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First trimester placental vascular indices and volume by three-dimensional ultrasound in pre-gravid overweight women

C.Y. Chen[a,b,*], H.T. Chang[b], C.P. Chen[b], F.J. Sun[c]

[a] Department of Medicine, Mackay Medical College, New Taipei City, Taiwan
[b] Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan
[c] Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan

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ABSTRACT

Objectives: To investigate changes of placental vascular indices and volume in pre-gravid overweight Chinese women during the first trimester using three-dimensional power Doppler ultrasound.
Methods: This was a prospective observational study of the morphology of placentas in pre-gravid overweight (body mass index (BMI) ≥ 24 kg/m^2) and non-overweight (BMI < 24 kg/m^2) Chinese women during the first trimester of pregnancy. Data on placental vascular indices (vascularization index, flow index, and vascularization flow index (VFI)), placental volume, uterine artery pulsatility index (PI), and neonatal outcomes were obtained during the first trimester and analyzed. Linear regression analysis was used to evaluate confounding factors between BMI and ultrasound indices.
Results: Of the 429 pregnant women enrolled, 68 (15.9%) were pre-gravid overweight. Placental VFI was significantly lower in the overweight group ($p = 0.037$). Conversely, placental volume was significantly larger in the overweight group ($p = 0.044$), and uterine artery PI was significantly higher in the overweight group ($p = 0.021$). After adjustments for confounding factors, there were still significant differences in placental VFI (unstandardized coefficient (B) −0.666, 95% confidence interval (CI) −1.306 – (−0.025)), placental volume (B 2.458, 95% CI 0.071–4.844), and uterine artery PI (B 0.152, 95% CI 0.030–0.274) between the two groups.
Conclusions: Placental vascular indices using three-dimensional power Doppler ultrasound can provide an insight into placental vascularization in pre-gravid overweight women in early pregnancy. Alterations in placental VFI, placental volume, and uterine artery PI occur during the first trimester in pre-gravid overweight women.

1. Introduction

Maternal obesity increases pregnancy-associated complications and there are increased societal and economic costs on maternal obesity, which is a global health concern [1]. The increased maternal and neonatal risks associated with maternal pre-gravid obesity include miscarriage, preeclampsia, gestational diabetes mellitus (GDM), respiratory complications, thromboembolic events, and cesarean deliveries [2,3]. In addition, increased rates of congenital anomalies, macrosomia, birth trauma, and mortality have also been reported in the neonates of obese women [3,4]. Furthermore, long-term implications of maternal obesity in the children such as obesity, diabetes, and cardiovascular disease have also been noted through fetal metabolic programming [5,6]. Compared with Caucasians, Chinese women have a higher percentage of body fat at the same body mass index (BMI), thus Chinese categorizations of BMI ≥ 24 for overweight and ≥28 for obesity have been suggested [7].

Pathophysiologic studies have revealed that maternal obesity during pregnancy is related to metabolic deterioration and redox imbalance in the mother-placenta-fetus unit, and that these changes contribute to an inflammatory environment of increased maternal insulin resistance, lipotoxicity, and oxidative stress, resulting in maternal and fetal complications [8,9]. Histologic studies have also revealed that maternal pre-gravid obesity is associated with villous immaturity and dysfunctional angiogenesis of the placenta [10].

The influence of maternal obesity on placental structure and function may occur in the first trimester. Previous studies have demonstrated that insulin receptors are more abundant in first-trimester syncytiotrophoblasts [11], and that pre-gravid obesity can increase the maternal insulin response in early pregnancy, possible due to an increase in placental insulin receptors on villous membranes [12]. On the other hand, obesity-associated insulin resistance programs the placental transcriptome to become refractory to insulin, and this effect has been

* Corresponding author. No. 92, Section 2, Chung-Shan North Road, Taipei, 10449, Taiwan.
E-mail address: f122481@mmh.org.tw (C.Y. Chen).

