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Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies

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Key words
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Conflicts of interest
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Abstract

Objective. Hypertensive disorders during pregnancy remain a major health burden. Normal pregnancy is associated with systemic cardiovascular adaptation. The augmentation index and pulse wave velocity measures may serve as surrogate markers of cardiovascular pathology, including pre-eclampsia. We evaluated these parameters during and after normotensive and pre-eclamptic pregnancies. *Design.* Longitudinal cohort trial involving a case–control analysis of healthy women and women with pre-eclampsia. *Setting.* University hospital. *Population.* Fifty-three healthy pregnant women between 11^{+6} and 13^{+6} gestational weeks, as well as 21 patients with pre-eclampsia. *Methods.* The augmentation index and pulse wave velocity were measured seven times during pregnancy and postpartum. *Main outcome measures.* Changes in augmentation index and pulse wave velocity during and after healthy pregnancies were measured. The influence of early-onset and late-onset pre-eclampsia on these measurements both during and after pregnancy was evaluated. *Results.* The normotensive pregnancies exhibited a significant decrease in the augmentation index from the first trimester to the end of the second trimester; however, the normotensive pregnancies showed an increase in the augmentation index during the third trimester as term approached. The patients with early-onset and late-onset pre-eclampsia displayed a significantly elevated augmentation index during pregnancy. The postpartum augmentation index and pulse wave velocity were significantly elevated in the early-onset pre-eclampsia group. *Conclusion.* After pregnancy, early-onset and late-onset pre-eclamptic patients exhibit differences in vascular function. This result indicates the presence of a higher cardiovascular risk in patients after early-onset pre-eclampsia.

Abbreviations: AIx, augmentation index; BMI, body mass index; NT-proBNP, N-terminal pro-brain natriuretic peptide; PWV, pulse wave velocity.

Key Message

In healthy pregnancies, the augmentation index and pulse wave velocity values are comparable to the normal values in healthy non-pregnant women. However, these values reflect the physiological circulatory adaptations that occur during pregnancy. After pregnancy, patients with early-onset and late-onset pre-eclampsia exhibit differences in vascular function.

Introduction

Hypertensive disorders, such as pre-eclampsia, remain a major cause of perinatal and maternal morbidity and mortality in the developed world. Approximately 5% of pregnancies worldwide are complicated by pre-eclampsia (1). The course of an uneventful pregnancy usually involves increases in maternal cardiac output, heart rate,

and intravascular volume, and these changes are accompanied by decreased vascular resistance (2,3). We recently reported increased levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) during early pregnancy; these values decreased during midterm pregnancy and increased again as term approached, which is consistent with the published data on cardiovascular adaptation during pregnancy (4).

Augmentation index (AIx) and pulse wave velocity (PWV) are well-studied diagnostic tools that are used in internal medicine to estimate arterial stiffness among patients with cardiovascular diseases (5,6). High arterial stiffness in non-pregnant patients is associated with risk factors for cardiovascular disease, such as hypertension, hypercholesterolemia, and renal disease (6–8). The AIx value depends on arterial stiffness and is influenced by the wave reflections of the arterial vessel tree. AIx is an indicator of increased work by the left ventricle during systole and may be a more direct measure of vasoconstriction than PWV. The normal AIx is less than −10% and the normal PWV is less than 10 m/s in non-pregnant healthy women measured with the TensioClinic TL1 Arteriograph (TensioMed Ltd., Budapest, Hungary) (9).

The few publications that have focused on AIx and PWV in hypertensive pregnant women (10–12) indicate that AIx is elevated during pre-eclampsia. However, only limited data about AIx or PWV in early pregnancy in patients who later developed pre-eclampsia are available. Recently, Khalil et al. reported the development of pre-eclampsia during late pregnancy among women who had displayed elevated AIx levels during the early stages of pregnancy (13,14).

Despite the relatively high incidence of pre-eclampsia, its long-term effects are not well known. Two studies have analyzed data on AIx and PWV after pregnancies that had been complicated by hypertensive disorders (15,16). These studies reported elevated AIx levels after the patients developed pre-eclampsia.

Using a longitudinal model, the aim of the present study was to establish the normal AIx and PWV values during healthy normotensive pregnancies. These values were compared with the AIx and PWV values in patients with pre-eclampsia. To assess the influence of pre-eclampsia on postpartum vascular function, the AIx and PWV values were also measured 3–6 months after delivery.

