

# Nomogram of Placental Thickness, Placental Volume and Placental Vascular Indices in Healthy Pregnant Women between 12 and 20 Weeks of Gestation

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**Objective:** To generate the nomogram of placental thickness, volume, and vascular indices in healthy pregnant women between 12 to 20 weeks of gestation.

**Material and Method:** An experimental cross sectional study of pregnant women, which were categorized into nine groups according to their gestational age ranging from 12 to 20 weeks of gestation, was done. Placental parameters that included placental thickness, volume, and vascular indices were measured using a Voluson E8 ultrasound machine. The measurements were correlated with gestational age.

**Results:** Two hundred ninety four subject were included in this study. The study indicated that the placental thickness and volume significantly increased with gestational age ( $r_p = 0.481$ ,  $p < 0.001$  and  $r_p = 0.837$ ,  $p < 0.001$ ). The correlation between the placental volume and gestational age can be formulated according to this equation: Placental volume ( $\text{cm}^3$ ) =  $e^{7.584+42.45(\frac{1}{GA})}$ ;  $R^2 = 0.76$ . Nonetheless, there is a very low correlation between the vascularization index (VI), vascularization flow index (VFI), and the gestational age ( $r_p = 0.162$ ,  $p = 0.005$  and  $r_p = 0.158$ ,  $p = 0.007$ ). The flow index (FI) was shown to have no correlation with gestational age ( $r_p = -0.067$ ,  $p = 0.254$ ).

**Conclusion:** From the present study, the placental thickness and placental volume significantly increased with gestational age. The VI and VFI showed poor correlation with gestational age while the FI had no correlation with the gestational age.

**Keywords:** Gestational age, Healthy pregnant women, Placental thickness, Placental volume, Placental vascular indices

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During pregnancy, both the fetal growth and placental growth increase correspond to the increasing gestational age in a linear regression. The placental vascularization also increases in the same manner. At the end of pregnancy, the placental weight is about one-sixth of the neonatal weight<sup>(1)</sup>.

Currently, ultrasound is used for the evaluation of both the fetus and the placenta. Many studies have shown that increasing gestational age is correlated with placental thickness and placental volume<sup>(2-4)</sup>. Any abnormalities of these placental parameters can reflect certain fetal conditions. For example, one study showed that an abnormal increase of placental thickness was associated with the Bart's hydrops fetalis<sup>(5)</sup>. Another study found a correlation of placenta membranacea with intrauterine growth restriction<sup>(6)</sup>. Some studies

have shown that birth weight can be predicted by the placental volume determined in the first and second trimesters<sup>(7,8)</sup>. Fetuses with trisomy 13 and trisomy 18 were found to have lower placental volumes in the first trimester compared to the normal fetus<sup>(9)</sup>.

Data from previous studies have not been conclusive concerning the placental vascular indices, including the vascularization index (VI), flow index (FI) and vascularization flow index (VFI). Some studies have shown increasing indices in correlation with increasing gestational age while others have not<sup>(10-12)</sup>. Two studies have shown that the placental vascular indices deviate from normal values in pregnancy with abnormal fetus<sup>(10)</sup> and pregnancy with maternal complications<sup>(13)</sup>. However, there is no definite conclusion about the correlation between placental vascular indices and maternal and fetal pathologies.

In Thailand, there has been no study to date concerning placental volume and placental vascular indices in pregnant Thai women. The available data is extracted from Western countries; this can be subject to misinterpretation when it is used in relation to Thai

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women. The objective of this study was to create a nomogram of placental thickness, volume, and vascular indices in healthy Thai pregnant women between 12 to 20 weeks of gestation. The basic data will be used for further studies that are concerned with placental profiles.

### Material and Method

This project was reviewed and approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand prior to its commencement.

### Materials

#### Study population

Between September 2011 and March 2012, pregnant women within 12 to 20 weeks of gestation were recruited for this study at the antenatal care unit and maternal-fetal medicine unit of Siriraj Hospital. The subjects in the present study were pregnant women who (1) had regular menstruation with a recognized last menstrual period (LMP), (2) had a singleton pregnancy, (3) had no obstetric complications, (4) had no associated diseases and (5) were at least 18 years old. Excluded from this study were patients who (1) had a discrepancy of more than two weeks between gestational age from LMP and ultrasound calculation, (2) had abnormal pregnancy including abnormalities of the fetus, placenta, or amniotic fluid, and (3) had abnormal pregnancy outcomes, for example, intrauterine growth restriction, being large for gestational age, or aneuploidy.

