# Normal Reference Ranges of Uterine and Spiral Arteries Doppler at as Early as 6 Weeks of Gestation and its Significance

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**Original Article**

## ABSTRACT

**Background:** A high uterine artery pulsatility index (PI) reflects a defective development of placental bed spiral arteries. This study assesses early uterine and spiral arteries Doppler and their relation to adverse pregnancy events.

**Methods:** A retrospective cohort study was conducted on 291 pregnant women between 6 and 10+ weeks' gestation, where uterine and spiral arteries were assessed by transvaginal Doppler ultrasound at 6-10+ and 11-13+ weeks' gestation. All participants were followed up regarding the risk for miscarriage, PIH, and the need for neonatal ICU admission.

**Results:** Normal reference ranges were obtained for mean uterine PI and spiral resistance index (RI) during 6-10+ weeks' gestation. There was a significantly increased risk of miscarriage in women with higher uterine PI (p=0.042). Besides, there was a moderate positive correlation (r=0.61) between mean uterine PI and spiral RI during the first scan (6 - 10+ weeks). Also, there was a fair, positive correlation (r=0.33) between the mean uterine PI during the first and the second ultrasound scans.

**Conclusion:** Early measurement of uterine and spiral arteries Doppler may benefit as an early tool for detecting those at risk of miscarriage.

**Key Words:** Pulsatility index; pregnancy-induced hypertension, resistance index; spiral artery; uterine artery.

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## INTRODUCTION

Uteroplacental circulation space (UPCS) is developed in two phases. The first phase occurs at 8-10 weeks of pregnancy. It starts when the trophoblast cells form endovascular plugging within the spiral arteries. The trophoblast cells then begin to invade and destroy the musculo-elastic media in the intradecidual segments of the spiral arteries[1,2]. The second phase occurs at 14-16 weeks of pregnancy, where the trophoblast cells start to invade the spiral artery segments within the inner third of the myometrium[3].

Spiral artery impedance, determined by measuring its pulsatility index (PI) and peak systolic velocity, decreases between the 5$^{th}$ and the 10$^{th}$ week of pregnancy. This reflects an early increase in the blood flow at 5-7 weeks of pregnancy. On the other hand, the uterine and arcuate arteries' hemodynamics show no change until after the 8th week of pregnancy. This delay could be due to the upstream effects of placental development following significant downstream events[4]. A developmental defect in the spiral arteries of the placental bed, which could be complicated by hypertension in pregnancies and fetal growth restriction (FGR), is determined by the high uterine artery PI[5].

Between the 6$^{th}$ week and the 12$^{th}$ week of pregnancy, increased resistance index (RI) of the spiral arteries are associated with adverse pregnancy outcomes such as spontaneous abortion, missed abortion, preterm labor, FGR, pregnancy-induced hypertension (PIH), and abruptio placentae. This finding, however, was not statistically significant[6].

Uterine artery Doppler ultrasound has become an essential procedure for indirect assessment of the

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uteroplacental circulation from early pregnancy[7]. Therefore, it has been considered as a possible screening method to detect PIH[8].

In 2014, uterine artery Doppler during the first trimester was declared as a helpful method to predict adverse pregnancy outcomes, in particular, early-onset preeclampsia. A large meta-analysis study on 55974 women has found that the sensitivity and specificity of abnormal uterine artery flow velocity waveform (FVW) to predict early-onset preeclampsia were 47.8% and 92.1%, respectively, and to predict early-onset FGR were 39.2% and 93.1%, respectively. The sensitivity and specificity to predict any preeclampsia (not only early-onset) were 26.4% and 93.4%, respectively, and to predict any FGR (not only early-onset) were 15.4% and 93.3%, respectively[9].

In a previous study, there were no significant results between high uterine or spiral arteries Doppler and adverse pregnancy outcomes such as spontaneous abortion, missed abortion, preterm labor, FGR, preeclampsia, and placental abruption[6]. This may be due to the low sensitivity and specificity of uterine artery Doppler alone in predicting cases of preeclampsia and FGR. However, uterine artery Doppler screening in the first trimester is still recommended in the early prediction of preeclampsia[10].