Material and methods

This study was conducted as a longitudinal cohort trial involving healthy pregnant women. Fifty-three pregnant women between 11^{+6} and 13^{+6} gestational weeks were enrolled. The gestational age was defined by ultrasound at first-trimester screening. The patients were measured seven times during pregnancy (at 11–13 weeks, 14–16 weeks, 19–21 weeks, 24–26 weeks, 29–30 weeks, 33–35 weeks, and 37–38 weeks of gestation) and once after delivery (at 3–6 months). The exclusion criteria were hypertension, extreme obesity [body mass index (BMI) >40 kg/m^2], renal disease, a history of malignancy, previous or current gestational diabetes, and pre-existing diabetes. Pregnancy losses were also excluded, and the data were not used in the analysis. None of the patients in the longitudinal cohort developed pregnancy-induced hypertensive disorders or pre-eclampsia.

Twenty-one patients who presented with pre-eclampsia were included for a case–control analysis. Following the current guidelines, pre-eclampsia was defined as a blood pressure $\geq$140/90 mmHg and proteinuria $\geq$300 mg/24 h (17,18). The pre-eclampsia group (n = 21) was subdivided into patients with early-onset (n = 11) and late-onset (n = 10) pre-eclampsia. Early-onset pre-eclampsia was defined as a diagnosis of pre-eclampsia before 34 weeks of gestation (16). All patients with early-onset and late-onset pre-eclampsia were measured once at the onset of disease and once 3–6 months postpartum. For each patient with pre-eclampsia one control woman was matched according to week of gestation. If more than one suitable control woman was available for matching, the control with the least date difference between the measurements was chosen. When appropriate, drop-outs from the healthy group were replaced for the postpartum comparison.

Detailed histories were obtained from all the patients to identify any previous cardiovascular disorders or pre-eclampsia. The clinical evaluation included blood pressure measurements and tests for proteinuria. Beginning at 18 weeks of gestation, each visit included fetal sonography with biometry and Doppler measurements of the umbilical artery. The presence of bilateral uterine artery notching was documented at 22 weeks of gestation. The study protocol was approved by the local ethics board (Ludwig Maximilians University, Munich – Study number 183/05) and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all the patients.

The patients' AIx and PWV were measured with the TensioClinic TL1 Arteriograph and TensioClinic software (TensioMed Ltd.). This device uses an oscillometric method to determine blood pressure and to assess arterial stiffness and wave reflection (9). The TL1 Arteriograph can be used to assess the pressure impulse in the cuff that is caused by the heartbeat, as well as the shape and characteristic parameters of the registered pressure impulse. Patients are positioned in a recumbent position and rest for 5 min before the measurement is performed on their right upper arm. First, a routine blood pressure

measurement is performed. For the oscillometric PWV and AIx measurements, the cuff automatically inflates to 35 mmHg above the systolic pressure. The AIx value represents the percentage difference between the first and second systolic peaks of the pulse pressure. AIx values were automatically recalculated and standardized to a heart rate of 80 beats per min. The distance between the jugulum and the symphysis was used to calculate the PWV.

This method is easy to perform and non-invasive. The TL1 Arteriograph and its measuring functions have been validated according to the 2002 European Society of Hypertension International Protocol (19). This method has high reproducibility and is in good accordance with previously applied measurement systems (9).

Statistical analysis

The AIx and PWV values were normally distributed. Sequential data from predefined time-points during the normotensive pregnancies were compared using analysis of variance and were corrected for multiple comparisons with a Bonferroni correction. The groups in the case–control analyses were compared using an unpaired Student's *t*-test for continuous data sets and a chi-squared test for nominal parameters. The data are presented in the Tables as the means and standard deviations or percentages. A two-sided *p*-Value of 0.05 or less was considered to be significant. The software PASW Statistics 18.0.3 (IBM, Armonk, NY, USA) was used for the statistical analysis and to create the figures.

