Food restriction alters pregnancy-associated changes in IGF and IGFBP in the guinea pig


Food restriction alters pregnancy-associated changes in IGF and IGFBP in the guinea pig. Am. J. Physiol. 274 (Endocrinol. Metab. 37): E410–E416, 1998.—The effect of moderate food restriction on pregnancy-associated changes in weight gain, body composition, and circulating insulin-like growth factors (IGF-I and II) and IGF-binding proteins (IGFBP-1 through -4) and their relationship was determined in the guinea pig. Pregnancy did not stimulate weight gain but reduced fat deposition in ad libitum-fed animals and increased weight gain and fat deposition in food-restricted animals relative to their respective virginal group. Pregnancy increased the abundance of circulating IGF-I regardless of food intake and increased that of IGF-II in food-restricted animals only. Pregnancy also increased circulating IGFBP-1 and -2 in ad libitum-fed and food-restricted animals and IGFBP-4 in ad libitum-fed animals. Multiple regression analysis showed that maternal weight gain was negatively associated with circulating IGF-II and IGFBP-2. Fetal weight was positively associated with maternal circulating IGF-II and negatively associated with maternal circulating IGFBP-1 and -2. Significant interactions indicate, however, that the role of IGF-II and IGFBP-1 on fetal growth is dependent on the nutritional status of the mother.

DURING PREGNANCY, the maternal body undergoes a number of physiological adaptations, including anabolic increases in the size of many maternal tissues, which may compete with the developing conceptus for essential substrates. The mechanisms behind the partitioning of nutrients between the maternal body and the fetus are poorly understood; however, substantial pregnancy-associated changes in the insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) occur in several species, consistent with a role for this axis (18). IGFs are polypeptide growth factors, expressed in most tissues in the body but present in highest abundance in blood, largely in association with IGFBPs. They induce proliferation, differentiation, and metabolic changes on a wide variety of cell types (12), and their abundance and expression, together with those of the IGFBPs, are regulated by nutritional and other factors (24).

Substantial increases in IGF-I in maternal blood occur from early in pregnancy in several species (2, 9, 17). The abundance of IGF-II in maternal serum also increases during pregnancy in some species such as humans and rabbits (4, 17). These changes may promote maternal anabolism, since exogenous IGF-I, IGF-II, or IGF analogs can stimulate nitrogen retention, general growth, and food-conversion efficiency (12). Thus IGF-I administered to pregnant rats during the second half of pregnancy increases maternal weight gain but does not enhance fetal and placental growth (5). Conversely, anti-rat growth hormone (GH) antiserum treatment of pregnant rats, which reduces circulating GH and IGF-I in late gestation, concomitantly reduces growth of maternal skeletal muscle while enhancing fetal growth (20). Similarly, severe food restriction in the pregnant rat inhibits the normal pregnancy-induced increase in circulating IGF-I and GH and reduces maternal growth to a greater extent than fetal growth in early pregnancy (16), consistent with the hypothesis that maternal IGF-I primarily targets maternal anabolism rather than the conceptus.

Nevertheless, increasing the concentration of IGF-I in the blood of pregnant mice and rats abolishes the typically negative relationship seen between litter size and fetal weight (7), suggesting that circulating IGF-I in the mother could also improve or maintain nutrient transfer to the fetus. Consistent with this, exogenous IGF-I in pregnant sheep may increase placental uptake of amino acids and increases maternal plasma levels of glucose, which should promote glucose transfer (14).

Thus the increased abundance of systemic maternal IGF-I in pregnancy may influence both maternal anabolic processes and nutrient delivery to the fetus. Pregnancy also alters the abundance and stability of the IGFBPs, which modulate the actions of the IGFs. The most abundant binding protein in blood, IGFBP-3, is subject to modification by a pregnancy-specific protease in some species (2, 15) and appears to bind IGFs less well. The concentration of the glucoregulatory IGFBP-1 in maternal plasma increases early in pregnancy and is negatively correlated with maternal weight gain, birth weight, and placental weight in women (9).

