Association of Cord Blood Insulin-Like Growth Factor-1 and Leptin Levels and Changes in Fetal Weight Gain in the Third Trimester of Pregnancy

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Association of Cord Blood Insulin-Like Growth Factor-1 and Leptin Levels and Changes in Fetal Weight Gain in the Third Trimester of Pregnancy

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ABSTRACT

Context: Insulin-like growth factor-1 (IGF-1) and leptin are hormones impacting somatic growth regulation and organ development in early fetal life. **Aims:** The study aimed to investigate the correlation between IGF-1 and leptin levels with birth weight and fetal weight gain during pregnancy third trimester. **Settings and Design:** A cohort study included 52 newborns from Semarang, Indonesia. **Subjects and Methods:** Serum IGF-1 and leptin were taken from the umbilical cord, and the estimated fetal weight in the third trimester was measured by ultrasound. Anthropometric data were plotted to the World Health Organization Fetal Growth Chart 2017. We divided three categories, i.e., weight gain faltering, if the infant decreased of two major percentiles (G1), normal weight gain (G2), and accelerated weight gain, whose increased more than two major percentiles (G3). **Statistical Analysis Used:** Fetal growth and other parameters were analyzed using Pearson's or Spearman's rho correlation. The comparison of IGF-1 and leptin levels among G1, G2, and G3 was analyzed by one-way ANOVA, least significant difference *post hoc* test, Kruskal–Wallis, and Mann–Whitney tests. **Results:** The mean IGF-1 level in G1 was 82.9 (25.9) ng/mL, G2 was 86.2 (28.9), and G3 was 134.8 (33.9), and there were significant differences between G1–G3 and G2–G3. Meanwhile, the levels of leptin among groups were not different. Birth weight was correlated with the level of IGF-1 ($r = 0.456$, $P = 0.001$) and leptin ($r = 0.39$, $P = 0.004$), and maternal body mass index was correlated with cord blood leptin. **Conclusions:** This study indicated that a higher IGF-1 and leptin cord blood level is correlated with larger birth weight.

KEYWORDS: *Birth weight, fetal weight, insulin-like growth factor-1, leptin, pregnancy*

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INTRODUCTION

A poor status during intrauterine has an essential role in susceptibility of metabolic syndrome in later life.[1-3] Some hormones play in metabolic regulation, energy expenditure, somatic growth, and development, including insulin-like growth factor-1 (IGF-1) and leptin.[4,5] IGF-1 is a polypeptide that acts as a paracrine and autocrine mediator,[6-8] meanwhile leptin regulates body fat.[9,10] High protein intake in pregnant women increases fetal growth[11] but will cause a linear slowdown of fetus in another study.[12] The aim of this study was to investigate the correlation between IGF-1 and leptin levels with fetal weight.

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SUBJECTS AND METHODS

We recruited 52 mothers out of 79 from 9 health centers and 5 hospitals in Semarang who had healthy full-term

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infants and ultrasound confirmation. The inclusion criteria were pregnant in the third semester with a normal pregnancy, a single fetus, age <40 years, and full-term babies with bodyweight between 2500 and <4000 g. Mothers with preeclampsia/eclampsia, diabetes mellitus or gestational diabetes, a history of hypertension, severe anemia in pregnancy (Hb <7 g/dL),[13] and perinatal asphyxia or respiratory distress at birth were excluded. Mothers who moved from the public health area and did not wish to participate in this research anymore, had a miscarriage, suffered from an illness, or died during the observation period were considered as dropped out.

Estimated fetal weight (EFW) was measured during the third trimester of pregnancy by ultrasound. Anthropometry of the newborn babies was recorded at birth, consisting of weight, length, and head circumference using a standard scale measured by the attending midwife. To measure maternal food intake including energy and protein intake, a 3-day food recall survey was taken by a nutritionist. Before delivering the placenta, 3 mL of cord blood samples was taken from the umbilical cord into non-EDTA tubes. The tubes were centrifuged at 3000 rpm for 10 min until serum was obtained. Then, IGF-1 and leptin were determined by the enzyme-linked immunosorbent assay (human IGF-1, R and D Systems, USA, and human leptin, R and D Systems, USA) at the Central Laboratory Diponegoro National Hospital, Faculty of Medicine, Diponegoro University, Indonesia.

