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Carbohydrate-lipid interactions during gestation and their control by insulin

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1. During the first two thirds of gestation, coinciding with a minimal accretion by the conceptus, the mother is in an anabolic state which is supported by her hyperphagia and the more efficient conservation of exogenous nutrients when she eats. During this phase maternal fat deposits are accumulated thanks to the enhancement in adipose tissue lipogenic and glycerolgenic activity. In contrast, in the latter part of gestation, the rapid fetal growth is sustained by the intense transfer of nutrients from maternal circulation.

2. Glucose is quantitatively the most abundant of the several substrates that cross the placenta and despite increased maternal gluconeogenesis this transfer is responsible for the maternal tendency to hypoglycemia. This causes a switch to a net catabolic state which is especially evident in the net breakdown of fat depots.

3. Enhanced release of adipose tissue lipolytic products, free fatty acids (FFA) and glycerol, facilitates the liver synthesis of triglycerides and their later release into circulation associated to very low-density lipoprotein (VLDL). Glycerol is also used as an important gluconeogenic substrate and FFAs are broken down through β-oxidation for ketone body synthesis. Flow through these pathways becomes increased when food is withheld and this actively contributes to the availability of fuels to the fetus which becomes partially preserved from maternal metabolic insult. Increased liver production of VLDL-triglycerides and decreased extrahepatic lipoprotein lipase contribute to exaggerated maternal hypertriglyceridemia which, besides being a floating metabolic reserve for emergency conditions such as starvation, constitutes an essential substrate for milk synthesis around parturition in preparation for lactation.

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4. While the maternal anabolic tendencies found during the first two-thirds of gestation seem to be facilitated by hyperinsulinemia in the presence of a normal responsiveness to the hormone, it is proposed that most of the metabolic changes taking place during the last third of gestation seem to be caused by the insulin-resistant state which is consistently present at this stage, since its reversion caused by sustained exaggerated hyperinsulinemia also reverts several of these metabolic adaptations.

Key words: pregnancy, gluconeogenesis, lipolysis, lipoprotein lipase, insulin, insulin sensitivity.

Introduction

Pregnancy may be considered a physiologic event wherein the intermittently feeding mother must provide a continuous supply of nutrients to the continuously growing fetus. Among these nutrients, glucose is quantitatively the most important, followed by amino acids (Herrera et al., 1985; Lasunción et al., 1987), and the continuous dependence of the fetus on these compounds is well known. Thus the mother tends to develop both hypoglycemia (Herrera et al., 1969b) and hypoaminoacidemia (Zorzano et al., 1986).

In order to support the continuous extraction of nutrients by the fetus, the mother has to adapt her own metabolism. One of the parameters most affected in the mother is her lipid metabolism, in spite of the fact that with the exception of ketone bodies and free fatty acids (FFA), the placenta is practically impermeable to lipids (Herrera et al., 1990a, 1992a).

During gestation there are at least two clearly differentiated metabolic situations. During the first two-thirds of gestation, coinciding with a minimal weight increase by the conceptus, the mother conserves more exogenous nutrients whenever she eats, and this, together with her hyperphagia (Knopp et al., 1975; Ludeña et al., 1983), results in an increase in the weight of her own structures (Figure 1) which is especially manifested in her accumulation of fat deposits. In the latter part of gestation, rapid fetal growth (Figure 1) is sustained by the intense transfer of nutrients from maternal circulation. This causes a switch to a net catabolic state which is especially evident in adipose tissue (Knopp et al., 1970a,b; Chaves and Herrera, 1980a) and must be responsible for the decline in the conceptus-free maternal body weight (Figure 1). The catabolic condition at late gestation becomes especially exaggerated when food is withheld (Freinkel et al., 1970b; Freinkel, 1980), and the consequent heightened ketogenesis and gluconeogenesis contribute to the availability of fuels to the fetus which in this manner becomes partially protected from the maternal metabolic insult.

This paper reviews these metabolic changes that occur during pregnancy, with special emphasis on the carbohydrate-lipid interactions, and analyzes
Carbohydrate-lipid metabolism in gestation

![Graph showing changes in maternal or conceptus weight and fetal weight over gestation days.](image)

Figure 1 - Increase in maternal body weight free of the conceptus (■), and conceptus (x) and fetus (○) weights, during gestation in the rat. Data are reported as means ± SEM for 8 rats.

their nutritional implications for both the mother and her offspring. Since changes in circulating insulin levels and in insulin sensitivity that take place during gestation parallel some of those metabolic events, we will also analyze the possible role of insulin in their control.