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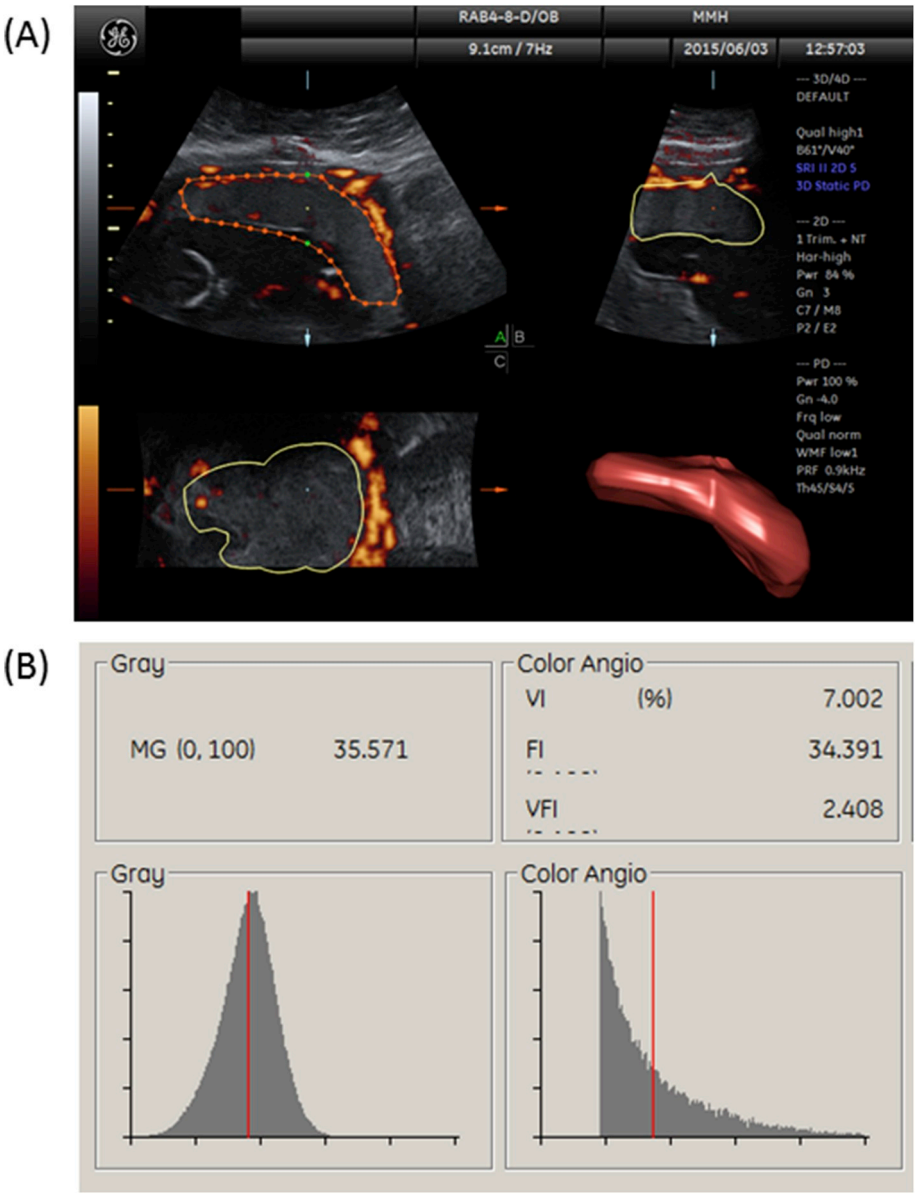

Fig. 1. Assessment of placental vascular indices and placental volume using Virtual Organ Computer-aided AnaLysis (VOCAL™) imaging software. (A) Measurement of placental volume. (B) Placental vascular indices determined by three-dimensional power Doppler ultrasound.

noted in the first trimester of pregnancy [13].