Results

The biometric data are presented in Table 1. There were no significant differences in BMI, age or previous pregnancies between the groups. No patients had pre-existing diabetes, and none developed gestational diabetes mellitus. At the postpartum assessment, the patients with early-onset pre-eclampsia had a significantly higher BMI than did the healthy controls. The systolic and diastolic blood pressure measurements were significantly increased among the patients with pre-eclampsia during pregnancy and among the women with early-onset pre-eclampsia after delivery. The birthweights were 1326 ± 555 and 2375 ± 518 g in the early-onset and late-onset pre-eclampsia births, respectively, which were significantly lower than those of the matched controls (3538 ± 268 and 3444 ± 400 g, respectively; $p < 0.001$ for both groups). The gestational ages at delivery were 30 ± 4 and 37 ± 2 weeks in the patients with early-onset and late-onset pre-eclampsia, respectively, and were also significantly lower than those of the matched controls (40 ± 1 and 40 ± 1 weeks; $p < 0.001$ for both groups).

The normotensive pregnancies exhibited a significant AIx decrease from the first measurement in the first trimester to the end of the second trimester, whereas there was an increase from the third trimester to postpartum ($p = 0.041$ and $p < 0.001$, respectively; Figure 1). The postpartum AIx was also significantly increased compared with the first measurement ($p = 0.025$).

Compared with the normotensive matched controls, the patients with both early-onset and late-onset pre-eclampsia

Table 1. Baseline characteristics.

	Early-onset pre-eclampsia			Late-onset pre-eclampsia		
	Disease (n = 11)	Control (n = 10)	p-value	Disease (n = 10)	Control (n = 9)	p-value
Diagnosis						
Age (years)	32 ± 5	32 ± 4	n.s.	33 ± 6	32 ± 5	n.s.
BMI (kg/m^2)	29.3 ± 6.0	24.2 ± 1.8	n.s.	29.7 ± 6.5	26.8 ± 3.3	n.s.
BPsys (mmHg)	170 ± 18	106 ± 9	<0.001	172 ± 13	110 ± 6	<0.001
BPdia (mmHg)	97 ± 13	64 ± 7	<0.001	103 ± 8	67 ± 6	<0.001
Week of gestation	28 ± 3	28 ± 2	n.s.	36 ± 2	36 ± 2	n.s.
Previous births (median)	0 (0–1)	0 (0–1)	n.s.	0 (0–1)	0 (0–1)	n.s.
Pre-existing hypertension	55%	0%	0.012	40%	0%	n.s.
	Disease (n = 8)	Control (n = 8)	p-value	Disease (n = 8)	Control (n = 8)	p-value
Postpartum						
Age (years)	35 ± 7	34 ± 4	n.s.	33 ± 6	34 ± 4	n.s.
BMI (kg/m^2)	28.8 ± 4.9	23.2 ± 4.0	0.028	23.9 ± 5.7	23.2 ± 4.0	n.s.
BPsys (mmHg)	135 ± 19	114 ± 12	0.038	123 ± 17	114 ± 12	n.s.
BPdia (mmHg)	82 ± 13	66 ± 9	0.005	76 ± 12	66 ± 9	n.s.

BMI, body mass index; BPsys, systolic blood pressure; BPdia, diastolic blood pressure; n.s., not significant.
Data represent the means ± standard deviation.

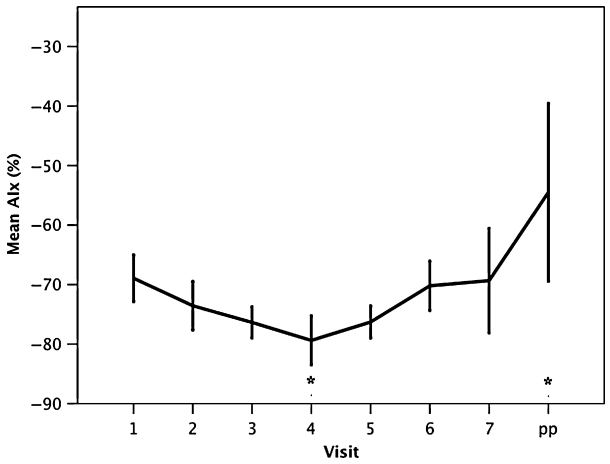

Figure 1. Augmentation index (AIx) in healthy pregnancy. Visits 1–7: continuous measurements during pregnancy, beginning at the 11th week of gestation; pp: measurement at 3–6 months postpartum; error bars: 95% confidence interval; *$p < 0.05$ compared with Visit 1.

