

Maternal serum concentrations of insulin-like growth factor (IGF)-I and IGF binding protein-1 before and during pregnancy in relation to maternal body weight and composition and infant birth weight

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Maternal nutritional status, e.g. body weight and composition, is associated with fetal growth. It has been suggested that the insulin-like growth factor (IGF) system may be a mediator of this relationship. In twenty-three healthy Swedish women, we studied (1) the relationships before and during pregnancy between maternal serum concentrations of IGF-I and IGF binding protein-1 (IGFBP-1) and maternal body weight and composition; (2) interactions between serum concentrations of IGF-I (before and in early pregnancy) and maternal nutritional status in relation to infant birth weight. We found that serum IGF-I during pregnancy was positively correlated with maternal body weight (r 0.47–0.56) and fat-free body weight (r 0.61–0.65), whereas serum IGFBP-1 was negatively correlated with maternal body weight (r –0.44 to –0.69) and body fat (r –0.64 to –0.76) before and during pregnancy. Women with a lower body fat content (%) before pregnancy had greater increases in serum IGFBP-1 during pregnancy than women with a higher prepregnant body fat content (%). In addition, significant fractions of the variation in corrected infant birth weight were explained by variables related to the maternal nutritional status when these were combined with serum concentrations of IGF-I in gestational week 14 (adjusted r^2 0.25–0.44, $P=0.001$ –0.021), but not when they were combined with such concentrations before pregnancy (adjusted r^2 0.11–0.12, $P=0.105$ –0.121). These results suggest mechanisms by which the IGF system may be a mediator between maternal nutritional status and fetal growth.

Insulin-like growth factor-I: Insulin-like growth factor binding protein-1: Body fat: Fat-free body weight: Infant birth weight

The association between maternal nutritional status and fetal growth is well known. For example, the weight, BMI and fat content of the maternal body correlate positively with infant birth weight^(1,2). The maternal insulin-like growth factor (IGF) system has been suggested to be a mediator between maternal nutritional status and fetal growth⁽³⁾, because it is affected by nutritional status⁽⁴⁾ and influences placental development, function and nutrient transfer^(5,6), as well as maternal retention of nutrients⁽⁷⁾. This system includes the ligands IGF-I and IGF-II (IGF) and six binding proteins (IGF binding protein (IGFBP)-1–6). Free IGF have either immediate anabolic insulin-like effects on protein and carbohydrate metabolism or long-term effects on cell replication and differentiation⁽⁸⁾. In the circulation, most IGF are bound to binding proteins. This provides a mechanism to regulate the biological activity of the free IGF. Binding protein IGFBP-3 binds 80–90% of all IGF in serum. However, during pregnancy, proteases degrade IGFBP-3^(9–12), which decreases its affinity for IGF. This may increase the metabolic action of IGF-I on target cells such as those in the placenta,

possibly stimulating fetal growth. IGFBP-1 binds only about 2% of serum IGF⁽¹³⁾, but it is important for the short-term regulation of IGF activity, and has a role in blood glucose regulation⁽¹⁴⁾.

Reports of relationships between serum concentrations of IGF-I in pregnant women and birth weight of their babies are contradictory as some studies^(15–18), but not all⁽¹⁹⁾, have shown such relationships to be positively significant. In a previous study on healthy, pregnant, Swedish women, we found serum concentrations of IGF-I to be significantly correlated with fetal weight in the third trimester⁽¹²⁾. In these women, we also observed a decrease in the serum concentration of IGF-I in the very beginning of pregnancy. Women with a high concentration before pregnancy had a more pronounced decrease in this concentration than women with a low concentration before pregnancy⁽¹²⁾. Furthermore, we identified significant negative correlations between the maternal serum concentration of IGFBP-1 in gestational weeks 20, 32 and 35 and birth weight of infants⁽¹²⁾. A few studies have investigated relationships in pregnant and

Abbreviations: IGF, insulin-like growth factor; IGFBP, IGF binding protein.