#### Sample size determination

Because the present study was cross sectional study, the sample size was calculated by the following formula<sup>(14)</sup>:

$$N = \frac{Z^2 \times \sigma^2}{d^2}$$

From this formula, the authors determined a need for 30 pregnant women for each gestation. Since there were nine specified gestations in this study ranging from 12 to 20 weeks, the number of subjects required, including an added number to take account of the possibility of later exclusion of the subjects was 300.

There was no available data from any study of other parameters, including placental volume, VI, FI, and VFI. Therefore, we performed pilot studies for the calculation of the sample size of these parameters and the same formula mentioned above was used. The sample sizes were calculated to be 20, 30, 27, and 23

subjects for each gestation for the study of placental volume, VI, FI, and VFI respectively.

In conclusion, from the calculations, the sample size needed for the present study was 300 pregnant women.

### Methods

#### Equipment for measurement

The 3D power Doppler ultrasound system (GE Voluson E8) with high definition flow and VOCAL mode was used for the calculation of the parameters in the present study. A 3.5 MHz abdominal transducer was used for the examinations.

#### Technique for measurement

Placental thickness was calculated by 2D ultrasound and defined by the thickness of placenta measured from the upper edge of the placenta starting from the point of placental cord insertion then vertically down to the lower edge of placenta.

The placental volume was evaluated by 3D ultrasound using VOCAL mode for calculation of the volume in two steps. In the first step, the whole placenta was calculated by the 3D ultrasound using an angle of sampling volume that varied from 60 to 98 degrees depending on different gestational ages. In the second step, the 3D picture of the whole placenta was divided into 6 sections. Each section was further measured individually until all the sections had been measured. The total placental volume was then automatically created and calculated by the machine, as shown in Fig. 1.

The placental vascular indices were calculated using the same technique as mentioned for the measurement of the placental volume and in addition

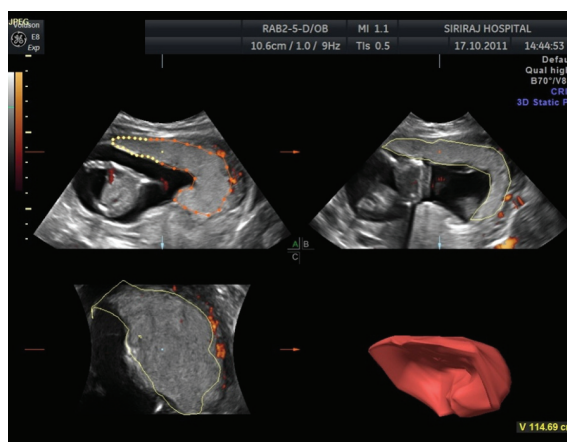


Fig. 1 Creation of placental volume using VOCAL mode.

with the power Doppler and volume histogram modes. The pulse repetition frequency and filter of power Doppler study were adjusted to be 0.9 and 2 for evaluation of all indices.

There are three placental vascular indices: (1) vascularization index (VI) is the ratio of the color voxel to total voxel, and represents the number of the vessels within the placenta; (2) flow index (FI) is the ratio of the weighted color voxel to total color voxel, and represents the number of blood cells that are being transported at the time of the 3D sweep; and (3) vascularization flow index (VFI), which is the ratio of the weighted color voxel to total voxel, and represents the number of vessels and the number of transported blood cells.

### Procedure

The process for the present study was explained to all the recruited subject and they were asked to sign a consent form before the procedure was performed. All the parameters of the subjects including placental thickness, volume, and vascular indices (VI, FI, and VFI) were then calculated using the techniques mentioned above.

All parameters in the present study were measured three times for each calculation to create the mean value of each parameter to be used in the analytical process.

### Statistical analysis

The descriptive data was expressed as mean  $\pm$  standard deviation (SD). The qualitative data was expressed in number and percentages.

The Pearson's correlation analysis ( $r_p$ ) was used to evaluate the correlations of gestational age and placental thickness, placental volume, and placental vascular indices.

Multiple regression analysis was applied to create the model of correlation. All calculations were performed by using the Excel and SPSS 18.0 programs. Differences were considered to be significant when the p-value was less than 0.05.

### Results

The present study consisted of 302 pregnant women. However, eight women were excluded as follows: two obese women because we were unable to identify the whole portion of the placenta, two women with gestational diabetes mellitus, three fetuses that were too small for gestational age and one woman whose fetus had uretero-pelvic junction obstruction.

