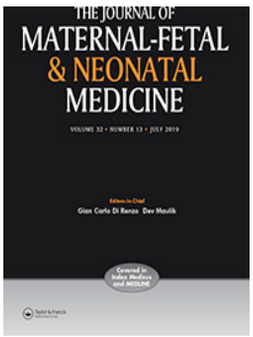

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ORIGINAL ARTICLE

The correlation between birth weight and insulin-like growth factor-binding protein-1 (IGFBP-1), kisspeptin-1 (KISS-1), and three-dimensional fetal volume

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ABSTRACT

Purpose: This study aimed to determine the relationship between birth weight, and maternal serum insulin-like growth factor-binding protein-1 (IGFBP-1) and kisspeptin-1 (KISS-1) levels, and first-trimester fetal volume (FV) based on three-dimensional ultrasonography.

Materials and methods: The study included 142 pregnant women at gestational week 11°–13^6. All fetuses were imaged ultrasonographically by the same physician. Maternal blood samples were collected at the time of ultrasonographic evaluation and analyzed for IGFBP-1 and KISS-1 levels *via* enzyme-linked immunosorbent assay (ELISA). Maternal and neonatal weights were recorded at birth. Birth weight ≤10th and the >90th percentiles was defined as small and large for gestational age (SGA and LGA), respectively.

Results: Median crown-rump length (CRL), FV, and maternal serum IGFBP-1 and KISS-1 levels were 58.2 mm (35.3–79.2 mm), 16.3 cm^3 (3.8–34.4 cm^3), 68.1 ng mL^{-1} (3.8–377.9 mL^{-1}), and 99.7 ng L^{-1} (42.1–965.3 ng L^{-1}), respectively. First-trimester IGFBP-1 levels were significantly lower in the mothers with LGA neonates ($p < .05$). There was a significant positive correlation between CRL and FV, and between the IGFBP-1 and KISS-1 levels. IGFBP-1 levels and maternal weight at delivery were negatively correlated with neonatal birth weight. There was no correlation between CRL or FV and maternal IGFBP-1 or KISS1 levels ($p > .05$). The maternal IGFBP-1 level during the first trimester was a significant independent factor for SGA and LGA neonates (Odds ratio (OR): 0.011, 95%CI: 1.005–1.018, $p < .001$; and OR: 1.297, 95%CI: 1.074–1.566, $p = .007$, respectively). There was no significant relationship between SGA or LGA, and CRL, FV, or the KISS-1 level.

Conclusions: As compared to the maternal KISS-1 level, the maternal IGFBP-1 level during the first trimester might be a better biomarker of fetal growth. Additional larger scale studies are needed to further delineate the utility of IGFBP-1 as a marker of abnormal birth weight.

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Birth weight; fetal volume; insulin-like growth factor-binding protein; kisspeptin; ultrasonography

Introduction

Birth weight plays an important role in human health. Multiple factors affect fetal growth, including maternal, fetal, and placental parameters. Although the most important factors remain unclear, maternal blood biochemical status is thought to be a significant factor affecting fetal growth. The insulin-like growth factor (IGF) family and their binding proteins (IGFBPs) are foundational to fetal growth and development. During pregnancy, insulin-like growth factor-binding protein-1 (IGFBP-1) is relatively resistant to pregnancy-related proteolysis; therefore, it is the major IGF-binding protein [1]. IGFBP-1 plays an important role in mitosis, trophoblastic invasion, trophoblastic implantation, and decidualization [2]. Although numerous effects on pregnancy of the IGF family and its binding proteins were reported, findings regarding their relationship with birth weight and the optimal gestational age for evaluating fetal growth are inconsistent [3–7].

Kisspeptin, another biochemical marker, is a peptide hormone that transmits signals via the G protein-coupled kisspeptin receptor (KISS1R). Kisspeptin plays an important role in physiological and pathological reproductive functions, including puberty and angiogenesis, placentation, and trophoblastic invasion during pregnancy [8], and therefore may be important for

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fetal growth. The literature includes only a few studies on the relationship between kisspeptin and birth weight that are characterized by inconsistent findings; some noting a positive correlation with birth weight [9,10] and other showing no association [8].