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non-pregnant women between serum concentrations of IGF-I and IGFBP-1 and body weight, BMI or body composition. In non-pregnant women of reproductive age, the results are contradictory^(20–22). Thus, Jernström & Olsson⁽²¹⁾ reported a positive correlation between IGF-I serum concentrations and body weight, whereas others have reported that such concentrations are unrelated to body fat⁽²²⁾ and BMI⁽²⁰⁾. In pregnant women, Hills *et al.*⁽¹⁹⁾ reported a significant positive relationship between serum IGF-I and body weight. Comparable studies for IGFBP-1 demonstrate that the serum concentration of this protein is negatively related to body weight, BMI and/or the body fat content of women before⁽²²⁾ as well as during pregnancy^(19,23,24). However, to understand whether the maternal IGF system represents a mediator between maternal nutritional status and fetal growth, further studies of the relationships between serum concentrations of IGF-I and IGFBP-1 and nutritional status in terms of body weight and composition are needed in women.

Our previous study in healthy Swedish women included longitudinal assessments, before and during pregnancy, of an extensive set of variables including components of the IGF system as well as accurate measures of body composition. This dataset has been used in a number of studies on pregnancy in relation to, for example, energy metabolism^(25,26), body composition^(26–28) and serum concentrations of hormones^(25,29), including the IGF system⁽¹²⁾. In the present study, we took advantage of the longitudinal design when testing the hypothesis that the maternal IGF system may act as a mediator between maternal nutritional status and fetal growth. This was carried out, first, by investigating relationships, before and during pregnancy, between maternal serum concentrations of IGF-I and IGFBP-1 and maternal body weight and composition. In addition, we explored how concentrations of IGF-I, before and in early pregnancy, may impact infant birth weight when combined with maternal body weight and composition.

Subjects and methods

Subjects

Thirty-nine women planning pregnancy were recruited via the health care system or via advertisements in a local newspaper in the city of Linköping. Twenty-three of these became pregnant and completed the study. The women were all healthy non-smokers with no eating disorders and with

a BMI before conception ranging from 18 to 39. Before pregnancy, the women had normal concentrations of blood glucose and serum insulin, and none was diagnosed with gestational diabetes⁽¹²⁾. Data regarding their serum insulin concentrations and insulin resistance before and during pregnancy have been published previously⁽²⁹⁾. Relevant data regarding the women and their infants are given in Table 1. Body weight and composition of the women before and during pregnancy have been described previously⁽²⁶⁾. Infant birth weight and serum IGF-I and IGFBP-1 data have been reported by Olausson *et al.*⁽¹²⁾. Each woman delivered one healthy infant after 280 (SD 10; range 256–296) d of pregnancy. At birth, the infants weighed 3740 (SD 510; range 2600–4540) g and were 51 (SD 2; range 46–57) cm long.

Study outline

The measurements were done before conception and at weeks 14 and 32 of pregnancy. Women arrived early in the morning after an overnight fast for measurements of body weight, blood collection and administration of a dose of ²H. Stage of gestation was assessed using ultrasound, generally at weeks 12–14⁽³⁰⁾. Infant body weight and length were measured just after delivery. The study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Research Ethics Committee of the University of Linköping, Sweden. Verbal informed consent, witnessed and formally recorded, was obtained from all subjects.

Body composition and anthropometry

Women. Body weight was recorded using a digital balance (KCC150; Mettler-Toledo, Albstadt, Germany). Fat-free body weight was calculated from total body water estimated using ²H dilution as described previously⁽²⁷⁾. Total body water was divided by the appropriate hydration fraction (before pregnancy, 0.718; week 14, 0.722; and week 32, 0.747) to assess fat-free body weight⁽²⁷⁾. Body fat was calculated as body weight minus fat-free body weight.

Infants. Body weight was recorded using an electronic column scale, and length using a length board. These measurements were obtained from hospital records. Corrected infant birth weight, to account for differences in birth weight due to gestational age and sex, was calculated as recorded birth weight times the ratio of recorded birth weight and mean

Table 1. Characteristics of women before pregnancy and in gestational weeks 14 and 32 (Mean values, standard deviations and ranges, *n* 23)

