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Increase of augmentation index (AIx@75): a promising tool for screening hypertensive pregnancy disorders

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Abstract

Background Screening tools in the first trimester of pregnancy for hypertensive pregnancy disorders need to be determined.

Objectives To compare cardiovascular parameters between pregnant (PG) and non-pregnant women (NPG) and to evaluate the sensitivity and specificity of arterial stiffness indices in screening for hypertensive pregnancy disorders and their possible association with the mean uterine artery pulsatility index (MUA-PI).

Methods This study included 77 pregnant women (11-13.6 gestational weeks) and 77 age-matched non-pregnant women. Cardiovascular parameters were non-invasively measured using Mobil- O-Graph®, a cuff-based oscillometric device. The Doppler Ultrasonographic was used to evaluate the MUA-PI.

Results Augmentation index (AIx@75) was significantly higher in PG compared to NPG. ROC curve of AIx@75 showed area under curve (AUC): 0.7303, Sensitivity: 74.03% and Specificity: 64.94% and Cutoff: 22.50%. The systolic volume index was lower and the heart rate was higher in PG compared to NPG. Of the 77 pregnant women, 12 had an unfavorable outcome with hypertensive changes. Central systolic blood pressure (109.1 ± 8.84mmHg) and AIx@75 (31.97 ± 5.47%) were significantly higher in the group of pregnant women with outcome compared to the group without outcome (103.0 ± 8.53mmHg and 26.80 ± 8.71%). ROC curve showed better performance of the AIx@75 [AUC: 0.7179, Sensitivity: 83.33% and Specificity: 60.00%, Cutoff: 27.67%] compared to MUA-PI [AUC: 0.5098, Sensitivity: 8.333% and Specificity 98.44%].

Conclusions AIx@75 was significantly higher in PG compared to NPG. We compared the AIx@75 of PG with and without outcomes. ROC curve analysis showed that this index could discriminate between PG with and without an outcome. Differently, the MUA-PI did not differ between PG with and without outcome, suggesting the superiority of AIx@75 in relation to MUA-PI as a method of screening in the first trimester for hypertensive disease of pregnancy. AIx@75 did not assotiate with MUA-PI. Prospective studies will be needed to confirm these findings.

Keywords Eclampsia, Preeclampsia, Arterial stiffness, Hypertension, Systolic blood pressure

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Introduction

According to the Pan American Health Organization and the World Health Organization, maternal mortality rates are unacceptably high. Pre-eclampsia is a complication present in 2–4% of pregnancies worldwide [1]. It is associated with approximately 46,000 maternal deaths and 500,000 fetal and neonatal deaths annually [2].

Greater understanding of the pathophysiology of pregnancy-induced hypertensive disorders, such as gestational hypertension and preeclampsia/eclampsia, led to the emergence of studies aimed at the development and validation of screening methods, such as clinical history, biomarkers and Doppler ultrasound of the uterine arteries [3–5]. To increase the efficiency of screening for hypertensive pregnancy disorders, the association of these factors was tested. Doppler ultrasound assessment in the first trimester of pregnancy can predict 47.8% of cases of early pre-eclampsia (7.9% false positive rate), 39.2% of cases of early fetal growth restriction (6.7% false positive rate) and 26,4% of pre-eclampsia cases at any time during pregnancy (6.6% false positive rate) [5]. Studies using Doppler ultrasonography have had some success, as isolated screening or combined with clinical-epidemiological data and serological markers, however, with low sensitivity, high cost and operator dependence, which makes screening far from the economic reality of the vast majority of the world's population [5, 6].

Therefore, in order to develop and validate screening methods that can provide clinical support for early therapeutic decision-making, arterial stiffness indices, with emphasis on AIx@75, have been increasingly studied and showing a growing number of favorable evidence for their use. Studies have demonstrated that increased AIx@75 is directly and independently associated with increased risk of cardiovascular complications and events. Although AIx@75 depends on arterial stiffness and is a measure of the amplitude of wave reflection, it cannot be used interchangeably with pulse wave velocity (PWV), which is considered the gold standard for measuring arterial stiffness [7].

Studies show increased arterial stiffness in women with pre-eclampsia, whose changes are detected early, even before changes in blood pressure, which reinforces the possibility of using stiffness indices to predict outcomes throughout pregnancy [7–9]. Furthermore, arterial stiffness indices and wave reflection are early screening tools for preeclampsia, which can be used to contribute to the clinical management of high-risk pregnancies [9, 10]. In the context of arterial stiffness indices, AIx@75 is higher in pregnancies complicated by hypertensive pregnancy disorders which may reflect a progression in the severity of the arterial stiffness abnormality and worsening of the clinical picture [7, 9]. In this perspective, local vascular adaptations during pregnancy may justify the low sensitivity in screening by Doppler assessment of the uterine arteries. On the other hand, AIx@75 provides a systemic assessment of vascular behavior. Systemic endothelial dysfunction, excessive inflammation and subsequent maternal and fetal manifestations in hypertensive pregnancy disorders could be attributed to the increased sensitivity of AIx@75 [3, 11].

The importance of using screening methods in the first trimester of pregnancy is due to the fact that the administration of aspirin, low-cost and easily accessible treatment at a dose of 150 mg/day from 11 to 14 up to 36 weeks of gestation, was associated with a reduction in the incidence of pre-eclampsia of 80% in pregnancies up to 34 weeks, 62% in the incidence of pre-eclampsia in pregnancies up to 36 weeks and a 15% reduction in pregnancies above 37 weeks of gestation compared to the use of placebo [12–15]. Hypertensive disorders of pregnancy have a major impact on public health around the world, particularly in low- and middle-income countries. Most of these deaths are considered preventable. It is necessary to invest in the validation of new screening methods that are low-cost, easy to use and highly sensitive. In order to establish these new methods, the assessment of arterial stiffness has already been studied on a small scale and has shown great promise as a valuable tool [16–22]. AIx@75 presents itself as an independent and sensitive method for early screening of hypertensive pregnancy disorders. This study, the first in Brazil, contributes to strengthening the use of the assessment of arterial stiffness indices, especially the AIx@75, as a screening tool in the first trimester of pregnancy for hypertensive disease of pregnancy.

