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Normative Values of Uterine Artery Doppler Pulsatility Index using Transvaginal Ultrasound in Women between 18-24^{+6} weeks of Gestation at Rajavithi Hospital

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ABSTRACT

Objectives: To establish the normative values of uterine artery Doppler pulsatility index (UtA-PI) obtained using transvaginal ultrasound in an unselected population at 18-24^{+6} weeks of gestation and to ascertain the relationship between UtA-PI and gestational age.

Materials and Methods: A prospective cross-sectional study was conducted at Rajavithi Hospital from December 2018 to June 2019. The mean UtA-PI was calculated using color Doppler ultrasound with uterine artery gated at the level of the internal os. Mean UtA-PI in relation to gestational age (GA) was reported, and linear regression was used to calculate the 5th, 10th, 50th, 90th and 95th percentiles of the UtA-PI.

Results: A total of 185 singleton pregnancies were enrolled in this study. Nineteen cases (10.2%) were excluded, leaving a total of 166 cases to be analyzed. The mean UtA-PI ranged from 1.19 at 18 weeks to 0.81 at 24 weeks of gestation. The best-fit curve of mean UtA-PI as a function of GA was a linear function: mean UtA-PI = 2.33-0.0634*GA (R2 = 0.271).

Conclusion: Normative values for the mean UtA-PI at 18-24^{+6} weeks of gestation using transvaginal ultrasound were established. A decrease in mean UtA-PI with advancing GA was observed.

Keywords: uterine artery pulsatility index, normative values, second trimester.

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ค่ามาตรฐานดัชนีความต้านทานของหลอดเลือดแดงมดลูกโดยอัลตราซาวด์ทางช่องคลอดในช่วงอายุครรภ์ 18-24^{+6} สัปดาห์ ณ โรงพยาบาลราชวิถี

ลลิตา ทรงสถาพร, ลัลธพร พัฒนาวิจารย์, เด่นนพพร สุดใจ

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาค่ามาตรฐานดัชนีความต้านทานของหลอดเลือดแดงมดลูกโดยการวัดทางช่องคลอด ในหญิงตั้งครรภ์อายุครรภ์ 18-24^{+6} สัปดาห์ และศึกษาความสัมพันธ์ระหว่างดัชนีความต้านทานของหลอดเลือดแดงมดลูกกับอายุครรภ์*

วัสดุและวิธี: *เป็นการศึกษาเชิงพรรณนา แบบไปข้างหน้า ในโรงพยาบาลราชวิถี ตั้งแต่เดือนธันวาคม พ.ศ. 2561 ถึง มิถุนายน พ.ศ. 2562 โดยวัดค่าเฉลี่ยความต้านทานของหลอดเลือดแดงมดลูกโดยการใช้คลื่นเสียงความถี่สูงและใช้ดอปเปลอร์ ตรงตำแหน่งขอบด้านในของปากมดลูก โดยใช้การวิเคราะห์การถดถอยเชิงเส้นในการคำนวณเปอร์เซ็นต์ไทล์ที่ 5, 10, 50, 90, และ 95 ของค่าดัชนีความต้านทานของหลอดเลือดแดงมดลูก*

ผลการศึกษา: *หญิงตั้งครรภ์เข้าร่วมการศึกษาทั้งหมด 185 ราย ถูกคัดออก 19 ราย วิเคราะห์ข้อมูลจากหญิงตั้งครรภ์ 166 ราย พบว่าค่ามาตรฐานดัชนีความต้านทานของหลอดเลือดแดงมดลูกเท่ากับ 1.19 ที่อายุครรภ์ 18 สัปดาห์ และ 0.81 ที่อายุครรภ์ 24 สัปดาห์ โดยความสัมพันธ์ระหว่างค่าดัชนีความต้านทานของหลอดเลือดแดงมดลูก และอายุครรภ์ เป็นความสัมพันธ์เชิงเส้น ดังสมการ 2.33-0.0634*อายุครรภ์ (R2=0.271)*

สรุป: *การศึกษานี้ได้ตรวจวัดค่าดัชนีความต้านทานของหลอดเลือดแดงมดลูกโดยการวัดทางช่องคลอด เพื่อสร้างค่ามาตรฐานในช่วงอายุครรภ์ 18-24+6 สัปดาห์*

คำสำคัญ: *ดัชนีความต้านทานของหลอดเลือดแดงมดลูก, ค่ามาตรฐาน, ไตรมาสที่2*

Introduction

Examination of uterine artery impedance using Doppler ultrasonography is widely used for evaluation of trophoblast development[1]. There is evidence that uterine artery Doppler ultrasound provides more accurate predictions when performed in the second rather than in the first trimester[2]. A series of Doppler ultrasound screening studies have demonstrated that increased impedance to flow in the uterine arteries at 18-24 weeks of gestation is associated with an increased risk of subsequent development of preeclampsia[3].