The mean age was  $29.48 \pm 5.81$  years, mean hematocrit was  $36.34 \pm 2.89\%$  and mean body mass index was  $21.35 \pm 3.49$  kg/m<sup>2</sup>. Of the 294 women included in the present study, 148 (50.3%) had anterior placental location, 126 (42.9%) had posterior location, and 20 (6.8%) had the placenta attached at the uterine fundus.

There was a significant correlation between gestational age and placental thickness, but this correlation was poor ( $r_p = 0.481$ ,  $p < 0.001$ ) as shown in Fig. 2.

The mean placental volume increase was significantly correlated with increasing gestation age in the first half of pregnancy as shown in Fig. 3. There was a strong correlation in an almost linear fashion

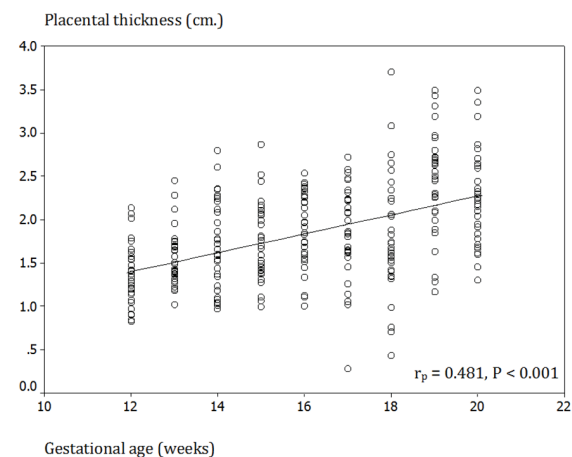


Fig. 2 Correlation between gestational age and placental thickness.

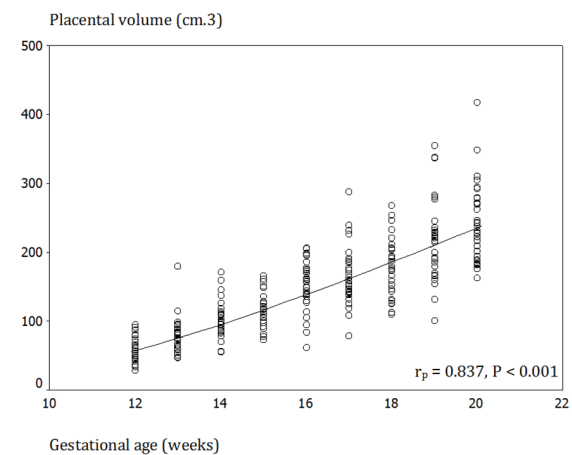
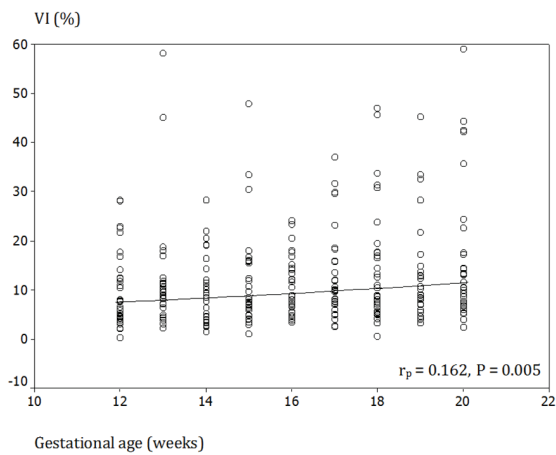
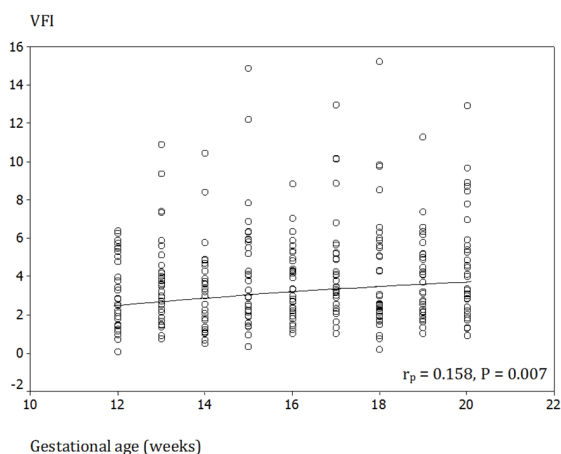


Fig. 3 Correlation between gestational age and placental volume.