First-trimester ultrasonographic fetal evaluation can be achieved via measurement of crown-rump length (CRL) and/or fetal volume (FV). Measurement of FV using three-dimensional (3D) ultrasonography provides substantial information about fetal growth during early gestation [11] and might be more useful for irregularly shaped objects [12]. Accordingly, minor differences between normal and abnormal fetal growth during the first trimester may be easier to differentiate via 3D ultrasonography than 2D ultrasonography [12]. Furthermore, combining ultrasonographic and biochemical findings makes the prediction of obstetric features and outcomes more accurate. To the best of our knowledge the literature is devoid of any data on the relationship between first-trimester FV and maternal IGFBP-1, and KISS-1 levels.

The present study aimed to determine the relationship between birth weight and maternal serum IGFBP-1, and KISS-1 levels, and first trimester FV based on 3D ultrasonography, as well as the relationship between maternal IGFBP-1 and KISS-1 levels, and first-trimester FV.

Materials and methods

This study included 142 pregnant women that presented between January and June 2013 to the outpatient clinic of our education and research hospital during their first trimester (gestational week 11°–13^{6}). Exclusion criteria were multiple gestation, fetal anomalies, pregestational or gestational diabetes mellitus, and pregestational or gestational hypertensive disorders. Gestational week was calculated according to the first day of the last menstrual period and was confirmed *via* obstetric ultrasonography. The Institutional Review Board (IRB) approved the study protocol (165/14) and all the patients provided written informed consent.

All fetal ultrasonographic measurements were performed using a Voluson® 730 Sonography Pro System (GE Healthcare, Zipf, Austria). CRL was measured using a 2D transabdominal transducer. Ultrasonographic FV was measured via fast volume acquisition and a 3D transabdominal transducer (Rab 4–8 L, 4–8 MHz convex). FV data were stored on a hard disk for offline analysis. The sagittal plane was chosen for the reference image and thereafter a virtual organ computer-aided analysis (VOCAL) program (4D View® v.10.x, GE Healthcare, Zipf, Austria) was activated. We opted for six sequential planes. In each section the outer border of the fetus was delineated, yielding an area and thereafter VOCAL automatically yielded a final FV. The same physician (GKC) with extensive experience in ultrasonography performed the 2D and then the 3D scan in each case.

Following ultrasonographic fetal evaluation, maternal venous blood samples were collected into EDTA tubes, and then centrifuged at 2000 RPM for 20 min (Nüve® NF 800, Ankara, Turkey). Each patient's supernatant was stored at $-40\,^{\circ}C$ until analysis. Maternal IGFBP-1 and KISS-1 levels were measured via enzyme-linked immunosorbent assay (ELISA) using a Dynex® device, and human IGFBP-1 (CK-E10159) and KISS-1 (CK-E90502) kits (EASTBİOPHARM®). The sensitivity of the IGFBP-1 and KISS-1 kits was $3.12\,ng\,mL^{-1}$ and $12.14\,ng\,L^{-1}$, respectively. Maternal demographics (age, gestational age, medical, and obstetric history) and pregnancy characteristics at the time of delivery, including maternal weight, maternal weight gain during pregnancy, delivery method, amnion fluid index (AFI), pregnancy complications, birth weight and height, newborn gender, Apgar score, and admittance to the neonatal intensive care unit, were obtained from the patients' files. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Neonatal birth weight was converted to a percentile using the Fenton fetal growth chart, in consideration of gestational age at delivery [13]. Birth weight percentiles of newborns were categorized to three group as a 10th percentile or less ($\leq$P10), between 10th and 90th percentile (P10–90), and more than 90th percentile ($>$P90). Newborns with $\leq$P10, P10$-$90, and $>$P90 were defined as small for gestational age (SGA), appropriate for gestational age (AGA), and large for gestational age (LGA), respectively.

Data were analyzed using SPSS Statistics for Windows v17.0 (SPSS, Inc, Chicago, IL). Descriptive statistics are expressed as mean $\pm$ SD and median (interquartile range) for continuous variables, and number and percentage for categorical variables. The normality of the distribution of variables and homogeneity of variance were determined using the Kolmogorov–Smirnov test and Levene test, respectively. Correlations between numeric variables were evaluated using Spearman's rank-order correlation test. Following correction of ultrasonographic measurements (CRL and FV) according to gestational age, CRL and FV were compared with percentile groups. For continuous variables with normal distribution mean values were compared using Student's *t*-test and one-way ANOVA when there were $>$2 groups.

For continuous variables with abnormal distribution, mean values were compared using the Mann–Whitney *U* test and the Kruskal–Wallis test when there were >2 groups.

