Insulin-Like Growth Factors (IGFs) and IGF-Binding Proteins (IGFBP-1, -2 and -3) in Diabetic Pregnancy: Relationship to Macrosomia

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Abstract. To evaluate the role of insulin-like growth factors (IGFs) and IGF-binding proteins (IGFBPs) in excessive fetal growth (macrosomia) in diabetic pregnancy, 84 insulin-treated diabetic mothers and their infants were tested for serum concentrations of IGF-I, IGF-II, and IGFBP-1, -2 and -3. These parameters were correlated with the birth weight of neonates and placental weight. IGF-I and II levels were determined by specific radioimmunoassays (RIAs) after serum samples were extracted with aid-ethanol. IGFBPs were measured by Western immunoblot with specific antibodies to the respective IGFBP species. Serum concentrations of both IGF-I and IGF-II in mothers with either IDDM or NIDDM increased with the gestational period, reached a plateau at the third trimester, and returned to non-pregnant levels within 7 days after delivery. These values were not different from those in normal mothers before and throughout pregnancy. As previously reported, IGF-I concentrations in cord serum of neonates born to diabetic mothers were (P<0.01) higher than those of newborns of normal mothers. Likewise, cord blood IGF-II levels were 2-fold higher in babies of diabetic mothers (P<0.001). Fetal IGF-I and IGF-II correlated with each other and with maternal HbA1c, and they positively correlated with either birth weight or placental weight. Cord IGFBP-3 concentrations were significantly higher in diabetic pregnancy, but IGFBP-2 concentrations were not different from those in normal pregnancy. Cord IGFBP-1 concentrations were significantly higher only in babies of mothers with IDDM. None of these cord IGFBP concentrations correlated with birth weight or placental weight. The data suggest that fetal IGF-II, like IGF-I, is involved in fetal and placental growth in diabetic pregnancy. The role of IGFBPs remained to be determined.

Key words: Diabetic pregnancy, Macrosomia, Insulin-like growth factor-I, -II (IGF-I, IGF-II), Insulin-like growth factor-binding proteins (IGFBP-1, -2, -3)

INSULIN-LIKE growth factors (IGFs), which include IGF-I and IGF-II, are a class of GH-dependent serum growth factors that are structurally related to proinsulin [1]. Both IGFs circulate in the blood bound to specific, high-affinity IGF-binding proteins (IGFBPs), forming IGF-BP complexes. At least six distinct classes of IGFBPs (IGFBP-1–IGFBP-6) have been identified. They all bind both IGF-I and IGF-II, but not insulin, and differ in terms of function, tissue distribution and regulation [2]. The physiological significance of IGFBPs is not completely understood, but they may provide a storage pool and prolong the biological half-life of the IGFs in circulation. They may also inhibit the actions of the IGFs by complexing with the IGFs, or potentiate the actions of the growth factors, depending on the type of IGFBP or target cell.

It is now established that IGF-I plays a major role in both fetal and postnatal growth in human.
In contrast, the role of IGF-II in human fetal growth is still not clear, although IGF-II has been shown to be essential to normal intrauterine growth in rodents [3, 4]. Several studies have shown that maternal serum IGF-II levels increased in late pregnancy [5–8], and in a study by Bennet et al. [9], cord IGF-II levels were shown to positively correlate with the birth weight of infants born to normal mothers. Furthermore, Samaan et al. [10] reported higher IGF-II in large-for-gestational-age neonates than in average-for-gestational neonates. These studies suggest that IGF-II is directly or indirectly involved in human fetal growth. On the other hand, a number of studies failed to detect a positive correlation of umbilical cord IGF-II with birth weight in non-diabetic pregnancy [7, 11–14].

Macrosomia is frequently seen in babies born to diabetic mothers. Although the mechanism is not completely clear, fetal hyperglycemia and hyperinsulinemia are the hallmark of such infants in utero [15]. In addition, earlier studies [5, 16] have shown that the concentration of IGF-I in cord blood is higher in babies born to diabetic mothers than in newborns of normal mothers, suggesting that IGF-I, as well as insulin, is a factor responsible for the development of macrosomia. It is not clear, however, whether IGF-II is also involved in fetal macrosomia, although Hall et al. [17] and Gelato et al. [6] have previously shown that the IGF-II concentration in cord blood is higher in babies born to diabetic mothers. These observations are inconsistent with a study by Susa et al. [18] which failed to show any difference between newborns of normal and diabetic mothers in the cord IGF-I or IGF-II levels.