**Fig. 4** Correlation between gestational age and vascularization index (VI).



**Fig. 5** Correlation between gestational age and vascularization flow index (VFI).

between gestational age and placental volume ( $r_p = 0.837$ ,  $p < 0.001$ ) and the formula of the placental volume that could be formed from this correlation is as follows:

$$\text{Placental volume (cm}^3\text{)} = e^{7.584-42.45(\frac{1}{GA})}$$

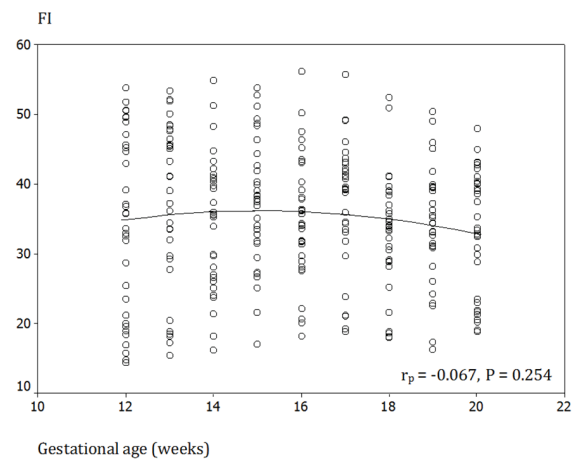
$R^2$  (coefficient of determination) = 75.8%, mean square error = 38.34, e (exponential value) = 2.718281828.

There was a weak correlation between gestational age and VI ( $r_p = 0.162$ ,  $p = 0.005$ ), and gestational age and VFI ( $r_p = 0.158$ ,  $p = 0.007$ ), both of which slightly increased with gestational age as shown in Fig. 4 and 5 respectively. No correlation between gestational age and FI ( $r_p = -0.067$ ,  $p = 0.254$ ) was found as shown in Fig. 6.

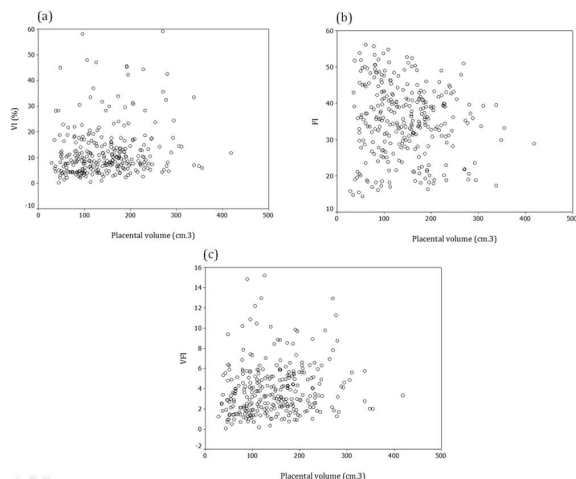
There was no correlation between placental volume and placental vascular indices, as shown in Fig. 7.

## Discussion

Over the last decade, the quality of the ultrasound machine has been continuously developed with better technology. The benefits of this are the better quality of techniques to evaluate the fetus and to clearly demonstrate all aspects of pregnancy. This gives obstetricians who use the ultrasound scan greater confidence in counseling patients.



**Fig. 6** Correlation between gestational age and flow index (FI).



**Fig. 7** (a) Correlation between placental volume and vascularization index (VI); (b) correlation between placental volume and flow index (FI); (c) correlation between placental volume and vascularization flow index (VFI).

The evaluation of many aspects of the placenta such as placental thickness, placental volume, and placental vascular indices can be now performed more easily and accurately than before. All the above-mentioned placental profiles can be used to predict the outcomes of the neonate such as birth weight<sup>(7,8)</sup>, abnormal chromosomes<sup>(9,10)</sup>, and complications of the mother such as preeclampsia<sup>(13)</sup>.

In the study by Thongsong and Boonyanurak<sup>(2)</sup> placenta thickness was shown to increase along with the gestational age ( $r = 0.82$ ). However, their study did not clearly define the location of the placenta that would be measured. The location of measurement might vary depending only on the physician's judgment and this could affect the results of the study.

Because of this problem, we used the placental cord insertion as the landmark for the measurement of the placental thickness. However, the placental cord insertion also varied in its location. It might be located at the center, the edge, or any other locations on the placenta. This causes variations of placental thickness within each gestational age group. The low correlation between the placental thickness and the gestational age could be caused by this defect of this technique. Considering both the previous study and the present study, the best location for the measurement of the placental thickness still needs to be explored.

