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Original Article

Changes in maternal serum insulin-like growth factor-I during pregnancy and its relationship to maternal anthropometry

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Abstract

Background: Insulin-like growth factor (IGF)-I is primarily produced by the liver under the stimulation of growth hormone, and has systemic growth effects. Placental growth hormone in maternal circulation increases from early pregnancy and is responsible for the increment in maternal serum IGF-I. The purpose of this study was to evaluate the changes in maternal serum IGF-I during pregnancy and their relationship to maternal anthropometry, including body weight (BW) and body mass index (BMI).

Methods: We obtained 332 blood samples from 114 expectant mothers at different gestational ages (Gas) without adverse medical history. Serum IGF-I levels were measured by immunoradiometric assay. Linear regression analysis for continuous variables and *t* test for comparisons of categorical variables were used to test for significance.

Results: Maternal serum IGF-I during pregnancy was significantly correlated not only to GA ($p < 0.001$, $r = 0.358$), but also to maternal BW ($p = 0.001$, $r = 0.202$), and maternal BMI ($p < 0.001$, $r = 0.263$). The mean maternal IGF-I was highest in the third trimester [1st vs. 2nd, $p < 0.001$, 95% confidence interval (CI) = −70.17 to −28.22; 1st vs. 3rd, $p < 0.001$, 95% CI = −138.02 to −76.94; 1st vs. 3rd, $p < 0.001$, 95% CI = −88.86 to −27.71].

Conclusion: Maternal serum IGF-I is significantly related to GA, maternal BW, and BMI during pregnancy.

Keywords: body mass index; body weight; gestational age; insulin-like growth factor-I; pregnancy; trimester

1. Introduction

Insulin-like growth factor (IGF)-I, also known as somatomedin C, is primarily produced by the liver as an endocrine hormone. However, it also functions in a paracrine/autocrine fashion in selected target tissues. Its production can be stimulated by growth hormone (GH) and decreased by malnutrition, growth hormone insensitivity, and lack of GH receptors. The molecular structure of IGF-I is similar to that of insulin, and its primary action is mediated by binding to its specific receptor, IGF-I receptor, which is present on many tissues. Binding to its receptor, IGF-I stimulates systemic body growth and has growth-promoting effects on almost every cell in the body, especially skeletal muscle, bone, cartilage, liver, kidney, nerves, skin, hematopoietic cells, and lungs, as well as cellular DNA synthesis. Consequently, deficiency of either GH or IGF-I results in diminished stature.

Hypertrophy of the mammary glands during pregnancy results in increased concentration of IGF-I; hence, a relationship between the development of the mammary glands and IGF-I can be found.[1] Moreover, IGF-I can also be found in the intervillous space during pregnancy.[2] The placental syncytiotrophoblast produces a variant of pituitary GH (variant GH or placental GH)[3] that gradually replaces pituitary GH in maternal circulation, which starts at 8 weeks of gestation and becomes elevated during pregnancy.[4] Placental GH is thought to be responsible for the increase in maternal serum levels of IGF-I.[5] Fetal growth during pregnancy may be mediated by placental GH via regulation of IGF-I.[6] Previous studies have

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demonstrated increases in maternal serum levels of IGF-I with the combined changes of fetal size, maternal weight, and placental mass during pregnancy.[7–9] Theoretically based on the above findings, changes in maternal IGF-I during pregnancy should be evident. However, the relationships among maternal IGF-I and gestational age (GA), as well as changes in maternal anthropometry have rarely been reported, and this was the purpose of our present study.

2. Methods

2.1. Samples

Blood samples were collected after obtaining written consent from singleton women without an adverse medical history during their first prenatal visit, Down's screen test, 50-g glucose challenge test, hepatitis B markers test, and admission for delivery. Samples were drawn during the daytime when possible to avoid the effect of time bias, spun at 4000 *g* for 10 minutes, and stored at −20 °C until assay. The study project was approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB No. 2011-12-017IB#1).