In most studies of undernourished pregnant animals, food intake has been restricted only during pregnancy or during a short period of pregnancy. The physiological changes induced by pregnancy can certainly be different in an animal already adapted to undernutrition than in an animal suddenly subjected to severe food restriction. A model using chronic moderate undernutrition from before conception would also be more relevant to the situation of many women. Furthermore, the species most often studied have been rats and mice. These species do not produce significant amounts of IGF-II postnatally, and thus the role of this growth factor during pregnancy in general and in undernourished pregnant animals in particular remains to be clarified. The guinea pig expresses substantial amounts...
of IGF-II and thus offers a possibility to use a small-animal model to study also the role of IGF-II during reproduction. Furthermore, this species has offspring with considerable amounts of body fat at birth, as does the human. The latter may be important, since the partitioning of nutrients between mother and conceptus and its regulation could vary according to whether substantial amounts of lipid, in addition to other substrates, must be accumulated by the fetus.

In this study, the following questions were therefore addressed. What are the effects of chronic moderate food restriction, from before conception, on maternal adaptation to pregnancy in mid- and late gestation with regard to the maternal IGF axis, as reflected by circulating IGF-I, IGF-II, and IGFBPs, weight gain, body composition, and plasma metabolites as well as on fetal and placental growth? Are changes in the IGF axis related to the outcomes for maternal anabolism or conceptus growth?

**MATERIALS AND METHODS**

**Experimental Design**

Nulliparous female guinea pigs (IMVS colored strain), 472 ± 56 g, 3–4 mo old, were obtained from the Gilles Plains Animal Resource Centre (Gilles Plains, SA, Australia). The animals were housed in individual wire-bottom cages in a room with a 12:12-h light-dark cycle and a temperature of 25°C. They were fed a guinea pig-rabbit ration from Milling Industries Stockfeeds (Murray Bridge, SA, Australia) supplemented with vitamin E (165 mg/kg). The animals had free access to tap water containing vitamin C (400 mg/l).

The guinea pigs were divided into two groups, one fed ad libitum (n = 34) and one subjected to food restriction (n = 41). After 4 wk of adaptation to the feeding regimen, a subgroup of animals in each feeding group was mated. A female found to be in estrus was put with a male overnight, and the female was assumed to be pregnant if a vaginal copulatory plug was found the following morning.

Animals were killed by an intraperitoneal overdose of pentobarbital sodium. The pregnant ad libitum-fed and food-restricted animals were killed on day 30 or 60 of gestation (term ~70 days). Virginal animals from both food regimens were killed after being subjected to the dietary regimen for the same length of time (30–60 days) as pregnant animals. There were no significant differences between virginal animals within each food regimen killed at the time corresponding to day 30 or 60 with regard to any of the parameters studied. Virginal animals were therefore treated as one ad libitum-fed group and one food-restricted group. Six groups of animals were studied (number of animals and body weight on day 1 of gestation or corresponding period): ad libitum-fed virgin, n = 14, 581 ± 42 g, ad libitum-fed pregnant, day 30 (n = 10, 611 ± 42 g), ad libitum-fed pregnant, day 60 (n = 10, 574 ± 42 g), food-restricted virgin, n = 21, 468 ± 39 g, food-restricted pregnant, day 30 (n = 10, 530 ± 54 g), and food-restricted pregnant, day 60 (n = 10, 524 ± 56 g). To make the ad libitum-fed and food-restricted animals comparable with regard to time between food intake and time of death, the food-restricted animals were killed in the afternoon, 3–4 h after they had received their daily food ration, whereas the ad libitum-fed animals were killed in the morning.

