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The significance of placental ratios in pregnancies complicated by small for gestational age, preeclampsia, and gestational diabetes mellitus

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Objective
This study aimed to evaluate the placental weight, volume, and density, and investigate the significance of placental ratios in pregnancies complicated by small for gestational age (SGA), preeclampsia (PE), and gestational diabetes mellitus (GDM).

Methods
Two hundred and fifty-four pregnant women were enrolled from August 2005 through July 2013. Participants were divided into four groups: control (n=82), SGA (n=37), PE (n=102), and GDM (n=33). The PE group was classified as PE without intrauterine growth restriction (n=65) and PE with intrauterine growth restriction (n=37). Birth weight, placental weight, placental volume, placental density, and placental ratios including birth weight/placental weight ratio (BPW) and birth weight/placental volume ratio (BPV) were compared between groups.

Results
Birth weight, placental weight, and placental volume were lower in the SGA group than in the control group. However, the BPW and BPV did not differ between the two groups. Birth weight, placental weight, placental volume, BPW, and BPV were all significantly lower in the PE group than in the control group. Compared with the control group, birth weight, BPW, and BPV were higher in the GDM group, whereas placental weight and volume did not differ in the two groups. Placental density was not significantly different among the four groups.

Conclusion
Placental ratios based on placental weight, placental volume, placental density, and birth weight are helpful in understanding the pathophysiology of complicated pregnancies. Moreover, they can be used as predictors of pregnancy complications.

Keywords: Birth weight/placental weight ratio; Complicated pregnancies; Placental volume

Introduction

Common pregnancy complications include small for gestational age (SGA), preeclampsia (PE), and gestational diabetes mellitus (GDM). The incidence of complicated pregnancies has gradually increased by 5% to 10% for SGA [1], 2% to 5% for PE [2], and 2% to 13% for GDM [3] worldwide. Recent studies have shown that pregnancies can be complicated by placental pathologies and fetal growth changes. The placenta, a temporary organ responsible for controlling nutrition from the mother to the fetus, has been observed to influence birth weight [4],

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and its weight has been shown to be directly associated with birth weight [5,6]. Some studies suggest that placental factors play an important role in fetal growth restriction and all macroscopic and microscopic pathological changes point towards reduced blood flow caused by vascular damage [1]. Roberts and Lain [2] showed that PE was secondary to the interactions of reduced placental perfusion with diverse maternal factors that alter endothelial function. Other studies suggest that placental pathological changes in diabetic women, such as significant thickening of trophoblastic basal membranes, separation of capillary basal membranes in basal capillaries, distention and proliferation of endothelial cells, disarrangements of perivascular space, and decrease of terminal villous vascular surface, are significant factors contributing to fetal growth in pregnancies complicated by diabetes mellitus [7].

Placental pathologies can be classified as functional or morphological. Functional changes are related to protein alteration, receptor expression, cytokines, chemokines, and hormones [8,9]. Conversely, morphological changes are detected by measuring placental weight, placental volume, birth weight/placental weight ratio (BPW), and the microscopic shape of placental villi. Recent studies have investigated the association between placental morphological changes and complicated pregnancies. Janthanaphan et al. [10] showed that placental weight increased with birth weight, and the BPW decreased slightly with advancing gestational age in normal pregnancies. In diabetic pregnancies, placental weight as well as the BPW was higher than that in non-diabetic pregnancies [11]. Bortolus et al. [12] showed that the mean placental weight from large for gestational age (LGA) pregnancies was significantly increased compared with that from SGA pregnancies, whereas the placental ratio (BPW) tended to increase in LGA pregnancies compared with that in SGA pregnancies. Some researchers have compared placentas from control, intrauterine growth restriction (IUGR), PE without IUGR, and PE with IUGR pregnancies based on microscopic findings such as villous membrane exchange surface area, villous membrane thickness, and villous membrane diffusive conductance [13].

Thus far, studies investigating the relationship between placental morphological changes and fetal growth in complicated pregnancies have been fragmentary, and lacked a systematic approach and comparisons between different groups of complicated pregnancies. Considering the role of the placenta in fetal growth, placental morphological characteristics such as placental weight, placental volume, and its ratio with birth weight could have significance in complicated pregnancies. This study aimed to evaluate the placental weight, volume, and density, and compare the significance of placental ratios in complicated pregnancies.