The placental volume in the present study was measured by VOCAL mode that was easily performed with reliable values in digit numbers. There was a significantly strong correlation between gestational age and placental volume in the present study ( $r_p = 0.837$ ,  $p < 0.001$ ), which is similar to the findings of Paula et al<sup>(12)</sup>. However, even though it is very easy to perform, there are some limitations to the measurement of placental volume, especially in the second half of pregnancy and beyond, due to the limitation of capturing the whole picture of the placenta for measurement.

Paula et al reported placental volumes measuring from 12 to 40 weeks of gestation and suggested that the technique for measurement in the later half of pregnancy should involve adjusting the location of measurement or degree of probe movements across the abdomen<sup>(12)</sup>. However, following Paula's suggestion, the measurement of placental volume in latter half of pregnancy was still unable to cover the entire area of the placenta. This was our reason for only measuring the placental volume at up to 20 weeks of gestation. A further limitation to the present study concerned the obese

pregnant women: the thick adiposity of abdominal wall caused poor vision of placental volume.

In future, if it was possible to obtain a picture of the whole portion of the placenta throughout gestation, it should show an even more remarkable association of placental volume and gestational age. Once the formula of placental volume is performed, it would be able to predict the expected placental volume. The abnormal placental volume might be found in the case of abnormal pregnancy, such as too small for gestational age and preeclampsia.

The results of the placental vascular indices and gestational age vary in different studies. The study by Rizzo et al indicated an increasing VI, FI, and VFI in a narrow range of gestational age between 11 weeks and 13 weeks six days<sup>(10)</sup>. Merce et al showed that FI increased during weeks 14 to 40 of gestation while the VI increased gradually until the thirtieth week of gestation and then it was stable before decreasing after the 37 week<sup>(11)</sup>. However, the limitation of Merce et al's study was the small sample (86 subjects) and the fact that the placental vascular indices were only for a small part of the total placental volume (mentioned as the placental biopsy technique). The VI, FI, and VFI were found to be constant between weeks 12 and 40 of gestation, but these values seemed to decrease when the placental volume was increased<sup>(12)</sup>. The results from these studies are not conclusive with regard to the aspect of correlation with the gestational age.

In the present study, the authors used the whole placenta to identify the placental vascular indices and correlated them with a wider range of the gestational age than in the study of Rizzo et al<sup>(10)</sup>. The present study showed the poor correlation between gestational age and VI ( $r_p = 0.162$ ,  $p = 0.005$ ) and VFI ( $r_p = 0.158$ ,  $p = 0.007$ ) and no correlation between gestational age and FI ( $r_p = -0.067$ ,  $p = 0.254$ ).

The parameter expressed in the VI is the ratio of the color voxel to the total voxel, which reflects the number of vessels in the placenta. The poor correlation between the VI and gestational age may arise from the almost proportionate increase in the number of vessels and placental volume, which makes it a rather constant ratio at any gestational age. That is why the poor correlation between VI and gestational age was demonstrated from the calculation of the ratio. The VFI parameter is expressed as the ratio of weighted color voxel to total voxel, which reflects the number of vessels and volume of blood cells in the voxel of the study. The poor correlation between the

VFI and gestational age can be explained in the same way as the correlation of VI and gestational age.

The parameter for the FI is expressed as the ratio of the weighted color voxel to the total color voxel, which reflects the volume of blood cells in the voxel under study. The fact there was no correlation between FI and gestational age may be due to the proportionate increase in the volume of the blood cells and volume of the placenta at every gestational age.

The other limitations of the placental vascular indices' measured in the present study are the location of placenta, the movement of the fetus, and the breathing of the mother while the measurement was taking place. The position of the placental attachment at the posterior portion of the uterus made it difficult to evaluate the placental vascular indices. If the fetus is lying down above the placenta, it is more difficult to measure the placental vascular indices because of the decreasing flow of the color Doppler. The movement of the fetus and the breathing of the mother caused the turbulent flow of the color Doppler, which can lead to the misinterpretation of the data.

### Conclusion

The present study found a poor correlation of gestational age with placental thickness, while a strong correlation was found between gestational age and placental volume. The correlation of placental volume and gestational age can be expressed by the formula:

$$\text{Placental volume (cm}^3\text{)} = e^{7.584-42.45(\frac{1}{GA})}; R^2 = 0.76$$

The present study showed poor correlations of VI, and VFI with gestational age and no correlation between FI and gestational age.