Materials and methods

The study was conducted between August 2020 and March 2022 by the *Faculdade Ciências Médicas de Minas Gerais (FCM-MG)* with participation of the Municipal Center for Diagnostic Imaging of the Municipality of Belo Horizonte (CMDI), specialized in Ultrasonography in Gynecology and Obstetrics. This study was approved by the Research Ethics Committee of the Medical Sciences Faculty of Minas Gerais (CEPCM-MG; opinion number: 4,400,617). All the participants signed informed consent form.

A total of 100 pregnant women at 11-13.6 gestational weeks were eligible to participate in this study. According to the International Society of Ultrasound in Obstetrics and Gynecology guidelines [23] the gestational age was defined by ultrasound (crown-rump length, 42–84 mm). Of the 100 pregnant women, 23 were excluded due to a previous diagnosis of gestational diabetes, use of vasoactive medication, arterial hypertension, twin pregnancy, fetal anomaly, spontaneous abortion or fetal death before 24 weeks, pregnancy-specific hypertensive disease,

autoimmune diseases, or chronic kidney disease. The control group consisted of women considered healthy, recruited through an active search in the general community, and matched by sex and age. In addition, participants who did not agree to sign an informed consent form or those who wished to interrupt their participation at any time were excluded.

The current study has a mixed design, which involves collecting both cross-sectional and longitudinal data used to screen the outcomes. The cross-sectional study compared cardiovascular parameters between pregnant women and a control group composed of age-matched women considered healthy. During the period leading up to the expected delivery date, pregnant women were contacted in order to collect information regarding the pregnancy outcome. The medical records of pregnant women were also analyzed in the hospitals where the birth took place. From then on, pregnant women were categorized into pregnant women with and without outcome (Hypertensive disorders of pregnancy), according to definitions and diagnostic criteria for Hypertensive Disorders of Pregnancy [11].

Hypertensive pregnancy disorders are classified according to the International Society for the Study of Hypertension in Pregnancy (ISSHP) into 4 categories: (1) pre-eclampsia/eclampsia; (2) chronic hypertension (of any cause); (3) chronic hypertension with superimposed preeclampsia; (4) gestational hypertension [24].

The patients included in this study belonged to the pre-eclampsia/eclampsia and gestational hypertension groups, that is, groups of pregnancy-specific hypertensive disease [24, 25].

For accurate diagnosis, it is crucial to have documented normal blood pressure either prior to pregnancy or early in pregnancy, and without any of the abnormalities that were previously discussed and define preeclampsia. Blood pressure was measured using a sphygmomanometer and then using Mobil-O-Graphy. The patient provided the information about blood pressure before pregnancy or in medical records. The ultrasound examination confirmed that the women were in the first trimester of pregnancy.

Sample calculation

The statistical analysis was done considering the power of the sample comparing AIx@75 between pregnant and non-pregnant women and comparing AIx@75 between pregnant women with and without outcome. The power of the AUC from the ROC curve for AIx@75 to discriminate pregnant women from controls was performed using package pROC of R version 4.4.0 software [26]. Considering 77 cases and 77 controls, for AUC 73.03% and 5% of significance, the power reached was 99.96%. The power of the AUC from the ROC curve for AIx@75 to discriminate pregnant women without the outcome from those with the outcome was performed the same way. Considering 12 cases with the outcome and 67 pregnant without the outcome, for AUC 71.79% and 5% of significance, the power reached was 69.69%.

Experimental protocol

Initially, anthropometric data and information on parity, history of previous illnesses, use of medications, smoking, physical activity, among other data relevant to the study, were collected. A cardiovascular assessment was then performed followed by an ultrasound examination. In the period close to the expected date of delivery, pregnant women were contacted to collect information about the outcome of the pregnancy with or without the occurrence of gestational hypertensive disease.

Ultrasound assessment of pregnant women

Therefore, 100 pregnant women scheduled by spontaneous demand in ultrasound clinics at the *Centro Municipal de Diagnóstico por Imagem da Prefeitura de Belo Horizonte (CMDI)* were considered participants and underwent the ultrasound examination as scheduled. At this meeting, pregnant women were invited to undergo Doppler assessment of the uterine arteries and their stiffness. The Doppler Ultrasonographic evaluation was carried out using the brand/model device Mindray DC-70 with X-Insight, including all necessary technological resources [23]. A single examiner with expertise in the area performed the ultrasound evaluation. Examiners involved in screening for hypertensive disease during pregnancy must have up-to-date knowledge about the main risk factors for the disease.

The Doppler technique of the uterine arteries was extensively studied in the gestational period of 11-13.6 weeks. For the transabdominal assessment of the resistance of the uterine arteries, a mid-sagittal section of the body and cervix must initially be obtained. When using color Doppler, the transducer has to be angled to each side in order to identify the uterine arteries with high-speed flow in their lateral course to the uterus and cervix. The pulsed Doppler sample volume should be about 2 mm and may be positioned in both the ascending and descending branches of the uterine artery at the point closest to the internal cervical orifice, with an insulation angle < 30. The peak systolic velocity should be over 60 cm/s to confirm that the vessel examined is the uterine artery. Pulsatility index (PI) is measured when at least three flow velocity waves are obtained. Standardized method and described in Guidelines ISUOG. Another alternative measurement, the mean PI of the uterine arteries, is performed by viewing the cervix in a transverse plane. The PI values obtained using the proposed method are comparable to those obtained using

the conventional sagittal approach in terms of reliability and reproducibility. These findings suggest that the proposed method can be reliably used even in the most challenging situations [27]. The 95th percentile for mean PI of uterine arteries obtained transabdominal between 11 and 13.6 weeks is 2.35. The PI of the uterine artery is also altered by maternal factors, including ethnic origin, body mass index (BMI) and previous hypertensive disease. Therefore, the inclusion of PI in a multifactorial tracking model, whenever possible, is preferable to its use with absolute cutoff points [28].