Materials and methods

1. Study population

All pregnant women who delivered at the Konkuk University Medical Center from August 2005 through July 2013 were enrolled in this study. Participants were divided into four groups: control, SGA, PE, and GDM. The PE group was classified as PE without IUGR and PE with IUGR. Preeclamptic placentas were obtained during the study period of 8 years. The other placentas were included in this study from August 2012 to July 2013. During this period, all cases that the pathologic examination for each placenta according to the clinician's decision was performed were included in this study. In our hospital, the inclusion criteria for the routine placental pathologic study have been preterm birth, PE, chorioamnionitis, and twin pregnancy. The gestational diabetes, SGA, and fetal distress cases were occasionally included for the pathologic study of placenta. The control group was defined as preterm birth cases and term pregnant women with the pathologic review, and selected with gestational age matched pregnancies between August 2012 and July 2013. SGA was diagnosed when the birth weight was below the 10th percentile. PE was defined as systolic blood pressure ≥140 mmHg or diastolic pressure ≥90 mmHg, combined with proteinuria ≥+2 on dipstick testing or ≥300 mg in a 24-hour urine sample after 20 weeks' gestation. Routine screening for GDM at 26 to 28 weeks' gestation with a non-fasting 50-g oral glucose tolerance test (OGTT) was performed for all pregnant women. If the glucose level was ≥140 mg/dL, the participant was referred for a 100-g fasting OGTT. For the 100-g OGTT, normal results were a fasting blood glucose level of <95 mg/dL at baseline, < 180 mg/dL at 1 hour, <155 mg/dL at 2 hours, and <140 mg/dL at 3 hours [14]. Women with at least 2 abnormal results on the 100-g OGTT were classified as having GDM. We obtained clinical data on the control, SGA, PE, and GDM groups from medical records. Pregnant women with a history of overt diabetes, multiple pregnancies, chronic hypertension, renal disease, fetal anomalies, and other medical conditions, and the cases with chorioamnionitis, succenturiate placenta, circumvallate placenta, and other abnormal shaped placenta were excluded from this

study. The Hospital Review Board approved this retrospective study.

2. Placental analysis

The placental weight and size were measured after placental delivery. All placentas included in this study were measured in the department of pathology. Placental parameters included placental weight, volume, and density. In this study, the placenta weight was measured by an electronic scale within one hour after placental delivery. The umbilical cord was clamped at its placental insertion to prevent loss of fetal blood. The membranes were carefully trimmed at the placental margin. After the placenta was laid down on the table, the largest radius and its vertical radius on the decidual base of the placenta were obtained, and the largest length of height was measured. After the long radius, short radius, and height of each placenta were obtained, each placental volume was calculated arithmetically and geometrically by assuming that the placenta was dome-shaped. Azpurua H et al. [15] used the formula for an elliptical cylinder. Major (A) and minor (B) diameters and height (H) of placenta were measured on a flat surface, which were then used to calculate actual placental volume, where V=πABH. The placental volume in this study was calculated using the formula for a dome-shaped volume (Fig. 1). The placental density was calculated using the placental weight and volume. Because the birth weight per unit volume or placental weight can be used to evaluate placental function, placental ratios such as the BPW and birth weight/placenta volume ratio (BPV) were arithmetically calculated.

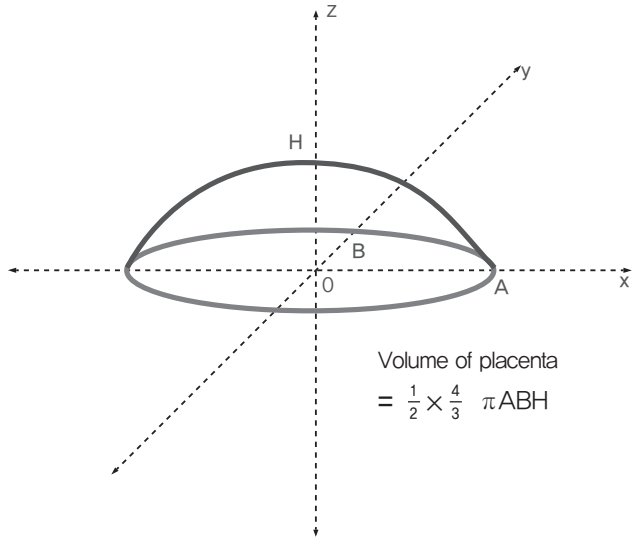

Fig. 1. Measurement of placental volume. The placental long radius (A), short radius (B), and height (H) were used to calculate the dome-shaped placental volume.