Few data are available on the levels of IGFBP-1, -2 and -3 in cord blood in babies born to diabetic mothers. We therefore attempted to determine whether maternal or fetal IGFs and IGFBPs are related to fetal growth in diabetic pregnancy.

### Research Design and Methods

#### Subjects

Ten normal pregnant and 84 diabetic pregnant women (41 IDDM, 43 NIDDM) and their babies were included in the present study. The profiles of the subjects are summarized in Table 1. There was no significant difference between the normal pregnant women and the diabetic women in mean age. All the diabetic mothers were treated with insulin, and serum HbA1c concentrations were 3.9–9.2% at the time of delivery. Fasting serum samples from the pregnant women were collected at blood sampling for routine antenatal care, at the time of delivery and within 7 days after delivery, with informed consent. Umbilical venous blood samples were obtained by direct puncture of the cord vein. Serum IGF-I and IGF-II were determined throughout the gestation period in available serum samples from 36 (18 IDDM and 18 NIDDM) diabetic patients. The 10 normal, and randomly selected 20 diabetic pregnant women (10 NIDDM and 10 IDDM) and their babies were studied for IGFBP-1, -2 and -3 concentrations in sera obtained at the time of delivery. All samples were stored at -20 °C until analysis.

#### Methods

RIA for IGF-I and IGF-II: Human recombinant human IGF-I was from Fujisawa Pharmaceuticals (Osaka, Japan). Monoclonal antibodies to IGF-I and 125I-IGF-I (specific activity 37TBq/mmol) were purchased from Amersham International Plc (Buckinghamshire, England). Human recombinant IGF-II and monoclonal antibody to IGF-II were obtained from Amano Pharmaceuticals (Nagoya, Japan). 125I-IGF-II (specific activity: 74TBq/mmol)

### Table 1. Profile of normal and diabetic pregnant women

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Gestational period (months)</th>
<th>HbA1c (%)</th>
<th>Placental weight (g)</th>
<th>Birth weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=10)</td>
<td>28.6 ± 2.0</td>
<td>39.2 ± 0.5</td>
<td>ND</td>
<td>ND</td>
<td>2990 ± 203</td>
</tr>
<tr>
<td>NIDDM (n=41)</td>
<td>30.9 ± 5.1</td>
<td>38.5 ± 1.4</td>
<td>6.3 ± 1.2</td>
<td>621 ± 142</td>
<td>3266 ± 486*</td>
</tr>
<tr>
<td>IDDM (n=43)</td>
<td>28.8 ± 3.6</td>
<td>38.4 ± 1.8</td>
<td>5.9 ± 1.3</td>
<td>635 ± 129</td>
<td>3293 ± 571*</td>
</tr>
</tbody>
</table>

The values are the mean ± SD. *difference from normal group is significant (P<0.05). ND: not determined.
was purchased from Amersham. Serum samples were extracted with acid-ethanol as previously reported [19]. Extracted samples were lyophilized and diluted to desired concentrations with assay buffer (50 mMTris/HCl, pH 7.4) and assayed for IGF-I and IGF-II, as reported from our laboratory [20, 21]. Antibody-bound labeled IGF-I or IGF-II was separated from unbound IGF-I or IGF-II by adding ice-cold polyethylene glycol 6000 (final concentration: 12.5%), with 0.2% bovine gamma globulin as the carrier. The sensitivity of the assay was 30 pg for IGF-I and 20 pg for IGF-II. Interassay coefficients of variation for these assays were 5% for IGF-I and 11% for IGF-II.