Many studies have performed uterine artery Doppler pulsatility index (UtA-PI) in the second trimester using the transabdominal approach rather than the transvaginal approach because the former is more feasible and less invasive. Some studies have suggested that transabdominal UtA-PI measurements make waveforms unclear, significantly lowering bilateral notching; furthermore, there have been suspicious that, unlike the transvaginal approach, it has limitations when used with obese women[4, 5]. The Fetal Medicine Foundation (FMF) has demonstrated that UtA-PI can be measured by either transabdominal or transvaginal sonography in the second trimester[6]. When using transvaginal ultrasound (TVS), the transducer is closer to the vessel, and the angle of insonation is generally near the optimal 0 degrees[1, 6-7]. TVS offers easy identification of the uterine arteries at the level of the internal cervical os and gives clearer waveforms; moreover, evaluation of UtA-PI can be achieved at the same time as cervical length assessment is carried out during second trimester scan in order to estimate the risk of premature delivery[8-9].

Examination using the TVS approach provides higher uterine artery pulsatility index (UtA-PI) values than measurement by transabdominal ultrasound (TAS)[1]. Since differences in UtA-PI have been observed between the two methods, different reference charts should be used for these approaches.

As mentioned above, increases in UtA-PI are associated with increased risk of the development of preeclampsia. The normal values of this parameter using the TVS approach are not as yet available for a Thai population; therefore, this study aimed to establish the normative values of uterine artery Doppler PI (UtA-PI) obtained using transvaginal ultrasound in a low-risk population at 18-24^{+6} weeks of gestation, and to ascertain the relationship between UtA-PI and gestational age (GA).

Materials and methods

This prospective, cross-sectional study was performed at the Department of Obstetrics and Gynecology, Rajavithi Hospital, Bangkok, Thailand. The study was approved by the ethics committee of Rajavithi Hospital, and all participants gave written informed consent.

We enrolled 185 pregnant women between the gestational ages of 18 and 24^{+6} weeks who underwent prenatal visit for a routine anomaly scan between December 2018 and June 2019. The study population consisted of singleton low-risk pregnant women whose gestational age was based on their last menstrual period (LMP) and confirmed by ultrasonography before 18 weeks of gestation. Because the aim of this study was to establish normative values, women were excluded if they subsequently were unable to follow-up, had complications, including hypertension, gestational diabetes, preterm birth, small and large for gestational age, intrauterine death and fetus with chromosome or structural abnormalities.

Maternal baseline characteristics such as age, parity, pre-pregnancy BMI, gestational age at time of delivery, route of delivery and delivery information including birth weight and fetal abnormality were collected.

In the study protocol, ultrasound examinations were performed using 4C-RS microconvex endocavitary transducer 4-10 MHz (Voluson S8 Expert, GE; Medical Systems), and all measurements were recorded by a single operator. Before including patients in the study, a researcher reviewed landmarks in order to assess the uterine artery in accordance with the recommendations of the Fetal Medicine Foundation. The women were asked to empty their bladders and were placed in the

dorsal lithotomy position. A clean vaginal probe covered by a sterile condom was inserted slowly into the anterior fornix of the vagina. A transvaginal scan was done to measure cervical length, as a method of screening for preterm delivery[9]. Measurements of UtA-PI were then obtained as follows: the ultrasound probe was placed first into the left and then the right lateral fornix; the uterine arteries were identified using color Doppler at the level of the internal cervical os magnified to 50-75% of the image; after identification of each uterine artery, pulsed wave Doppler was used with the sampling gate set at 2 mm. to cover the whole vessel (Fig. 1). Care was taken during measurement to maintain the angle of insonation at less than 30 degrees. It was important that the peak systolic velocity was greater than 60 cm per second to differentiate the uterine artery from the arcuate artery. After three similar consecutive waveforms had been obtained, the pulsatility index (PI) was measured, and the mean UtA-PI of the left and right arteries were calculated[6]. UtA-PI was measured three times on each side in order to reduce the effect of intra-observer variability, and the presence or absence of uterine artery notching was also noted, with a notch was defined as a persistent decrease in blood flow velocity in early diastole, below the diastolic peak velocity. The mean UtA-PI and uterine artery notching patterns were recorded, and each subject was examined once during the 18-24^{+6} weeks period of gestation.