Table 1. Demographic and clinical data in the control, SGA, PE, and GDM groups

	Control (n=82)	SGA (n=37)	PE (n=102)	GDM (n=33)	*P*-value[a]
Maternal age (yr)	33 (22–44)	34 (26–41)	34 (25–45)	36 (24–47)[b]	0.011
BMI (kg/m^2)	26 (18–37)	26 (18–36)	27 (17–41)[b]	27 (21–42)[b]	0.009
Pregnancy duration (wk)	38 (33–41)	38 (34–40)	35 (24–40)[b]	38 (32–40)	<0.001
Birth weight (g)	3,003 (1,880–4,105)	2,358 (1,236–2,810)[b]	1,960 (455–3,995)[b]	3,295 (1,900–4,470)[b]	<0.001
Blood pressure (mmHg)					
Systolic	116 (87–187)	117 (89–137)	146 (114–204)[b]	118 (95–147)	<0.001
Diastolic	72 (41–101)	73 (56–97)	98 (72–137)[b]	74 (54–98)	<0.001
MAP	86 (59–129)	87 (70–108)	147 (127–163)[b]	88 (68–124)	<0.001
MAP					
Hb (g/dL)	11.9 (9.2–14.2)	12.1 (8.0–14.9)	12.7 (8.5–16.1)[b]	12.0 (9.0–14.0)	0.002
BUN (mg/dL)	9.76 (6–15)	10.6 (6-19)[b]	12.9 (5–32)[b]	9.4 (5–41)	<0.001
Creatinine (mg/dL)	0.54 (0.35–0.90)	0.60 (0.38–1.10)	0.80 (0.34–1.40)[b]	0.59 (0.40–1.20)	<0.001
AST (IU/L)	20 (11–55)	20 (11–83)	26 (12–480)[b]	19 (11–43)	0.001
ALT (IU/L)	12 (4–62)	12 (5–69)	15 (4–290)[b]	11 (7–42)	0.001

Values are given as median (range).

SGA, small for gestational age; PE, preeclampsia; GDM, gestational diabetes mellitus; BMI, body mass index; MAP, mean arterial pressure; Hb, hemoglobin; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

[a]The *P*-value was calculated by ANOVA and considered significant if the value was <0.05; [b]Statistical significance (*P*<0.05) was tested by Student's *t*-test. The SGA, PE, and GDM groups were compared with the control pregnancy group.

Table 2. Clinical data showing the birth weight, placental parameters, and placental ratios in the control, SGA, PE, and GDM groups

	Control (n=82)	SGA (n=37)	PE (n=102)	GDM (n=33)	*P*-value[a]
Birth weight (g)	3,003 (1,880–4,105)	2,358 (1,236–2,810)[b]	1,960 (455–3,995)[b]	3,295 (1,900–4,470)[b]	<0.001
Placenta characters					
Placenta weight (g)	498 (280–856)	386 (188–660)[b]	387 (114–650)[b]	491 (296–966)	<0.001
Placenta volume (cm^3)	772 (271–1,665)	589 (302–1,140)[b]	613 (241–1,335)[b]	744 (321–1,610)	<0.001
Placenta density (g/cm^3)	0.65 (0.19–1.20)	0.66 (0.41–1.25)	0.63 (0.27–1.74)	0.66 (0.36–1.23)	0.381
Birth weight/placenta character ratios					
Birth weight/placenta weight	6.0 (3.9–11.1)	6.1 (3.1–10.3)	5.1 (2.1–9.3)[b]	6.7 (4.1–12.3)[b]	<0.001
Birth weight/placenta volume	3.9 (1.1–7.3)	4.0 (2.0–8.3)	3.2 (1.0–6.8)[b]	4.4 (2.7–9.6)[b]	<0.001

Values are given as median (range).
SGA, small for gestational age; PE, preeclampsia; GDM, gestational diabetes mellitus.
[a]The *P*-value was calculated by ANOVA and considered significant if the value was <0.05; [b]Statistical significance (*P*<0.05) was tested by the Student's *t*-test. The SGA, PE, and GDM groups were compared with the control pregnancy group.