Assessment of cardiovascular parameters in pregnant and non-pregnant women

Cardiovascular parameters were assessed non-invasively using the device Mobil-O-Graph (IEM, Stolberg, Germany) in accordance with previous studies by our group [29, 30]. This device calculates the aortic or central pulse wave from the oscillometric recording of brachial pressure using a conventional arm cuff equipped with a high-fidelity pressure sensor. The circumference of the arm was measured to choose the correct cuff, which was positioned 2 cm from the cubital fossa of the left arm.

At the beginning, the device measures peripheral diastolic and systolic pressures and sequentially inflates at the diastolic blood pressure level for 10 s and records brachial pressure waveforms. Using a transfer function, central pressure curves are obtained and processed using the ARCSolver algorithm (Austrian Institute of Technology, Vienna, Austria) [31]. This system calculates central arterial pressure, aortic pulse wave velocity, and additional centralhemodynamic indices, all based on oscillometric recording of brachial artery pulse waves. Systolic/diastolic blood pressure calibration was used [32]. The augmentation index corrected for heart rate of 75 beats per minute (AIx@75) was calculated by the relationship between augmentation pressure (AP) and central pulse pressure (cPP) (AIx@75 = PA/cPP *100). Augmentation pressure, which corresponds to the increase in cSBP caused by the reflection wave, is evaluated by the difference between the second (P2) and the first systolic peak (P1) of the aortic pressure wave. The hemodynamic parameters evaluated were stroke volume (SV), cardiac output (CO), cardiac index (CI), total vascular resistance (TVR), and heart rate (HR).

The ARCSolver transfer function includes an algorithm to check signal quality. In a first step, the recorded pulse waves are checked for plausibility and classified according to predefined quality criteria. In this study, only excellent or good quality results were analyzed, i.e., > 80% or > 50% of the signals used for the transfer function, respectively. Three measurements of each variable were taken and the average was considered for final analysis.

Statistical analysis

The data are presented in frequency tables with absolute frequencies and their respective percentages as well as descriptive measures (mean, median, standard deviation) for quantitative data. Quantitative variables were tested for normality using the Kolmogorov–Smirnov test. T-test was used to examine normal distribution variables (t-test for independent groups) and Mann–Whitney U test was used for those without a normal distribution variables. Effect size was calculated with Cohen's d. The interpretation guideline used was 0.1–0.4 (small), 0.5–0.7 (moderate), and > 0.8 (large effect) [33]. The receiver operating characteristic curve receiver operating characteristic (ROC) was constructed to determine the sensitivity and specificity of AIx@75 to differentiate pregnant women with and without outcome. In all tests, the significance level adopted was $p < 0.05$. The software used for the analysis was SPSS version 25.0, and GraphPad Prism 9.4.1.

Results

A total of 100 pregnant women at 11-13.6 gestational weeks were eligible to participate in this study. Of the 100 pregnant women, 23 were excluded due to a previous diagnosis of gestational diabetes, use of vasoactive medication, arterial hypertension, twin pregnancy, fetal anomaly, spontaneous abortion or fetal death before 24 weeks, pregnancy-specific hypertensive disease, autoimmune diseases, or chronic kidney disease. The control group consisted of women considered healthy, recruited through an active search in the general community, and matched by age (Fig. 1).

Comparison of anthropometric variables and cardiovascular parameters between the group of pregnant women and the control group

Table 1 presents the comparison of anthropometric data from the group of pregnant women with the control group. The pregnant group had a significantly higher BMI than the control group. None of the participants had a history of smoking before or during pregnancy. BMI was recorded on the same day as cardiovascular and ultrasound data collection.

Table 2 presents cardiovascular variables. pDBP was lower and cPP was higher in the pregnant group. The effect size was moderate to reduce the pDBP [Cohen's d = (70.59–75.84)/8.935911 = 0.587517] and to increase the cPP [Cohen's d = (45.23–39.64)/8.224992 = 0.679636].

Regarding central vascular pressures, it was observed that the cDBP [Cohen's d = (72.29–77.2) / 8.880056 = 0.552924] and cMAP [Cohen's d = (82.85–86.7) / 8.338825 = 0.461696] were significantly smaller in the pregnant group and the effect size was moderate for both measurements. On the other hand, cPP was