Throughout the experiment, food intake and body weight of animals were monitored three times per week, and the average daily food intake per kilogram of body weight was calculated. During the 4-wk adaptation period, the food-restricted animals were given 70% of the average food intake per kilogram of body weight of the ad libitum-fed animals over the previous 2 or 3 days. During the first 34 days of pregnancy, the food-restricted animals were given 70% of the average food intake per kilogram of body weight of the ad libitum-fed pregnant animals, and then between days 35 and 60 of gestation, they were given 90% of the average food intake per kilogram of body weight of the latter animals. The virginal animals were also given 70 and then 90% of the intake of the ad libitum-fed virginal guinea pigs’ intake over the same period.

Immediately after death, 10 ml of blood were collected from the animals by cardiac puncture. Blood was stored on ice until centrifugation at 4°C, 10, 2,500 rpm. The plasma was harvested and frozen at –20°C until analysis.

The weight of the following organs or tissues was recorded: adrenals, kidneys, spleen, pancreas, liver, gastrointestinal tract (consisting of cleaned stomach, small intestine, cecum, and large bowel), retroperitoneal fat, interscapular fat, parametral fat, heart, lungs, thymus, thyrads, biceps brachii, soleus, and gastrocnemius as well as individual fetal and placental weights for the pregnant animals. The fat pads were chosen based on the fact that they were easy to identify and represent both subcutaneous and visceral fat depots. The parametral fat pad has previously been argued to be a specific pregnancy depot, although studies in rats have shown that the retention of body fat during pregnancy is evenly distributed in the body (22).

This study was approved by the Animal Ethics Committee of the University of Adelaide.

**Analyses**

IGF-I and -II radioimmunoassay. IGF-I and -II were analyzed according to Kind et al. (13). IGFS were dissociated from IGFBPs before radioimmunoassay (RIA) by size-exclusion high-performance liquid chromatography of plasma at pH 2.5. Individual plasma samples were extracted with Freon according to Owens et al. (19) and then injected onto a Protein-Pak 125 exclusion column (Waters/Millipore, Lane Cove, NSW, Australia). To establish where IGFs were eluting under these conditions, 0.25-min fractions were collected from plasma of pregnant and virgin animals between 6 and 12 min of elution, and each fraction was subjected to IGF-I and -II RIA. On the basis of the elution profile of the IGFs, chromatogram fractions were collected at 6.25–8.25, 8.25–8.75, 8.75–10.75, and 10.75–11.25 min. The third fraction contained the IGFs (26). Recombinant human IGF-I and -II were used as radioligand and standard. In the IGF-I RIA, a rabbit anti-human (h) IGF-I (MAC 89/1), having a cross-reactivity with hIGF-II of <1%, was used at a final dilution of 1:60,000. In the IGF-II RIA, a mouse anti-rat IGF-II monoclonal antibody (IGF S1-F2, a generous gift from Dr. K. Nishikawa, Kanazawa Medical University, Ishikawa, Japan) was used, with a cross-reactivity with hIGF-II of 2.5%, at ng/reaction tube. The intra- and interassay coefficients of variation, assessed by repeated analysis of the same sample, were 5.5 and 6.9%, respectively, for IGF-I and 7.8 and 10.1%, respectively, for IGF-II.

Western ligand blotting. Individual binding proteins were identified by Western ligand blotting. Samples (20 ml of a 5% dilution) were subjected to nonreducing discontinuous sodium dodecyl sulfate-polyacrylamide gel electrophoresis on a 4% stacking gel and a 10% polyacrylamide separating gel for 2 h at 20 mA followed by overnight at 8 mA. A sample containing a mixture of plasma from ad libitum-fed pregnant and virgin as well as plasma from food-restricted pregnant
and virginal animals was run on each gel as a control. Molecular masses of IGFBP bands were calculated from 14C-labeled "rainbow" molecular-weight markers (Amersham International, Bucks, UK). Separated proteins were transferred onto nitrocellulose filters at 250 mA for 3.5 h. Membranes were blocked and probed with 125I-IGF-I or -II as described by Hossenlopp et al. (10) and exposed to X-ray film at −80°C for 1 (IGFBP-3) or 2 (IGFBP-1, -2, and -4) wk. The relative amount of IGFBP was assessed by densitometry (ImageQuant, version 3:22, Computing Densitometer, model 300A, Molecular Dynamics, Sunnyvale, CA). Each band was expressed as a percentage of the control sample.