3. Statistical analyses

Values were expressed as the median and ranges. Student's *t*-test was used to compare maternal age, body mass index, pregnancy duration, birth weight, blood pressure, blood laboratory values, placental weight, placental volume, placental density, BPW, and BPV between control and complicated preg-

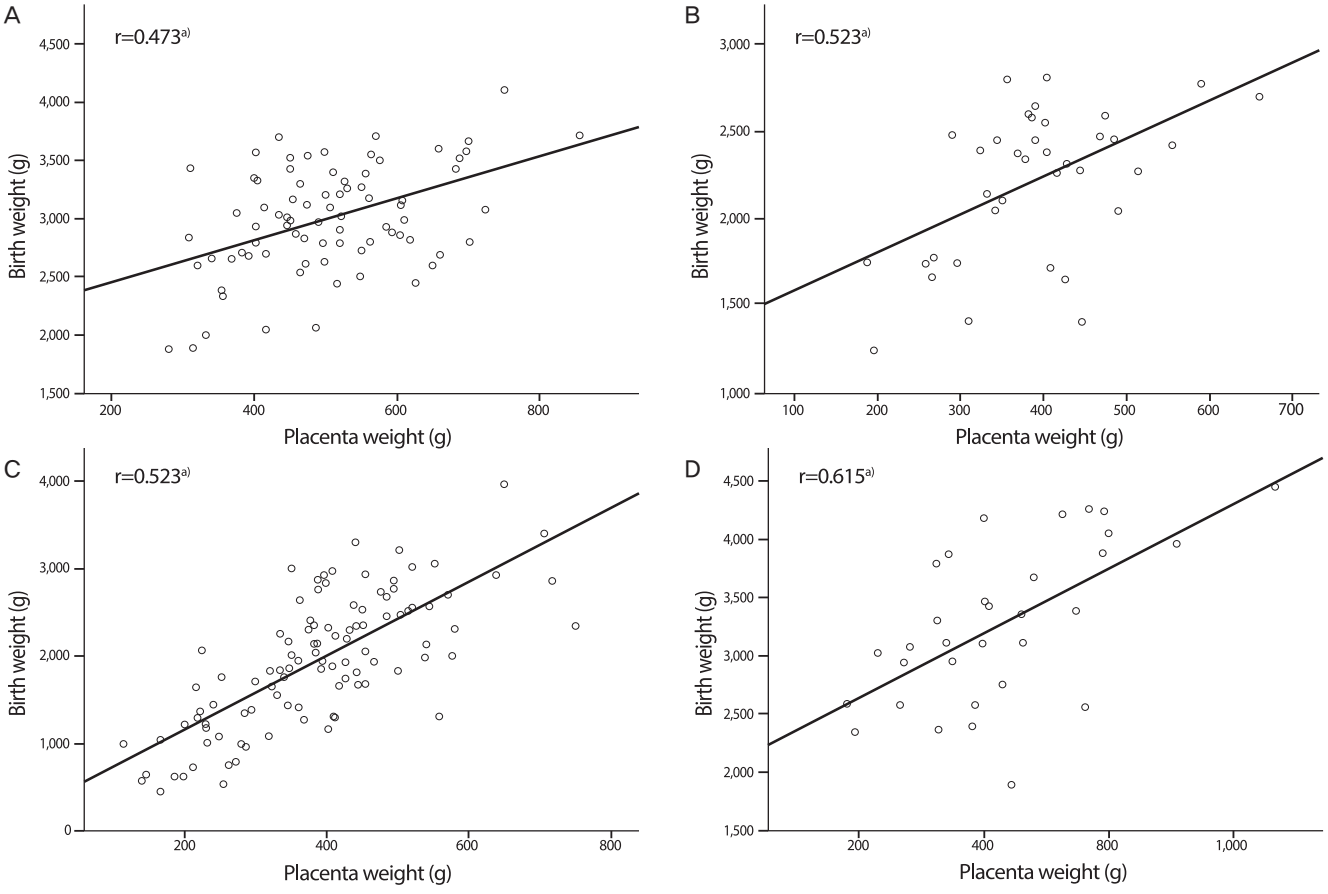

Fig. 2. Correlation between birth weight and placental weight. The control, small for gestational age (SGA), preeclampsia (PE), and gestational diabetes mellitus (GDM) groups show a positive correlation between birth weight and placental weight. [a]The correlation coefficients were r=0.473 in the control group (A), r=0.523 in the SGA group (B), r=0.736 in the PE group (C), and r=0.615 in the GDM group (D) (Pearson's rank correlation test, *P*<0.01).

nancies. Statistical significance was determined using multiple comparisons performed by a one-way ANOVA test among the groups. The strength of the association between birth weight and placental weight in control and complicated pregnancies was estimated by Pearson's correlation coefficient (r). Data analysis was performed using the SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA). A *P*-value <0.05 with a 95% confidence interval was considered statistically significant.