When the *p* value from one-way ANOVA or Kruskal–Wallis test was statistically significant, *post-hoc* Tukey's HSD or Conover's multiple comparison test was used to determine which group differed from others. The most important factor(s) for fetal birth weight was determined based on multiple linear regression analysis after adjustment for gestational age at delivery. Additionally, coefficients of regression, 95%CIs, and *t* statistics were calculated. The best predictor(s) which has an effect on percentiles of newborn after adjustment for all possible confounding factors was determined using multinomial logistic regression analysis. Odds ratios, 95%CIs, and Wald's statistics for each independent variable were also calculated. The level of statistical significance was set at $p < .05$.

Table 1. Clinical and biochemical findings of all cohort.

Maternal age[a] (year)	28 ± 4.5
Gestational age[b] (week)	12 (11–13[6])
Gestational age at delivery[b] (week)	39 (33–42)
CRL[a] (mm)	58.4 ± 11.28
FV[a] (cm^3)[d]	16.5 ± 7.64
Maternal IGFBP-1[c] (ng/mL)[d]	68.1 (34.0–96.3)
Maternal KISS-1[c] (ng/L)[d]	99.7 (91.0–136.7)
Maternal weight (at the beginning of pregnancy)[a] (kg)	62.8 ± 6.5
Maternal weight gain[b] (kg)	13 (7–22)
Maternal weight[a] (kg)[e]	75.7 ± 7.7
Maternal BMI[a] (kg/m^2)[e]	28.7 ± 2.4
Birth weight[a] (g)	3271.4 ± 517
Birth height[a] (cm)	50 ± 3
Percentile[f] *n* (%)	
≤P10	10 (7.2%)
P10–90	117 (84.7%)
>P90	11 (9.3%)

CRL: crown-rump length; BMI: body mass index IGFBP-1: Insulin-like growth factor binding protein-1; FV: fetal volume; KISS-1: Kisspeptin-1.
[a]Mean ± SD.
[b]Median (min-max).
[c]Median (IQR).
[d]At first trimester (11–13[6] weeks).
[e]At delivery.
[f]Birth weight Fenton scale: ≤P10: neonates with 10th percentile or less; P10-90: neonates between 10th and 90th percentile; >P90: neonates with more than 90th percentile [13].

Results

In all, four of the participants had early pregnancy loss and were excluded from the study. Among the remaining 138 women, first-trimester mean maternal age was 28 ± 4.5 years and median gestational age was 12 weeks (min: 11°- max: 13[6] weeks). Maternal clinical and biochemical findings are given in Table 1. Mean maternal weight at delivery was 75.7 ± 7.7 kg. In total, 98 (71%) of the women had vaginal delivery and 40 (29%) had cesarean delivery. Newborn characteristics (weight and height) and birth weight percentiles are shown in Table 1.

Maternal age, first-trimester CRL and FV, or the maternal KISS-1 level did not differ significantly among the percentile groups (Table 2). Mean maternal weight was significantly higher in the >P90 group (83.1 kg, 95%CI: 79.3–86.9) than in the ≤P10 (72.3 kg, 95%CI: 66.7–77.9) and P10-90 (75.3 kg, 95%CI: 73.9–76.7) groups ($p = .003$ and $p = .003$, respectively). Median weight gain was also significantly higher in the >P90 group than in the ≤P10 and P10–90 groups ($p = .022$ and $p = .008$, respectively). A statistically significant difference was found among percentile groups in terms of maternal IGFBP-1 levels ($p < .05$). The highest maternal IGFBP-1 levels were recorded in ≤P10 group and the lowest maternal IGFBP-1 levels were found in >P90 group (Table 2, Figure 1).

Table 2. The associations between maternal or fetal characteristics and percentiles of newborns.

	≤P10	P10-90	>P90	*p*
Maternal age[e] (years)	27.0 ± 3.1	27.9 ± 4.5	27.0 ± 4.3	.678[h]
Maternal weight[e] (kg)	72.3 ± 7.8[a]	75.3 ± 7.5[b]	83.1 ± 5.7[a,b]	**.002**[h]
Maternal weight gain[f] (kg)	12 (8–17)[a]	13 (7–22)[b]	15.5 (13–21)[a,b]	**.036**[i]
Gestational age[f] (weeks[d])	12.3 (11.0–13.3)	12.2 (11.0–13.6)	12.4 (11.0–13.1)	.905[i]
CRL[e] (mm)	57.8 ± 12.7	58.6 ± 11.4	57.1 ± 9.9	.906[h]
FV[e] (cm^3)	15.9 ± 8.3	16.7 ± 7.8	15.2 ± 5.8	.797[h]
Maternal IGFBP-1[g] (ng/mL)	163.1 (132.7–239.1)[a,c]	68.7 (41.2–93.4)[b,c]	5.0 (4.9–13.6)[a,b]	<**.001**[i]
Maternal KISS-1[g] (ng/L)	152.3 (97.8–248.7)	99.7 (90.0–135.8)	98.4 (79.7–103.5)	.227[i]