Women	Before pregnancy			Week 14			Week 32		
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
Body weight (kg)	67.3	12.6	51.0–95.0	69.7	12.6	51.9–95.4	79.1	13.0	58.3–101.2
Fat-free body weight (kg)	44.6	5.5	35.3–52.9	45.7	6.0	36.2–55.5	52.2	5.9	41.2–60.6
Body fat (%)	32.6	7.8	17.2–49.8	33.5	7.1	23.0–51.3	33.3	7.3	16.9–47.8
Body fat (kg)	22.6	8.9	8.9–43.1	24.0	8.9	12.6–46.0	27.0	9.5	11.3–46.0
IGF-I (µg/l)	273	90	150–460	183	45	87–262	391	148	193–709
IGFBP-1 (µg/l)	21	12	7–56	145	61	57–296	140	59	42–268

IGF-I, insulin-like growth factor-I; IGFBP-1, IGF binding protein-1.

birth weight of healthy Swedish newborns with the appropriate gestational age and sex⁽³¹⁾.

Analyses of blood samples

Blood was collected by cubital vein puncture. Samples were kept at +4°C for a maximum of 4 h before being centrifuged at 1500g for 10 min. Serum was harvested and stored at -70°C. Total IGF-I in serum was measured using RIA after acid-ethanol extraction⁽³²⁾. The intra-assay CV were 4.3% at 149 µg/l and 8.6% at 526 µg/l, while the inter-assay CV was 11%. IGFBP-1 was analysed using RIA as described by Póvoa *et al.*⁽³³⁾. The intra-assay CV were 8.4% at 18 µg/l and 6.0% at 90 µg/l. The inter-assay CV was 10%.

Statistical analyses

Results presented are means and standard deviations. Simple linear regression and correlation analyses were used. To identify significant differences between slopes of regression lines, we evaluated whether there was an interaction between an independent variable and stage of gestation in the effect on the dependent variable. This evaluation was carried out using multiple regression analysis including an interaction term between the independent variable and stage of gestation. Multiple regression analysis was also used to explore how corrected infant birth weight varied in response to two independent variables (serum IGF-I concentration in combination with body weight and body fat). $P \leq 0.05$ was considered statistically significant. Statistical analyses were carried out using Statistica 6.1 (StatSoft, Inc., Tulsa, OK, USA) and SPSS (version 6.0; Chicago, IL, USA).

Results

Serum concentrations of insulin-like growth factor-I and insulin-like growth factor binding protein-1 in relation to maternal body weight and composition

Correlation coefficients for relationships between serum concentrations of IGF-I and variables describing body weight and composition are given in Table 2. Before pregnancy, no correlations were found between serum IGF-I and body weight, body fat (kg and %) or fat-free body weight (kg). However, in gestational weeks 14 and 32, significant positive correlations with serum IGF-I were found for body weight and fat-free body weight, while body fat (kg and %) was not correlated with serum IGF-I on these measurements. Table 2 also shows the corresponding correlations for serum concentrations of IGFBP-1. Before pregnancy and in gestational weeks 14 and 32, serum concentrations of IGFBP-1 were significantly correlated with body weight and body fat (kg and %), but not with fat-free body weight. Fig. 1 shows the regression lines obtained when IGFBP-1 in serum is regressed on body fat (%) in gestational week 14 and before pregnancy (Fig. 1(a)) and on body fat (%) in gestational week 32 and before pregnancy (Fig. 1(b)). The slope of the regression line obtained before pregnancy was significantly different from the corresponding value obtained in gestational week 14 ($P=0.0001$) as well as from the corresponding value obtained in gestational week 32 ($P=0.0001$). In addition,

Table 2. Correlation coefficients (*r*) and their probabilities (*P*) for linear relationships obtained when serum concentrations of insulin-like growth factor-I (IGF-I) or IGF binding protein-1 (IGFBP-1) are regressed on body weight, body fat and fat-free body weight, respectively*

	IGF-I (µg/l)		IGFBP-1 (µg/l)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Before pregnancy				
Body weight (kg)	0.08	>0.05	-0.44	0.033
Body fat (kg)	-0.08	>0.05	-0.64	0.001
Body fat (%)	-0.20	>0.05	-0.72	0.0001
Fat-free body weight (kg)	0.29	>0.05	0.08	>0.05
Gestational week 14				
Body weight (kg)	0.56	0.005	-0.63	0.001
Body fat (kg)	0.36	>0.05	-0.70	0.0002
Body fat (%)	0.11	>0.05	-0.69	0.0002
Fat-free body weight (kg)	0.65	0.001	-0.30	>0.05
Gestational week 32				
Body weight (kg)	0.47	0.024	-0.69	0.0003
Body fat (kg)	0.27	>0.05	-0.76	0.00003
Body fat (%)	0.07	>0.05	-0.74	0.00005
Fat-free body weight (kg)	0.61	0.002	-0.30	>0.05

* Results were obtained from twenty-three healthy women before pregnancy and in gestational weeks 14 and 32.