The objective of Doppler ultrasound screening at this stage (11 to 13+ weeks) is to identify pregnant women who are at high risk for preterm preeclampsia (<37 weeks) and to reduce such risk through the prophylactic use of Aspirin (150 mg/day from 11-14 to 36 weeks). The ASPRE trial has shown that aspirin administration to pregnant women who are at high risk for preeclampsia reduces the rate of early preeclampsia (<32 weeks) and preterm preeclampsia (<37 weeks) by about 90% and 60%, respectively. Prophylactic use of Aspirin does not reduce the incidence of term preeclampsia[11].

In previous research, very early uterine artery Doppler examination (6-10 weeks of pregnancy) was not considered to predict preeclampsia. This study aimed to assess the uterine and spiral arteries Doppler in very early pregnancy and their relation to the increased uterine artery resistance in the late first trimester and their relation to other pregnancy-related complications, such as early miscarriage, PIH, and the need for neonatal ICU admission.

## METHODS

A retrospective cohort study was conducted on 291 pregnant women between 6 and 10+ weeks gestational age. Inclusion criteria were fetal viability, 6-10+ weeks gestational age at first scan determined by the crown-rump length, and absence of treatment with Aspirin or Heparin before enrollment. Fetuses with chromosomal/structural abnormalities or maternal risk factors for vascular disease, immune disease, and pregestational diabetes were excluded from the study.

Women underwent routine scans at 6-10+ weeks of gestational age to assess fetal viability and at 11-13+ weeks to conduct the routine first-trimester scan. Transvaginal ultrasound with Doppler was done by a single experienced operator who had received a certificate of competence in Doppler from the Fetal Medicine Foundation (www.fetalmedicine.com).

The transvaginal transducer was used for the uterine artery Doppler to obtain the sagittal section of the cervix. The probe was then moved laterally, and Color Doppler imaging was used to identify the uterine artery at the cervico-corporeal junction level, where uterine Doppler measurements were assessed. For the spiral arteries Doppler, a sagittal section of the fetus was searched for, where then crown-rump length was measured. Afterward, the operator followed the umbilical cord to reach its origin from the future placenta. The spiral arteries appeared by putting the color Doppler beneath this placenta. Then, using a pulsed-wave Doppler, the resistance index was measured (Figure 1).

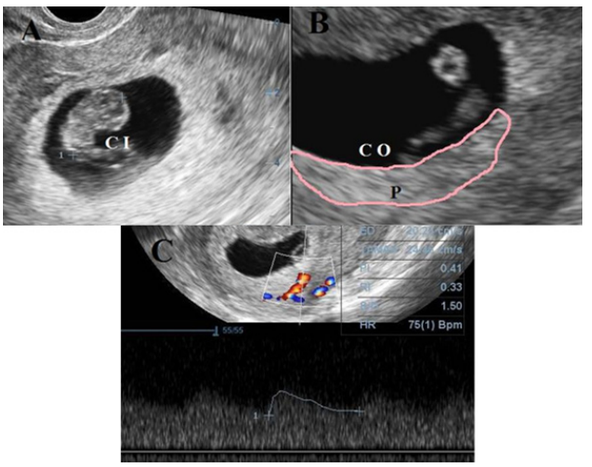


**Fig. 1:** Location of spiral arteries (CI: cord insertion; CO: cord origin, P: placenta)

In all measurements, the insonation angle was less than 30º, and the wall motion filter was 60. The gate was adjusted to the artery width (2 mm for uterine arteries and 0.5 mm for spiral arteries). All women were followed up regarding the risk for miscarriage, signs of PIH, and the need for neonatal ICU admission.

### *Statistical analysis*

The statistical method designed by Royston and Wright to estimate reference ranges was used[9]. The normal distribution of the collected data was checked using the Shapiro test. Z-scores were calculated using the

equation (measurement - mean/SD). Centile curves were calculated by the equation (mean + K x SD), where K is the corresponding centile of the standard normal distribution. Statistical procedures were performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Qualitative variables were expressed in the form of numbers and percentages. The chi-square test was used to compare between groups, and the Spearman correlation was used to correlate different variables with the gestational age. *P-value* was assumed to be significant if less than 0.05 and highly significant if less than 0.001.