Western immunoblotting: Relative amounts of IGFBP-1, -2 and -3 were determined by Western immunoblotting as described by Hossenlopp et al. [22]. Briefly, the serum sample (2–6 µl) was diluted in 0.062 mol/L Tris-HCl (pH 6.8) in the presence of 2.0% sodium dodecyl sulfate, 10% glycerol, and 0.5% bromphenol blue (sample buffer). After heating for 5 min at 95 °C, the samples were subjected to the 10% gel SDS-gel electrophoresis in the absence of a reducing agent with a constant current (40 mA/gel). The gels were electroblotted onto a nitrocellulose sheet (Bio-Rad) in transfer buffer at 15 °C and 80 V for 2 h. The paper was blocked with 5% skim milk and then incubated with polyclonal antibody (Update Biotechnology Incorporated, NY) to human IGFBP-1 (dilution 1:1000), IGFBP-2 (1:2000) or IGFBP-3 (1:1000). After extensive washing of the sheet, the immune complexes were visualized by means of an enhanced chemiluminescence system (Amersham Japan, Tokyo). The bands on X-ray films were scanned with a densitometer and the integrated optic densities were measured for each band. The relative amount of IGFBP-1, -2 and -3 were determined with reference standard serum and expressed in arbitrary units.

Statistics
Statistical analysis of differences between groups was carried out by Student's t-test. The difference was considered significant when the P value was less than 0.05.

Results

Serum IGF in diabetic women during pregnancy
Both IGF-I and IGF-II levels in serum were determined in the normal and diabetic women throughout gestation and in their neonates. The concentrations of serum IGF-I before pregnancy in normal women were not significantly different from those in patients with IDDM or NIDDM. As shown in Table 2, the IGF-I levels in the maternal serum were significantly (P<0.05) higher than those before pregnancy in both normal and diabetic women, and the values returned to the pre-pregnant levels within 7 days after delivery. Serum levels of IGF-II in the majority of patients with either IDDM or NIDDM increased with the gestational weeks and reached a plateau at the third trimester, then returned to the pre-pregnant levels within 7 days after delivery, as in the normal group (Fig. 1).

IGF-I and IGF-II levels in cord blood
Confirming previous reports, the IGF-I and IGF-II concentrations in cord blood were significantly (P<0.01) lower than the maternal values in serum obtained at delivery in all three groups (Table 2). The IGF-I levels in the cord blood of infants born to both IDDM and NIDDM mothers were significantly (P<0.01) higher than those of newborns of

| Table 2. Serum IGF-I and IGF-II concentrations in mothers and their infants |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | Before pregnancy            | At delivery                 | Postpartum                  | Fetal                       |
|                            | IGF-I | IGF-II | IGF-I | IGF-II | IGF-I | IGF-I | IGF-I | IGF-II |
| Normal                     | 11.1 ± 2.4 | 54.0 ± 17.4 | 16.0 ± 6.6* | 92.0 ± 28.3** | 10.3 ± 4.1 | 61.4 ± 14.4 | 1.7 ± 0.9 | 8.3 ± 2.0 |
| NIDDM                      | 11.1 ± 3.4 | 61.4 ± 16.7 | 16.9 ± 6.3* | 92.4 ± 33.0** | 12.0 ± 4.7 | 62.3 ± 20.1 | 4.7 ± 2.9† | 13.0 ± 5.0 |
| IDDM                       | 8.7 ± 2.9 | 53.3 ± 18.4 | 15.1 ± 6.3** | 93.4 ± 32.0** | 9.6 ± 5.1 | 58.6 ± 19.7 | 4.3 ± 3.7‡ | 16.9 ± 5.36 |

The values are the mean ± SD expressed as nmol/L. *P<0.05 vs. before pregnancy, **P<0.01 vs. before pregnancy. †P<0.05 vs. postpartum. ‡P<0.01 vs. normal. §P<0.001 vs. nonpregnant levels.
normal mothers. Cord IGF-II levels were also significantly (P<0.001) higher in babies born to diabetic mothers. As shown in Fig. 2, there was a highly significant correlation between the cord blood IGF-I and IGF-II levels (r=0.772, P<0.001), but no correlation was found between the IGF levels in maternal and postpartum sera. There was a positive correlation between maternal HbA1c and cord IGF-I (r=0.6, P<0.001) or IGF-II (r=0.374, P<0.001) levels, as shown in Fig. 3.