Plasma metabolites. Plasma metabolites (glucose, albumin, and free fatty acids) in individual animals were analyzed enzymatically, in duplicate, using a Cobas Mira automated analyzer (Roche Diagnostic Systems). The interassay coefficients of variation, assessed by repeated analysis of the same sample, ranged from 1.4 to 7.8% for the different metabolites.

Statistics

Data were analyzed using BMDP Statistical Software (Los Angeles, CA). The values were analyzed by one-way analysis of variance in the ad libitum-fed and food-restricted groups, respectively, with virginal and days 30 and 60 as between factors. A Bonferroni post hoc test was used for the following comparisons: virginal against day 30, virginal against day 60, and day 30 against day 60. Student’s t-test for independent means was used to assess differences in total and net weight gain and food intake between pregnant groups and their corresponding virginal groups and to assess differences in number of fetuses and fetal and placental weights between ad libitum-fed and food-restricted guinea pigs. Associations between IGFs and IGFBPs on the one hand and net maternal weight gain and average fetal weight on the other were analyzed by multiple linear regression analysis on the days 30 and 60 of gestation, respectively. Nutrition (ad libitum fed, coded 1; food restricted, coded 0), IGFs, IGFBPs, and the interaction between nutrition and IGFs-IGFBPs were independent variables, and fetal weight and net maternal weight gain were dependent variables.

RESULTS

During the first 30 days of gestation, ad libitum-fed pregnant animals had similar total and net weight gains compared with virginal animals (Fig. 1). However, by day 60, ad libitum-fed pregnant animals had gained more total weight but less net weight than their virginal counterparts. There was no difference in food intake between ad libitum-fed pregnant and virginal animals (data not shown). In marked contrast, by day 30 of gestation, food-restricted pregnant animals had gained more total weight, but not more net weight, than their virginal counterparts.

Fetal and placental weights were significantly reduced in the food-restricted group by 17% at day 30, and by 39% and 30%, respectively, at day 60 (Table 1). Food restriction increased the placental-to-fetal weight ratio by 11% and 14% at days 30 and 60 of gestation, respectively. The ad libitum-fed and food-restricted dams had an average of three and two fetuses per dam, respectively.

Table 1. Reproductive outcome of ad libitum-fed and food-restricted guinea pigs

<table>
<thead>
<tr>
<th>Time of Death:</th>
<th>Ad Libitum Fed</th>
<th>Food Restricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal wt, g</td>
<td>Day 30</td>
<td>Day 60</td>
</tr>
<tr>
<td>Placental wt, g</td>
<td>0.67 ± 0.08*</td>
<td>4.52 ± 0.78†</td>
</tr>
<tr>
<td>Placental/fetal wt ratio</td>
<td>0.55 ± 0.06*</td>
<td>0.07 ± 0.01†</td>
</tr>
<tr>
<td>No. of fetuses/dam</td>
<td>3.4 ± 0.8*</td>
<td>3.0 ± 0.7†</td>
</tr>
<tr>
<td>Total fetal and placental wt, g</td>
<td>6.29 ± 1.39*</td>
<td>22.12 ± 40.8†</td>
</tr>
</tbody>
</table>

Values are means ± SD. *Significantly different (P < 0.05) from corresponding value for food-restricted, day 30 group. †Significantly different (P < 0.05) from corresponding value for food-restricted, day 60 group.

By day 60 of gestation, the ad libitum-fed pregnant animals had relatively larger (expressed as percentage of net body weight) adrenals, biceps, and soleus but smaller retroperitoneal and interscapular fat pads and thymus compared with the virginal group (Fig. 2). There were no differences in relative organ weights between ad libitum-fed pregnant and virginal animals on day 30 of gestation or between any of the ad libitum-fed groups regarding the other organs or tissues at day 60 of gestation (data not shown). The food-restricted pregnant animals had relatively smaller kidneys and thymus on days 30 (data not shown) and 60 of gestation and relatively larger interscapular and parametrial fat pads on day 60 of gestation compared with the food-restricted virginal animals (Fig. 2).