Fig. 2 illustrates the relationships obtained when the serum concentrations of IGFBP-1 during pregnancy minus the corresponding values obtained before pregnancy were regressed on body fat (%) before pregnancy. These regression lines were significant with negative slopes when values in gestational week 14 (a) as well as in gestational week 32 (b) were used.

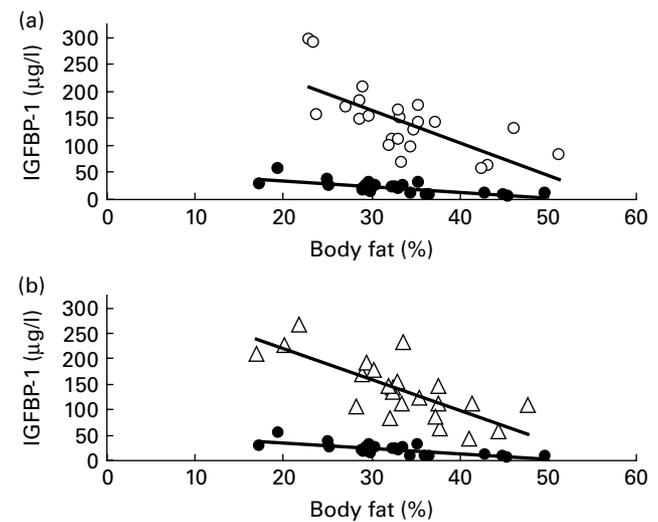


Fig. 1. Serum concentration of insulin-like growth factor binding protein-1 (IGFBP-1; µg/l) (*y*) regressed on body fat (%) (*x*) (a) before pregnancy (●) and in gestational week 14 (○; *n* 23), and (b) before pregnancy (●) and in gestational week 32 (△; *n* 23). Regression equations are as follows: $y = 56.4 - 1.1x$, $r = 0.720$, $P = 0.0001$ (before pregnancy); $y = 346.0 - 6.0\ddagger x$, $r = 0.693$, $P = 0.0002$ (gestational week 14); $y = 333.8 - 6.0\ddagger x$, $r = 0.743$, $P = 0.00005$ (gestational week 32). † The slope of the regression line was significantly different from the corresponding value before pregnancy assessed after identification of an interaction between body fat (%) and stage of gestation in the effect on the serum concentration of IGFBP-1 ($P = 0.0001$). This assessment was made by means of multiple regression analysis, where an interaction term between body fat (%) and stage of gestation was included.