Carbohydrate metabolism during pregnancy

Maternal hypoglycemia develops during late gestation after short or prolonged fasting periods (Bleicher et al., 1964; Herrera et al., 1969b). Since glycogen stores are depleted during this fasting situation, hypoglycemia may be the result of decreased gluconeogenesis, an enhanced rate of glucose utilization, or both.

The circulating levels of gluconeogenic substrates fluctuate during fasting in late pregnancy. As shown in Figure 2, whereas in the pregnant fasted rat plasma levels of lactate or pyruvate are maintained similar to those in virgin...
controls, gluconeogenic amino acids are decreased and glycerol levels are increased. We found that after the *in vivo* administration of 1 mmol of uniformly labelled alanine or glycerol, their conversion into glucose in the fasted pregnant rat is always greater than in virgin controls, although the effects were much greater when glycerol rather than alanine was provided as gluconeogenic substrate (Zorzano et al., 1986; Herrera et al., 1992b, 1993). However, when lower amounts of these substrates (0.2 mmol/rat) were administered, the rate of gluconeogenesis from alanine appeared to be similar in pregnant rats and in virgin animals, whereas the enhanced gluconeogenesis from glycerol was still demonstrable in the pregnant rats (Zorzano et al., 1986; Herrera et al., 1992b).
It may be concluded that although gluconeogenesis from these three carbon substrates is enhanced in the late pregnant fasted rat, alanine, and probably other gluconeogenic amino acids as well, are not used as preferential substrate in this pathway because of their reduced availability. Placental transfer of amino acids is carried out through an active transport system which results in their concentration in fetal plasma being even higher than in maternal plasma in which hypoaminoacidemia develops (Herrera et al., 1985). It may then be proposed that, as shown in Figure 3, under fasting conditions, maternal hypoglycemia and the efficient transfer of alanine through the placenta at late gestation interfere with the maternal glucose-alanine cycle that normally takes place between the liver and skeletal muscles.

Another conclusion that may be reached from in vivo gluconeogenetic experiments in the late pregnant rat described above is that glycerol is one of the most efficient substrates in its conversion into glucose. This conclusion is not surprising since, as shown in Figure 4, unlike most other substrates, the pathway of glycerol to glucose does not require intramitochondrial steps which, together with the high glycerokinase activity in liver and kidney cortex (Lin, 1977), allow this metabolite to be rapidly converted into glucose, thus becoming an efficient gluconeogenic substrate in pregnancy under both fed and fasting conditions (Chaves and Herrera, 1980b; Zorzano and Herrera, 1986; Zorzano et al., 1986).

Figure 3 - The glucose-alanine cycle in the fasting condition as modified in pregnancy by the presence of the conceptus. The arrow corresponding to the flow of alanine to the fetus has been enlarged proportionally to indicate the active transfer against gradient, as also occurs for other amino acids.

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Figure 4 - Metabolic interactions between gluconeogenesis (glucose synthesis), glycolysis (glucose conversion into pyruvate), the citric acid cycle and the metabolism of FFA and glycerol in the liver.

Since reduced gluconeogenic activity probably does not explain the tendency to hypoglycemia during gestation, it must be the result of an overall enhanced use of glucose in spite of the fact that the rates of glucose utilization by maternal tissues in several species are lower in pregnant than in nonpregnant females (Leturque et al., 1986, 1987). This effect, therefore, is mainly due to the extensive use of glucose by the conceptus, which may represent up to 50% of overall maternal glucose expenditure (Leturque et al., 1986; DiGiacomo and Hay, 1990), contributing very actively to the rapid disappearance of glucose from maternal circulation.

The importance of the fetal consumption of maternal metabolites may be inferred from the quality and quantity of their placental transfer. As shown in Figure 5, obtained from our studies on the maternal-fetal transfer of a variety of substrates in the late pregnant rat in situ (Herrera et al., 1985, 1991; Lasunción et al., 1987), glucose transfer is much higher than the transfer of alanine, palmitic acid, glycerol and triglycerides. This preponderance of placental glucose transfer is justified, because despite the fact that under normal conditions the fetus cannot synthesize glucose (Palacín et al., 1987), this metabolite is a major fuel in its metabolic economy (Hay et al., 1990; Marconi et al., 1993).