## RESULTS

In this study, 291 pregnant women were recruited. Regarding women's characteristics, the mean age is 23.46 ± 2.73, and the mean body mass index (BMI) is 26.87 ± 3.17. All women underwent an early sonographic scan at 6-10 weeks of pregnancy, where uterine and spiral arteries Doppler were assessed.

According to the mean uterine PI, women were divided into two groups: normal PI for gestational age (group 1, n=263) and high PI for gestational age, who are above the 90th percentile (group 2, n=28). The mean uterine PI was decreased with the increase of gestational age (Figure 2). Similarly, the mean spiral RI was reduced with the increase of gestational age, especially among the participants in group 1 (Figure 3). The percentiles of mean uterine PI and spiral RI for group 1 were presented in (Table 1). Regarding the relation between the mean uterine PI and spiral RI during the first scan (6-10 weeks of pregnancy), there was a moderate positive correlation (r=0.61, $p$<0.001) (Table 2).

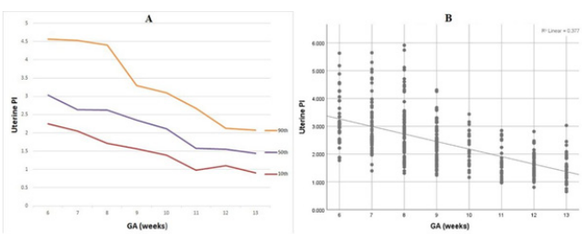


**Fig. 2:** a) Growth curve for mean uterine PI, b) Distribution of mean uterine PI

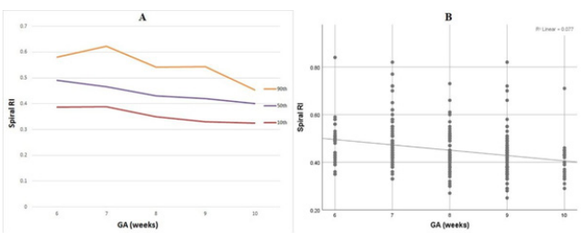


**Fig. 3:** a) Growth curve for Spiral RI, b) Distribution of spiral RI

**Table 1:** Reference ranges for mean uterine PI and spiral RI

| | GA | 10th | 50th | 90th |
|---|---|---|---|---|
| Mean Uterine PI | 6 weeks | 2.253 | 3.035 | 4.562 |
| | 7 weeks | 2.050 | 2.638 | 4.531 |
| | 8 weeks | 1.711 | 2.625 | 4.403 |
| | 9 weeks | 1.562 | 2.345 | 3.298 |
| | 10 weeks | 1.388 | 2.110 | 3.096 |
| | 11 weeks | 0.982 | 1.578 | 2.675 |
| | 12 weeks | 1.101 | 1.553 | 2.120 |
| | 13 weeks | 0.901 | 1.445 | 2.081 |
| Spiral RI | 6 weeks | 0.387 | 0.490 | 0.580 |
| | 7 weeks | 0.389 | 0.465 | 0.623 |
| | 8 weeks | 0.349 | 0.430 | 0.551 |
| | 9 weeks | 0.330 | 0.420 | 0.544 |
| | 10 weeks | 0.324 | 0.400 | 0.453 |

* PI: pulsatility index * RI: resistance index

**Table 2:** Relation between the mean uterine PI during the first scan (6-10+ weeks) with the spiral RI during the first scan (6-10+ weeks) and the mean uterine PI during the second scan (11-13+ weeks)

| | High uterine PI (1st scan) | Normal uterine PI (1st scan) | *P-value* |
|---|---|---|---|
| High spiral RI (1st scan)<br>Normal spiral RI (1st scan) | 8 (28.6%)<br>20 (71.4%) | 18 (6.9%)<br>245 (93.1%) | <0.001* |
| High uterine PI (2nd scan)<br>Normal uterine PI (2nd scan) | 4 (25%)<br>12 (75%) | 7 (9.1%)<br>95 (93.1%) | 0.02* |

Data presented as № (%) * *P-value* < 0.001 is highly significant

Unfortunately, only 118 women from all participants underwent a second sonographic scan, including a uterine Doppler scan, at 11-13+ weeks of pregnancy. There was a significant correlation between the mean uterine PI during the second sonographic scan (11-13+ weeks of pregnancy) and the mean uterine PI during the first sonographic scan (6-10 weeks of pregnancy) with a p-value of 0.02 and a fair, positive correlation (r=0.33) (Table 2).