CRL: crown-rump length; FV: fetal volume; IGFBP-1: Insulin-like growth factor-binding protein-1; wk: week; KISS-1: Kisspeptin-1.
[a]≤P10 versus > P90 ($p < .01$).
[b]P10-90 versus > P90 ($p < .01$).
[c]≤P10 versus P10-90 ($p < .001$).
[d]At first trimester.
[e]Mean ± SD.
[f]Median (min-max).
[g]Median (IQR).
[h]One-way ANOVA.
[i]Kruskal–Wallis test.
Birth weight Fenton scale: ≤P10: neonates with 10th percentile or less; P10-90: neonates between 10th and 90th percentile; >P90: neonates with more than 90th percentile [13].
Statistically significant values are indicated in bold ($p < .05$).

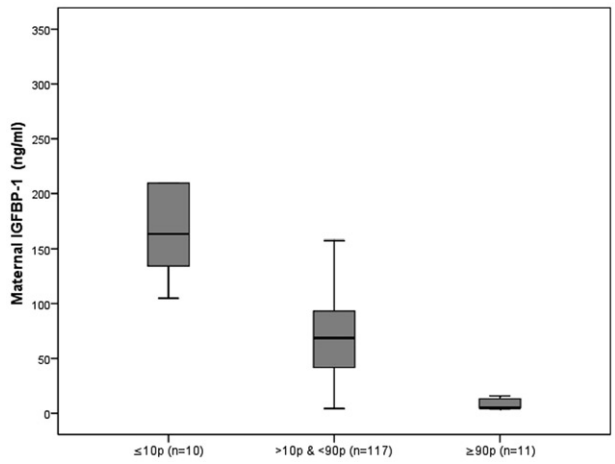

Figure 1. Comparison of the maternal IGFBP-1 level according to birth weight percentile groups. Horizontal lines in the middle of each box indicate the median maternal IGFBP-1 level, whereas the top and bottom borders of the box denote the 25th and 75th percentiles, respectively. The whiskers above and below the box mark indicate the maximum and minimum levels.

Table 3. Factors affected the neonatal birth weight after the correction of other possible risk factors according to multiple linear regression analysis.

		95%CI			
Variables	Coefficient of regression	Lower limit	Upper limit	*t*-test	*p**
Constant term	−5.219	−8.117	−2.322	−3.563	**<.001**
Maternal weight[a]	0.022	0.010	0.033	3.639	**<.001**
Maternal IGFBP-1	−0.009	−0.010	−0.007	−11.688	**<.001**
Maternal KISS-1	0.001	−0.0002	0.001	−1.372	.172
Gestational age[a]	0.111	0.043	0.178	3.225	**.002**

IGFBP-1: Insulin-like growth factor binding protein-1; KISS-1: Kisspeptin-1; CI: Confidence interval.
*p Value $<.05$ is statistically significant.
[a]At delivery.
Statistically significant values are indicated in bold ($p<.05$).

There was a significant positive correlation between CRL and FV ($r=0.920$, $p<.001$), and between maternal IGBP-1 and KISS1 levels ($r=0.182$, $p=.032$). There was no correlation between CRL or FV and maternal IGFBP-1 or KISS1 levels ($p>.05$). Birth weight was positively correlated with maternal weight and BMI at the time of delivery ($r=0.352$ and $p<.001$, and $r=0.209$ and $p=.014$, respectively) and negatively correlated with maternal IGFBP-1 and KISS-1 levels ($r=-0.886$ and $p<.001$, and $r=-0.186$ and $p=.029$, respectively); however, birth weight was not correlated with CRL or FV ($p>.05$). Newborn gender was not associated with CRL, FV, or maternal IGFBP-1 and KISS1 levels.

Multivariate analysis showed that only the IGFBP-1 level and maternal weight at delivery were associated with birth weight (Table 3). The first-trimester maternal IGFBP-1 level was an independent significant biomarker of fetal growth (Table 4). The risk of a neonate being in the SGA group significantly increased as the maternal IGFBP-1 level increased (OR: 1.011; 95%CI: 1.005–1.018; $p<.001$). A 10 ng mL^{-1} increase in the maternal IGFBP-1 level was associated with a 53.1 g decrease in birth weight (95%CI: 45.4–136.2; $p<.001$). Maternal weight and IGFBP-1 level were independent factors associated with delivering an LGA neonate. The risk of a delivering an LGA newborn significantly increased as the maternal IGFBP-1 level decreased (OR: 1.297; 95%CI: 1.074–1.566; $p=.007$) (Table 4).