Adipose tissue metabolism

Lipolytic activity

Maternal hypoglycemia even under mild dietary deprivation seems to be responsible for the heightened catecholamine excretion found during late gestation in the rat (Herrera et al., 1969a; Young and Landsberg, 1979), since it is known that the adrenal medulla is selectively activated by reductions in blood glucose (Goldfien et al., 1958; Garber et al., 1976). This increased sympathoadrenal activity, together with the increased amount of gestational hormones released by the placenta and ovary, may be responsible for the accelerated mobilization of fat deposits that occurs during late gestation under both fed and fasting conditions (Knopp et al., 1970a; Freinkel et al., 1970a; Chaves and Herrera, 1980a).

Enhanced adipose tissue lipolysis increases the release of both FFA and glycerol into maternal circulation where they reach high plasmatic values (Knopp et al., 1970a; Freinkel et al., 1970a; Chaves and Herrera, 1980a; Herrera et al., 1987). As shown in Figure 5, the placental transfer of these two lipolytic products is low (Lasunción et al., 1987; Herrera et al., 1992a) whereas, the maternal liver is their main receptor (Carmaniu and Herrera, 1979; Mampel et al., 1985). In the liver, after being converted into their respective active forms, FFA to acetyl-CoA and glycerol to α-glycerol-phosphate, they may be used for esterification in the synthesis of glycerides (see Figure 4). Other pathways used for these compounds are: β-oxidation to acetyl-CoA and ketone body production in the case of FFA, and glucose synthesis in the case of glycerol (Figure 4). As commented above, glycerol is the preferential gluconeogenic substrate used during gestation, and we showed that the use of glycerol for glyceride glycerol synthesis is also very
efficient in the liver of the fed 21-day pregnant rat (Zorzano and Herrera, 1986). This effect, together with the increased transfer of FFA and glycerol to the liver from adipose tissue lipolysis justifies their enhanced esterification in the liver and the consequent heightened very low-density lipoprotein (VLDL)-triglycerides production by this organ during late pregnancy (Wasfi et al., 1980).

Under fed conditions, the fetus does not directly benefit from these changes since maternal triglycerides do not directly cross the placental barrier (see Figure 5 and reference Herrera et al., 1992a). However, in the fasting condition the use of both FFA for ketogenesis (Scow et al., 1964; Herrera et al., 1969b) and glycerol for gluconeogenesis (Zorzano et al., 1986) is greatly enhanced in the liver of the pregnant mother. Ketone bodies freely cross the placenta (Herrera et al., 1992a) and may be used as fetal fuels (Shambaugh III, 1985; Shambaugh III et al., 1992) or even as substrates in brain lipid synthesis (Patel et al., 1975). Increased glycerol levels in maternal circulation together with

![Graph showing metabolite transfer](image)

Figure 5 - Placental transfer of metabolites in 21-day pregnant rat measured in situ as a function of the radioactivity that appeared in fetuses after infusing the respective labelled tracer through the left uterine artery. Data was corrected for the specific activity dilution of the tracer and uterine blood flow as described by Herrera et al. (1985) and Lasunción et al. (1987). Data are reported for 6 rats.

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both the preferential use of this metabolite as a gluconeogenic substrate and the efficient transfer of glucose to the fetus commented above, therefore, also benefit the fetus under conditions of reduced availability of other substrates such as amino acids (Zorzano et al., 1986; Zorzano and Herrera, 1986; Herrera et al., 1992b).

As summarized in Figure 6, the active adipose tissue lipolytic activity in the mother, thus, plays a critical role for the fetus, especially under fasting conditions. It also benefits maternal tissues since the lipolytic products, and especially FFA and ketone bodies, may be used as alternative fuels to spare glucose.