In the ad libitum-fed pregnant group, the plasma concentrations of albumin and glucose decreased during gestation, whereas that of free fatty acids tended (P = 0.1) to be increased at the end of pregnancy (Fig. 3). In the food-restricted pregnant group, the concentrations of albumin and free fatty acids did not change.
during pregnancy, whereas the concentration of glucose was increased at day 30 of gestation.

In ad libitum-fed animals, pregnancy increased plasma concentrations of IGF-I to 280 and 201% of those of the virginal animals at days 30 and 60 of gestation, respectively (Fig. 4). Similarly, in food-restricted animals, pregnancy increased the plasma concentrations of IGF-I to 223 and 167% of those of the corresponding virginal animals at days 30 and 60 of gestation, respectively. The plasma concentration of IGF-I decreased late in pregnancy in the ad libitum-fed animals but not in the food-restricted animals. Pregnancy did not alter the concentration of IGF-II in the ad libitum-fed animals (Fig. 4). In food-restricted animals, however, pregnancy increased the plasma concentration of IGF-II on day 30 of gestation compared with food-restricted virginal animals.

Figure 5 shows the IGFBPs of pooled plasma in ad libitum and food-restricted animals as assessed by Western ligand blotting. The blot shows a distinct 46-kDa band (IGFBP-3), 30-kDa band (IGFBP-2), 28-kDa band (consisting of IGFBP-1 but possibly also other binding proteins), and 24-kDa band (IGFBP-4). The bands were identified as particular IGFBPs as described above on the basis of their apparent molecular mass. There was no evidence of any protease activity in pregnancy, since the band representing IGFBP-3 remained at high levels at days 30 and 60 of gestation. The presence of protease activity was also tested for by incubating plasma from the ad libitum-fed virginal group with plasma from ad libitum-fed or food-restricted pregnant animals, which was then subjected to Western ligand blotting, according to Gar-gosky et al. (6). No reductions in the intensity of the band corresponding to IGFBP-3 could be found after exposure to pregnancy plasma, suggesting that pregnancy does not induce protease activity in the guinea pig, at least of a type that can be detected by this method in the guinea pig (data not shown). IGFBP-3 was the most abundant binding protein in all treatment groups, followed by IGFBP-2, -1, and -4. Preg-
negatively related with IGFBP-1 and -2 on day 30 of gestation and those of IGFBP-1 and -2 at day 60 of gestation but had no effect of those of IGFBP-3 in ad libitum-fed animals (Fig. 6). In food-restricted animals, pregnancy increased plasma levels of IGFBP-1 at days 30 and 60 of gestation and those of IGFBP-2 and IGFBP-4 on day 60 of gestation but had no effect on plasma level of IGFBP-3.

Fetal weight was positively related with IGF-II and negatively related with IGFBP-1 and -2 on day 30 of gestation (Table 2). These associations were significant independent of nutrition. There were, however, significant interactions between IGF-II and nutrition and between IGFBP-1 and nutrition, showing that the associations between these growth factors and fetal growth were different in ad libitum-fed and food-restricted animals. Net maternal weight gain (days 1–60) was negatively associated with IGF-II and IGFBP-2. These associations were significant independent of nutrition. There was a significant interaction between IGF-II and nutrition, showing that the association between this growth factor and net maternal weight gain was different in ad libitum-fed and food-restricted animals. No significant associations were found between fetal weight and IGF axis on day 60 of gestation or between net maternal weight gain and IGF axis on day 30 of gestation (data not shown).