EFW and birth weight were plotted to the World Health Organization Fetal Growth Chart 2017.[14] We considered weight gain faltering (Group I [G1], if the percentile of growth decreased for more than two major percentiles), normal weight gain (Group II [G2], if the fetus growth was on the same percentile), and accelerated weight gain (Group III [G3], if the fetus growth increased for more than two major percentile).

This study's minimum sample size was 38, based on the sample size calculation for correlation studies. The correlation between fetal growth and IGF-1, leptin, or maternal protein intake was analyzed using Pearson or Spearman's rho correlation. The comparison of IGF-1 and leptin levels among Groups I, II, and III was analyzed by the one-way ANOVA, least significant difference *post hoc* test, Kruskal–Wallis, and Mann–Whitney tests.

The Medical Ethics Review Committee of Faculty of Medicine, Diponegoro University/Dr. Kariadi Hospital, approved this study, and informed consent was obtained from all participants.

RESULTS

Our analysis included 52 pregnant women and their offspring who underwent ultrasound in the third trimester and had cord blood taken during labor. The majority of the subjects were boys (61.5%) with a gestational age of 39 weeks at delivery. The characteristics of subjects are presented in Table 1, and the comparisons between maternal protein intake, IGF-1 levels, and leptin with their relationship to fetal weight gain are depicted in Tables 2 and 3. The mean IGF-1 level in G1 was 82.9 (25.9) ng/mL, G2 was 86.2 (28.9) ng/ml, and G3 was 134.8 (33.9) ng/ml. There were significant differences between G1–G3 and G2–G3. However, there was no difference of maternal protein intake, maternal BMI, and leptin cord level among G1–G2–G3 groups [Table 2]. Figure 1 describes the comparison among the IGF-1 cord blood level in different fetal weight gain groups. Birth weight was correlated with IGF-1 and leptin levels, meanwhile maternal BMI was correlated with cord blood leptin [Table 3]. We did not find any relation between maternal dietary intake with IGF-1 and leptin cord blood. However, protein daily intake in our study (mean 58 ± 15.0 g/day) was lower than Angka Kecukupan Gizi Indonesia (Indonesian Dietary Recommendation) for pregnant women.[15]

Table 1: Participants' characteristics

	n (%)
Maternal characteristics, mean (SD)	
Age (years)	28.9 (5.68)
Weight (kg)	63.1 (0.43)
Height (cm)	155 (5.7)
BMI (kg/m^2)	26.3 (4.2)
Fetal characteristic, mean (SD)	
Gestational age (week)	26 (6.1)
Estimated fetal weight (g)	1207 (844)
Infant characteristics	
Male, *n* (%)	32 (61.5)
First pregnancy, *n* (%)	17 (32.7)
Gestational age (week), mean (SD)	39 (1.9)
Birth weight (g), mean (SD)	3084 (401.8)
Length (cm), mean (SD)	48.9 (1.9)
Maternal intake during the 3rd semester of pregnancy, mean (SD)	
Energy (kcal)	1764 (462.2)
Protein (g)	58 (15.0)
Fat (g)	64 (4.0)
Cord blood samples (ng/mL), mean (SD)	
IGF-1	91.5 (32.98)
Leptin	5.85 (1.871)

IGF-1: Insulin-like growth factor-1, BMI: Body mass index, SD: Standard deviation

Table 2: Comparison of maternal protein intake, insulin-like growth factor-1 level, and leptin level in different groups of fetal weight gain