Results

From August 2005 through July 2013, 254 pregnant women were enrolled in this study. Participants were divided into four

Table 3. Demographic and clinical data in the preeclampsia without IUGR and preeclampsia with IUGR groups

	Preeclampsia without IUGR (n=65)	Preeclampsia with IUGR (n=37)	*P*-value
Maternal age (yr)	34 (25–45)	35 (25–45)	0.356
Body mass index (kg/m^2)	27 (18–41)	27 (17–34)	0.224
Pregnancy duration (wk)	35 (24–40)	33 (24–40)	0.066
Birth weight (g)	2,246 (580–3,995)	1,763 (455–2,570)	<0.001[a]
Blood pressure (mmHg)			
Systolic	145 (114–204)	147 (120–189)	0.539
Diastolic	100 (72–137)	105 (76–137)	0.265
MAP	115 (86–159)	118 (94–154)	0.434
Blood laboratory value			
Hb (g/dL)	12.3 (8.5–14.5)	12.9 (8.8–16.1)	0.062
BUN (mg/dL)	12.5 (5–32)	13.4 (9–29)	0.338
Creatinine (mg/dL)	0.8 (0.34–1.40)	0.9 (0.49–1.30)	0.081
AST (IU/L)	26 (12–382)	30 (15–480)	0.554
ALT (IU/L)	13 (4–214)	19 (6–290)	0.725

Values are given as median (range); *P*<0.05 with a 95% confidence interval was considered significant.
IUGR, intrauterine growth restriction; MAP, mean arterial pressure; Hb, hemoglobin; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]Statistical significance was tested by the Student's *t*-test.