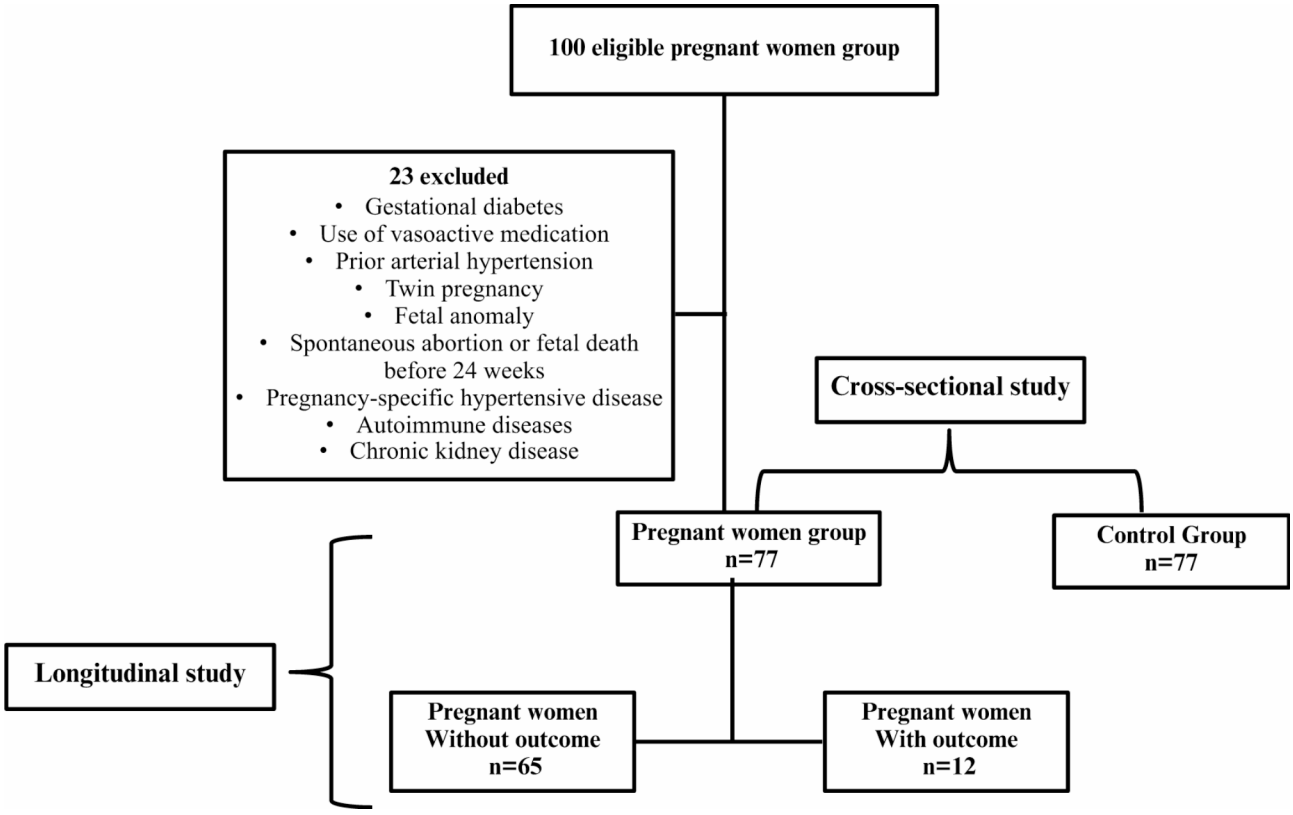

Fig. 1 Selection of participants for the control and pregnant groups

Table 1 Anthropometric data from the group of pregnant women and the control group

Variables	Control (*n* = 77)	Pregnant (*n* = 77)	*P*-value
Age (years)	25.10 ± 5.02	26.86 ± 6.49	0.0672[M]
Height (cm)	1.62 ± 0.06	1.62 ± 0.07	0.5800[M]
Weight (kg)	63.50 ± 15.05	67.24 ± 15.10	0.1257[M]
BMI (Kg/cm^2)	24.09 ± 5.59	25.72 ± 5.27	0.0063[M]*

BMI: Body mass index. Arterial stiffness as screening for gestational hypertensive disease. M means Mann-Whitney test. *$p < 0.05$ Pregnant group in relation to control group

significantly higher in the pregnant group compared to the control group and the effect size was moderate [Cohen's d = (31.71–28.55)/6.20561 = 0.509217].

Several adaptations were observed in the hemodynamic parameters of pregnant women in relation to the control group. The systolic index of the pregnant group was significantly lower than that of the control group, with strong effect size was [Cohen's d = (31.52–37.07) / 6.398008 = 0.867458]. On the other hand, heart rate was significantly higher in the group of pregnant women with strong effect size [Cohen's d = (84.74–75.56) / 9.865191 = 0.930545]. Similarly, aortic pulsatility was higher in the group of pregnant women with moderate effect size [Cohen's d = (0.39 – 0.34) / 0.088278 = 0.566393].

Regarding arterial stiffness indices, it was observed that c-fPWV did not differ between the control and pregnant groups. AIx@75 and augmentation pressure were significantly higher in the group of pregnant women and corresponded, respectively, to strong [Cohen's d = (27.61–21.39)/7.518938 = 0.827044] and small effect size [Cohen's d = (7.5–6.16)/2.68628 = 0.498831].

ROC curve analysis showed that the maximum AIx@75 sensitivity and specificity in differentiating pregnant group and control group was occurred at 22.50% (Fig. 2).

Comparison of anthropometric variables, MUA PI and cardiovascular parameters between the group of pregnant women without and without gestational hypertensive pregnant disorders and with gestational hypertensive disease

The anthropometric data of the groups of pregnant women with and without outcome are presented in Table 3. Weight and BMI were, respectively, 15% and 15.98% higher in the group of pregnant women with an outcome than in the group without an outcome.

When comparing vascular parameters (Table 4), it was observed that cSBP and AIx@75 were significantly higher in the group of pregnant women with an outcome. The mean effect size was moderate to cSBP [Hedges g = 0.71 (95% CI 109.1–103)] and to AIx@75 [Hedges g = 0.57

Table 2 Comparison of peripheral and central vascular pressures in the group of pregnant women with the control group

Peripheral blood pressure	Control (*n* = 77)	Pregnant Group (*n* = 77)	*P*-value
pSBP (mmHg)	115.50 ± 8.39	115.80 ± 9.84	0.8169[T]
pDBP (mmHg)	75.84 ± 9.59	70.59 ± 8.23	0.0004[T]*
pMAP (mmHg)	93.76 ± 8.46	90.30 ± 7.10	0.0618[T]
pPP (mmHg)	39.64 ± 6.81	45.23 ± 9.43	< 0.0001[M]*
Central blood pressure			
cSBP (mmHg)	105.70 ± 8.42	104.00 ± 8.81	0.1916[M]
cDBP (mmHg)	77.20 ± 9.58	72.29 ± 8.12	0.0008[T]*
cMAP	86.70 ± 8.88	82.85 ± 7.76	0.0048[T]*
cPP (mmHg)	28.55 ± 5.24	31.71 ± 7.04	0.0088[M]*
Pulse pressure amplification	1.40 ± 0.13	1.44 ± 0.13	0.0953[T]
Hemodynamic parameters			
Stroke volume (ml)	61.81 ± 10.23	54.09 ± 8.43	< 0.0001[M]*
Stroke volume index (ml/m^2)	37.07 ± 6.71	31.52 ± 6.07	< 0.0001[T]*
Cardiac output (l/min)	4.60 ± 0.46	4.54 ± 0.46	0.4824[M]
Heart rate (bpm)	75.56 ± 10.18	84.74 ± 9.54	< 0.0001[T]*
TVR (s*mmHg/ml)	1.24 ± 0.13	1.22 ± 0.10	0.1087[M]
Cardiac index (l/min/m^2)	2.76 ± 0.35	2.66 ± 0.33	0.0754[T]
Aortic pulsatility	0.34 ± 0.081	0.39 ± 0.095	0.0006[M]*
Arterial Stiffness indices			
Pulse wave velocity (m/s)	4.97 ± 0.39	5.08 ± 0.45	0.1200[M]
AIx@75 (%)	21.39 ± 6.43	27.61 ± 8.47	< 0.0001[T]*
Reflexion coefficient (%)	58.53 ± 6.66	60.28 ± 6.43	0.983[T]
Augmentation pressure (mmHg)	6.16 ± 2.21	7.50 ± 3.09	0.0129[M]*