	Mean (SD)	*P*	Comparison	*P*
Maternal protein intake (g)				
Weight gain faltering (G1)	59 (15.3)	0.878[#]	G1-G2	0.990[¶]
Normal weight gain (G2)	57 (17.6)		G2-G3	0.998[¶]
Accelerated weight gain (G3)	56 (11.1)		G1-G3	0.918[¶]
Maternal BMI (kg/m^2)				
Weight gain faltering (G1)	26.2 (4.51)	0.875[b]	G1-G2	0.986[§]
Normal weight gain (G2)	26.1 (3.71)		G2-G3	0.676[§]
Accelerated weight gain (G3)	27.0 (3.67)		G1-G3	0.617[§]
IGF-1 cord level (ng/mL)				
Weight gain faltering (G1)	82.9 (25.9)	<0.001[b]	G1-G2	0.743[§]
Normal weight gain (G2)	86.2 (28.9)		G2-G3	0.001[§]
Accelerated weight gain (G3)	134.8 (33.9)		G1-G3	<0.001[§]
Leptin cord level (ng/mL)				
Weight gain faltering (G1)	5.80 (1.70)	0.262[#]	G1-G2	0.716[¶]
Normal weight gain (G2)	5.48 (2.67)		G2-G3	0.374[¶]
Accelerated weight gain (G3)	6.50 (1.47)		G1-G3	0.093[¶]

[b]One-way ANOVA, [§]LSD *post hoc* tests, [#]Kruskal-Wallis, [¶]Mann-Whitney. BMI: Body mass index, IGF-1: Insulin-like growth factor-1, BMI: Body mass index, LSD: Least significant difference

Table 3: The correlation between insulin-like growth factor-1 and leptin levels and their variables

Variables	*R*	*P*
Cord blood IGF-1		
EFW (g)	−0.219	0.120[b]
Birth weight (g)	0.456	0.001[b]
Birth length (cm)	0.229	0.116[b]
Maternal BMI (kg/m^2)	0.248	0.080[b]
Energy intake/day (kcal)	0.015	0.918[b]
Protein intake/day (g)	0.081	0.569[b]
Cord blood leptin	0.372	0.007[#]
Cord blood leptin		
EFW (g)	−0.144	0.308[#]
Birth weight (g)	0.392	0.004[#]
Birth length (cm)	−0.001	0.994[#]
Maternal BMI (kg/m^2)	0.360	0.010[#]
Energy intake/day (kcal)	0.078	0.583[#]
Protein intake/day (g)	0.091	0.520[#]

[b]Pearson correlation, [#]Spearman correlation. IGF-1: Insulin-like growth factor-1, BMI: Body mass index, EFW: Estimated fetal weight

DISCUSSION

The present study found that the IGF-1 cord blood was correlated with fetal weight gain and birth weight. The mean of IGF-1 cord blood level was 91.5 ± 32.98 ng/ml, with the level being 82.9 ± 25.9 ng/mL in the weight gain faltering group, 86.2 ± 28.9 ng/ml in the normal weight gain group, and 134.8 ± 33.9 ng/ml in the accelerated weight gain group. The IGF-1 level in this study was similar with Randomized Control Trial of Low Glycemic Index Diet Study in Dublin, Ireland, with a mean 113.4 ± 37.3 ng/ml,[16] and in a study which compares cord blood IGF-1 from

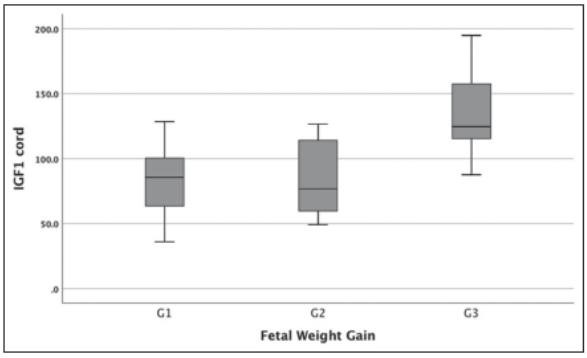

Figure 1: Comparison of IGF-1 cord blood level among infants with gain faltering group (G1), normal weight gain group (G2), and accelerated weight gain group (G3). There were significant differences between G1 and G3 and G2 and G3, but not the IGF-1 between G1 and G2. IGF-1: Insulin-like growth factor-1, G1: Group I, G2: Group II

subjects in Boston (98.4 ± 37.8 ng/mL) and Shanghai (79 ± 48.9 ng/ml).[17] Whereas, a study in infants from preeclamptic mothers and small-for-gestational age (SGA) infants had lower IGF-1 level (73.2 ± 48.69 ng/ml and 33.2 ± 32 ng/ml, respectively).[18,19]

