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# Reference range of uterine artery Doppler parameters between the 11<sup>th</sup> and 14<sup>th</sup> pregnancy weeks in a population sample from Northeast Brazil

*Valores de referência para parâmetros dopplervelocimétricos das artérias uterinas entre a 11<sup>a</sup> e 14<sup>a</sup> semanas de gestação em uma amostra populacional do Nordeste do Brasil*

## Original Article

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Ultrasonography, Doppler  
Pregnancy trimester, first  
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### Palavras-chave

Ultrassonografia Doppler  
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### Abstract

**PURPOSE:** To establish reference values for the first trimester uterine artery resistance index (UtA-RI) and pulsatility index (UtA-PI) in healthy singleton pregnant women from Northeast Brazil. **METHODS:** A prospective observational cohort study including 409 consecutive singleton pregnancies undergoing routine early ultrasound screening at 11–14 weeks of gestation was performed. The patients responded to a questionnaire to assess maternal epidemiological characteristics. The left and right UtA-PI and UtA-RI were examined by color and pulsed Doppler by transabdominal technique and the mean UtA-PI, mean UtA-RI and the presence of bilateral protodiastolic notching were recorded. Quartile regression was used to estimate reference values. **RESULTS:** The mean±standard deviation UtA-RI and UtA-PI were 0.7±0.1 and 1.5±0.5, respectively. When segregated for gestation age, mean UtA-PI was 1.6±0.5 at 11 weeks, 1.5±0.6 at 12 weeks, 1.4±0.4 at 13 weeks and 1.3±0.4 at 14 weeks' gestation and mean UtA-RI was 0.7±0.1 at 11 weeks, 0.7±0.1 at 12 weeks, 0.6±0.1 at 13 weeks and 0.6±0.1 at 14 weeks' gestation. Uterine artery bilateral notch was present in 261 (63.8%) patients. We observed that the 5th and 95th percentiles of the UtA-PI and UtA-RI uterine arteries were 0.7 and 2.3 and, 0.5 and 0.8, respectively. **CONCLUSION:** Normal reference range of uterine artery Doppler in healthy singleton pregnancies from Northeast Brazil was established. The 95th percentile of UtA-PI and UtA-RI values may serve as a cut-off for future prediction of pregnancy complications studies (i.e., pre-eclampsia) in Northeast Brazil.

### Resumo

**OBJETIVO:** Estabelecer valores de referência para os índices de resistência (UtA-IR) e de pulsatilidade (UtA-IP) das artérias uterinas em mulheres com gravidezes saudáveis do nordeste do Brasil. **MÉTODOS:** Um estudo de coorte observacional prospectivo, incluindo 409 gestações únicas consecutivas submetidas a exame de ultrassonografia de rotina entre 11 e 14 semanas de gestação, foi realizado. As pacientes responderam a um questionário para avaliar características epidemiológicas maternas. Os índices UtA-IR e UtA-IP das artérias uterinas esquerda e direita foram examinadas através de Doppler colorido e pulsátil por técnica transabdominal. A média UtA-IP, a média UtA-IR e a presença de incisura protodiastólica bilateral foram registradas. Regressão quartil foi utilizada para estimar os valores de referência. **RESULTADOS:** A média±desvio-padrão de UtA-IR e UtA-IP foram de 0,7±0,1 e 1,5±0,5, respectivamente. Quando separadas por idade gestacional, a média de UtA-IP foi de 1,6±0,5 com 11 semanas, 1,5±0,6 com 12 semanas, 1,4±0,4 com 13 semanas e 1,3±0,4 em uma gestação de 14 semanas e a média de UtA-IR foi de 0,7±0,1 com 11 semanas, 0,7±0,1 com 12 semanas, 0,6±0,1 com 13 semanas e 0,6±0,1 com 14 semanas de gestação. Incisura bilateral das artérias uterinas estava presente em 261 (63,8%) pacientes. Observou-se que os percentis 5 e 95 de UtA-IP e UtA-IR foram 0,7 e 2,3 e 0,5 e 0,8, respectivamente. **CONCLUSÃO:** A curva de valores de referência dos índices de dopplervelocimetria das artérias uterinas no primeiro trimestre foi estabelecida para gestações únicas e saudáveis do nordeste do Brasil. Os valores do percentil 95 para os índices UtA-IP e UtA-IR podem servir como ponto de corte para estudos de predição de complicações em gravidezes (por exemplo, pré-eclâmpsia) no nordeste do Brasil.