Data presented as mean ± standard deviation. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MAP: Mean arterial pressure. PP: Pulse pressure. TVR: Total vascular resistance. M means Mann-Whitney test and T means t-test. *$p < 0.05$ Pregnant group in relation to control group. Arterial stiffness as screening for gestational hypertensive disease

Table 3 Comparison of anthropometric data of groups of pregnant women with and without outcome

Variables	Pregnant Without outcome (*n* = 65)	Pregnant With outcome (*n* = 12)	*P*-value
Age (years)	26.86 ± 6.76	26.58 ± 5.054	0.8227[T]
Height (cm)	1.62 ± 0.07	1.62 ± 0.07	0.9920[T]
Weight (kg)	65.70 ± 14.35	75.56 ± 16.95	0.0368[T]*
BMI (Kg/cm^2)	25.10 ± 4.718	29.11 ± 6.934	0.0146[T]*
UtA- PI	1.562 ± 0.53	1.512 ± 0.548	0.7649[T]

BMI: Body mass index. UtA-PI: Uterine artery pulsatility index. M: Mann Whitney test. Arterial stiffness as screening for gestational hypertensive disease. T means t-test. *$p < 0.05$ Pregnant with outcome group in relation to pregnant without outcome group

(95% CI 31.97–26.8)] in the group Pregnant with outcome compared to the group without outcome. The other cardiovascular parameters were similar in both groups.

ROC curve analysis showed that the maximum AIx@75 sensitivity and specificity in differentiating Pregnant without outcome group and Pregnant with outcome group occurred at 27.67% (Fig. 3). Differently, the ROC of MUA PI was not able to differentiate the two groups.

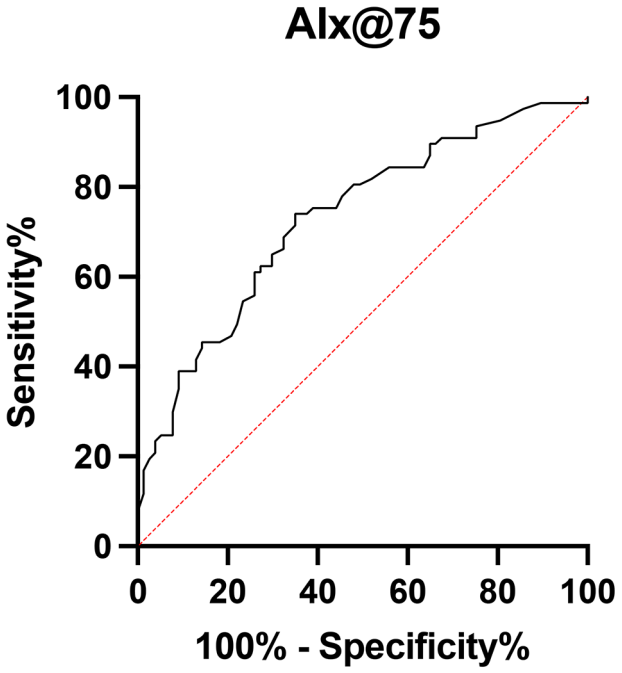

Fig. 2 Receiver operating characteristic (ROC) curve of pregnant and control group. A - ROC curve of augmentation index (AIx@75). AUC: 0.7303 (95%CI: 0.6515 to 0.8091). Sensitivity %: 74.03 and Specificity %: 64.94, Cut-off: 22.50%

Similary to AIx@75, the ROC curve of cSBP was also able to differentiate the two groups.

Discussion

In this study, we show that the development of hypertensive pregnancy disorders is preceded by an increase in cSBP and AIx@75, assessed between 11 and 13.6 weeks. Additionally, we observed that these indices were able to discriminate early between pregnant women with and without an outcome. Differently, the MUA-PI did not differ between pregnant women with and without an outcome and the ROC curve did not show good discriminatory capacity in differentiating between pregnant women with and without an outcome. These results suggest that these data may be used as a basis for future investigations into the role of aortic pulse wave analysis in predicting disorders that can interfere with cardiovascular adaptation related to pregnancy and consequently the possibility of prophylaxis.