There were differences in IGF-1 levels on fetal weight gain, especially in Group 3 (accelerated weight gain) compared to other groups [Table 2]. IGF-1 was also associated with birth weight (Pearson correlation: 0.456, $P = 0.001$) but not correlated with maternal protein intake [Table 6]. This result is similar to Geraghty *et al*., where birth weight centile was associated with IGF-1 (Pearson correlation: 0.331, $P < 0.001$). Maternal IGF-1 was higher than cord IGF-1 because IGF-1 was

mainly expressed at the maternal–fetal interface in early human pregnancy.[18] IGF-1 mediates the effects of the growth hormone (GH) and has an important role in regulating somatic growth and organ development.[4] Besides GH, other hormones that play an essential role in increasing IGF-1 expression during pregnancy are the platelet-derived growth factor, the epidermal growth factor, and the basic fibroblast growth factor.[18,20] These growth-related factors do not cross the placental barrier but may affect fetal growth through their effects on the placenta. Therefore, IGF-1 level in preeclampsia mothers is lower than normotensive mothers.[18]

Another hormone that affects fetal growth is IGF-2. IGF-2 levels are lower in 28-week premature infants with SGA compared to the infant with appropriate for gestational age (AGA) at the same age. However, when the premature babies reached the chronological age of 37 weeks, the levels of IGF-2 in the two groups were not significantly different.[21] Similarly, IGF-2 of SGA fetuses taken from chorionic villus sampling at 11–13 weeks' gestation were lower than AGA fetuses.[22] Thus, it is concluded that IGF-2 plays a crucial role in the first to the third trimester of fetal life. We did not analyze the IGF-2 level from cord blood because our subjects were full-term newborns.

The mean cord blood leptin level in our study was 5.85 ± 1.87 ng/mL. There was no difference in leptin levels between G1 (weight gain faltering), which was 5.80 ± 1.70 ng/mL, G2 (normal weight gain) 5.48 ± 2.67 ng/mL, and G3 (accelerated weight gain) 6.50 ± 1.47 ng/mL (P = 0.262). Panjeta's study found that the leptin cord blood level in normal pregnancy was 10.02 ± 4.57 ng/mL,[18] so the average leptin level in our study was slightly lower than in previous studies. Leptin appears to be an important factor in fetal growth, including contributing to maintaining pregnancy. This hormone is produced by the maternal and fetal adipose tissue, as well as by the placenta. Leptin in the placenta is produced by the fetal adipose tissue and it is detected at 18 weeks of gestation, increasing significantly after 34 weeks. *In vitro* studies reveal that 95% of placental leptin is distributed to the maternal circulation.[3,9] It was found that the leptin concentration in the umbilical vein was higher compared to the leptin level in the umbilical artery. Leptin in the umbilical arteries is thought to have a closer correlation with neonatal anthropometry, whereas leptin levels in veins are more closely related to maternal characteristics.[3,23] We did not distinguish the origin of cord blood leptin from the umbilical vein or the artery.

This study showed that leptin level was correlated with birth weight (r = 0.392, P = 0.004) and maternal BMI (r = 0.36, P = 0.01). Several studies have shown a positive relationship between cord blood leptin concentration and birth weight, reflecting the contribution of body fat mass in determining leptin levels.[24] Leptin levels decreased after the 6th day of life. A study showed that the rapid decline of leptin on day 4 is associated with an increased weight gain in neonates and infants.[10] Another study found that high cord blood leptin levels are associated with lower increases in adiposity and a slower weight gain during infancy.[25] A previous study in Taiwan found a positive correlation between leptin level and maternal BMI (r = 0.466, P = 0.001), and it was similar to our research (r = 0.360, P = 0.01). This result might be caused by maternal and placental leptin provided to a higher quantity of their serum leptin concentration.[26]