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Conflict of interests: nothing to declare.

## Introduction

Pre-eclampsia (PE) remains the leading cause of maternal and perinatal mortality and morbidity worldwide; in particular, it has been estimated that 10–15% of the 500 000 maternal deaths that occur each year are caused by hypertensive diseases of pregnancy. The ability to predict which women will be at high risk for PE has been a focus of recent research. At present, the first trimester appears to be the preferred gestational period for PE screening; this preference for early screening has been reinforced by recent evidence suggesting that the prophylactic use of low-dose aspirin beginning in early pregnancy (prior to 16 weeks) can reduce the prevalence of PE by as much as 50% and significantly decrease rates of perinatal death<sup>1,2</sup>.

Although no single screening procedure for predicting PE has been widely adopted in clinical practice, uterine artery Doppler is certainly the most widely studied clinical test available for this purpose. Uterine artery Doppler ultrasound has become a useful method for the indirect assessment of uteroplacental circulation in early pregnancy (11–14 weeks). If combined with examination of maternal history, mean arterial pressure (MAP) and certain biochemical markers (pregnancy-associated plasma protein A and placenta growth factor), uterine artery Doppler may be regarded as an adjunct screening tool for predicting PE and intrauterine growth restriction. Abnormal uterine artery Doppler results are strongly correlated with adverse maternal and perinatal outcomes<sup>1-8</sup>.

The clinical use of uterine artery Doppler ultrasound requires the existence of reference values. Reference values for mean uterine artery Doppler indices between 11 and 14 weeks of gestation have not previously been reported for our study population. The objective of this study was to determine reference values for the uterine artery resistance index (UtA-RI) and uterine artery pulsatility index (UtA-PI) between weeks 11 and 14 of gestation among singleton pregnant women from Fortaleza, located in the Northeastern region of Brazil.

## Methods

This prospective observational cohort study recruited patients who visited the Maternal-Fetal Medicine Service of Fortaleza General Hospital (*Hospital Geral de Fortaleza*, HGF) in the Ceará state in Northeastern Brazil for routine first trimester Down syndrome screening between August 2009 and February 2011. The women were followed up until late postpartum. Information regarding the evolution of these patients' pregnancies and maternal and perinatal outcomes was obtained from the patients' hospital records.

The patients were invited to undergo an ultrasound scan to measure fetal crown-rump length and to confirm gestational age (GA). Nuchal translucency and uterine artery Doppler index measurements were also obtained during

this ultrasound. GA was established using menstrual dates and confirmed by first trimester ultrasound; the ultrasound-based GA estimate was utilised if the GA estimates from menstrual and ultrasound data differed by more than 7 days. This study was approved by the Research Ethics Committee of Fortaleza General Hospital.

The inclusion criteria for this study were singleton pregnant women recruited in the first trimester who delivered a phenotypically normal stillborn or live-born infant at or after 24 weeks of gestation without experiencing hypertensive disease.

The exclusion criteria were pregnancies with major fetal abnormalities, pregnancies ending in miscarriage or fetal death prior to 24 weeks, twin pregnancies, cases lost of follow-up and patients with fetal growth restriction, PE and/or gestational hypertension (GH).

Patients responded to a questionnaire that included the following items: age, race (white, non-white or others), method of conception (spontaneous conception or assisted conception requiring the use of ovulation drugs), the smoking of any number of cigarettes per day during pregnancy (yes or no), the intake of any volume of alcohol during pregnancy (yes or no), drug use during pregnancy (yes or no), medical history, including not only whether the patient has been diagnosed with chronic hypertension or diabetes mellitus but also whether there exists a familial history of PE in the patient's mother or sister (Fam-PE; scored as yes or no) and obstetric history, including parity and the occurrence of PE in a previous pregnancy (Previous PE; scored as yes or no).