### Table 2. Significant associations between fetal and net maternal weight gain (dependent variables) and nutrition (ad libitum fed and food restricted) IGFs and IGFBPs (independent variables) in guinea pigs on gestational days 30 and 60

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>P Value</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fetal wt (day 30)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>-0.6453</td>
<td>0.0126</td>
<td></td>
</tr>
<tr>
<td>IGF-II</td>
<td>0.0002</td>
<td>0.0175</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>-0.0003</td>
<td>0.0397</td>
<td>0.7082</td>
</tr>
<tr>
<td>Nutrition</td>
<td>-0.075</td>
<td>0.2573</td>
<td></td>
</tr>
<tr>
<td>IGF-II</td>
<td>-0.0007</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>0.0009</td>
<td>0.0088</td>
<td>0.7618</td>
</tr>
<tr>
<td>Nutrition</td>
<td>-0.0947</td>
<td>0.3271</td>
<td></td>
</tr>
<tr>
<td>IGFBP-1</td>
<td>-0.0011</td>
<td>0.0495</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>0.0012</td>
<td>0.2539</td>
<td>0.6651</td>
</tr>
<tr>
<td><strong>Net maternal wt gain (days 1–60)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>34.1626</td>
<td>0.4678</td>
<td></td>
</tr>
<tr>
<td>IGF-II</td>
<td>-0.0633</td>
<td>0.029</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>0.1197</td>
<td>0.0039</td>
<td>0.8097</td>
</tr>
<tr>
<td>Nutrition</td>
<td>20.2979</td>
<td>0.7544</td>
<td></td>
</tr>
<tr>
<td>IGFBP-2</td>
<td>-0.4136</td>
<td>0.0423</td>
<td></td>
</tr>
<tr>
<td>Interaction</td>
<td>0.7343</td>
<td>0.1351</td>
<td>0.7528</td>
</tr>
</tbody>
</table>

IGF, insulin-like growth factor; IGFBP, IGF-binding proteins.

This study has shown that, in the ad libitum-fed guinea pig, pregnancy substantially increases the abundance of IGF-I but not that of IGF-II in maternal blood. Previous studies of more limited numbers of animals found either no consistent changes in circulating IGFs within the mother or a substantial decrease in IGF-I in late gestation (1, 3). Thus pregnancy-associated changes in the IGFs in the guinea pig generally resemble those in humans and nonhuman primates rather than those seen in small rodents and other polytocous species. We have also characterized circulating IGFBPs in the pregnant guinea pig for the first time using Western ligand blot analysis. The major IGFBP in guinea pig plasma, IGFBP-3, is unchanged during pregnancy, and proteolytic activity directed against IGFBP-3 or other IGFBPs is not evident using Western ligand blotting.

Despite the pregnancy-associated increases in circulating IGF-I in the ad libitum-fed guinea pig, net maternal weight gain is unaltered at midgestation and reduced in late gestation compared with nonpregnant animals. This suggests that if systemic maternal IGF-I has any anabolic actions, they may be directed toward nonmaternal tissues, such as the placenta and fetus, especially in late gestation. Maternal tissues were also differentially affected by pregnancy in late gestation, with the adrenals and skeletal muscles being larger and the fat depots and thymus being reduced compared with those of nonpregnant animals. The tissues whose growth is most sensitive to IGFs postnatally are the adrenals, kidney, spleen, and gut (12), suggesting that the altered pattern of maternal growth in late gestation cannot be readily explained by changes in IGF-I abundance alone. Our results indicate that pregnancy imposes a high metabolic demand on the maternal body, as shown by a slowing of growth and smaller fat depots late in gestation. The nutritional requirements of the conceptus thus seem to take priority over the mother.

Circulating IGF-I levels increased during pregnancy also in the food-restricted animals. In guinea pigs subjected to more severe restriction of food intake (60% of ad libitum), pregnancy also increased circulating levels of IGF-I in maternal plasma at day 25 of gestation, with subsequent decline by day 65 of gestation (3). The food-restricted guinea pigs in our study also had low plasma IGF-II concentrations, which increased during pregnancy, in contrast with ad libitum-fed guinea pigs.
pigs and with previous studies (1, 3). At the same time, the food-restricted group responded to pregnancy by a slightly increased maternal weight gain during the first half of pregnancy compared with their virginal counterparts. Interestingly, the major difference in body composition between food-restricted virginal and pregnant animals was the larger fat depots in the pregnant animals.