It was also found that SGA infants have lower leptin levels at birth compared to AGA infants.[27] However, there is a feedback mechanism where lower cord blood leptin levels are associated with faster infant growth in the 1st year of life.[28] This is in accordance with our study which found that infants on G1 (weight gain faltering) had lower leptin levels than G3 (accelerated weight gain) infants even though it was not statistically significant. Our result was also similar to Panjeta's study, which found that leptin levels in preeclampsia mothers who generally have SGA babies were higher compared to those of normotensive mothers.[18] On the contrary, Zareaan *et al*. found that leptin levels in intrauterine growth restriction infants were lower compared to normal infants (7.42 ± 4.08 ng/mL and 30.49 ± 14.50 ng/mL, respectively).[29]

We did not detect a relationship between maternal protein intake and fetal growth even though maternal protein intake in G1 (less weight gain) was higher (59 ± 15.3 g/day) compared to G2 group (normal weight gain), which was 57 ± 17.6 g/day and G3 (accelerated weight gain) which was 56 ± 11.1 g/day. There were also no correlations between energy and protein intake during pregnancy with birth weight, birth length, IGF-1 levels, and leptin levels. This result was similar to Geraghty *et al*.'s study that did not find any relation between IGF-1 intake with any measure of maternal protein intake during pregnancy.[16]

Maternal protein intake in our study (mean 58 ± 15.0 g/day) was lower than the Indonesian Dietary Recommendation that has been suggested to Indonesian pregnant women, which is 90 g/day.[15] A study in Hamburg found that protein intake in pregnant women, especially animal protein, raised significantly from 76 ± 24 g/day at the first trimester and 82 ± 23 g/day

at the third trimester.[30] The study by Borazjani *et al*. in India proved that a protein intake of 70 g and milk of 465 mL/day in pregnant women increase fetal growth measured by ultrasound, with better results than the control group with <50 g protein and 155 mL of milk per day.[11] Another study conducted in India, women with a low BMI, who received an additional daily intake with 300 kcal/day of energy and 15 g of protein/day from 12 weeks of gestation until delivery, found that no increment in the infant's weight, whole protein kinetics, or serine and glycine fluxes.[31] Furthermore, a study found that pregnant women that consumed dairy milk in the 34th week of pregnancy had higher cord IGF-1 level and bigger placenta than pregnant women who did not consume dairy milk.[32]

The Healthy Start Study of 1040 mother-offspring pairs found that increasing 1% saturated fatty acids in maternal food would increase neonatal adiposity. However, this study did not find an association between macronutrient intake with a fat-free mass increase in the offspring. There was also no relationship between protein intake and neonatal fat mass.[33] Likewise, a study in the USA found that in populations with a relatively high protein intake, giving a diet with high protein during pregnancy would cause a linear slowdown of the fetus until mid-childhood.[12] However, this study failed to prove the relationship between maternal protein intake and fetal weight gain. The explanation for this may be caused by dietary intake and BMI supposed to have no direct effects on fetal growth but from the change of maternal metabolic hormones such as insulin, IGF-1, and leptin, which influence placental nutrient transport, and finally altered fetal nutrient supply and growth.[34]

Our study's limitation was that IGF-1 and leptin levels were only taken from cord blood, not differentiated, whether derived from maternal or infant. Furthermore, we only measured the total maternal protein intake, and as a result, we found no difference between animal protein and milk products. For further research, maternal blood samples of IGF-1 and leptin are proposed to take as a comparison, and subsequent cohort studies are needed to assess the role of IGF-1 and leptin in infant growth.

Conclusions

Our study found a significant correlation between cord blood IGF-1 level with birth weight and fetal weight gain. Meanwhile, the leptin level was correlated with birth weight and maternal BMI. This study indicated that a higher IGF-1 level is correlated with larger birth weight.

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Conflicts of interest

There are no conflicts of interest.

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