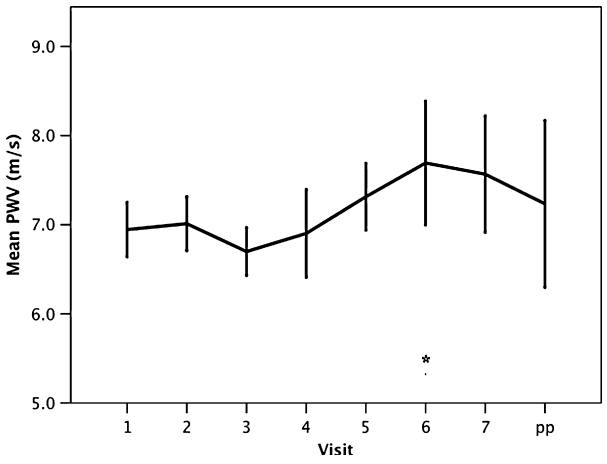

Figure 2. Pulse wave velocity (PWV) in healthy pregnancy. Visits 1–7: continuous measurements during pregnancy, beginning at the 11th week of gestation; pp: measurement at 3–6 months postpartum; error bars: 95% confidence interval; *$p < 0.05$ compared with Visit 3.

had significantly elevated AIx values (Table 2). The postpartum AIx remained significantly elevated in the early-onset pre-eclampsia group compared with the normotensive and late-onset pre-eclampsia groups. There were no significant postpartum differences between the patients with late-onset pre-eclampsia and the normotensive controls. In the healthy pregnancies, the lowest PWV values occurred at 20 weeks of gestation and the peak values at 35 weeks of gestation ($p = 0.015$; Figure 2). These values were similar to the pre-eclamptic PWV values in both groups during pregnancy. However, the postpartum PWV was significantly higher in the early-onset pre-eclampsia group compared with matched controls (Table 2).

Discussion

Both AIx and PWV provide a comprehensive assessment of arterial function that is highly reproducible and has been validated in both healthy subjects and patients with cardiovascular disease (20). Our results describe the values of AIx and PWV in a longitudinal healthy pregnant study cohort. Both parameters, including their 95% confidence intervals, were in the normal range for healthy non-pregnant women.

We found evidence that the healthy pregnant women underwent distinct hemodynamic adaptations during pregnancy. The AIx values decreased significantly from the first to the second trimester. Similar to the results of Robb et al. (21), the AIx increased from the beginning of the third trimester and returned to the first-trimester level by term. Interestingly, the AIx at 3–6 months postpartum was higher than the AIx at term. The PWV followed a similar course, but with lower variability over the course of the pregnancy. Our results are consistent with data from Bosio et al. (3) that showed that the peripheral

Table 2. Augmentation Index (AIx) and pulse wave velocity (PWV) in patients with early-onset and late-onset pre-eclampsia.

	Early-onset pre-eclampsia			Late-onset pre-eclampsia		
	Disease ($n = 11$)	Control ($n = 10$)	*p*-value	Disease ($n = 10$)	Control ($n = 9$)	*p*-value
Diagnosis						
AIx (%)	9.8 ± 18.8	−72.3 ± 12.9	<0.001	11.5 ± 29.8	−72.9 ± 11.9	<0.001
PWV (m/sec)	8.1 ± 0.7	7.3 ± 1.5	n.s.	9.0 ± 0.7	8.4 ± 1.5	n.s.
	Disease ($n = 8$)	Control ($n = 8$)	*p*-value	Disease ($n = 8$)	Control ($n = 8$)	*p*-value
Postpartum (5.0 ± 1.5 months)						
AIx (%)	−10.7 ± 21.1	−60.4 ± 10.3	0.001	−50.2 ± 16.3	−60.4 ± 10.3	n.s.
PWV (m/sec)	9.9 ± 1.6	7.0 ± 1.2	0.006	7.6 ± 1.0	7.0 ± 1.2	n.s.

n.s., not significant.
Data represent the means ± standard deviation.

resistance in normal pregnancies peaks at the beginning of the pregnancy, gradually decreases until the middle of the third trimester and undergoes a non-significant increase at term. In the present study, the AIx decrease between the first and second trimesters suggests that the maternal circulation adaptation is completed after the first trimester and remains constant during the second trimester. These findings are consistent with previously published data for NT-proBNP (4). In this previous trial, NT-proBNP significantly decreased between the first and second trimesters and increased again as term approached.