Food restriction reduced litter size as well as fetal and placental growth and hence overall conceptus size. Thus, although fetal growth was compromised, maternal growth during food restriction was stimulated compared with that of virginal guinea pigs. Moderately food-restricted pregnant rats also accumulate considerable amounts of fat and lean tissue within their own bodies, even though fetal growth is reduced (22). Together with the findings of the current study, this suggests that when food intake is limited during pregnancy, nutrients are not necessarily repartitioned from the maternal body to the conceptus; instead, maternal priorities may dominate over fetal needs.

Circulating IGF-II was positively related with fetal weight and negatively related with net maternal weight gain, suggesting a possible role for this growth factor in the partitioning of nutrients between mother and fetus. Furthermore, the results indicate that IGF-II may have different roles in ad libitum-fed and food-restricted animals. The role of IGF-II during pregnancy could be resolved by directly determining the consequences for growth of the mother and the conceptus in the abundance of IGF-II relative to that of the IGFBPs by, for example, administering exogenous IGF-II to well-fed and food-restricted pregnant guinea pigs. The negative associations between fetal weight and IGFBP-1 and -2 and between net maternal weight gain and IGFBP-2 support previous studies showing that these binding proteins have inhibitory effects on the anabolic actions of IGFs (8). In human pregnancy, the gestational increase in circulating maternal IGF-BP-1 is enhanced by severe preeclampsia (25) and in utero-placental insufficiency by intrauterine growth retardation (14). The increased abundance of IGFBP-1 in food restriction and pregnancy may serve to inhibit stimulation of glucose utilization by tissues by the small but potent free IGF pool, as has been previously suggested, and may contribute to the increase in plasma glucose concentrations in these animals.

In the ad libitum-fed animals, the concentration of albumin and glucose in maternal plasma decreased during pregnancy, whereas that of free fatty acids tended to increase, which is in agreement with previous observations in pregnant women (21) and guinea pigs (11, 23). The consequences of these metabolic changes may be a switch of maternal metabolism from glucose to free fatty acid utilization, making more glucose available to the conceptus (21). In the food-restricted group, however, the concentration of glucose in maternal plasma was increased during pregnancy. This may reflect induction of insulin resistance by undernutrition together with increased inhibition of the metabolic actions of the IGFs due to increased abundance of some IGFBPs.

The interaction between maternal nutrition, endocrine changes and fetal growth is a complex one. Progesterone and insulin have been suggested to stimulate retention of adipose tissue in the maternal body during the first part of gestation, whereas placental prolactin may promote the increased insulin resistance and lipolysis observed late in gestation. There are studies indicating that IGFs and IGFBPs may partly mediate the actions of these hormones during pregnancy (18). Because the IGF axis is highly dependent on the nutritional status, it is conceivable that IGFs and IGFBPs may modify the action of pregnancy-specific hormones according to the nutritional status of the animal. Further studies of what tissues express IGFs and IGFBPs during pregnancy in ad libitum-fed and food-restricted animals and how exogenously administered IGF-I and IGF-II to undernourished animals affect fetal growth, maternal weight gain, and body composition could give an increased understanding of this complex question.

In conclusion, pregnancy increases the abundance of IGF-I in maternal blood normally and during undernutrition in the guinea pig and that of IGF-II during undernutrition. Ad libitum-fed animals respond to pregnancy by a decreased growth rate and smaller fat depots, whereas food-restricted animals show an increased growth rate and larger fat depots despite compromised fetal growth. The findings suggest that IGF-II may be involved in the partitioning of nutrients between mother and fetus but that this role is dependent on the nutritional status of the animal.

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