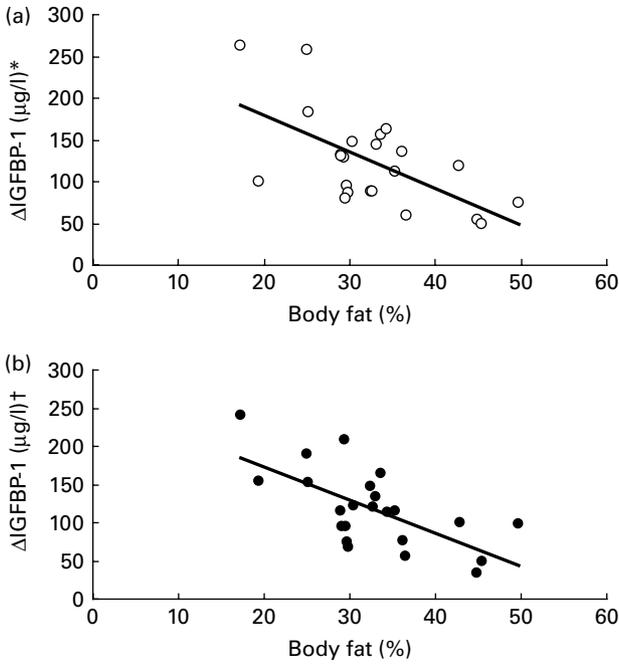


Fig. 2. Difference in insulin-like growth factor binding protein-1 (Δ IGFBP-1) serum concentrations ($\mu\text{g/l}$) (y) (a) between values obtained in gestational week 14 and before pregnancy (n 23), and (b) between values obtained in gestational week 32 and before pregnancy (n 23) regressed on body fat (%) before pregnancy (x). Regression equations are as follows: (a) $y = 267 - 4.4x$, $r = 0.613$, $P = 0.002$; (b) $y = 260 - 4.3x$, $r = 0.664$, $P = 0.001$. * Δ IGFBP-1: the serum concentration in gestational week 14 minus the corresponding concentration before pregnancy. † Δ IGFBP-1: the serum concentration in gestational week 32 minus the corresponding concentration before pregnancy.

Serum concentrations of insulin-like growth factor-I before pregnancy and in gestational week 14 and maternal body weight and composition in relation to corrected infant birth weight

Both maternal body weight (kg) and body fat content (kg) before pregnancy were significantly correlated with corrected infant birth weight (r 0.436, $P = 0.038$ and r 0.443, $P = 0.034$, respectively). Similarly, in gestational week 14, significant correlations were observed between maternal body weight (kg) and corrected infant birth weight (r 0.449, $P = 0.032$), as well as between the body fat content (kg) and corrected infant birth weight (r 0.438, $P = 0.037$). No significant correlations were observed between serum IGF-I ($\mu\text{g/ml}$) and corrected infant birth weight either before pregnancy (r 0.015, $P = 0.947$) or in gestational week 14 ($r = 0.174$, $P = 0.428$).

Table 3 shows adjusted r^2 for multiple linear relationships relating corrected infant birth weight (y) to two independent variables, including the serum concentration of IGF-I (either before pregnancy or in gestational week 14) and either maternal body weight or body fat content (before pregnancy or in gestational week 14). Combinations including IGF-I in gestational week 14 explained significant ($P = 0.001$ – 0.021) fractions of the variation in corrected infant birth weight (adjusted r^2 0.251–0.435), while combinations including IGF-I before pregnancy did not explain any significant ($P = 0.105$ – 0.121) fraction of this variation (adjusted r^2 0.109–0.122). Fig. 3 shows a graphical representation of two of the relationships given in Table 3. These relationships

Table 3. Multiple linear regression analyses relating corrected infant birth weight (dependent variable, y)* to two independent variables, including insulin-like growth factor-I (IGF-I) in maternal serum (before pregnancy or in gestational week 14) and a variable describing maternal body weight or body fat (n 23)

First independent variable	Second independent variable	Regression equation	Standard error of coefficients	Adjusted r^2 (P)
IGF-I before pregnancy ($\mu\text{g/l}$) (x_1)	Body weight (kg) before pregnancy (x_3)	$y = 1626.2 - 0.193x_1 + 35.13x_3$	2.15 for x_1 16.21 for x_3	0.109 (0.121)
	Body fat (kg) before pregnancy (x_4)	$y = 2706.48 + 0.527x_1 + 48.05x_4$	2.14 for x_1 21.62 for x_4	0.118 (0.110)
	Body weight (kg) in gestational week 14 (x_5)	$y = 1542.91 + 0.042x_1 + 34.19x_5$	2.13 for x_1 15.22 for x_5	0.122 (0.105)
	Body fat (kg) in gestational week 14 (x_6)	$y = 2544.51 + 0.842x_1 + 48.46x_6$	2.16 for x_1 21.82 for x_6	0.118 (0.110)
IGF-I in gestational week 14 ($\mu\text{g/l}$) (x_2)	Body weight (kg) before pregnancy (x_3)	$y = 2026.05 - 14.48x_2 + 67.84x_3$	21.82 for x_2 4.26 for x_3	0.435 (0.001)
	Body fat (kg) before pregnancy (x_4)	$y = 4096.94 - 9.07x_2 + 66.45x_4$	16.10 for x_2 4.21 for x_4	0.282 (0.014)
	Body weight (kg) in gestational week 14 (x_5)	$y = 2121.21 - 13.29x_2 + 61.01x_5$	21.32 for x_2 4.20 for x_5	0.415 (0.002)
	Body fat (kg) in gestational week 14 (x_6)	$y = 3936.91 - 8.145x_2 + 62.22x_6$	15.03 for x_2 4.21 for x_6	0.251 (0.021)

* Corrected infant birth weight was calculated as recorded birth weight times a ratio between recorded birth weight and mean birth weight of healthy Swedish newborns with the appropriate gestational age and sex⁽³¹⁾.