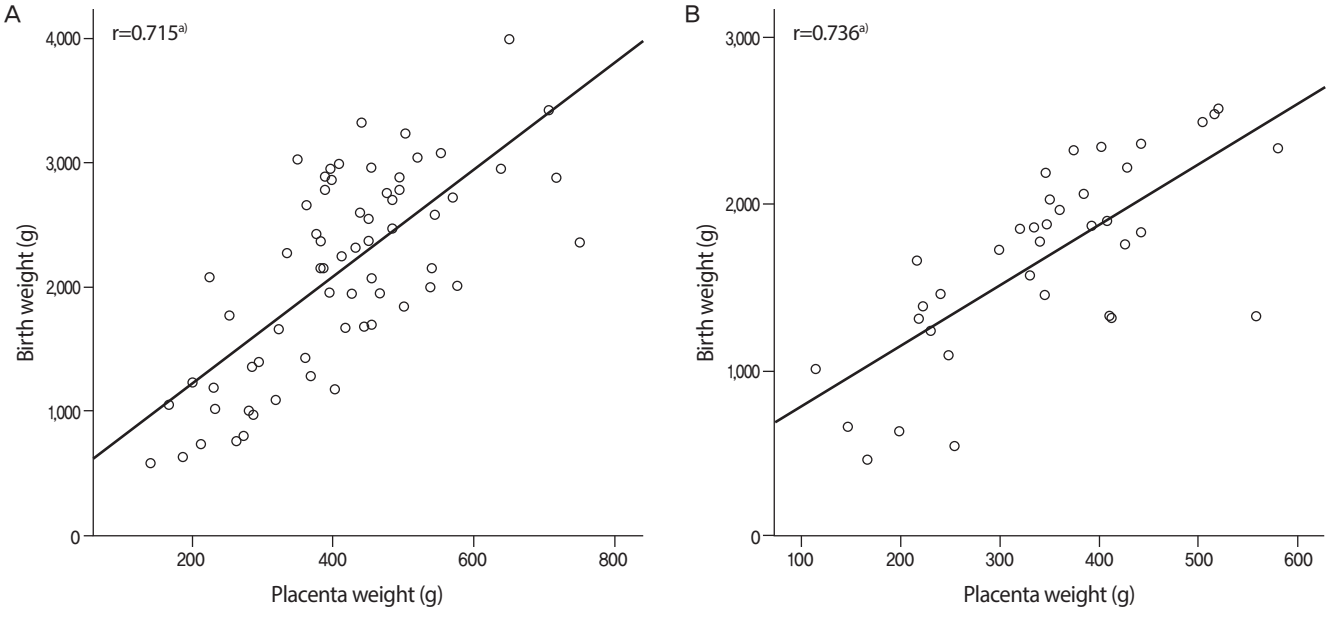

Fig. 3. Correlation between birth weight and placental weight. [a]The correlation coefficients were r=0.715 in the preeclampsia (PE) without intrauterine growth restriction (IUGR) group (A) and r=0.736 in the PE with IUGR group (B) (Pearson's rank correlation test, *P*<0.01).

groups: control (n=87), SGA (n=37), PE (n=102), and GDM (n=33). Maternal characteristics and blood laboratory values in each group are shown in Table 1. Blood pressure and blood laboratory values significantly differed in the PE group compared with those in the other groups. Birth weight, placental parameters (placental weight, volume, and density), BPW, and BPV in each group are shown in Table 2. While the placental weight and volume in the SGA and PE groups were smaller than those in the control group, the placental weight and volume in the GDM group did not significantly differ from those in the control group. However, the placental density did not significantly differ between the control and complicated pregnancies. In control and complicated pregnancies, the placental weight is positively correlated with the birth weight (Fig. 2). There was no difference in the BPW and BPV between the control and SGA groups. However, compared with the control group, BPW and BPV were lower in PE group, and higher in the GDM group.

The demographic and clinical data were compared between the PE without IUGR and PE with IUGR groups, as shown in Table 3. Although blood pressures and blood laboratory values did not statistically differ between the two groups, an increasing trend was noted in the PE with IUGR group. Positive correlations between birth weight and placental weight in the PE without IUGR and PE with IUGR groups are shown in Fig. 3. We compared the placental parameters, BPW, and BPV between these two groups (Table 4). Although the placental weight and volume were lower in the PE with IUGR group, the placental density and the BPW and BPV ratios remained unchanged.

Discussion

In this study, the placental morphological characteristics and ratios were compared between control pregnancies and pregnancies complicated with SGA, PE, and GDM. Birth weight, placental weight, and placental volume were lower in the SGA and PE groups and higher in the GDM group than in the control group. The placental density, BPW, and BPV described in this study have rarely been evaluated in placental morphological studies. In this study, new parameters were evaluated to allow comparisons between groups and to evaluate placental function in complicated pregnancies. Placental density indicates placental structural characteristics, whereas the BPW and BPV indicate placental function calculated using the birth weight per unit weight or placental volume. One study showed that compared with the group with normal BPW ratios, those in the high BPW group had increased rates of admission to the neonatal intensive care unit, Apgar scores of <7 at 5 minutes, breech presentation, and delivery by caesarean section [16]. Although complicated pregnancies may be associated with placental functional and morphological pathologies, no difference in placental density was found among groups in this study. In other words, placental density is not affected by the type of complicated pregnancy. BPW and BPV were similar in the control and SGA groups, but lower in the PE group and higher in the GDM group than in the control group.

Some studies showed the relation between placental volume and birth weight. Higgins et al. [17] showed an association between maternal diabetes and increased terminal villous vol-

Table 4. Clinical data showing the birth weight, placental parameters, and placental ratios in the preeclampsia with IUGR and preeclampsia with IUGR groups

	Preeclampsia without IUGR (n=65)	Preeclampsia with IUGR (n=37)	*P*-value
Birth weight (g)	2,246 (580–3,995)	1,763 (455–2,570)	<0.001[a]
Placenta characters			
Placenta weight (g)	432 (140–750)	346 (114–580)	0.012[a]
Placenta volume (cm^3)	725 (229–1,335)	569 (141–990)	0.043[a]
Placenta density (g/cm^3)	0.60 (0.27–1.09)	0.61 (0.40–1.74)	0.811
Birth weight/placenta character ratios			
Birth weight/placenta weight	5.2 (2.9–9.3)	5.1 (2.1–8.8)	0.433
Birth weight/placenta volume	3.1 (1.3–6.8)	3.1 (1.0–6.6)	0.987

Values are given as median (range); $P<0.05$ with a 95% confidence interval was considered significant.
IUGR, intrauterine growth restriction.
[a]Statistical significance was tested by the Student's *t*-test.

ume by stereological study of the placenta in type 1 and type 2 diabetes. One study revealed that first trimester placental volume is strongly associated with fetal and placental growth [18]. However, studies for placental volume are limited to first trimester data, ultrasonographic results, and microscopic findings. To our knowledge, this is the first study providing data of birth weight/ placental volume ratio.