The expected date of delivery was calculated based on the first day of the last menstrual period when pregnancy was detected immediately after a missed period. When no reliable menstrual dates were available or menstrual cycles were irregular, ultrasound was used to date the pregnancy. Maternal characteristics including body height, body weight (BW), and GA of each blood test, as well as the time of delivery were all recorded. Body mass index (BMI) was calculated using the formula weight/height.[2]

2.2. IGF-I assay

The serum concentrations of IGF-I were measured with ACTIVE non-extraction IGF-I IRMA (immunoradiometric assay; Diagnostic Systems Laboratories, Webster, TX, USA) by the Department of Nuclear Medicine. The procedure used a two-site IRMA principle described by Miles et al,[10] and was designed to detect IGF-I. The IRMA was a noncompetitive assay in which the analyte (recombinant human IGF-I) to be measured was sandwiched between two antibodies. The first antibody was immobilized to the inside walls of the tubes and the other antibody was radiolabeled (iodine-125-labeled anti-IGF-I) for detection. The analytes present in the unknowns, standards, and controls were bound by both antibodies to form a sandwich complex. Unbound reagents were removed by decanting and washing the tubes. The minimal detectable concentration of IGF-I was 2.06 ng/mL. The intra- and interassay coefficients of variations (CVs) were 4.8% and 5.1%, respectively.

2.3. Statistical analysis

Statistical analysis for linear regression between continuous variables, and *t* test for comparison of categorical variables were done with SPSS software for Windows, version 20 (IBM SPSS Inc. Chicago, IL, USA), with $p < 0.05$ as significant.

3. Results

There were 332 blood samples obtained from 114 expectant mothers in this study. The average age of the participants was 29.9 ± 4.0 years with a range of 19–40 years. The range of gravidity was 1–7 with a mean of 2.3 ± 1.2. Mean parity was 0.7 ± 0.7 with a range of 0–3. The average maternal height was 159.8 ± 5.0 cm and ranged between 147 cm and 170 cm. The mean preconceptional BW was 52.3 ± 7.1 kg and the range was 39.5–81.3 kg. The preconceptional BMI was 15.4–34.3 kg/m^2 with a mean of 20.5 ± 2.7 kg/m^2. The mean maternal BW at delivery was 67.1 ± 7.9 kg with a range of 49.0–92.0 kg. The range of maternal BMI at delivery was 19.5–37.9 kg/m^2 with an average of 26.3 ± 3.0 kg/m^2. The gestational age at delivery ranged between 37 weeks and 42 weeks with a mean of 38.8 ± 1.3 weeks. There were 82 natural spontaneous deliveries and 32 cesarean sections. There were 55 male and 59 female newborns. The mean number of blood samples offered by the expectant mothers was 2.8 ± 1.3, ranging from 1 sample to 5 samples (Table 1).

Throughout the whole course of pregnancy, maternal serum levels of IGF-I ranged from 10.0 ng/mL to 735.4 ng/mL. IGF-I was significantly correlated to GA ($p < 0.001$, $r = 0.358$; Fig. 1), maternal BW ($p = 0.001$, $r = 0.202$; Fig. 2), and maternal BMI ($p < 0.001$, $r = 0.263$; Fig. 3). Both maternal BW and BMI were related to GA (BW vs. GA, $p < 0.001$, $r = 0.603$; BMI vs. GA, $p < 0.001$, $r = 0.600$). Seemingly, maternal BW is significantly correlated to BMI ($p < 0.001$, $r = 0.905$; Table 2).

In the first trimester (GA < 13 weeks), 37 blood samples were collected and serum levels of IGF-I ranged from 14.2 ng/mL to 215.1 ng/mL, with an average of 93.8 ± 44.2 ng/mL. There was no significant correlation between maternal serum levels of IGF-I with early GA ($p = 0.241$, $r = 0.221$), maternal BW ($p = 0.597$, $r = 0.101$), and maternal BMI ($p = 0.717$, $r = 0.069$). Nevertheless, maternal BW was correlated with BMI ($p < 0.001$, $r = 0.809$), but neither was

Table 1
Demographic data of patients.

	Average (range)
No.	114
Age, y	29.9 ± 4.0 (19–40)
Gravidity	2.3 ± 1.2 (1–7)
Parity	0.7 ± 0.7 (0–3)
Blood tests, samples	2.8 ± 1.3 (1–5)
Maternal body height, cm	159.8 ± 5.0 (147–170)
Preconceptional body weight, kg	52.3 ± 7.1 (39.5–81.3)
Preconceptional body mass index, kg/m^2	20.5 ± 2.7 (15.4–34.3)
Body weight at delivery, kg	67.1 ± 7.9 (49.0–92.0)
Body mass index at delivery, kg/m^2	26.3 ± 3.0 (19.5–37.9)
Gestational age at delivery, wk	38.8 ± 1.3 (37–42)
Delivery methods	
NSD	82
C/S	32
Newborn sex	
Male	55
Female	59

C/S = cesarean section; NSD = normal spontaneous delivery.