**Fat accumulation**

The availability of sufficient maternal fat deposits is necessary to sustain her accelerated adipose lipolytic activity. Accumulation of body fat is one

![Diagram](image)

*Figure 6 - Metabolic response to starvation in late pregnancy showing the quantitatively significant role of adipose tissue lipolysis as the source of substrates for both ketogenesis and gluconeogenesis.*

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of the most striking features of gestation in both women (Hytten and Leitch, 1971) and experimental animals (Beaton et al., 1954; Moore and Brassel, 1984; López-Luna et al., 1991). Actually, during gestation both in women and in the rat, body fat accumulation accounts for most of the conceptus-free maternal body weight increase (Herrera et al., 1988; López-Luna et al., 1991; Villar et al., 1992).

From studies in the pregnant rat model, fat accumulation during the first two trimesters of gestation has been associated with three major changes: hyperphagia, increased lipogenesis and increased lipoprotein lipase activity. Hyperphagia supervenes shortly after mating and increases as gestational time advances both in women (Murphy and Abrams, 1993) and rats (Knopp et al., 1975; Ludeña et al., 1983). This change enhances the availability of exogenous substrates and must contribute to the maternal accumulation of fat deposits since it is not observed under conditions of food restriction (Beaton et al., 1954; Lederman and Rosso, 1980; Moore and Brassel, 1984).

Glucose utilization for fatty acids and glycerol synthesis by peritoneal adipose tissue in situ in pregnant rats has been estimated at different days of gestation (Palacín et al., 1991). Both lipogenesis (fatty acid synthesis) and glycerologenesis (glyceride glycerol synthesis) increased until day 20 and then decreased sharply on day 21. This active lipid synthetic activity must contribute to the fat accumulation occurring during the first two trimesters of gestation.

Lipoprotein lipase is an enzyme which controls the so-called “fat uptake” in adipose tissue. It is located on the capillary endothelium where it hydrolyzes the triglycerides circulating in plasma in the form of triglyceride-rich lipoproteins, chylomicrons and VLDL, and facilitates the uptake of the hydrolytic products, FFA and glycerol, by the subjacent tissue (Lasunción and Herrera, 1983) (Figure 7). Lipoprotein lipase activity in lumbar fat pads is higher at day 12 of gestation in the rat than in nonpregnant animals (day 0) (Herrera et al., 1990a). We suggest that at this time of gestation maternal adipose tissue actively hydrolyses and takes up circulating triglycerides and that this action may also contribute to the accumulation of body fat occurring during the first part of gestation.

Lipoprotein lipase activity in adipose tissue decreases during late gestation in the rat (Otway and Robinson, 1968; Hamosh et al., 1970; Ramirez et al., 1983; Herrera et al., 1988, 1990a). This effect, together with the reduction in fatty acids and in glyceride glycerol synthesis as compared to its rise at mid gestation (Palacín et al., 1991) and the increased lipolytic activity commented on above, results in the net increase in fat depot breakdown that occurs before parturition. The benefits of this striking transition from an anabolic to a catabolic condition in the maternal lipid metabolism are not yet completely understood, because, although this transition coincides with the maximal fetal growth phase (Herrera et
Figure 7 - Role of lipoprotein lipase activity (LPL) present in the capillary endothelium on the metabolism of triglyceride-rich lipoproteins, very low-density lipoproteins (VLDL) and chylomicrons, and the hydrolysis and tissue uptake of circulating triglycerides (tg). FFA, Free fatty acids; Glyc, glycerol.

al., 1988; López-Luna et al., 1991), lipids can only cross the placental barrier with difficulty (Herrera et al., 1992a) (Figure 5). As will be discussed below, this situation permits maximal development of maternal hypertriglyceridemia which, together with the presence of lipoprotein lipase activity in both the placenta and the mammary gland (Ramírez et al., 1983; Herrera et al., 1988), may warrant the access of essential fatty acids to the fetus and the newborn.

Maternal hypertriglyceridemia

Hypertriglyceridemia is a common feature in normal pregnancy both in women (Desoye et al., 1987; Herrera et al., 1988; Knopp et al., 1992; Montelongo
et al., 1992) and in the rat (Montes et al., 1978; Argiles and Herrera, 1981; Ramirez et al., 1983). Although, from a longitudinal study in pregnant women at different stages of gestation we know that hypertriglyceridemia corresponds to an enrichment of triglycerides in all circulating lipoproteins (Montelongo et al., 1992), quantitatively, the greatest change is found in the plasma VLDL-triglyceride levels. These lipoproteins are synthesized in the liver and the triglycerides that carry them must proceed either from the fatty acids and glycerol that are synthesized within this organ or from those that reach the liver from the circulation after their release from adipose tissue lipolysis (Figure 8). The plasma concentration of VLDL-triglycerides increases progressively with gestational

Figure 8 - Schematic representation of the metabolic fate of the adipose tissue lipolytic products and production by the liver of very low-density lipoproteins (VLDL) for their catabolism by extrahepatic tissues.