Table 4. Factors affected the neonatal birth weight after adjustment for possible risk factors according to multinominal logistic regression analysis.

	OR	95%CI	Wald	*p* Value
≤P10				
Maternal age	0.940	0.800–1.106	0.555	.456
Maternal weight	0.945	0.845–1.056	0.995	.318
Maternal IGFBP-1[a]	1.011	1.005–1.018	10.876	**<.001**
Maternal KISS-1	1.002	0.998–1.006	0.751	.386
>P90				
Maternal age	0.596	0.345–1.028	3.458	.063
Maternal weight	1.346	1.033–1.756	4.824	**.028**
Maternal IGFBP-1[a]	1.297	1.074–1.566	7.325	**.007**
Maternal KISS-1	0.995	0.976–1.015	0.209	.648

IGFBP-1: Insulin-like growth factor-binding protein-1; KISS-1: Kisspeptin-1; OR: Odds ratio; CI: confidence interval.
[a]Decreasing in each 1 ng/ml.
Birth weight Fenton scale: ≤P10; neonates with 10th percentile or less, >P90; neonates with more than 90th percentile [13].
Statistically significant values are indicated in bold ($p<.05$).

Discussion

In the present study, there was a strong negative correlation between the maternal IGFBP-1 level and birth weight, whereas there wasn't any relationship between birth weight and the maternal KISS-1 level or first trimester FV. The present findings show that the first-trimester maternal IGFBP-1 level and pre-partum maternal weight are independent parameters associated with birth weight, indicating that the first-trimester maternal IGFBP-1 level might be considered as a significant indicator of fetal growth.

First-trimester ultrasonographic fetal evaluation has been used as an important tool for assessing fetal growth and pregnancy outcomes. Many researchers have reported that there is a significant correlation between CRL and FV, but findings regarding the correlation between CRL and FV, and birth weight have been inconsistent [11,14–16]. Vafaei et al. [17] noted an association between CRL and low-birth weight (LBW; <2500 g), and suggested that first-trimester fetal measurements play an important role in fetal growth. Van Uitert et al. [18] reported that there is a significant

positive correlation between birth weight and late first-trimester (gestational week 10–13) CRL, but there is no correlation between birth weight and early first--trimester (gestational week 8–9) CRL. In addition, the correlation between birth weight and FV (measured at gestational week 11°–13^{6}) was stronger than the correlation between birth weight and CRL (measured at gestational week 11°–13^{6}) [19]. Smeets et al. [20] reported that early fetal growth retardation is more likely to be predicted by FV than CRL, because the weekly increase in FV is greater than that in CRL. Smeets et al. [21] also reported that the predictive value of first-trimester FV for LBW was extremely low. In contrast, other researchers did not observe an association between first-trimester ultrasonographically measured CRL or FV, and birth weight or birth weight percentile categories (SGA or LGA) [22–25]. In the present study, there was a significant positive correlation between CRL and FV; however, neither measured at gestational week 11°–13^{6} was associated with birth weight or birth weight percentile. Additionally, the present findings show that first-trimester maternal IGFBP-1 and KISS-1 levels are not associated with CRL or FV.

The possible role of IGFBP-1 in fetal growth, as a mediator or regulator, is supported by two primary facts. First, during pregnancy the serum IGFBP-1 level increases more rapidly than that of other members of the IGF family. Second, IGFBP-1 is resistant to pregnancy-related proteolysis [1,4]. Clinical studies have reported that there is an inverse correlation between the maternal serum IGFBP-1 level and birth weight [4–6], but these findings are of limited value because the gestational week for maternal blood sample collection was not standardized across studies. Jonsson et al. [6] reported that birth weight increases as the third-trimester maternal serum IGFBP-1 level decreases, but that the first-trimester maternal serum IGFBP-1 level and birth weight are not correlated. Verhaeghe et al. [7] noted that the maternal IGFBP-1 level at gestational week 24–29 is not predictive of birth weight.