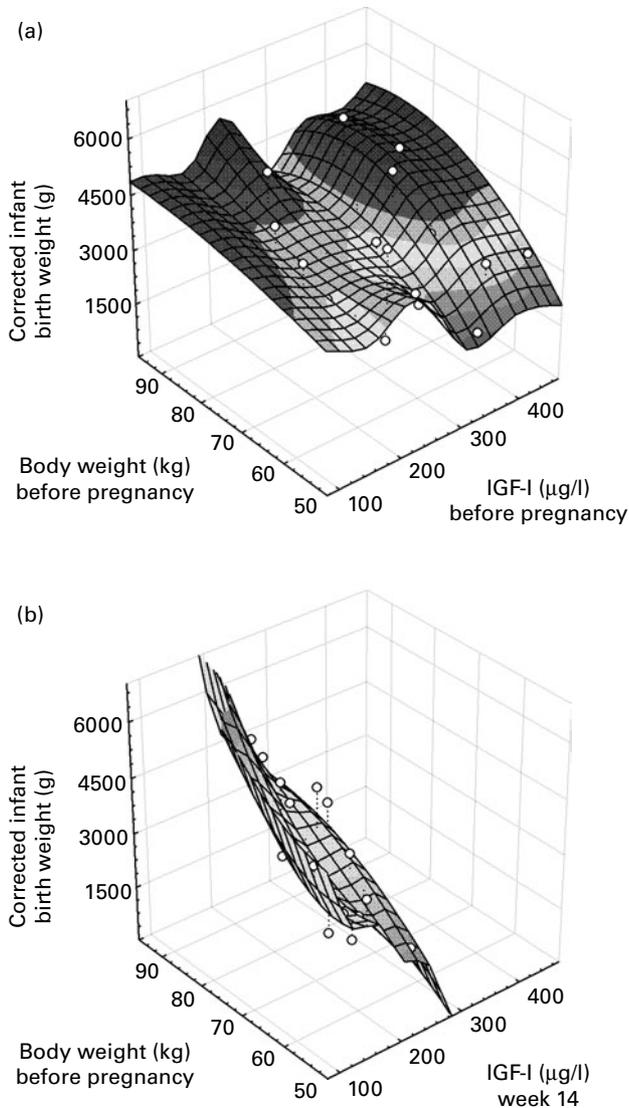


Fig. 3. A graphical representation of the relationships between corrected infant birth weight (g) (dependent variable) and the maternal serum concentration of insulin-like growth factor-1 (IGF-I; $\mu\text{g/l}$) (first independent variable) before pregnancy (a) or in gestational week 14 (b), and maternal body weight (kg) before pregnancy (second independent variable). Regression equations are given in Table 3.

show the effect on corrected infant birth weight of using the serum concentration of IGF-I before pregnancy (a) *v.* in gestational week 14 (b) as one of the two independent variables when body weight before pregnancy was the second independent variable.

Discussion

In a previous paper⁽²⁸⁾ based on the dataset that was the same as that used in the present study, we reported relationships between maternal body weight and composition and infant birth weight. In the present paper, we investigated whether the maternal IGF system has a role in mediating the kind of relationships observed in our previous study⁽²⁸⁾. Our dataset provided a unique opportunity to investigate this area for the following reasons: it has a longitudinal design and includes

measurements before conception and in early pregnancy, as well as information on infant birth weight. Furthermore, our body composition results are based on assessments of total body water using ^2H dilution and application of appropriate hydration factors, a procedure known to result in accurate estimates of body fat. A combination of these accurate and longitudinal data, thus, provided a unique opportunity to study interactions between maternal body weight and composition, the maternal IGF system and infant birth weight.