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time in women, attaining the highest value at the 3rd trimester and declining rapidly after parturition (Montelongo et al., 1992).

Multiple factors probably contribute to this increase in VLDL-triglycerides. One of them must be the active adipose tissue breakdown which is especially intense during late gestation, as commented on above. The enhanced arrival of the lipolytic products, FFA and glycerol, to the liver would facilitate their use for triglyceride synthesis and the export of triglycerides to the circulation in the form of VLDL (see Figure 8). An increased production of VLDL-triglycerides has been demonstrated directly in perfused liver from pregnant rats (Wasfi et al., 1980), and the same conclusion has been reached from indirect experiments (Humphrey et al., 1980). The progressive and intense increase of estrogens occurring during gestation may be responsible for the increase in liver VLDL production (Knopp et al., 1992).

Another factor that may contribute to the increment of VLDL-triglycerides in maternal circulation is the reduction in adipose tissue lipoprotein lipase activity commented on above. Since this enzyme controls the catabolism of the VLDL-triglycerides, the reduction of its activity in adipose tissue could be compensated for by a change in the opposite direction in other tissues, as was shown to occur in the heart, placenta, and, especially, in the mammary gland (Ramirez et al., 1983). However, when measuring post-heparin lipoprotein lipase activity as an index of the overall activity of this enzyme in the whole body in pregnant women, we recently found that it is decreased at the 3rd trimester of gestation as compared to earlier stages of gestation and post-partum (Herrera et al., 1992c). This indicates that the overall reduction in lipoprotein lipase activity in maternal tissues, at least in part, impedes a normal catabolic rate of the exaggerated amount of VLDL-triglycerides that are present in the mother during the last gestational trimester and therefore contributing to their exaggerated increase.

In addition to being a circulating energy source for rapid use under emergency conditions such as starvation, where circulating triglycerides may be used as substrates for liver ketogenesis (Herrera et al., 1988), the major physiological role of maternal hypertriglyceridemia is its active contribution to milk synthesis in preparation of lactation (Herrera et al., 1994). We showed that following an oral load of labelled triglyceride there is a rapid appearance of labelled lipids in the mammary gland (Argiles and Herrera, 1989) and that blocking the increase in mammary gland lipoprotein lipase activity by treatment with progesterone in the late pregnant rat completely inhibits the decline in plasma triglycerides normally occurring near parturition in the rat (Ramirez et al., 1983). These findings demonstrate that the rapid and intense increase in mam-
mary gland lipoprotein lipase activity before parturition facilitates the clearance of circulating triglycerides and their use in milk synthesis.

Role of maternal insulin in the metabolic adaptations which occur during gestation

We have seen above that during the early part of gestation the mother is in an anabolic condition as indicated by the progressive increase in her net body weight (see Figure 1), which mainly corresponds to fat accumulation (López-Luna et al., 1986, 1991; Herrera et al., 1988; Villar et al., 1992). This net anabolic condition lasts until about day 15 of gestation in the rat and may be driven by insulin since it is well known that insulin is the most efficient anabolic hormone, and as shown in Figure 9, its circulating levels are already greatly increased at this time during gestation, remaining high until late gestation. It could be argued, however, that decreased insulin sensitivity could be counteracting the hyperinsulinemia, as is known to occur during late gestation (see below). However, as shown in Figure 10, the intravenous responsiveness to insulin is not modified in the 15-day pregnant rat as compared to virgin controls whereas, in the 20-day pregnant rat the response

Figure 9 - Effect of pregnancy on the plasma insulin levels in the rat. Insulin was measured by radioimmunoassay (Heding, 1972). Data are reported for 5-7 rats in each group. *P<0.01 compared to nonpregnant rats (t-test).
is clearly decreased, as would be expected. This result agrees with our recent findings which showed a normal or even an increased oral glucose tolerance by the 15-day pregnant rat (Muñoz et al., 1992), indicating that at this stage of gestation insulin sensitivity is still unchanged. Hyperinsulinemia in the presence of unchanged insulin sensitivity, therefore, may drive the anabolic tendencies of the mother during the first two-thirds of gestation.