As quantitative variables, UtA-RI and UtA-PI were measured. Transabdominal ultrasound examinations were performed using a Voluson 730 Pro (General Electric, USA) ultrasound system. This system, which was equipped with a 3.5-MHz convex transducer, has been described in previously published studies<sup>5-10</sup>. Pulsed Doppler ultrasound was used to obtain flow velocity waveforms from the ascending branch of the uterine artery at the point closest to the internal os. When three similar consecutive waveforms were obtained, UtA-RI and UtA-PI were measured, and mean index values were calculated using the values obtained for the left and right arteries. The presence or absence of a protodiastolic notch was also recorded<sup>5,8-12</sup>.

Values of quantitative variables were analysed for each categorical variable. The  $\chi^2$  test and Fisher's exact test were used to analyse unpaired categorical variables, and Student's *t*-test and analysis of variance were used to assess continuous variables.  $p < 0.05$  was considered statistically significant. The Doppler indices were analysed by quartile regression. The average values, standard deviations (SDs) and 5th, 50th and 95th percentile values of these indices were calculated for each GA between 11 and 14 weeks of pregnancy. All calculations were performed using the Stata 10 program (Stata Corp., College Station, TX, USA).

## Results

The examined cohort initially consisted of 550 consecutive, singleton pregnancies with a live fetus between gestational weeks 11 and 14. However, 45 of these cases (8.1%) were excluded due to loss of follow-up. Among the remaining 505 cases, women who developed PE or GH (n=78), women who did not develop PE or GH but delivered newborns who were small for their GA (n=12) and women with pregnancies resulting in fetal death or miscarriage prior to gestational week 24 (n=6) were all excluded from the study.

This study included 409 women whose pregnancies progressed to term without the occurrence of hypertensive disorders. The mean age of the participants was 26.1 years (range: 15–43 years). With respect to race, the women were predominantly non-white. The majority of study participants had low parity as the subjects included 201 nulliparous women (49.1%), 115 primiparous women (28.1%) and 93 multiparous women (22.8%). Only 25 study subjects (6.1%) smoked during their pregnancies, and 41 study subjects (11.2%) had consumed alcohol during their pregnancies. Nine participants presented a history of chronic hypertension, and 12 participants were diabetic (type I or II). The mean body mass index (BMI) of the study subjects was  $25.0 \pm 4.9$  (range: 15–38), and 56 subjects (13.6%) had a BMI greater than 30. The mean systolic and diastolic pressures of the study participants were 105.1 mmHg and 65.5 mmHg, respectively. The average MAP was  $78 \pm 10$  mmHg (range: 53–117 mmHg) (Table 1).

The presence of risk factors for PE, such as chronic hypertension, diabetes, a family history of PE, a prior history of PE and obesity, was not associated with significant changes in mean UtA-RI and mean UtA-PI values during the first trimester of pregnancy. The intake of folic acid, smoking, alcohol consumption and miscarriage risk also did not appear to significantly affect the values of these Doppler indices (Table 2).

This study examined 61 women at 11 weeks, 188 women at 12 weeks, 133 women at 13 weeks and 27 women at 14 weeks. Deliveries occurred at approximately 39 weeks, and the mean birth weight of the infants was 3272 g.

Overall, the means  $\pm$  standard deviation for the UtA-RI and UtA-PI values measured in this study were  $0.7 \pm 0.1$  and  $1.5 \pm 0.5$ , respectively. After breaking down the results by GA, the mean UtA-PI values ranged from  $1.6 \pm 0.5$  at 11 weeks to  $1.3 \pm 0.4$  at 14 weeks (Table 3). As pregnancies progressed from 11 to 14 weeks, a decrease in the presence of a bilateral notch and the mean values of the impedance indices (UtA-RI and UtA-PI) were observed (Tables 3 and 4).