At the study's end, only 25 women were missed during follow-up. Therefore, 241 women from the first group and 25 women from the second group had completed the study. (Table 3) shows a comparison between both groups regarding pregnancy outcomes. There was a significantly higher incidence of miscarriage in group 2 than in group 1 (*p-value* 0.042). On the contrary, there were no significant differences regarding the incidence of PIH and neonatal admission to neonatal ICU.

**Table 3:** Comparison between the two groups regarding the outcome

| | Group 1 (n=241) | Group 2 (n=25) | *P-value* |
|---|---|---|---|
| Miscarriage | 4 (1.7%) | 2 (8%) | 0.042* |
| Pregnancy-induced hypertension | 13 (5.4%) | 3 (12%) | 0.186 |
| NICU admission | 21 (8.7%) | 4 (16%) | 0.235 |

Data presented as № (%) *: *P-value* is significant

## DISCUSSION

Doppler ultrasound examination has been used to assess blood flow resistance in the uterine artery branches such as spiral arteries. In harmony with the physiological changes that occur during placentation, there is a significant decline in the impedance of blood flow in uterine artery branches with the increase of gestational age[6].

This study shows that, in early pregnancy, uterine PI and spiral RI decrease with increased gestational age. This regressive course aligns with its attitude through pregnancy[8]. We have noticed a difference between left and right uterine PI measurements in many cases due to different placental sites. To get accurate results, we measured both left and right uterine artery PI for each woman and then calculated the mean uterine PI.

Examining pregnant women during very early pregnancy (6-10+ weeks gestational age) for routine viability check and during the first trimester for routine chromosomal abnormality scan allowed us to develop reference ranges for mean uterine PI and spiral RI between 6 and 10+ weeks of gestation. We assumed the 90th percentile of our results is the limit to differentiate normal from abnormal measurements, as there is no valid reference range until now for the mean uterine PI and spiral RI at this very early gestational age.

The ASPRE trial previously stated that high uterine PI at 11-13+ weeks is a high risk for preterm preeclampsia[11]. So, we thought it would benefit if there is an earlier method to predict any Doppler change. Our results showed a moderate positive correlation between the mean uterine PI during the early sonographic scan at 6-10+ weeks gestational age and the uterine PI during the second sonographic scan at 11-13+ weeks gestational age. Therefore, we could use early uterine doppler as a differentiation tool between normal pregnant women and those with a risk of adverse pregnancy outcomes. When we compared the incidence of miscarriage between the two groups (below and higher 90$^{th}$ percentile uterine PI), we found that early high uterine PI (as early as six weeks) significantly increased the miscarriage incidence. This may be due to impaired blood flow to the future placenta. This assumption is strengthened by the strong positive correlation between uterine PI and spiral RI during the first scan at 6 to 10+ weeks of gestation.

On the other hand, when we followed the high uterine PI group until delivery, we could not significantly correlate with PIH. This may be due to the relatively small number of patients. These insignificant results may be changed if the study is applied on a large scale. Similarly, the incidence of neonatal ICU admission in the high uterine PI group was higher than that of the normal uterine PI group but with no significant difference, which may be attributed to relatively small numbers of patients.

## LIMITATION OF THE STUDY

The study's main limitation is that only 118 women from all participants completed the study and underwent a second sonographic scan at 11-13+ weeks of pregnancy.

## CONCLUSION

Early measurement of uterine and spiral arteries Doppler at 6-10+ weeks gestational age may help early detect those at risk of miscarriage due to impaired uteroplacental circulation. Those patients may benefit from the early administration of anticoagulants as early as six weeks of gestational age.

## HIGHLIGHTS

- First-trimester uterine artery Doppler is a useful tool for predicting PIH.
- Uterine PI and spiral RI decrease with increased gestational age.
- Screening of uterine and spiral arteries Doppler could be beneficial as early as 6 weeks of gestation to detect women at risk of miscarriage.

## CONFLICT OF INTEREST

There are no conflicts of interest.

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