Maternal and fetal IGFBP

We measured the serum concentrations of IGFBPs in the normal and diabetic women in 10 samples from each group obtained before pregnancy and at the time of delivery, and compared the values with those of their fetal cord blood (Table 3). A representative Western blot is shown in Fig. 4. When the data were analyzed by densitometry, the maternal level of IGFBP-1 was 3.8-6.7-fold higher (difference is significant, P<0.001) than the level before pregnancy in both the normal and NIDDM patients. In the IDDM patients, the concentrations were significantly (P<0.01) higher than those in the normal women before pregnancy and at the time of delivery. The values in the cord blood of newborns of IDDM patients were significantly (P<0.01) higher, but those in infants of NIDDM mothers were not different from the concentrations in infants of normal mothers. Umbilical IGF-I and IGF-II levels were not related to the IGFBP-1 levels.

The maternal serum concentrations of IGFBP-2 were approximately 60% lower than those before pregnancy in both normal and diabetic patients, and the difference was significant (P<0.01) in all three groups. Those in cord blood were 10-11.3-fold higher than in maternal blood, and there was no difference between the neonates of non-diabetic mothers and those of diabetic mothers in cord IGFBP-2.

In Western immunoblotting, IGFBP-3 can be de-
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There was no difference between the normal women and the diabetic patients before pregnancy (data not shown). In the maternal serum, the 41/38 KDa species disappeared completely and only the 30 KDa species were detected (see Fig. 4), due to the increased protease activity for IGFBP-3 in pregnant serum [24–26]. There was also no difference among the three groups in the amount of 30 KDa species (data not shown). In cord serum, however, IGFBP-3 (41/38 KDa) was detected as a 41/38 KDa doublet along with 30 KDa species, which represents degraded products of the 41/38 species.

Fig. 3. Positive correlation between maternal HbA1c and fetal IGFs. Maternal HbA1c were correlated with cord IGF-I levels (upper panel) and IGF-II (lower panel) in pregnant women with IDDM (open triangles) and with NIDDM (open squares).

Fig. 4. Identification of IGFBP-1, -2 and -3 in maternal and fetal serum. The serum samples were processed as described in the text. This figure shows a representative Western blot obtained for IGFBP-1, BP-2 and BP-3 in maternal and fetal serum.

Table 3. Serum concentrations of IGFBP-1, -2 and -3 in women before and at the time of delivery and in their babies

<table>
<thead>
<tr>
<th></th>
<th>BP-1</th>
<th>BP-2</th>
<th>BP-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0.298 ± 0.297</td>
<td>1.141 ± 0.357</td>
<td>0.687 ± 0.268</td>
</tr>
<tr>
<td>NIDDM</td>
<td>0.362 ± 0.186</td>
<td>1.008 ± 0.306</td>
<td>0.804 ± 0.160</td>
</tr>
<tr>
<td>IDDM</td>
<td>1.410 ± 0.515</td>
<td>1.651 ± 0.180</td>
<td>0.625 ± 0.233</td>
</tr>
<tr>
<td>At delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1.120 ± 0.438</td>
<td>0.525 ± 0.294</td>
<td>0.0</td>
</tr>
<tr>
<td>NIDDM</td>
<td>1.186 ± 0.285</td>
<td>0.722 ± 0.357</td>
<td>0.0</td>
</tr>
<tr>
<td>IDDM</td>
<td>2.011 ± 0.370</td>
<td>0.600 ± 0.192</td>
<td>0.0</td>
</tr>
<tr>
<td>Fetal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0.450 ± 0.090</td>
<td>5.876 ± 0.787</td>
<td>0.216 ± 0.076</td>
</tr>
<tr>
<td>NIDDM</td>
<td>0.474 ± 0.150</td>
<td>7.190 ± 2.001</td>
<td>0.402 ± 0.113</td>
</tr>
<tr>
<td>IDDM</td>
<td>0.681 ± 0.349</td>
<td>7.017 ± 2.480</td>
<td>0.357 ± 0.140</td>
</tr>
</tbody>
</table>