An intriguing observation is that the serum IGF-I concentration becomes correlated with maternal body weight and fat-free body weight after the serum concentration of IGF-I decreases during the first part of pregnancy. In addition, the multiple regression models presented in Table 3 and Fig. 3 suggest that lower concentrations of IGF-I in early pregnancy are favourable for fetal growth when combined with maternal body weight or fat content. A possible interpretation is that a regulatory activity is involved, originating in the product of conception with the purpose of controlling growth of the maternal body. Early pregnancy represents a period of balance between anabolism and catabolism, and it is important for the fetus that growth of the maternal body is maintained within appropriate limits. A certain proliferation of the maternal body is advantageous for the fetus, but if this growth becomes excessive, the fetus may be unable to compete successfully for available nutrients. It should be pointed out, however, that this interpretation certainly is speculative and requires confirmation. In this context, it is also relevant to note that an experimental study in animals has shown that maternal circulating concentrations of IGF-I from early gestation to mid-gestation may impact fetal growth and placental transport near term⁽⁵⁾.

Figs. 1 and 2 show that women with a low body fat content before pregnancy have higher increases during pregnancy in their serum concentrations of IGFBP-1 than women with a high body fat content before pregnancy. This is noteworthy since high serum concentrations of IGFBP-1 during the second half of pregnancy are associated with low birth weight⁽¹²⁾, and therefore also with slow fetal growth. This suggests the presence of a regulatory process responsible for maintaining a fetal growth rate appropriate to the nutritional status of the mother. It is possible that low serum concentrations of IGFBP-1 result in higher concentrations of free IGF-I, with the possible consequence being a stimulating effect on fetal growth via the stimulating actions of free IGF-I on the placenta. However, it is unlikely that this mechanism explains more than a part of the relationship between maternal serum IGFBP-1 concentrations and fetal growth rate since IGFBP-1 binds only about 2% of all IGF-I. Insulin and blood glucose also influence serum concentrations of IGFBP-1⁽¹⁴⁾, and therefore it is possible that the observed relationship between serum IGFBP-1 and fetal growth is due to the glucoregulatory effects of IGFBP-1 and its relationship to insulin. However, in our women, neither serum concentrations of insulin nor insulin resistance⁽²⁹⁾ was significantly correlated with corrected birth weight of their infants. In this context, it may be relevant to note that in our women, serum concentrations of insulin and insulin resistance were significantly correlated with body fat (%)⁽²⁹⁾. Insulin resistance during pregnancy is thought to promote fetal growth, since women with gestational diabetes tend to deliver infants with high birth weight⁽³⁴⁾. The mechanism behind the

enhanced fetal growth is thought to be increased exposure to all major fuel sources i.e. glucose, NEFA and amino acids⁽³⁵⁾. Franks *et al.*⁽³⁶⁾ recently reported that blood glucose concentrations are related to infant birth weight also in non-diabetic pregnant women. Hence, it is possible that the mechanisms explaining the relationships found in the present study regarding serum concentrations of IGFBP-1, the maternal body fat content and corrected infant birth weight are related to interactions between insulin, blood glucose and IGFBP-1.

One weakness of the present study is the small number of women studied. It is noteworthy, however, that their BMI before pregnancy and weight gain during pregnancy are quite typical for Swedish women of childbearing age, and our women are similar to many other such women in the Western countries. A potential problem with our small sample size is the risk for type II errors, e.g. a failure to identify existing relationships as significant. Using a simple linear regression model with twenty-three observations gives a power of 80% to identify a correlation coefficient of 0.55 as significant. All relationships identified as non-significant in Table 2 have correlation coefficients well below 0.55. This is also true for correlation coefficients obtained for the relationships between corrected infant birth weight and serum concentrations of IGF-I before pregnancy and in gestational week 14.

In conclusion, we have reported findings confirming and extending the statement that the IGF system has a role in mediating the effect of the maternal nutritional status on fetal growth. The present results provide new aspects on this role of the IGF system, and suggest that the mechanisms involved are complicated and interact in an intricate way. Studies in populations of pregnant women with different nutritional status may be valuable for increasing our understanding regarding the role of the IGF system in fetal growth regulation.

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