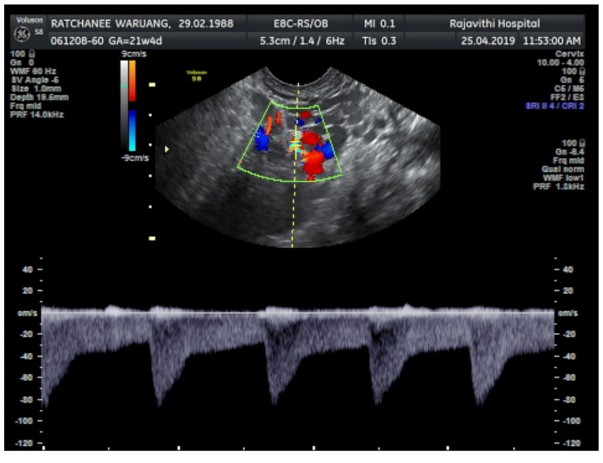

Fig. 1. Transvaginal ultrasound showing the uterine artery Doppler

Statistical analysis

The sample size was calculated to estimate single mean[10], with an estimated standard deviation (SD) of 1.14 and levels of and d of 0.05 and 0.56, respectively. The minimal sample size required for each GA was 16 cases; therefore, anticipating a dropout rate of 25%, the total sample size required was 20 cases per gestational age.

The baseline characteristics of the women and their fetal delivery information were calculated as mean and SD for continuous variables. Linear regression analysis was used to calculate the mean with 95% confidence interval and 5th, 10th, 50th, 90th, and 95th percentiles of the UtA-PI. Correlation analyses were performed using the Pearson product–moment correlation coefficient (normal distribution), and statistical significance was set at p value less than 0.05. Intraobserver reliability was calculated for 10 patients using intraclass correlation coefficient, with each patient examined three times. The data were analyzed with IBM SPSS version 22.

Results

Of 185 participants, five (2.7%) were lost to follow-up, another five developed preeclampsia (2.7%), three had fetal growth restriction (1.62%) and six

(3.24%) had preterm deliveries. A total of 166 pregnant women were therefore included in the final analysis.

The mean ± SD of maternal age was 30.5 ± 6.7 years, and mean ± SD of body mass index was 23.0 ±4.3 kg/m^2; these and other baseline characteristics are summarized in Table 1. The distribution of pregnant women in each GA period (weeks) were as follows: 18-18$^{+6\ (29)}$, 19-19$^{+6\ (24)}$, 20-20$^{+6\ (23)}$, 21-21$^{+6\ (23)}$, 22-22$^{+6\ (22)}$, 23-23$^{+6\ (22)}$, 24-24$^{+6\ (23)}$. When segregating into gestation age groups, mean UtA-PI values were 1.19 ± 0.21, 1.17 ± 0.29, 1.01 ± 0.23, 0.97 ± 0.19, 0.96 ± 0.21, 0.85 ± 0.17 and 0.83 ± 0.16 at 18, 19, 20, 21, 22, 23, and 24 weeks of gestation respectively. The prevalence of uterine artery notching was 7.57% (14/185): five cases (2.7%) demonstrated bilateral notching and nine (4.86%) had unilateral notching. Two women were excluded from analysis due to preeclampsia in one instance and preterm birth delivery in the other, while the remaining 12 pregnant women progressed to term without complication. Fig. 2. shows a scatterplot of observed mean UtA-PI with 95% confidence interval (CI) values against GA (weeks). Fig. 3. shows the relationship between mean UtA-PI and GA (weeks) in terms of linear regression (mean UtA-PI = 2.33-0.0634*GA) (R2=0.271). A significant correlation was confirmed by p value < 0.001 (R = 0.52). Gestational age-specific normative values for the 5th, 10th, 50th, 90th, and 95th percentiles of mean UtA-PI were established (Table 2).

Intra-observer variability in measurement of UtA-PI was analyzed and found good agreement, with intra-class correlation coefficient of 0.969 (95%CI 0.933-0.987, p < 0.001).

Table 1. Baseline characteristics.