Values relative to those for control serum (different control serum was used for BP-1, BP-2 and BP-3) were obtained by densitometry and are expressed as the mean ± SD (n=10). **P<0.01 vs. normal. +P<0.05 vs. normal.
with the maternal and fetal IGF-I, -II and IGFBP-1, -2, -3 (see Table 1). Numerous reports have demonstrated a positive correlation between birth weight and cord IGF-I in non-diabetic pregnancy and in diabetic pregnancy [16], which was confirmed by the present study (r=0.524, P<0.001). As shown in Fig. 6, there was also a positive correlation between cord IGF-II levels and birth weight, although the correlation (r=0.345, P<0.01) was less strong than that in IGF-I (r=0.524, P<0.001). Additionally, the maternal HbaA1c levels correlated to the birth weight of newborns of diabetic mothers (r=0.380, P<0.001). Figure 7 shows that fetal IGF-I positively correlated with placental weight (r=0.402,
P<0.05), and a stronger correlation was found between fetal IGF-II and placental weight (r=0.405, P<0.01). A strong correlation was also found between placental weight and birth weight (r=0.733, P<0.001). There was no correlation between birth weight and maternal of IGF-I, IGF-II, IGFBP-1, -2 and -3 or cord IGFBP-1, -2, and -3 (data not shown).

Discussion

The present study shows that maternal serum IGF-I levels in normal, IDDM, NIDDM women increased during gestation and IGF-I reached 1.4–1.5-fold higher values at delivery, consistent with a number of earlier studies [5, 7, 11, 17, 23], whereas IGF-II levels reached 1.5 fold higher values at delivery than the nonpregnant concentrations. Both IGF-I and -II showed by a prompt drop after delivery. There was no difference between serum IGF-I and IGF-II in normal and diabetic women before, during pregnancy and after delivery, which is not consistent with an earlier report [23] indicating that serum IGF-I concentrations in IDDM patients were lower throughout pregnancy. This discrepancy may be due to different patient populations or different methodologies. Earlier studies have shown that the concentrations increase slightly during the latter half of gestation [5–7], whereas Funakoshi et al. [11] could not find increased IGF-II during pregnancy in normal women. The marginal increase or failure to detect any elevation in IGF-II may be due to wide individual variation in serum IGF-II concentrations in these cross-sectional studies. Our longitudinal analysis clearly shows that serum IGF-II increased in all of the diabetic mothers during the latter half of gestation. It is most likely that the increase in serum IGF-II levels during pregnancy is mediated by placental factor(s), because the concentrations rapidly decreases after delivery. Hall et al. [27] showed that serum IGF-II increased during pregnancy in GH-deficient patients, indicating that the increase in IGF-II is GH-independent. Furthermore, it has been shown that both cord IGF-I and IGF-II concentrations are related to fetal placental lactogen levels in non-diabetic pregnancy [8, 13].

Although maternal IGF-I and IGF-II concentrations were not different between normal and diabetic patients during gestation, there was a significant increase in both IGF-I and IGF-II in the cord blood of infants of diabetic mothers, indicating a different regulation of IGFs in mother and fetus. A significant increase in cord IGF-II but not IGF-I in newborns of diabetic mothers was reported by Hall et al. [17]. There was no change in either IGF-I or IGF-II in one study [18]. Our data are consistent with those of Gelato et al. [6] who showed 2-fold higher values for IGF-I and 1.3-fold higher values for IGF-II in the cord blood of newborns of diabetic mothers. It has been reported that cord IGF-I [8, 9, 12, 14] and IGF-II [8, 9] concentrations correlate with gestational age. In the present study, however, the gestational age of infants of diabetic mothers did not differ from that.
of infants of non-diabetic mothers. There was a positive correlation between cord IGF-I and IGF-II concentrations, which, in turn, positively correlated with cord IGFBP-3 concentrations, as reported by Fant et al. [13]. These observations suggest that IGF-I and -II are coordinately regulated by fetoplacental factors.

In contrast to another study [18], we found a positive correlation between the maternal HbA1c and cord blood IGF-I and IGF-II concentrations, which is consistent with the hypothesis that maternal hyperglycemia or resultant events stimulate IGF productions. Although glucose is not a direct stimulator of IGFs in postnatal life, insulin has been shown to stimulate IGF-I production in adults [28].

The present study revealed a positive correlation between umbilical IGF-II levels and placental weight in diabetic pregnancy. The correlation was stronger than that for IGF-I. The positive correlation has been reported for IGF-I in non-diabetic pregnancy [13, 14], but these reports failed to show any correlation between cord IGF-II and placental weight. It is not clear why fetal IGF-II concentrations are correlated to placental growth. A recent study in mouse showed that disruption of the IGF-II gene in the fetus resulted in a decrease in placental weight [3]. This observation indicates the importance of the interaction of fetal IGF-II with placenta, but we have no evidence supporting this hypothesis in man.