However, the situation is substantially modified during late gestation, when both hyperinsulinemia and insulin resistance are consistently present in both humans (Spellacy and Goetz, 1963; Ryan et al., 1985) and rats (Knopp et al., 1970b; Leturque et al., 1984; Martín et al., 1986) (see Figures 9 and 10). On the basis of the well-known metabolic effects of insulin, it can be hypothesized that the decreased insulin responsiveness of maternal tissues could be responsible for several of the metabolic changes taking place during this late stage of gestation. To test this hypothesis, we recently were able to revert maternal insulin resistance in the pregnant rat by subjecting 17-day pregnant rats and virgin controls under conscious and unrestrained conditions to a continuous intravenous infusion with 50% glucose (35 ml/day) for 72 h. This causes a sustained exaggerated hyperinsulinemia in normoglycemic conditions which decreases insulin

Figure 10 - Hypoglycemic effect during the first 16 min of the intravenous administration of insulin (10 IU of porcine insulin, Actrapid monocomponent from Novo/kg body weight) in the conscious rat at different times of gestation. Blood was collected from the tail and glucose was measured (Hugget and Nixon, 1957) after protein precipitation (Somogyi, 1945). Data are reported for 5 rats per group. *P<0.001 compared to 0 days (t-test).
sensitivity in virgin rats, whereas it reverts insulin resistance in the pregnant rat, as tested by the euglycemic-hyperinsulineemic clamp technique (P. Ramos and E. Herrera, unpublished data). In agreement with this finding, the data in Figure 11 show that continuous intravenous infusion with glucose for 72 h increases the responsiveness to intravenous insulin in the 20-day pregnant rat when compared to pregnant controls, and the former group attains a value closer to that observed for untreated virgin rats. We have also shown that the glucose infusion causes a greater reduction of circulating FFA and a greater increase in the liver glycogen concentration in pregnant, than in virgin rats (P. Ramos and E. Herrera, unpublished data), indicating that decreased insulin sensitivity in the untreated pregnant rat contributes to the enhanced adipose tissue lipolytic activity (Knopp et al., 1970a) and the decreased glycogen storage capacity (Hagerman, 1962) normally demonstrable in the mother during late gestation.

We recently demonstrated that pregnant rats subjected to the same glucose-infusion protocol presented a larger increase in lumbar adipose tissue lipoprotein lipase activity than virgin rats (Herrera et al., 1990b; Martín et al., 1993). These data indicate that maternal insulin resistance is also responsible for the decreased lipoprotein lipase activity normally seen in adipose tissue during late gestation.

The mechanism by which insulin resistance develops during late gestation is not yet completely understood, but present findings indicate that it allows the mother to maintain an accelerated catabolic condition which is especially exaggerated when food is withheld. This guarantees the availability of substrates.

*Figure 11 - Effect of a continuous glucose infusion (35 ml 50% glucose/day) for 3 days (day 17 to 20 of gestation) on the hypoglycemic effect of intravenous insulin (1 IU of porcine insulin, Actrapid monocomponent from Novo/kg body weight) in 20-day pregnant rats under unrestrained conditions. Virgin and pregnant-control rats were infused for the same time with bidistilled water. Data are reported as means ± SEM glucose disappearance rate, $K_i$, as %/min for 6 rats per group measured during the first 16 min after insulin administration. Blood glucose was measured as indicated in the legend to Figure 10. *P<0.05 compared to virgin rats and †P<0.05 compared to pregnant-control rats (t-test).
to sustain the rapid fetal growth during the third part of gestation. This view is supported by the fact that, as shown in Figure 12, despite the fact that 24-h starvation causes a greater reduction of body weight in 20-day pregnant rats than in their age- and sex-matched virgin controls as a consequence of the greater catabolic condition of the former, their fetuses do not show any change in body weight, indicating an appropriate availability of nutrients.

Figure 12 - Effect of 24-h fasting on body weight of virgin and 21-day pregnant rats and their fetuses. Data are reported as means for 7 rats in each group. *P<0.01 compared to fed animals of the same group, filled bars. Open bars indicate fasted group.

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