Three-dimensional power Doppler ultrasound is a non-invasive practical tool used for placental vascular assessments. Previous studies have investigated placental vascular indices during the first trimester with regards to preeclampsia, fetal growth restriction, and diabetes [14–16]. To the best of our knowledge, this is the first pilot study to investigate placental vascular indices using three-dimensional power Doppler ultrasound in overweight women during the first trimester of pregnancy. We hypothesized that the placental endothelial structure and capacity in obese women may be altered in the first trimester. Therefore, the aim of this study was to investigate placental vascular changes and placental volume during the first trimester between pregnant women with and without obesity.

2. Methods

2.1. Study population

This prospective observational study was performed at the Mackay Memorial Hospital, Taipei, Taiwan from May 2013 to January 2016. Pregnant Chinese women who underwent ultrasound and serum examinations for aneuploidy screening during the first trimester (11 0/7 to 13 6/7 gestational weeks) were recruited into this study. The pregnant women were divided into two groups: pre-gravid overweight (BMI $\geq$ 24 kg/m^2) and non-overweight (BMI $<$ 24 kg/m^2) [7]. The exclusion criteria were: (1) mothers who smoked during pregnancy, (2) fetal chromosomal or structural anomalies, and (3) multifetal pregnancies. This study was approved by the Mackay Memorial Hospital Institutional Review Board, and all personal identifiers were anonymized prior to analysis.

Chronic hypertension during pregnancy was defined as hypertension (systolic blood pressure $\geq$ 140 mmHg and/or diastolic blood pressure $\geq$ 90 mmHg) first detected before 20 gestational weeks. Gestational hypertension was defined as the new onset of hypertension $\geq$20 gestational weeks in the absence of proteinuria. Preeclampsia was defined as gestational hypertension combined with proteinuria or new signs of end-organ dysfunction, according to the diagnostic criteria of the American College of Obstetricians and Gynecologists [17]. GDM

Table 1
Maternal characteristics and neonatal outcomes.

	BMI ≥24 (N = 68)	BMI < 24 (N = 361)	*p* value
Mother			
Age (years)	32.56 ± 4.36	31.55 ± 3.43	0.074
Gravida	1.78 ± 1.04	2.04 ± 1.10	0.066
Para	0.44 ± 0.66	0.57 ± 0.64	0.136
Placenta			
Cesarean delivery	17 (25.0)	84 (23.3)	0.722
Chronic hypertension	1 (1.5)	12 (3.3)	0.702
Gestational hypertension	0 (0.0)	3 (0.8)	> 0.999
Preeclampsia	1 (1.5)	6 (1.7)	> 0.999
Type 1 DM	0 (0.0)	2 (0.6)	> 0.999
Type 2 DM	4 (5.9)	1 (0.3)	0.003
GDM	1 (1.5)	29 (8.0)	0.065
Neonate			
Delivery age (weeks)	38.54 ± 1.69	38.60 ± 1.67	0.786
Birth weight (g)	3000.49 ± 465.90	3113.25 ± 456.58	0.078
Apgar score			
1 min	9.16 ± 0.99	9.17 ± 1.02	0.938
5 min	9.69 ± 0.53	9.68 ± 0.67	0.899
LGA	5 (7.4)	23 (6.4)	0.787

Continuous variables are presented as mean ± standard deviation and categorical variables as n (%).
BMI: body mass index; DM: diabetes mellitus; GDM: gestational diabetes mellitus; LGA: large for gestational age.

Table 2
Maternal serum markers, placental vascular indices, placental volume, and uterine artery PI between the study and control groups.