Hills et al. [5] observed that the maternal IGFBP-1 level measured at gestational week 11–42 was higher in patients with SGA neonates than in those with AGA neonates and lower than in those with LGA neonates. Wang et al. [26] reported that there isn't a difference in the maternal IGFBP-1 level measured during the third trimester between women with SGA and AGA neonates; however, they also reported that the cord blood IGFBP-1 level is significantly higher in SGA neonates. Sifakis et al. [27] observed that the maternal IGFBP-1 level at gestational week 11–13 is significantly lower in women with SGA neonates, but after adjusting for such maternal characteristics as race and smoking, which the rate of these were significantly higher in those with SGA neonates, the maternal IGFBP-1 level was not predictive of delivery of an SGA neonate. In the present study, there was a significant inverse correlation between the first-trimester maternal IGFBP-1 level and birth weight. Additionally, the maternal IGFBP-1 level was an independent significant marker for SGA or LGA newborns. The present findings are compatible with those of Hills et al. [5], who categorized birth weight into three percentile groups, which the point of discriminations was 10th and 90th percentiles, as in the present study; however, they differ greatly from those reported by Sifakis et al. [27]. In their study SGA neonates were defined as $<$5th percentile and non-SGA as all other percentiles [27]. In the present study, SGA was considered $\leq$10th percentile; therefore, differences in the present study's findings and theirs might be due to differences in birth weight percentile group definition. Additional large-scale population-based studies are needed to further clarify the effect of the first-trimester maternal IGFBP-1 level on fetal growth.

Only a few studies have evaluated the value of KISS-1 in pregnancy. Insulin plays an undeniably important role in fetal growth [28]. Some studies reported that KISS-1 stimulates insulin secretion [29,30], whereas other reported that it inhibits insulin secretion [31]. Such inconsistent findings in rat studies were attributed to the fact that a KISS-1 level in the nanomolar range suppresses insulin secretion and a micromolar KISS-1 level stimulates insulin secretion [30,32]. Nonetheless, Andreozzi et al. [33] reported that a nanomolar plasma KISS-1 level is inversely and independently associated with insulin secretion in humans. In the present study, there was a positive correlation between maternal IGBP-1 and KISS-1 levels, which indirectly supports Andreozzi et al.'s [33] findings.

Various biochemical markers might function via different mechanisms or pathways to affect fetal growth. For KISS-1, angiogenesis is thought to be a primary mechanism. Many studies reported a significant relationship between vascular disorders of pregnancy and KISS-1 [8,9,34]. Smets et al. [10] posited that defects in trophoblastic invasion in SGA fetuses lead to a decrease in the maternal KISS-1 level. They reported that the first-trimester plasma KISS-1 level was significantly lower in women with SGA neonates than in those with AGA neonates. Logie et al. [9] reported that there is an association between the maternal serum KISS-1 level at gestational week 16 and LBW; however, Armstrong et al. [8] did not find an association between KISS-1 at 16–20 weeks of gestation and birth weight. Additionally, in the present study there was no correlation between the maternal KISS-1 level and

birth weight, and the maternal KISS-1 level did not differ according to birth weight percentile groups, which might be because women with hypertension, diabetes mellitus, and collagen tissue disease, which can affect *in utero* angiogenesis, were excluded from the study. Therefore, we infer that KISS-1 levels in complicated pregnancies with impaired angiogenesis might clearly discern the mechanism of action responsible for its effect in fetal growth.

Maternal overweight and obesity were strongly associated with fetal macrosomia [35,36]. Yang et al. [37] reported that birth weight was significantly correlated with maternal weight. In the present study birth weight was associated with maternal weight at the time of delivery. Additionally, the present findings show that there was significant association between pre-partum maternal weight and BMI, and LGA newborns. Moreover, pre-partum maternal weight was an independent factor for having an LGA neonate.

To the best of our knowledge the present study is the first to examine the relationship between maternal IGFBP-1 and KISS-1 levels, as well as association between those levels and first-trimester ultrasonographically measured CRL and FV. This study's prospective design and the fact that the same physician performed all ultrasound examinations are its strengths. This is a preliminary study performed in general population where the results indicate that the mentioned biomarkers can be valuable for $\leq$ P10 and $>$ P90 groups. Nevertheless, the study's primary limitation is its small patient population. The value of these potential biomarkers can be re-explored in studies including large number of cases with abnormal fetal growth.

In conclusion, as compared to the maternal KISS-1 level, maternal IGFBP-1 might be a better biomarker for fetal growth. However, the available data is not enough to recommend for routine analysis to any patient population nowadays. Additional larger scale studies are needed to further delineate the utility of IGFBP-1 as a marker of abnormal birth weight.

Disclosure statement

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