Characteristics	Mean ± SD	Min-Max
Age (years)	30.5 ± 6.7	18 - 44
BMI (kg/m^2)	23.0 ± 4.3	15.2 - 34.9
Gravida (n)	1.9 ± 0.8	1 - 4
Mean arterial blood pressure (mmHg)	84.2 ± 9.0	66.7 - 106.7
Cervical length (mm.)	38.8 ± 4.6	28.3 - 53.4
Gestational age at delivery (weeks)	38.5 ± 1.0	37 - 41
Neonatal birth weight (grams)	2,913 ± 465	2,290 - 3,695

BMI: Body Mass Index

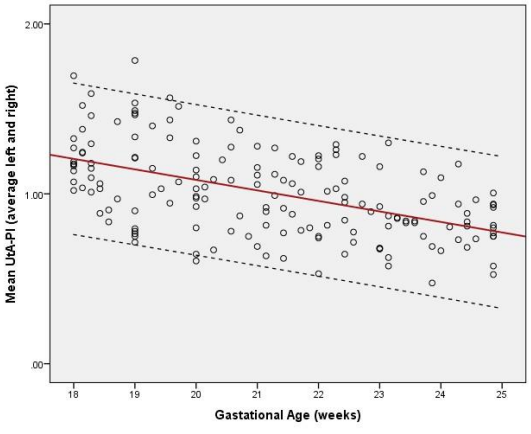

Fig. 2. Scatterplot of the mean uterine artery pulsatility index as function of gestational age (weeks).

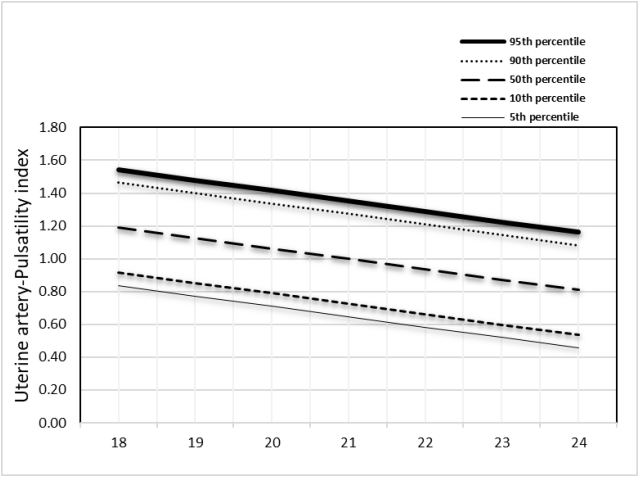

Fig. 3. Linear function relationship between gestational age in weeks and uterine artery pulsatility index from 18-24^{+6} weeks of gestation (The lines represent 5th, 10th, 50th, 90th, and 95th percentiles).

Table 2. Normal reference values for mean uterine artery pulsatility index with respect to gestational age.

GA (weeks)	(n)	P5	P10	P50	P90	P95
18	(29)	0.84	0.92	1.19	1.46	1.54
19	(24)	0.77	0.85	1.13	1.40	1.48
20	(23)	0.71	0.79	1.06	1.34	1.42
21	(23)	0.65	0.73	1.00	1.27	1.35
22	(22)	0.58	0.66	0.94	1.21	1.29
23	(22)	0.52	0.60	0.87	1.15	1.23
24	(23)	0.46	0.54	0.81	1.08	1.16

GA: gestational age

Discussion

UtA-PI Doppler ultrasound examination has become a valuable method of assessing uteroplacental circulation from early gestation and is considered to be a potential screening tool for the detection of preeclampsia[1,2]. In pregnancy, uteroplacental vascular adaptation is dependent on the invasion of spiral arteries by trophoblasts. The first wave of trophoblastic invasion involves the decidual portion of the spiral arteries and starts at 8 weeks of gestation, whereas the second wave involves the myometrial segments and occurs at 14-24 weeks[12].

Uterine artery Doppler ultrasound provides a more accurate prediction when performed in the second rather than in the first trimester[2]. Increased UtA-PI or presence of early diastolic notching has been shown in several studies to be associated with maternal and perinatal adverse outcomes[3,13]. The frequency of uterine artery notching in our study was 7.57% (14/185), with five cases (2.7%) of bilateral notching and nine (4.86%) of unilateral notching. Of these fourteen cases, only one developed preeclampsia. Phupong, et al[14] demonstrated values of uterine artery Doppler using PI combined with an early diastolic notch as a screening test for preeclampsia and/or having SGA infant in 400 healthy Thai pregnant women at 22 to 28 weeks of gestation. The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were

76.9%, 52.9%, 10.2%, and 97.1%, respectively. They concluded that women with an abnormal uterine artery Doppler were at a considerably higher risk of developing preeclampsia and/or having SGA infant. Another study by Sritippayawan, et al[15] assessed UtA-PI in 298 elderly gravida Thai women at 17-21 weeks of gestation and found that the sensitivity, specificity, PPV and NPV for detecting preeclampsia were 20%, 95.8%, 14.3%, and 97.2%, respectively. They concluded that women with mean PI > 95th of each gestational age had a high risk of developing preeclampsia. With the high NPV, this test may be useful in minimizing unnecessary interventions.