**Table 1.** Maternal epidemiologic characteristics between weeks 11 and 14 of gestation in 409 singleton pregnancies that evolved satisfactorily

Characteristics	Values
Age (years)	26.1 $\pm$ 6.7
Systolic BP	105.1 $\pm$ 11.5
Diastolic BP	65.5 $\pm$ 10.0
MAP	78.8 $\pm$ 10.0
Ethnicity	
Non-white	303 (74.0)
White	94 (23.0)
Others	12 (3.0)
Nulliparous	201 (49.1)
Parity	
1	115 (28.1)
2 or 3	82 (20.0)
4 or more	11 (2.8)
Previous PE	24 (5.8)
Family history of PE	60 (14.6)
Cigarette smoker	25 (6.1)
Alcohol consumption	46 (11.2)
BMI (kg/m <sup>2</sup> )	25.0 $\pm$ 4.6
Obesity (BMI>30)	56 (13.6)
Folic acid	334 (81.6)
Threatened miscarriage	78 (19.0)
History of chronic hypertension	9 (2.1)
History of pre-existing diabetes	12 (2.9)

Data are shown as mean  $\pm$  standard deviation or n (%) of sample.

BP: blood pressure; MAP: mean arterial pressure; PE: pre-eclampsia; BMI: body mass index.

**Table 2.** The mean values of resistance index and pulsatility index of the uterine arteries between weeks 11 and 14 of gestation among 409 singleton pregnancies that evolved satisfactorily, according to maternal epidemiological characteristics

Variables	Present	Absent	p-value	Present	Absent	p-value
	Resistance index			Pulsatility index		
Cigarette smoker	0.7	0.7	0.7	1.5	1.5	0.8
Alcohol consumption	0.7	0.7	0.8	1.5	1.5	0.9
Obesity (BMI>30)	0.6	0.7	0.4	1.4	1.5	0.2
Diabetes	0.7	0.6	0.6	1.6	1.5	0.6
Folic acid	0.7	0.7	0.8	1.5	1.4	0.1
Chronic hypertension	0.7	0.7	0.6	1.5	1.5	0.2
Threatened miscarriage	0.7	0.7	0.3	1.5	1.4	0.0
Nulliparous	0.6	0.7	0.4	1.5	1.5	0.3
Family history of PE	0.7	0.7	0.8	1.5	1.5	0.5

BMI: body mass index; PE: pre-eclampsia.

**Table 3.** Mean, standard deviation, 5th and 95th percentiles for mean uterine artery pulsatility index between weeks 11 and 14 of gestation among 409 singleton pregnancies that evolved satisfactorily

Week	n	Pulsatility index			
		Mean	SD	5th percentile	95th percentile
11	61	1.6	0.5	0.8	2.5
12	188	1.5	0.6	0.7	2.6
13	133	1.4	0.4	0.8	2.2
14	27	1.3	0.4	0.7	1.9

SD: standard deviation.

**Table 4.** Mean, standard deviation, 5th and 95th percentiles for mean uterine artery resistance index between weeks 11 and 14 of gestation among 409 singleton pregnancies that evolved satisfactorily

Week	Resistance index			
	Mean	SD	5th percentile	95th percentile
11	0.7	0.1	0.5	0.8
12	0.7	0.1	0.5	0.8
13	0.6	0.1	0.5	0.8
14	0.6	0.1	0.5	0.8

SD: standard deviation.

The difference in UtA-PI values between 11 and 14 weeks was statistically significant ( $p=0.02$ ), whereas the corresponding difference in UtA-RI values was nearly statistically significant ( $p=0.08$ ) (Table 4).

The 95th percentile values for mean UtA-PI and mean UtA-RI were 2.4 (range: 1.9–2.5) and 0.8 (range: 0.8–0.9), respectively. A bilateral notch occurred in 261 patients (63.8%).

## Discussion

Bilateral uterine artery Doppler waveforms were successfully obtained in all included cases. Analyses of the study results demonstrated the feasibility of assessing uteroplacental circulation by transabdominal ultrasonography in the first trimester of pregnancy (11–14 weeks) and confirmed the possibility of incorporating uterine artery Doppler into routine screening performed during this trimester. The application of this method, in combination with other markers, such as maternal history, MAP and biochemical markers, appears to be useful for identifying pregnancies at high risk for complications, and the increased monitoring of these pregnancies could improve maternal and perinatal outcomes<sup>5,10,13-16</sup>.

We observed that UtA-RI and UtA-PI values decreased as GA increased from 11 to 14 weeks. This finding suggested that trophoblastic invasion may be responsible for the observed decrease in impedance in uterine vessels during this time period and that this decrease is indicative of a good prognosis for a pregnancy<sup>16-20</sup>.