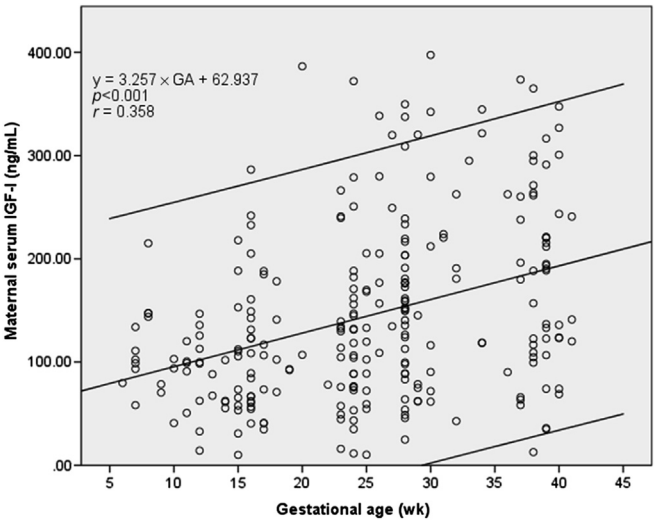

Fig. 1. Relationship between maternal serum insulin-like growth factor-I and gestational age (GA) throughout the whole pregnancy.

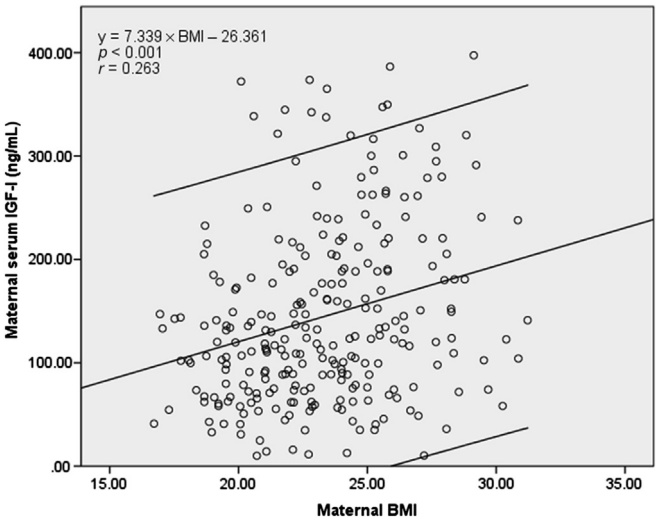

Fig. 3. Relationship between maternal serum insulin-like growth factor-I and maternal body mass index (BMI) throughout the whole pregnancy.

correlated with early gestation (BW vs. GA, $p = 0.235$, $r = 0.224$; BMI vs. GA, $p = 0.735$, $r = 0.064$; Table 2).

One hundred and ninety-one samples were obtained during the second trimester (defined by GA >12 weeks and <29 weeks). Maternal serum levels of IGF-I ranged between 10.0 ng/mL and 548.9 ng/mL. The mean value was 145.7 ± 104.6 ng/mL. A significant correlation was found between maternal serum levels of IGF-I and GA, with $p = 0.001$ ($r = 0.272$; Fig. 4). Although, IGF-I was not correlated with maternal BW ($p = 0.123$, $r = 0.126$), it was significantly related to maternal BMI ($p = 0.018$, $r = 0.192$; Fig. 5). At the same time, maternal BW was not only correlated with BMI ($p < 0.001$, $r = 0.860$), but also related to GA ($p < 0.001$, $r = 0.428$). Maternal BMI was significantly correlated with GA as well ($p < 0.001$, $r = 0.474$; Table 2).

There were 104 blood samples obtained in the third trimester. The IGF-I levels ranged between 11.2 ng/mL and 735.4 ng/mL with a mean of 202.5 ± 140.8 ng/mL. Serum IGF-I was not related to GA ($p = 0.818$, $r = 0.026$), maternal BW ($p = 0.612$, $r = 0.058$), or maternal BMI ($p = 0.662$, $r = 0.050$), although maternal BW was significantly related to both BMI ($p < 0.001$, $r = 0.838$) and GA ($p = 0.017$, $r = 0.267$). Significant correlation was also found between maternal BMI and GA ($p = 0.023$, $r = 0.256$; Table 2).

Comparison of maternal serum IGF-I among the three trimesters revealed the highest level of significance in the third trimester (1st vs. 2nd, $p < 0.001$, 95% confidence interval (CI) = −70.17 to −28.22; 1st vs. 3rd, $p < 0.001$, 95% CI = −138.02 to −76.94; 2nd vs. 3rd, $p < 0.001$, 95% CI = −88.86 to −27.71; Table 3).