IGFBP-3 is the main serum IGFBP which plays a major role in determining the free concentration of IGFs, which decreases during pregnancy because of proteinase activity [24, 25]. Actually, there was no 38/41 KSa species of IGFBP-3 in the maternal serum obtained at the time of delivery from the normal and diabetic women. The amount of degraded products of 38/41 KDa IGFBP-3 (30 kDa species) was similar in the normal and diabetic mothers. It appears, therefore, that proteinase activity in the serum of diabetic mothers is not different from that for normal mothers. The concentrations of IGFBP-2, the major BP in fetal life, were also not different in infants of diabetic and normal mothers. Although Langford and Miell [29] reported that cord IGF-I negatively correlated with IGFBP-2, this was not the case in the present study with diabetic patients. It appears that a change in glucose metabolism has little effect, if any, on IGFBP-2 production [39].

Numerous earlier studies have shown a positive correlation of cord C-peptide [15, 16, 18], or IGF-I [11, 16] levels, with the birth weight of neonates of diabetic mothers, suggesting the involvement of these factors in macrosomia. A positive correlation between birth weight and umbilical IGF-I levels has also been reported for non-diabetic pregnancy [11–14], but conflicting results have been obtained with regard to the correlation between cord IGF-II with birth weight. The abovementioned reports failed to detect any correlation between the two in non-diabetic pregnancy [11–14], whereas some reports suggested a positive role of IGF-II in fetal growth [9, 10]. Hall et al. [17] reported 50%
higher values in infants born to diabetic mothers, but no correlation of the IGF-II values with birth weight was shown. In contrast, Susa et al. [18] showed no difference in cord IGF-I and -II concentrations between infants of normal mothers and diabetic mothers. We demonstrated that cord IGF-II concentrations positively correlate with birth weight, though the correlation was weaker than that for IGF-I. These observations are compatible with the notion that fetal IGF-II, as well as IGF-I, is involved directly or indirectly in overgrowth of the fetus. It is accepted that most of the biological activity of IGF-II is mediated by the binding of IGF-I receptors (type I receptors). Thus, a combination of both IGFs would be important in promoting fetal growth.

It has been established that both IGF-I and -II are produced not only in fetal tissues [30, 40] but also by the placenta, suggesting an autocrine/paracrine role of IGFs in placental growth [41]. Furthermore, expression of the mRNA of IGFs is more abundant in placental tissues from diabetic mothers [42]. This may be, at least in part, responsible for the higher placental weight and, thereby, for the higher birth weight in diabetic pregnancy, since fetal growth is closely coupled to placental growth.

Recent studies have shown that IGFBPs act as modifiers of the biologic action of IGFs, but the role of IGFBPs in fetal growth is poorly understood. In one study [13], the umbilical IGFBP-3 concentration was positively correlated to birth weight, but neither BP-1 nor BP-2 was related to growth parameters. Other reports [35, 43], however, have shown that IGFBP-1 and IGFBP-2 concentrations are inversely correlated to birth weight. Maternal IGFBP-1 has also been shown to inversely correlate with birth weight [44]. The present study in diabetic pregnancy failed to show any correlation between cord IGFBP-1 or BP-2 with birth weight. It is therefore not clear whether fetal IGFBP-1 or IGFBP-2 is causally related to fetal growth. Like IGFs, IGFBPs can be produced by placental tissues [22, 45, 46]. They may be involved in placental and fetal growth by modifying the bioavailability of IGFs.

In summary, we showed that fetal IGF-II, like IGF-I, positively correlated with both birth weight and placental weight. Maternal HbA1C concentrations correlated with both cord IGF-I and IGF-II. Collectively, these data suggest that fetal IGF-II, like IGF-I or insulin, is involved in placental and fetal growth in diabetic pregnancy. Further studies are required to determine the autocrine/paracrine role of IGFs and IGFBPs in fetal and placental growth.

Acknowledgements

The present study was supported by grants from the Ministry of Education, from the Ministry of Health and Welfare and from the Institute of Growth Science.

References


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