Comparison of anthropometric variables and cardiovascular parameters between the group of pregnant women in the first trimester and the control group

In the present study, it was observed that the group of pregnant women had a significantly higher BMI than the control group. Gestational weight gain is related to fetal and maternal components. In the fetus, tissue gain is related to the development of the placenta, amniotic

Table 4 Comparison of peripheral and central vascular pressures in groups of pregnant women with and without outcome

Peripheral blood pressure	Pregnant Without outcome (*n* = 65)	Pregnant With outcome (*n* = 12)	*P*-value
pSBP (mmHg)	114.9 ± 9.68	120.6 ± 9.70	0.0660[T]
pDBP (mmHg)	70.14 ± 8.15	73.98 ± 8.60	0.2749[T]
pMAP (mmHg)	90.67 ± 7.43	94.75 ± 8.61	0.0919[T]
pPP (mmHg)	44.79 ± 9.90	47.61 ± 6.06	0.0821[M]
Central blood pressure			
cSBP (mmHg)	103.0 ± 8.53	109.1 ± 8.84	0.0266[T]*
cDBP (mmHg)	71.81 ± 8.12	74.86 ± 8.89	0.2418[T]
cMAP	82.22 ± 7.54	86.29 ± 8.38	0.0958[T]
cPP (mmHg)	31.23 ± 7.12	34.28 ± 6.20	0.1059[M]
Pulse pressure amplification	1.445 ± 0.13	1.405 ± 0.14	0.3333[T]
Hemodynamic parameters			
Stroke volume (ml)	54.06 ± 8.35	54.25 ± 9.23	0.3950[T]
Cardiac output (l/min)	4.52 ± 0.45	4.65 ± 0.53	0.4824[M]
Heart rate (bpm)	84.50 ± 9.59	86.03 ± 9.53	0.6137[T]
TVR (s*mmHg/ml)	1.22 ± 0.11	1.23 ± 0.06	0.6477[T]
Cardiac index (l/min/m^2)	2.68 ± 0.33	2.56 ± 0.37	0.2870[T]
Aortic pulsatility	0.38 ± 0.097	0.40 ± 0.0847	0.4760[M]
Arterial Stiffness indices			
Pulse wave velocity (m/s)	5.06 ± 0.47	5.20 ± 0.34	0.1808[M]
AIx@75 (%)	26.80 ± 8.71	31.97 ± 5.47	0.0157[M]*
Reflexion coefficient (%)	60.08 ± 6.55	61.33 ± 5.87	0.5394[T]
Augmentation pressure (mmHg)	7.50 ± 3.01	8.99 ± 3.30	0.1015[M]

Data presented as mean ± standard deviation. SBP: Systolic blood pressure. DBP: Diastolic blood pressure. MAP: Mean arterial pressure. PP: Pulse pressure. TVR: Total vascular resistance. M means Mann-Whitney test and T means t-test.*$p < 0.05$ Pregnant with outcome group in relation to Pregnant without outcome group. Arterial stiffness as screening for gestational hypertensive disease

fluid and fetal tissues. In women, weight gain is related to the increase in body water and blood volume to supply placental perfusion, deposition of tissue in the breasts for future breastfeeding, expansion of the uterus and deposition of fat in the stores [34]. However, the global prevalence of overweight and obesity in pregnancy is increasing and it represents a significant challenge for the management of pregnancy and birth.

Cardiovascular adaptations in pregnancy occur in different aspects. Peripherally, the SBP of the pregnant group was significantly reduced in relation to the control group. Similar results were observed centrally. cDBP and cMAP were significantly lower in the pregnant group compared to the non-pregnant group. These results are in line with those found by Wykrtowicz et al. [35] who compared pregnant women in the third semester of pregnancy with women considered healthy matched by age and height. These results may be related to an increase in intravascular volume, of aortic distensibility, complacency and decreased vascular resistance [36]. The reduction in peripheral and central diastolic pressures contributed to the increase in pPP and cPP, respectively. This result differs from those found by Wykrtowicz et al. who observed lower cPP in pregnant women compared to the control group and no difference in pPP [35]. This divergence of results may be related to the composition of the group of pregnant women. In the present study, of the 77 pregnant women, 12 of them developed hypertensive disease of pregnancy. Studies show that pregnant women who later develop hypertensive disease of pregnancy may have elevated cPP and pPP in the first trimester [9, 37].

Healthy pregnancy is characterized by a significant increase in stroke volume and cardiac output to meet metabolic needs [36]. In contrast to previous findings in the literature, the present study revealed a significant decrease in both systolic volume and systolic index among the pregnant group when compared to the control group. Despite this change, cardiac output and cardiac index did not differ between groups. This result can be explained by the higher heart rate observed in the pregnant group compared to the control group, as also observed in other studies [35].

In the present study, AIx@75 and the augmentation pressure and pulse pressure were significantly higher in the pregnant group when compared to the control group. It was demonstrated that the AUC of AIx@75 was 0.7303 (95% CI: 0.6515 to 0.8091) and that the maximum point of sensitivity and specificity was 22.50%.

In our results, we observed that aortic pulsatility, assessed by the cPP/cMAP ratio, was higher in the pregnant group when compared to the control group. The important dampening action performed by a healthy aorta reduces arterial pulsatility and protects the microvasculature from potentially harmful changes in blood flow and blood pressure [38]. In healthy young adults, the compliant aorta effectively dampens excess pulsatility caused by intermittent ejection of the left ventricle and exhibits a slow pulse wave velocity, which allows reflection waves to reach the heart during diastole, increasing coronary perfusion pressure and without systolic ventricular overload. On the other hand, excessive pulsatility in the aorta is transmitted preferentially to low-resistance vascular beds (such as the kidney, placenta and brain), as in these organs microvascular pressure is more directly coupled to fluctuations in aortic blood pressure [39]. Further studies will be needed to determine whether increased pulsatility in the aorta in pregnant women contributes to late pregnancy complications.

Comparison of anthropometric variables and cardiovascular parameters between the group of pregnant women in the first trimester with and without outcome

In the present study, weight and BMI were, respectively, 15% and 15.98% higher in the group of pregnant women