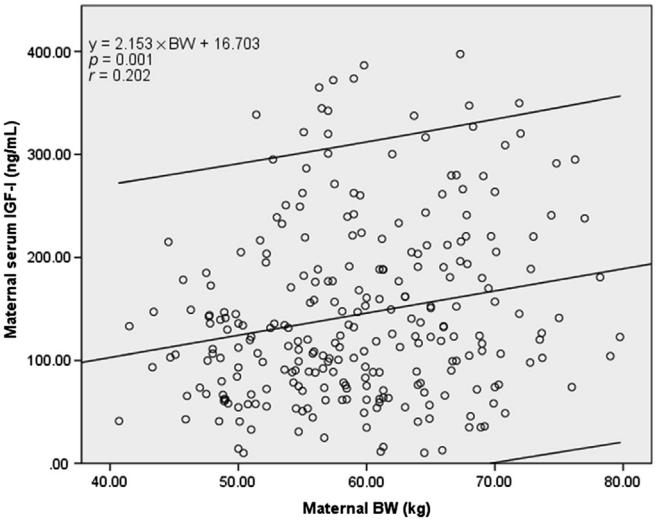

Fig. 2. Relationship between maternal serum insulin-like growth factor-I and maternal body weight (BW) throughout the whole pregnancy.

4. Discussion

Previous reports have discussed the relationship between neonatal outcomes, such as preterm birth, intrauterine growth restriction, or pregnancy-induced hypertension, and maternal serum IGF-I, IGF binding proteins (IGFBPs), IGF-I binding protein receptors.[11,12] However, the changes in levels of maternal serum IGF-I during pregnancy have seldom been mentioned. Holmes et al[11] reported a significant increase in maternal IGF-I and IGFBP-3 with advancing GA, and in cases of fetal growth restriction, maternal IGF-I was significantly lower ($p = 0.001$). Compared with that study, our sample size was larger and yielded more convincing results. Similar results were found by Wang et al[9] showing the highest significant maternal serum IGF-I during the third trimester. Nevertheless, the linear correlations between IGF-I and GA as well as maternal anthropometry were not shown.

Klauwer et al[12] presented the relationship between maternal serum levels of total IGF-I, free IGF-I, IGFBPs, and fetal or newborn growth in 1997. Free IGF-I has a direct effect on target tissues or cells. The methodology in this study used a two-site immunoradiometric assay to detect IGF-I in serum

Table 2
Inter-relationships of maternal serum IGF-1, BMI, BW, and GA during the three trimesters and throughout the whole pregnancy.

	First trimester		Second trimester		Third trimester		Whole pregnancy	
	p	*r*	*p*	*r*	*p*	*r*	*p*	*r*
IGF-1 vs. GA	0.241	0.221	0.001	0.272	0.818	0.026	<0.001	0.358
IGF-1 vs. BW	0.597	0.101	0.123	0.126	0.612	0.058	0.001	0.202
IGF-1 vs. BMI	0.717	0.069	0.018	0.192	0.662	0.050	<0.001	0.263
BW vs. GA	0.235	0.224	<0.001	0.428	0.017	0.267	<0.001	0.603
BMI vs. GA	0.735	0.064	<0.001	0.474	0.023	0.256	<0.001	0.600
BMI vs. BW	<0.001	0.809	<0.001	0.860	<0.001	0.838	<0.001	0.905

The values were compared by linear regression analysis.
BMI = body mass index; BW = body weight; GA = gestational age; IGF = insulin-like growth factor.

samples.[10] Hence, all the detected IGF-I was free form; therefore, additional detection of IGFBPs or total IGF-I was unnecessary.

Although a significant correlation between GA and maternal serum levels of IGF-I was found throughout pregnancy, there was no significant correlation between them in the first trimester. During this period, patients usually have sleep disturbance, dizziness, breast engorgement, headache, and gastrointestinal discomfort such as nausea, vomiting, and changes in appetite.[13] Consequently, major BW change in pregnant women during the first trimester is not commonly seen. The embryonic size and chorion frondosum do not have apparent increments in the first trimester, and maternal total body mass does not usually increase. As a result, maternal serum levels of IGF-I do not correlate with GA or maternal BW in the first trimester.