	BMI ≥24 (N = 68)	BMI < 24 (N = 361)	*p* value
Gestational age at scan (weeks)	13.01 ± 0.41	12.93 ± 0.44	0.197
CRL (mm)	68.66 ± 6.36	67.36 ± 5.88	0.099
PAPP-A (IU/L)	5.06 ± 2.92	6.15 ± 3.93	0.009
Free β-hCG (IU/L)	40.44 ± 23.85	56.63 ± 37.82	< 0.001
VI	19.52 ± 9.28	21.53 ± 9.69	0.115
FI	31.88 ± 10.31	32.41 ± 10.99	0.714
VFI	5.68 ± 2.24	6.35 ± 2.45	0.037
Placental volume (cm^3)	52.38 ± 10.34	49.98 ± 8.74	0.044
Uterine artery PI	1.81 ± 0.51	1.67 ± 0.45	0.021

Continuous variables are presented as mean ± standard deviation.
PI: pulsatility index; BMI: body mass index; CRL: crown-lump length; PAPP-A: pregnancy-associated plasma protein-A; β-hCG: beta human chorionic gonadotrophin; VI: vascularization index; FI: flow index; VFI: vascularization flow index.

was defined according to the National Diabetes Data Group criteria [18]. Furthermore, large for gestational age (LGA) was diagnosed when the birth weight was > 90th percentile, based on the nationwide singleton birthweight percentiles in Taiwan [19].

2.2. Ultrasound examinations

A Voluson E8 ultrasound machine (GE Medical Systems, Zipf, Austria) with a 2–8 MHz transabdominal probe was used in this study. The gestational age was determined by measuring the crown-lump length (CRL) during the first trimester. Placental vascular indices (vascularization index (VI), flow index (FI), and vascularization flow index (VFI)), placental volume, and uterine artery pulsatility index (PI) were measured. The three vascular indices were developed through specific algorithms based on the relative proportion of color voxels (three-dimensional pixels) and signal intensity within the defined volume of interest. VI means the number of color voxels in the volume, which represents the vascular density within the tissue and is expressed as a percentage. FI means the average color value of all the color voxels, which represents the average blood flow intensity. VFI is a combination of both factors derived through their multiplication, which represents both vascularization and blood flow [20]. The placental vascular indices were automatically calculated using Virtual Organ Computer-aided AnaLysis (VOCAL™) imaging software (GE Medical Systems, Zipf, Austria), and expressed on a scale of 0–100 (Fig. 1). To obtain the optimal placental volume, the probe was placed along the alignment of the placenta. Each woman was asked to hold her breath for 10 s, and then the margin of the placenta was delineated to obtain its maximum area. This procedure was repeated six times after rotating the probe 30° around the axis each time to acquire the full volume of the placenta. For laterally and posteriorly located placentas, the position of the probe was adjusted to fit the placental alignment as far as possible to obtain the optimal volume. All of the examined cases were measured using the same ultrasound instrument settings in the first trimester. Uterine artery PI was then measured using the transabdominal probe. A sagittal view of the uterus was attained, and the cervical canal and uterine artery were then identified. Pulsed wave Doppler with a sample volume of 2 mm was used to measure the uterine artery PI by three consecutive waveforms, with an angle of insonation < 30°. Uterine artery PI was calculated as the mean of the left and right uterine artery PI values. All of the ultrasound scans were performed by the same examiner (CYC), and the placental vascular indices and placental volume were measured twice in the first 20 cases to inspect the intra-rater reliability.

2.3. Serum examinations

Maternal blood samples (about 3 mL) were collected and immediately sent to the laboratory. The serum was separated by centrifugation and stored at −20 °C until analysis. Levels of maternal serum pregnancy-associated plasma protein-A (PAPP-A) and free beta human chorionic gonadotrophin (β-hCG) were measured using a Kryptor analyzer (Brahms GmbH, Henningsdorf, Germany).

2.4. Statistical analysis

SPSS version 21.0 (IBM, Armonk, New York) was used for all statistical analyses. The chi-square test or Fisher's exact test was used for categorical variables. Comparisons between continuous variables were made using the Student's *t*-test. Linear regression analysis was used to evaluate confounding factors associated with placental vascular indices, placental volume, and uterine artery PI. The intraclass correlation coefficient (ICC) was used to examine the intra-rater reliability of the placental vascular indices and placental volume. Pearson's correlation analysis was used to evaluate the relationships between placental vascular indices, placental volume and BMI. A p value < 0.05 was considered to be statistically significant.