A mid-trimester ultrasound has been conventionally employed in screening of both structural and chromosomal abnormalities[3,12]; in addition, evaluation of UtA-PI can be achieved at the same time as cervical length assessment is carried out during second trimester scan to estimate the risk of premature delivery.

Previous studies have found that the number of women attending their first antenatal visit after 16 weeks is often greater than 50% and can be as high as 88.5% in developing countries[17-19]. Screening for preeclampsia in the second trimester could still be beneficial, since close monitoring looking for early signs of preeclampsia permits timely treatment and delivery[2,20,21]. Low-dose aspirin prophylaxis is recommended in women at high risk of preeclampsia, and this should be initiated between 12 weeks and 28 weeks of gestation and be continued daily until delivery[22].

The authors have established the normative values of UtA-PI obtained using transvaginal ultrasound at GA 18-24^{+6} weeks, and demonstrated that values of mean UtA-PI progressively declined with advancing GA from 1.19 to 0.81 from 18 through 24 weeks of gestation. Likewise, Peixoto, et al[23], established reference ranges of mean UtA-PI using transvaginal ultrasound at 20-24^{+6} weeks of gestation in 847 low-risk participants in a Brazilian population, demonstrating a decrease in UtA-PI with advancing GA from 1.14 at 20 weeks to 0.95 at 24 weeks. These findings were in agreement with those of our study, which showed a trend toward a decrease in UtA-PI. Although, the authors' normative values of mean UtA-PI in each gestational age were slightly different from those previously reported[23], this might be explained by the different populations and sample sizes. Our observation of a significant decrease in the mean UtA-PI was in agreement with that reported by Gomez, et al[24] who established a chart from 11-41 weeks of gestation based on a cross-sectional study. Including 20 pregnancies at each gestational week, the study used transvaginal ultrasound until 14 weeks of gestation, and transabdominal ultrasound from gestational week 15. The authors concluded that UtA-PI decreased progressively between 11 and 34 weeks, whereas a stable plateau was then seen until 41 weeks. Their results were comparable to ours, with a decreasing UtA-PI in the second trimester of pregnancy.

Takahashi, et al[25], established a reference range of mean UtA-PI between 16 and 23 weeks of gestation in 1,266 singleton Japanese pregnant women. The best-fit curve was a logarithmic one that represented the relationship between mean UtA-PI and GA: log10 mean PI = - 0.0211*GA+0.438. Similarly, Nanthakomon, et al[26], examined UtA-PI in early second trimester using the transabdominal approach in 132 Thai women showed a linear decrease across gestation (Right UtA-PI=1.569-(0.033*GA), R2=0.03 and Left UtA-PI=1.690-(0.035*GA), R2=0.008. When compared to our study using the TVS approach, the relationship between mean UtA-PI and GA (weeks) was described by the following formula: mean UtA-PI=2.33–0.0634*GA, (R2=0.271), the lower the R-squared, the lesser the model fits the data. Therefore, the mean UtA-PI was higher in those having TVS than in those undergoing the TAS approach at the same GA. Our findings were in concordance with the study of Ferreira, et al[1], which compared the reproducibility of measurements of first and second trimester UtA-PI using TAS and TVS, concluding that when measuring UtA-PI, assessment by TVS provides higher values and better insonation angle compared with TAS.

The strengths of the present study were: 1) it provided the first nomogram of mean UtA-PI using the TVS approach in a Thai population; 2) its low intra-observer variation suggested high reproducibility of this measurement; 3) all cases followed-up until delivery,

so that we were able to accurately calculate normal reference ranges in normal low-risk pregnancies; and 4) evaluation of UtA-PI could be achieved at the same time as cervical length assessment was carried out to estimate the risk of premature delivery during second trimester scan. The limitations of the study were: 1) all measurements were performed by a single operator, so that interobserver variability was not investigated; and 2) the TVS approach might cause minimal discomfort with the insertion of the transducer into the vagina. TVS requires covering the ultrasound transducer in a sterile condom, which might cause a reaction in patients with a latex allergy.

Conclusion

UtA-PI decreased with advancing GA when the mean UtA-PI was measured at 18-24^{+6} weeks of gestation by means of transvaginal ultrasound. Finally, normative values were established for the mean UtA-PI at 18-24^{+6} weeks of gestation using the transvaginal ultrasound in an unselected population at Rajavithi Hospital, and the prevalence of notching in the study was 7.57%. We believe that these normative values may be of clinical value in daily obstetric practice.

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Potential conflicts of interest

The authors declare no conflict of interest.

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