Normally the greatest change in maternal BW is seen during the second trimester, resulting from improved appetite. It has been observed that there is an apparent increase in body mass and blood volume, hyperplasia of adipose tissue and mammary glands,[1] reinforcement of the skeletomuscular system,[14] and positive effects on other organs.[15] During this stage of pregnancy, there is additional fetal weight and placental mass increase with advancing GA. It has been noted that IGF-I is involved in these changes. Data from our present study support the significant correlation of maternal serum IGF-I with GA, maternal BW, as well as BMI in the second trimester of pregnancy. This finding is similar to the study performed by Clapp et al[16] in 2004 in which a robust relationship was noted between the increase in placental mass, neonatal fat mass, and maternal IGF-I levels after 16 weeks. A similar result was also found by Chellakooty et al[17] in their longitudinal study of intrauterine growth and placental growth hormone-insulin-like growth factor 1 axis in maternal circulation. They disclosed a highly significant association between the increase in placental growth hormone and the increase in IGF-I along with advancing GA.[17]

In the third trimester, although maternal BW and BMI correlated with GA, there was no significant relationship between maternal IGF-I and GA. At the same time, maternal BW and BMI were not correlated with maternal serum IGF-I. It is difficult to explain the relationship among these factors (IGF-I, maternal BW, BMI, and GA) in this period of gestation. This phenomenon may be caused by the catabolic effect of maternal adipose tissue and is probably due to the dilutional effect from expanded maternal plasma volume in the third trimester. However, further studies are needed to confirm this.

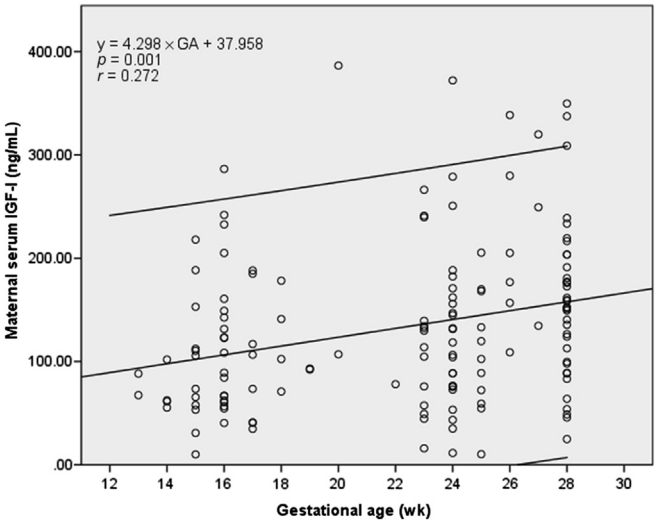

Fig. 4. Relationship between maternal serum insulin-like growth factor-I and gestational age during the second trimester.

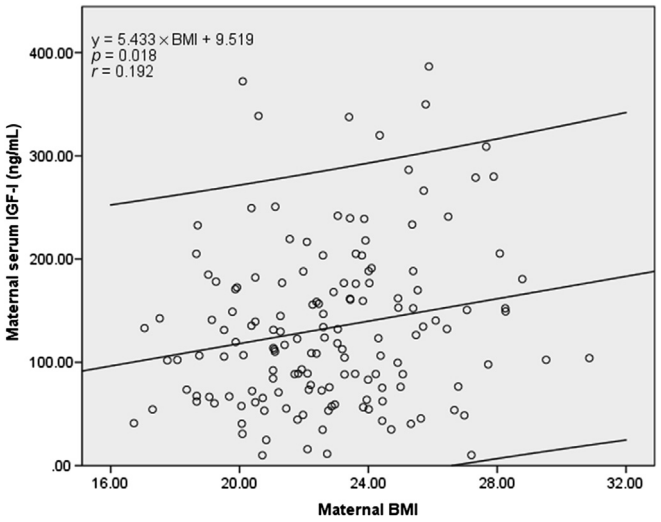

Fig. 5. Relationship between maternal serum insulin-like growth factor-I and maternal body mass index (BMI) during the second trimester.

Table 3
Comparisons of maternal IGF-I among the three trimesters with *t* test.

Trimester	*p*	95% CI
1st vs. 2nd	<0.001	−70.2, −28.22
1st vs. 3rd	<0.001	−138.02, −76.94
2nd vs. 3rd	<0.001	−88.86, −27.71

CI = confidence interval; IGF = insulin-like growth factor.

In conclusion, our study was able to identify the relationship between maternal IGF-I and GA through the entire course of pregnancy, showing the highest level of significance in the third trimester. It should also be noted that maternal IGF-I was significantly related to BW and BMI throughout pregnancy.

Acknowledgments

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