3. Results

Of the 429 pregnant women enrolled, 68 (15.9%) were pre-gravid overweight and 361 (84.1%) were non-overweight. Table 1 shows the maternal characteristics and neonatal outcomes. The mean maternal age was similar between the two groups, and there were no significant differences in rates of maternal chronic hypertension, gestational hypertension, preeclampsia, type 1 diabetes mellitus (DM), and GDM between the two groups. However, the rate of type 2 DM in the overweight group (5.9%) was higher than that in the control group (0.3%) ($p = 0.003$). There were no significant differences in delivery age, birth weight, and Apgar scores between the two groups.

Table 2 shows the results of maternal serum biomarkers, placental vascular indices, placental volume, and uterine artery PI between the two groups. No difference was noted in CRL between the two groups, however maternal serum levels of PAPP-A and free β-hCG were significantly lower in the overweight group compared to the control group (PAPP-A: $p = 0.009$; free β-hCG: $p < 0.001$). Although no significant

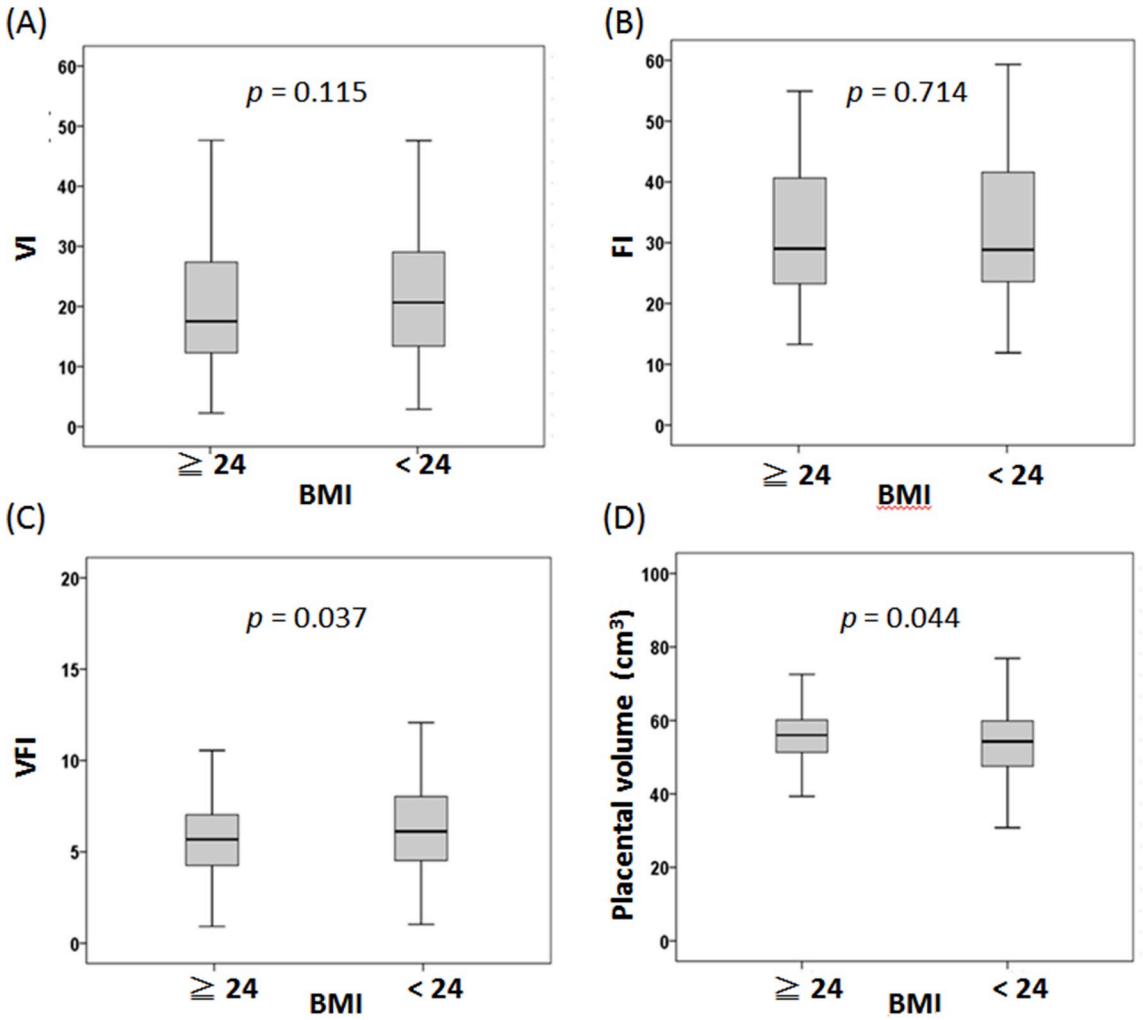

Fig. 2. Box-and-whisker plots of placental vascular indices and placental volume in the overweight and non-overweight groups. Boxes show median and interquartile range, and whiskers represent the 5th and 95th percentiles.

Table 3
Intraclass correlation coefficients of placental vascular indices and placental volume.

	ICC	95% CI	*p* value
VI	0.992	0.981–0.997	< 0.001
FI	0.954	0.884–0.982	< 0.001
VFI	0.975	0.936–0.990	< 0.001
Placental volume	0.968	0.919–0.987	< 0.001

VI: vascularization index; FI: flow index; VFI: vascularization flow index; ICC: intraclass correlation coefficient; CI: confidence interval.

differences were noted between the two groups in placental VI and FI, placental VFI in the overweight group was significantly lower than that of the control group ($p = 0.037$). Conversely, placental volume was significantly larger in the overweight group compared to the control group ($p = 0.044$) (Fig. 2). Moreover, uterine artery PI was significantly higher in the