Pre-eclampsia had a significant impact on AIx in this study, but the changes in PWV were less pronounced. We suggest that pre-eclampsia has a minor effect on arterial stiffness, which is the major contributor to PWV, but leads to significant vasoconstriction, which directly influences AIx. Increases in AIx among patients with pre-eclampsia have been found in previous studies (3,10–12,15,21). Our data confirm the presence of significant elevations in AIx among patients with early-onset and late-onset pre-eclampsia. To our knowledge, only two studies have evaluated AIx after delivery in patients with pre-eclampsia. Robb et al. found that AIx was higher at 7 weeks postpartum than at 16 weeks of gestation (21). However, the postpartum pre-eclamptic patients were not divided into early-onset and late-onset groups. In our study, the AIx values of both of these pre-eclampsia groups were significantly elevated during pregnancy. Interestingly, in the early-onset group, the AIx remained significantly elevated at 3–6 months after delivery. These findings are consistent with the results of a study by Yinon et al., which demonstrated alterations in AIx 14 months after delivery among patients with early-onset pre-eclampsia compared with the AIx values after normotensive pregnancies (16). However, Yinon et al. did not measure AIx during pregnancy. Our data confirm and augment the results of these two trials and are consistent with other studies that have demonstrated impaired endothelial function in postpartum women who experienced pre-eclampsia during pregnancy (22–24).

Our findings together with previous observations (15,25) suggest that early-onset but not late-onset pre-eclampsia is associated with increased arterial stiffness and vasoconstriction that extends beyond pregnancy and may contribute to adverse cardiovascular outcomes (16,25). It is not clear why only early-onset pre-eclampsia is associated with elevated AIx after pregnancy. Recent findings have suggested that circulating angiogenic factors released from the placenta can cause endothelial dysfunction and pre-eclampsia (26,27). It has been hypothesized that damage resulting from maternal exposure to these angiogenic factors during pregnancy may cause later maternal cardiovascular diseases, but our study, that of Yinon et al. (16) and other experimental data (22) challenge this view. After having early-onset pre-eclampsia, patients are at high risk of pre-eclampsia in subsequent pregnancies. Furthermore, patients with pre-existing arterial hypertension and nephrological disorders, both of which involve impaired endothelial function and elevated AIx, are known to have an increased risk of pre-eclampsia (28,29). Combining these previous data with our findings leads to the following proposed interpretation of our data: as we did not measure pre-pregnancy AIx values of the early-onset pre-eclampsia group, these patients may already have had an elevated AIx before pregnancy. If so, they might have had a higher risk of cardiovascular diseases and hypertensive disorders during pregnancy. Pregnancy may have unmasked this cardiovascular risk and led to pre-eclampsia, as when pregnancy leads to gestational diabetes and later type II diabetes mellitus (30). We acknowledge that there is only weak evidence for this theory; a large cohort study with measurements of AIx before planned pregnancies would provide confirmatory data.

A limitation of our study is the small number of patients with pre-eclampsia that were included. Furthermore, pre-eclamptic patients were included only after the onset of pre-eclampsia. A sub-analysis of patients comparing patients with de novo pre-eclampsia with patients with superimposed pre-eclampsia on pre-existing hypertension was not performed because of the small sample size. The limited sample size may also lead to the statistically similar BMI during pregnancy, although there was a tendency towards a higher BMI in the pre-eclamptic women. It is therefore possible that alterations in AIx may be, at least partly, a result of variations in BMI between groups. AIx has been compared by Pal and Radavelli-Bagatini (31) in obese, non-pregnant women and lean women. In that study, obese women had significantly higher AIx values than lean women. AIx was also positively associated with measurements of body composition, triglycerides and glucose levels, and systolic and diastolic blood pressure. Their data suggest that arterial stiffness is associated with obesity, but other metabolic abnormalities are also important contributors to AIx changes. In our opinion, taking the results of Pal and Radavelli-Bagatini (31) into account, a potential difference in BMI is not likely to be the only reason for the observed differences in AIx.

In conclusion, the AIx and PWV values in healthy pregnant women were in the range of the published normal values and reflected physiological circulatory adaptations during pregnancy. The patients with early-onset and late-onset pre-eclampsia differed in terms of their vascular function after pregnancy. This finding indicates a

higher cardiovascular risk in patients who have experienced early-onset pre-eclampsia.

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