In SGA pregnancies, the placental weight and birth weight were lower than those in control group, but there were no differences in placental density, BPW, and BPV. These results suggest that the SGA may not be caused by functional change in the placenta, but external obstetric factors such as uterine anomalies, genetic constitution, hypertension, malnutrition, anemia, and smoking. Some studies have shown that most SGA pregnancies were not associated with placental pathologies, and may be the result of fetal malnutrition, maternal anemia, and smoking [19-23]. In PE pregnancies, birth weight, placental weight, and placental volume, as well as BPW and BPV, were lower than those in control group. This suggests a decrease of both placental and fetal size, as well as the activity of fetal growth per unit tissue of placenta. This finding can be explained by a reduction in placental function. The PE group was divided into two groups, PE without IUGR and PE with IUGR to evaluate the independent IUGR effect in the PE group. Both the PE without IUGR and PE with IUGR groups had decreased placental and fetal size, but showed no difference in BPW and BPV as much alike as control and SGA groups have differences only in birth weight and placenta weight. So, we can hypothesize that IUGR in PE pregnancies may originate from non-placental causes. Kovo et al. [24] explained morphological changes in the placental villi in IUGR pregnancies complicated by pregnancy-induced hypertension and normotensive IUGR. This study showed that placental lesions in pregnancies complicated by hypertensive disorders were different from those in normotensive IUGR pregnancies. In the GDM group, the placental parameters (placental weight, volume, and density) did not differ from those in the control group. However, placental ratios (BPW and BPV) were significantly increased in the GDM group compared with those in the control group. Except for placental parameters, the fetal size as well as the fetal growth activity per placental unit tissue increased. Therefore, placental function in GDM pregnancies is increased, unlike in PE pregnancies, and excessive placental growth leads to fetal growth.

Previous studies retrospectively measured placental weight and fetal birth weight after delivery to predict adverse pregnancy outcomes. Our findings suggest that disease-specific BPW and BPV, as well as placental density, can be used to predict pregnancy complications before delivery. For example, we can assume birth weight and placental volume measured by two-dimensional and three-dimensional ultrasonography before delivery can be used to predict pregnancy complications. If placental volume, estimated fetal body weight (EBW), and estimated BPV (EBPV) are lower than those observed in control pregnancies, we can predict the probability that this pregnancy will be complicated by PE. If placental volume and EBW are lower and EBPV is similar, we can predict that the pregnancy will be complicated by SGA. Lastly, if EBW and EBPV are increased compared with control group and placental volume is similar, the pregnancy could be complicated by GDM. Future studies need to focus on confirming these findings. In addition, further research on functional changes associated with placental pathologies needs to be considered.

This study has some of limitations. The number of participants in each group was slightly heterogeneous. The median pregnancy duration in the PE group was 35 weeks' gestation, which is different from other groups. All cases enrolled in this study were not obtained during the same period. Until now, there have been no definite methods to measure the placental profiles such as weight, size, volume, and density. Considering the placental volume, there is one known method that after the placenta is soaked in water, the volume of overflowed water is measured as a placental volume. However, this method has also some limitations. So, we tried to measure the volume of placenta arithmetically and geometrically. There is a possibility that the calculated placental volume is not same to true volume of placenta. But, the calculated placental volume is well correlated with placental weight, and can be used for comparison among the groups. Though the preeclamptic placentas were measured by three persons due to long study period, the other placentas were evaluated by one. Because we don't have data for interobserver and intraobserver variability, we will study for the variability in the placental morphologic measuring in the near future. Strictly speaking, the control group is not the control group. Though the control group includes some preterm delivery cases, the placentas with chorioamnionitis or abnormal shape were excluded. Despite these weaknesses, the systematic approach and placental morphological comparisons included in this study contribute to understanding complicated pregnancies.

In conclusion, our study suggests that placental weight, volume, and density, as well as the birth weight and associated ratios, are helpful in understanding the pathophysiology of complicated pregnancies. Moreover, they can be used to predict pregnancy complications.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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