overweight group compared to the control group ($p = 0.021$). After adjustments for confounding factors such as hypertension, preeclampsia, and DM, there were still significant differences in placental VFI (unstandardized coefficient (B) −0.666, 95% confidence interval (CI) −1.306 – (−0.025), $p = 0.042$), placental volume (B 2.458, 95% CI 0.071–4.844, $p = 0.044$), and uterine artery PI (B 0.152, 95% CI 0.030–0.274, $p = 0.015$) between the two groups. The intra-rater reliability of placental vascular indices and placental volume was excellent, with ICC > 0.90 (Table 3).

Fig. 3 shows the changes in placental vascular indices and placental volume according to BMI. A negative correlation was observed between placental VFI and BMI ($r = -0.146$, $p = 0.003$). Conversely, a positive correlation was observed between placental volume and BMI ($r = 0.149$, $p = 0.002$).

4. Discussion

Our results showed that placental VFI during the first trimester was significantly lower in the pre-gravid overweight mothers. Few studies have investigated placental vascular changes and capacity in obese women, and most have focused on term placenta after delivery. Hayward et al. [21] examined the chorionic plate artery function of term placenta, and found that vasodilatation due to the nitric oxide donor sodium nitroprusside was decreased in obese mothers, suggesting that maternal obesity is associated with impaired placental vascular function. Loardi et al. [10] analyzed term placental structures in pre-gravid obese women using hematoxylin and eosin staining, immunohistochemical and morphometric examinations, and found that maternal obesity was associated with immature villous trees and angiogenetic defects of the placenta. Furthermore, several studies have reported that the influence of maternal obesity on placental structure and function may occur from the first trimester [11–13]. Three-dimensional power Doppler ultrasound is a valuable tool to quantitatively assess placental vascular changes before delivery, and previous studies have shown promising results in investigations of preeclampsia, fetal