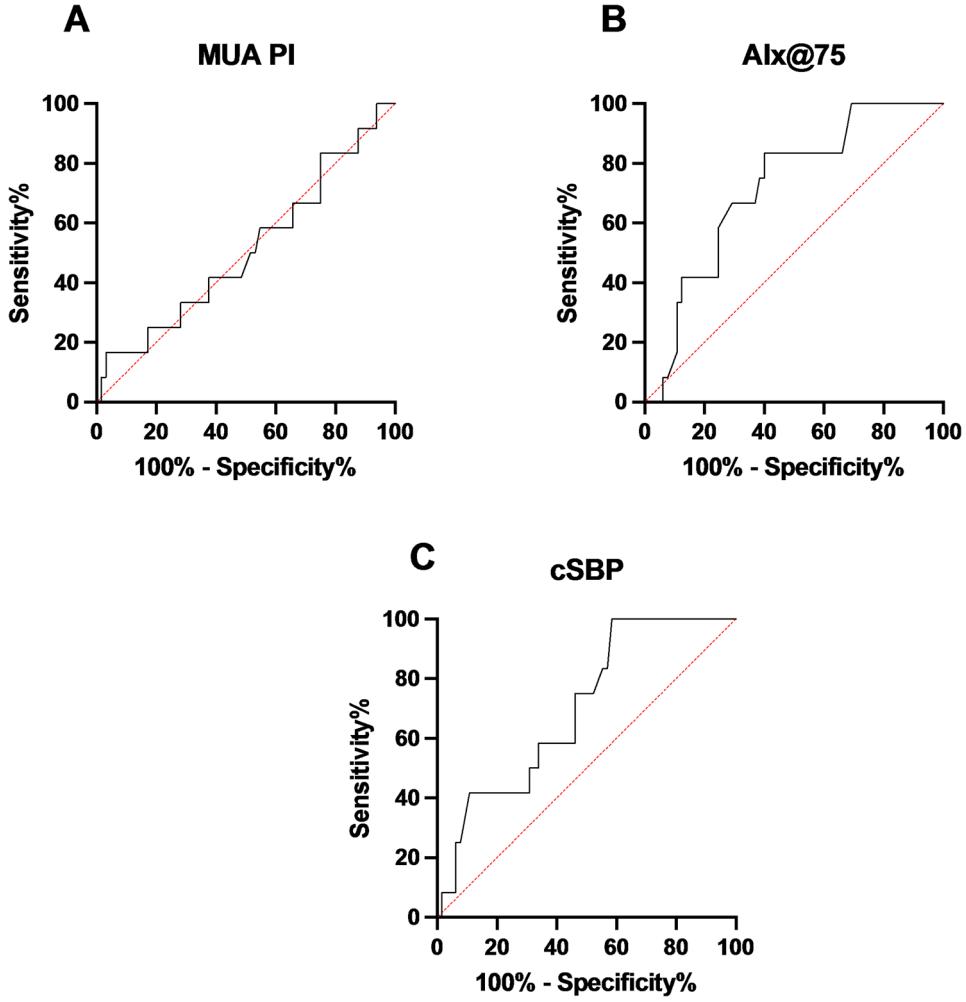

Fig. 3 Receiver operating characteristic (ROC) curve of pregnant with and without outcome. A - ROC curve of MUA-PI [AUC: 0.5098 (95% CI: 0.3240 to 0.5956). Sensitivity 8.333% and Specificity 98.44%]. B - ROC curve of augmentation index (AIx@75) [AUC: 0.7179 (95% CI: 0.5789 to 0.8570). Sensitivity 83.33% and Specificity 60.00%, Cutoff: 27.67%]. C - ROC curve of cSBP was not able to differentiate the two groups [AUC: 0.7013 (95%CI: 0.5590 to 0.8436). Sensitivity 100%: 74.03 and Specificity %: 41.54, Cutoff: 99.50%]

with an outcome than in the group without an outcome. Studies show that obesity, assessed by BMI, is a risk factor for the development of high blood pressure during pregnancy [34, 39]. In a systematic review and meta-analysis of large cohort studies, it was demonstrated that BMI > 30 kg/m^2 pre-pregnancy is an important risk factor for pre-eclampsia. As obesity is closely linked to chronic high blood pressure, reducing pre-pregnancy BMI could reduce these two important risk factors for pre-eclampsia. The BMI > 30 kg/m^2 increases the risk of pre-eclampsia by 2 to 4 times [5]. The risk of high blood pressure during pregnancy doubles for every 5 to 7 kg/m² increase in BMI [40, 41]. The mechanisms involved in the contribution of obesity to preeclampsia are not well known. Obesity is considered a chronic low-grade inflammatory condition, also known as "meta-inflammation." The presence of low-grade inflammation can induce endothelial dysfunction and placental ischemia through immunomodulatory mechanisms, which lead to the production of inflammatory mediators. These inflammatory mediators, in turn, can trigger an exacerbated maternal inflammatory response and develop arterial hypertension during pregnancy [42].

In the present study, peripheral blood pressures were similar between the groups with and without outcome. Differently, cSBP was significantly higher in the outcome group. A body of evidence suggests that cSBP is better correlated with future cardiovascular events than brachial blood pressure. The heart, kidneys, and major arteries supplying the brain are exposed to aortic pressure, suggesting that cardiovascular events may be more closely related to central blood pressure than to brachial blood pressure [43]. With the aim of evaluating whether cSBP would be able to differentiate pregnant women with and without an outcome, the ROC curve was constructed and maximal sensitivity and specificity were determined.

The AUC of cSBP was 0.7013 (95% CI: 0.5590 to 0.8436) and the maximum sensitivity and specificity point was 99.50 mmHg. These results show that cSBP is capable of discriminating, at the beginning of pregnancy, pregnant women with and without outcome.

BP and AIx@75 were significantly higher in the outcome group. Similar results were found by Avni et al. [44] who compared pregnant women with severe pre-eclampsia ($n = 5$), gestational hypertension ($n = 27$) and chronic arterial hypertension ($n = 14$) with 54 normal pregnancy. The authors observed that AIx@75 was significantly higher in women with gestational hypertension and pre-eclampsia compared to normal pregnancies and women with chronic hypertension. These results suggest that pulse wave analysis has potential as a possible screening tool in women at high risk of preeclampsia [4]. According to Velauthar et al. [5], Doppler of the uterine arteries can predict 47.8% and 26.4% of cases of pre-eclampsia in the first trimester of pregnancy and at any time of pregnancy, respectively.

