, in normal pregnancy.[26–28] Such NO-mediated vasodilation, possibly induced by estrogen,[21,22,29] may increase reflection site distance within the vasculature and reduce wave reflection amplitude; thus explaining the reduction in AIx. This contention is supported by the increase in pulse wave transient time observed in our pregnant population.

Normal pregnancy has been reported to be associated with decreased maternal PWV (carotid-femoral) compared to nonpregnant controls.[30] Maternal PWV has also been assessed in pregnancies complicated by preeclampsia and was found to be increased, but this increase could have been a mere consequence of the elevated MAP associated with preeclampsia.[13] In the present study, we did not find any difference in the carotid-radial or carotid-femoral PWV during pregnancy and compared to nonpregnant controls. This may imply that either there is no change in the stiffness of these arterial pathways or that the hemodynamic changes in pregnancy with increased aortic diameter, at least at the level of the left outflow tract,[2] and increased circulating blood volume, attributable to volume expansion,[31] may mask the alterations and consequently the usefulness of these parameters in the assessment of arterial stiffness in normal pregnancy.

In our study, the pregnant population contained significantly more smokers than the control group. Nevertheless, neither smoking nor ethnic group nor parity appeared to be significant predictors of AIx and PWV. Applanation tonometry is usually performed in supine position. However, in the present study, all the measurements were performed in the left lateral position to avoid vena cava compression by the uterus in the pregnant population. It is important to note that both controls and pregnant women were examined in the same position; therefore it is unlikely that position would have had any significant effect on our results. In addition, the investigators who performed the measurements had been fully trained in the technique of applanation tonometry, and every attempt was made to ensure that the waveforms were similar between pregnant and nonpregnant subjects and that these waveforms met the quality control standards (good amplitude of waves, low diastolic variability, and consistency of waveforms) contained within the Sphygmocor software.

Perspectives

Using the noninvasive method of applanation tonometry, we have shown that normal pregnancy is associated with profound alterations in central BP, despite relatively little change in peripheral BP, and a delay in wave reflection within the arterial tree. This is a significant new step over the already established knowledge in this area, which is so far based on the assessment of peripheral BP in pregnancy. It is also of particular interest because previous research has demonstrated that central and peripheral BP are not the same and several factors can exert differential effects on them.[10,18,19] These findings offer a new insight in the maternal adaptation to pregnancy and may prove to be useful in the early detection of pregnancies complicated by hypertensive disorders.

Conclusions

The results of the present study demonstrate that normal pregnancy is associated with profound alterations in central BP, despite relatively little change in the peripheral BP, and a delay in wave reflection within the arterial tree. Our findings offer a further insight in the pathophysiology of maternal cardiovascular adaptation to pregnancy. The degree to which this information will be useful in the detection of pathological pregnancies remains to be determined.

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Disclosures

None.

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