The mean UtA-PI value was 1.5 (range: 1.3–1.6). This mean UtA-PI value was similar to values obtained for the unaffected group in other studies that utilised

transabdominal uterine artery Doppler<sup>21-25</sup>. However, our observed mean UtA-PI value was lower than the mean UtA-PI value of 1.6 reported by another study conducted in Brazil that utilised transvaginal uterine artery Doppler to examine 344 pregnancies with normal pregnancy outcomes<sup>26</sup>.

We observed that mean UtA-RI and UtA-PI values were lower among women with previous pregnancies of over 24 weeks that resulted in normal outcomes than among nulliparous women. This finding may suggest that the occurrence of a prior healthy pregnancy is associated with improved placental adaptation<sup>19,20,27,28</sup>.

It is known that PE in a prior pregnancy, obesity, a family history of PE and nulliparity are risk factors for PE<sup>8-11,28</sup>. The presence of these risk factors did not significantly alter the mean UtA-RI and UtA-PI values in the first trimester of pregnancies that evolved satisfactorily.

High UtA-PI values have been associated with adverse pregnancy outcomes. An abnormal uterine artery Doppler pattern has been defined as a mean UtA-PI higher than the 95th percentile value, and this cut-off may be useful in clinical practice for PE screening among high-risk populations<sup>22,25,29-31</sup>. In our study, the 95th percentile value for mean UtA-PI was 2.3 (range: 1.9–2.5). The 95th percentile value for mean UtA-PI was lower in our study than in other published studies<sup>6,14,25</sup>.

One of these previously published investigations was a prospective study of 1091 patients that reported 95th percentile values for mean UtA-PI that ranged from a minimum of 2.3 (at gestational week 14) to a maximum of 3.1 (at gestational week 11). Another study by the same research group evaluated 620 patients and reported 95th percentile values for mean UtA-PI that ranged from 2.2 (at gestational week 14) to 2.7 (at gestational week 11)<sup>6,25</sup>. Less variation in the 95th percentile values of mean UtA-PI over time was observed in our investigation than in other studies; this discrepancy remains even if the comparison is restricted to only include other studies that also used the transabdominal uterine artery Doppler measurement technique. Differences among various investigations with respect to the characteristics of study population may explain this finding.

We observed that an average of 63.8% of pregnant women presented with a bilateral notch during the first trimester. We can therefore consider this finding normal for this gestational period. Martin et al.<sup>3</sup> performed transabdominal scanning of women in the first trimester of pregnancy and reported that bilateral notches were present in 55% of the 3045 examined cases.

Another recent prospective study with 280 pregnant women reported a sensitivity of 66.7% and a specificity of 96.5% when using the 95th percentile value for mean

UtA-PI during the first trimester as a cut-off for predicting PE<sup>32</sup>. This prospective study determined that the 95th percentile value for mean UtA-PI was 2.3, which was comparable to the 95th percentile that was calculated in our study.

Sample size may be regarded as a limiting factor in our study because we examined a few cases of chronic hypertension and diabetes, undermining attempts to comparatively analyse the impedance behaviour of uterine arteries in these cases. The examination of a greater number of patients with obesity, chronic hypertension and/or nulliparity may favour the emergence of statistically significant differences in uterine artery Doppler index values that are associated with these characteristics. The highlight of this study was the analysis of a sample

population consisting of pregnant women in Northeastern Brazil who were treated by the Brazilian National Health Service (*Sistema Único de Saúde*, SUS). These patients characteristically exhibited high levels of racial miscegenation and belonged to the most underprivileged socioeconomic strata of Brazil.

In summary, we observed that mean UtA-PI decreased as GA progressed from gestational week 11 to week 14; in addition, the mean UtA-PI observed in this study was lower than the corresponding values reported by other investigations. The presence of a family history of PE, diabetes, smoking, alcohol consumption, obesity and/or chronic hypertension at the beginning of a pregnancy did not significantly alter the mean UtA-RI and UtA-PI values in the first trimester of pregnancies that evolved satisfactorily.

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