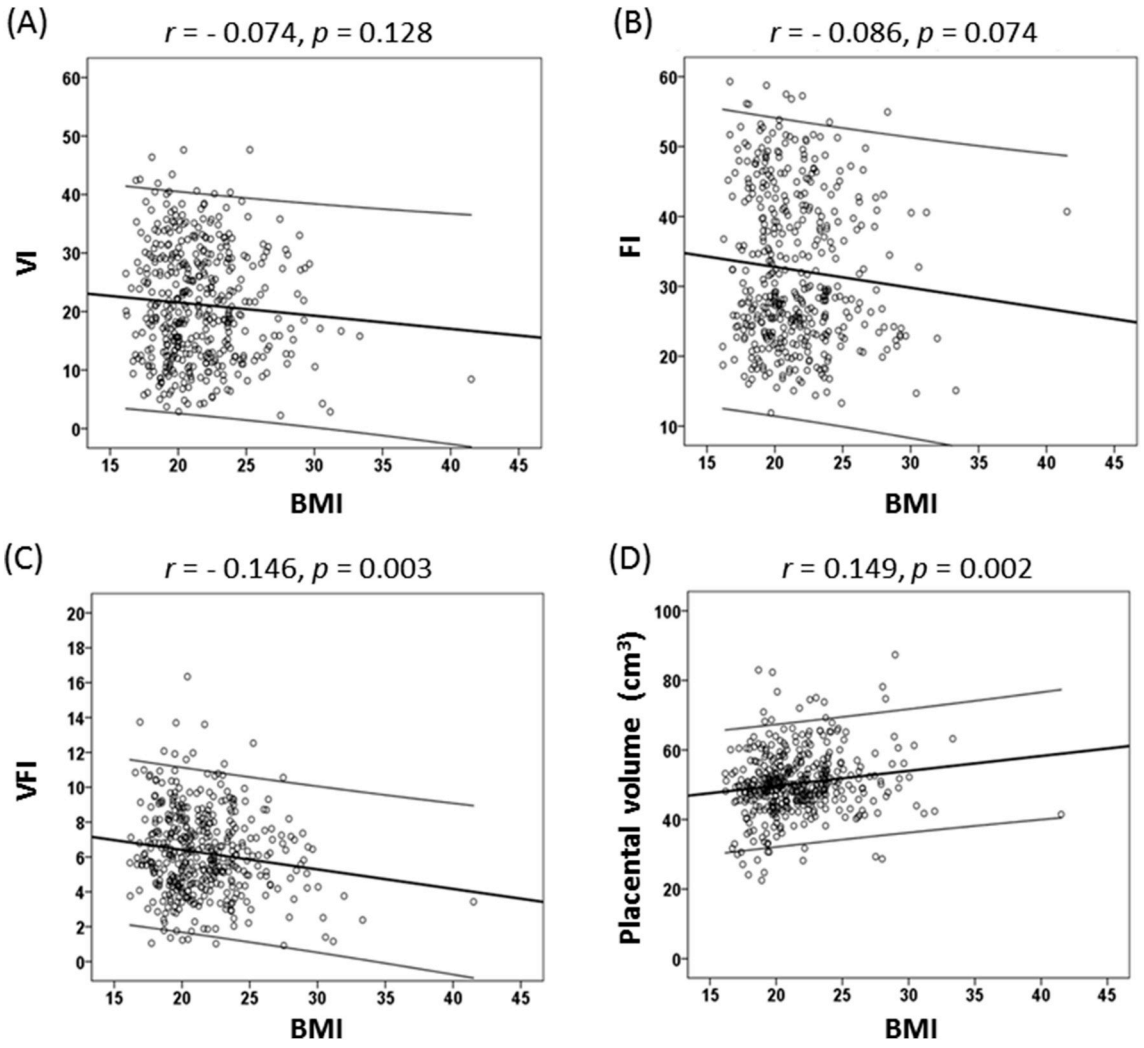

Fig. 3. Placental vascular indices and placental volume compared with BMI in the overweight and non-overweight groups, plotted on reference limits (mean, 5th and 95th percentiles).

growth restriction, and diabetes [14–16]. We found that the overweight group had a decreased placental VFI, suggesting that maternal obesity may lead to different uteroplacental circulation with intraplacental vascular lesions in the first trimester.