### What is already known on this topic?

A nomogram of placental thickness and placenta volume has been already reported. However, the techniques in the study are poor and the data is unreliable. The placenta vascular indices for each gestational age of pregnancy including vascular index (VI), vascular flow index (VFI) and flow index (FI) have also been already studied but without conclusive data.

### What this study adds?

The present study used a higher quality of ultrasound machine with the VOCAL mode technique that can be used to measure more accurately the placental thickness, placental volume, and placental vascular indices.

The present study found a significant correlation between the placental thickness and placental volume with gestational age. Vascular index (VI) and vascular flow index (VFI) showed a poor correlation with gestational age, while flow index (FI) revealed no correlation at all with the gestational age.

### Potential conflicts of interest

None.

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## Nomogram ของความหนา ปริมาตร และดัชนีหลอดเลือดของรกในสตรีตั้งครรภ์ปกติช่วงอายุครรภ์ 12 ถึง 20 สัปดาห์

วิทยา ธิฐาพันธ์, พนิดา เชิดชูเกียรติ

**วัตถุประสงค์:** เพื่อหาค่า nomogram ของความหนาของรก (placental thickness) ปริมาตรรก (placental volume) และดัชนีหลอดเลือดของรก (placental vascular indices) ในสตรีตั้งครรภ์ปกติช่วงอายุครรภ์ 12 ถึง 20 สัปดาห์

**รูปแบบการศึกษา:** การศึกษาแบบตัดขวาง เชิงการทดลอง (experimental cross sectional study)

**วัสดุและวิธีการ:** สตรีตั้งครรภ์ปกติในแต่ละอายุครรภ์ตั้งแต่ 12 ถึง 20 สัปดาห์ ซึ่งมารับบริการฝากครรภ์ที่โรงพยาบาลศิริราช ตั้งแต่วันที่ 1 กันยายน พ.ศ. 2554 ถึง 31 มีนาคม พ.ศ. 2555 ที่อยู่ในเกณฑ์คัดเข้าและไม่เข้าในเกณฑ์คัดออกที่สนใจเข้าร่วมโครงการวิจัยจะได้รับการตรวจด้วยคลื่นเสียงความถี่สูงเพื่อวัดหาค่าความหนา ปริมาตร และดัชนีหลอดเลือดของรก (ประกอบด้วย vascularization index (VI), flow index (FI) และ vascularization flow index (VFI)) หลังจากนั้นจะนำค่าของปัจจัยที่ศึกษาข้างต้นมาหาความสัมพันธ์กับอายุครรภ์

**ผลการศึกษา:** จากจำนวนผู้เข้าร่วมโครงการวิจัยทั้งหมด 302 คน ถูกคัดออกจากงานวิจัย 8 คน เหลือผู้เข้าร่วมโครงการวิจัย 294 คน จากการศึกษาครั้งนี้พบว่ารกมีความหนาเพิ่มขึ้นตามอายุครรภ์อย่างมีนัยสำคัญทางสถิติ ( $r_p = 0.481, p < 0.001$ ) ซึ่งเช่นเดียวกันกับปริมาตรรกที่เพิ่มขึ้นตามอายุครรภ์อย่างมีนัยสำคัญทางสถิติ ( $r_p = 0.837, p < 0.001$ ) และสามารถสร้างสูตรปริมาตรรกได้คือ ปริมาตรของรก (ลบ.ซม.) =  $e^{7.584-42.45(\frac{1}{GA})}$ ; โดยที่  $R^2 = 0.76$  ส่วนค่าดัชนีหลอดเลือดของรกทั้ง 3 ค่านั้น พบว่า VI และ VFI มีความสัมพันธ์ในระดับที่ต่ำมาก ( $r_p = 0.162, p = 0.005$  และ  $r_p = 0.158, p = 0.007$ ) ในขณะที่ FI ไม่สัมพันธ์กับอายุครรภ์เลย ( $r_p = -0.067, p = 0.254$ )

**สรุป:** ความหนาของรกและปริมาตรรกมีการเพิ่มขึ้นสัมพันธ์กับอายุครรภ์ที่เพิ่มขึ้นอย่างมีนัยสำคัญทางสถิติ ในขณะที่ค่า VI และ VFI มีความสัมพันธ์กับอายุครรภ์ที่เพิ่มขึ้นในระดับต่ำมาก จนแทบไม่มีความสัมพันธ์และ FI ไม่มีความสัมพันธ์กับอายุครรภ์เลย