The results of the present study demonstrate that the development of pregnancy-associated hypertensive disease was preceded by a significant increase in AIx@75 and cSBP, which is corroborated by several reports in the literature [7, 9, 19, 43]. AIx@75, using the ROC curve, it was shown to be capable of tracking hypertensive disease during pregnancy in a better way than the method most used at the time, Doppler ultrasound of the uterine arteries. The MUA-PI ROC curve showed a sensitivity of 8.333% and a specificity of 98.44%, and the AIx@75 ROC curve showed a sensitivity of 83.33% and a specificity of 60.00% (Fig. 3).This study adds to other studies in the literature, the importance of AIx@75 in screening for hypertensive pregnancy disorders [16, 19–21, 37, 45]. This fact shows that the circulatory adaptation of pregnancy can hide differences in these parameters between pregnant women with or without poor outcomes. Therefore, a simple comparison between arterial stiffness indices, such as the AIx@75 of healthy pregnant women and those who developed hypertensive syndrome may be insufficient to guarantee effective early screening, which highlights the importance of creating equations and/or reference values that enable the use of these indices as predictors of cardiovascular disorders. Both the AIx@75 as for c-fPWV provide a comprehensive assessment of arterial function that is highly reproducible, and its value has been validated in both healthy individuals and patients with cardiovascular disease [17, 18]. In our study, only AIx@75 and cSBP were able to stratify pregnant women who developed hypertensive disease of pregnancy or not. It is likely that this finding is related to a lesser influence of arterial structural changes in hypertensive syndromes during pregnancy, especially pre-eclampsia, which is influenced by vasoconstriction [45]. The changes in gestational hypertensive pathology in patients in the age range of our group would be more related to vasoconstriction and not to changes with aging/atherosclerosis, smoking, etc. AIx@75 is mainly influenced by vasoconstriction.

Strengths and limitations of the study

Strengths: 1. Studies show that AIx@75 can be modulated by age and height. In this study, the pregnant women group was matched by age and height with the control group with the aim of studying the changes imposed by pregnancy without the bias imposed by these two variables. 2.The assessment with Doppler ultrasound was performed according to international recommendations [19, 27] and by just one professional to reduce the operator-dependent bias peculiar to the technique. 3. The results of our study suggest the superiority of AIx@75 in relation to Doppler of the uterine arteries, as a screening method in the first trimester of pregnancy, regardless of whether the pregnant woman will develop gestational hypertension with or without target organ damage (more severe form). On the other hand, in most studies, the best screening performance by Doppler ultrasound assessment is achieved in the assessment of the second trimester of pregnancy and for hypertensive disease in its severe form (eclampsia) [24, 28, 46]. It is important to highlight that the most effective drug intervention in preventing hypertensive disease to date should be started in the first trimester of pregnancy [27, 47].

Limitations: 1.This is a cross-sectional study, considering the comparison between pregnant women and the control group. This type of study does not provide data on pregnancy-related longitudinal temporal variations in the variables of interest. 2. The population came from just one center, which compromises the external validity of the study.

Conclusions

AIx@75 was significantly higher in pregnant woman compared to control group. ROC curve analysis showed that this index is a sensitive and independent early screening measure of hypertensive pregnancy disorders. In addition, we compared pregnant women with and without outcome and our results suggest that the development of hypertensive pregnancy disorders is preceded by higher levels of cSBP and AIx@75. ROC curve analysis showed that AIx@75 and cSBP were able to discriminate between pregnant women with and without an outcome. Differently, the MUA-PI did not differ between pregnant women with and without outcome and the ROC curve did not show good discriminatory capacity in differentiating between these two groups. These results suggest that AIx@75 is more effective than MUA-PI for screening hypertensive disease of pregnancy in the first trimester.

AIx@75 did not associate with MUA-PI. Taken together, this study suggests the possibility of using cardiovascular parameters for screening in the first trimester compared with other data using MUA-PI in the second trimester. Prospective studies will be needed to confirm these findings.

Abbreviations

AIx@75	augmentation index corrected by 75 beats per minute
AP	Augmentation pressure
AUC	Area under curve
BMI	Body mass index
BP	Blood pressure
CI	Cardiac index
cAP	Central augmentation pressure
CMDI	Centro Municipal de Diagnóstico por Imagem em Ginecologia-Obstetrícia da Prefeitura de Belo Horizonte
CO	Cardiac output
cDBP	Central diastolic blood pressure
pDBP	Peripheral diastolic blood pressure
HR	Heart rate
ISUOG	International Society of Ultrasound in Obstetrics and Gynecology
MAP	Mean arterial pressure
MUA-PI	Mean uterine artery pulsatility index
NO	Nitric oxide
eNOS	Endothelial nitric oxide syntase
NPG	Non-pregnant women
PG	Pregnant
PI	Pulsatility index
PP	Pulse pressure amplification
cPP	Central pulse pressure
pPP	Peripheral pulse pressure
c-fPWV	Estimated pulse wave velocity between the carotid and femoral arteries
ROC	Receiver operating characteristic
SV	Stroke volume
S/D	Systole/diastole ratio
cSBP	Central systolic blood pressure
pSBP	Peripheral systolic blood pressure
TVR	Total vascular resistance
UtAPI-l- left	Left uterine artery pulsatility index
UtAPI-r- right	Right uterine artery pulsatility index

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Author contributions
PMAOG: conceptualization, investigation, data curation, formal analysis, and editing of the original draft. MLPB, MSMS, LFMS Data curation, methodological supporting, and revision of the original draft. JOFJ, BAR, BAFS, Conceptualization, formal analysis, investigation, methodological supporting, project administration, validation, and revision of the original draft. JFPS, MGRM: Conceptualization, formal analysis, statistical analysis, investigation, methodological support, project administration, supervision, validation, and revision of the original draft. All authors read and approved the final manuscript.

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Data availability
The dataset analyzed during the current study is available from the corresponding author upon reasonable request.

Declarations

Ethical approval
This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Research Ethics Committee of the Faculty of Medical Sciences of Minas Gerais (opinion number: 4,400,617).

Consent to participate
Written informed consent was obtained from all the participants before evaluation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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