Obesity increases maternal insulin resistance which promotes placental growth. It is well-known that increased placental weight at term is associated with maternal obesity [22]. However, few studies have focused on the relationship between placental volume and maternal obesity during the first trimester. Schwartz et al. [23] found that many ultimate placental morphologic features can be predicted in early pregnancy. In the present study, placental volume during the first trimester was significantly increased in the overweight group, which is consistent with the study by O'Tierney-Ginn et al. [12]. Insulin receptors are more abundant on syncytiotrophoblasts in early gestation than in late gestation [11], and pre-gravid obesity increases the maternal insulin response in early pregnancy, which can then result in placentomegaly in the first trimester.

Early uteroplacental circulation depends on trophoblast invasion of the spiral arteries, and impaired placentation results from decreased trophoblast invasion as represented by high resistance of uterine arteries [24]. Previous studies have revealed that increased uterine artery PI can reflect impaired placentation in the first trimester of pregnancy and predict adverse pregnancy outcomes such as early-onset preeclampsia and fetal growth restriction [25]. We found a significantly higher uterine artery PI in the overweight group compared to the control group, which is consistent with the study by Kim et al. [26], who found that pre-gravid obesity increased uterine artery PI during the third trimester and the rate of adverse pregnancy outcomes. Furthermore, we found that the impact of obesity on uterine artery PI occurred in the first trimester, which also implies that pre-gravid obesity may lead to different uteroplacental circulation in early pregnancy.

PAPP-A, a zinc-binding metalloproteinase produced by placental syncytiotrophoblasts and decidua, is found in maternal blood during early pregnancy, and its level increases during gestation until delivery. PAPP-A degrades insulin as with growth factor binding proteins and increases the bioavailability of insulin-like growth factors, which then modulates trophoblast invasion [27]. Human chorionic gonadotropin (hCG), a glycoprotein initially synthesized by placental syncytiotrophoblasts, consists of two noncovalently bound subunits, α and β. The α structure is essentially identical for the transactivation of receptors, whereas the β structure is transcribed from separate genes and confers the biological and immunological specificity of receptors [28]. Many studies have demonstrated that maternal serum PAPP-A and free β-hCG play a key role in placental development during the first trimester, and verified their predictive value for various adverse pregnancy outcomes [29]. We found that the levels of PAPP-A and free β-hCG in the overweight group were lower than those in the non-overweight group, which is consistent with previous studies [30]. This is probably because of the dilutional effect of higher blood volume in overweight mothers.

There are some limitations to this study. First, despite advances in sonographic instruments, maternal obesity may influence the performance of placental vascular indices measured by three-dimensional power Doppler ultrasound. However, we found both a decreased placental VFI and increased uterine artery PI during the first trimester, suggesting evidence of early changes in uteroplacental circulation in pre-gravid overweight women. Second, we did not perform placental histological examination to investigate placental endothelial changes, and thus we could not confirm the placental histopathological findings after delivery. Previous histologic studies have revealed that maternal pre-gravid obesity is associated with villous immaturity and dysfunctional angiogenesis of the placenta [10], which could support our findings. Third, because not all the women enrolled in the study have measured the placental vascular indices and placental volume in the second and third trimesters, we could not compare the differences of placental vascular indices and placental volume in mid and late pregnancy.

In conclusion, we demonstrated that placental VFI, placental volume, and uterine artery PI may be altered during the first trimester in pre-gravid overweight women, and that three-dimensional power Doppler ultrasound is a promising non-invasive tool to investigate these changes. The puffiness change of the placenta presented by lower VFI and larger volume in early pregnancy suggests that maternal obesity can result in early changes of placental endothelial structure and capacity. Further studies are necessary to elucidate the mechanisms between maternal pre-gravid obesity and feto-placental interactions in early pregnancy.

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