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Metabolic adaptations in pregnancy and their implications for the availability of substrates to the fetus

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During the first two-thirds of gestation, the mother is in an anabolic condition, increasing her fat depots thanks to both hyperphagia and enhanced lipogenesis. During the last third of gestation, the mother switches to a catabolic condition. Glucose is the most abundant nutrient crossing the placenta, which causes maternal hypoglycemia despite an increase in the gluconeogenic activity. Adipose tissue lipolytic activity becomes enhanced, increasing plasma levels of FFA and glycerol that reach the liver; consequently there is an enhanced production of triglycerides that return to the circulation in the form of very low density lipoproteins (VLDL). Glycerol is also used as a preferential gluconeogenic substrate, saving other more essential substrates, like amino acids, for the fetus. Under fasting conditions, fatty acids are converted into ketone bodies throughout the β -oxidation pathway, and these compounds easily cross the placental barrier and are metabolized by the fetus.

An enhanced liver production of VLDL-triglycerides together with a decrease in adipose tissue lipoprotein lipase (LPL) and an increase in plasma activity of cholesterol ester transfer protein causes both an intense increment in these lipoproteins and a proportional enrichment of triglycerides in both low and high density lipoproteins. Maternal triglycerides do not cross the placenta, but the presence of LPL and other lipases allows their hydrolysis, releasing fatty acids to the fetus. Under fasting conditions, the maternal liver uses circulating triglycerides as ketogenic substrates. Around parturition there is an induction of LPL activity in the mammary glands, driving circulating triglycerides to this organ for milk synthesis, allowing essential fatty acids derived from the mother's diet to become available to the suckling newborn.

Descriptors: gestation; gluconeogenesis; lipoproteins; lipolysis; lipoprotein lipase; adipose tissue
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Introduction

During pregnancy the mother eats intermittently but must continuously supply nutrients to the fetus in order to sustain its exponential growth (Hyttén & Leitch, 1971, Herrera *et al.*, 1994a). Glucose is quantitatively the most important substrate crossing the placenta, followed by amino acids (Herrera *et al.*, 1985; Lasunción *et al.*, 1987), and is responsible for the mother's tendencies to develop both hypoglycemia (Herrera *et al.*, 1969) and hypoaminoacidemia (Zorzano *et al.*, 1986). Lipid metabolism is especially affected during pregnancy, despite the fact that, except for free fatty acids (FFA) and ketone bodies, the placenta is practically impermeable to lipids (Herrera *et al.*, 1990, 1991, 1998).

From the metabolic point of view, there are two clearly differentiated stages during gestation. During the first one, corresponding to the first two thirds, when fetal growth is very limited, the mother stores a great proportion of the nutrients she eats, which together with her hyperphagia causes an accumulation of fat stores, as seen both in women (Villar *et al.*, 1992) and in rats (López Luna *et al.*, 1986, 1991). During the last third of gestation fetal growth is very rapid, being sustained by an enhanced transfer of nutrients throughout the placenta, which makes the mother to switch to a catabolic condition. This is specially reflected in an enhanced breakdown of lipid stores, of which adipose

tissue lipolysis is the most representative (Chaves & Herrera, 1978; Knopp *et al.*, 1970; Martín-Hidalgo *et al.*, 1994). Such an enhanced catabolic condition during late pregnancy is especially noticeable under reduced food intake conditions (Freinkel *et al.*, 1970b), in which the rates of both ketogenesis and gluconeogenesis become highly accelerated, allowing the continuous availability of nutrients to the fetus. Based in our own data, this paper reviews these metabolic adaptations that take place during pregnancy.

Carbohydrate and amino acid metabolism through gestation

During late pregnancy the mother tends to develop hypoglycemia, which is especially manifest during fasting (Bleicher *et al.*, 1964; Herrera *et al.*, 1969). Since under this condition liver glycogen stores are depleted, such hypoglycemia may be a consequence of either a decreased gluconeogenesis, an enhanced utilization of glucose or both factors together. Indirect studies in women (Assel *et al.*, 1993) and direct experiments in rats (Herrera *et al.*, 1969, 1991; Zorzano & Herrera, 1984; Zorzano *et al.*, 1986), show that the rate of gluconeogenesis is enhanced during pregnancy under fasting conditions. In addition, the effect of pregnancy enhancing gluconeogenesis depends on the type of substrate used; Figure 1 shows the *in vivo* synthesis of glucose from equimolecular amounts of three carbon compounds in 24 h fasted 21-day pregnant rats and virgin controls. The conversion of glycerol into glucose and the effect of pregnancy on it is even higher than that of other

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substrates, such as pyruvate and alanine, more commonly used as gluconeogenics. These results therefore indicate that the enzymatic capability to synthesize glucose when substrate is available is enhanced during late pregnancy under fasting conditions. It may, however, occur that endogenous gluconeogenic substrates could be decreased due to their transfer to the fetus, but although plasma levels of amino acids are decreased in pregnancy, pyruvate and lactate levels do not change while glycerol is significantly increased (Herrera *et al*, 1994a; Zorzano & Herrera, 1984).

It appears then that gestational hypoglycemia must be a consequence of an enhanced utilization of glucose, which occurs despite the well known decreased consumption of glucose by maternal tissues due to the insulin resistant condition of pregnancy (Martin *et al*, 1986; Ramos & Herrera, 1995). In fact, the enhanced utilization of glucose is due to its high utilization by the fetal-placental unit, which corresponds to up to 50% of the total glucose utilized by the mother. The placental transfer of glucose is much higher than any other metabolite, including amino acids (Herrera *et al*, 1985, 1991), and is highly dependent on the positive maternal-fetal glucose gradient (Herrera *et al*, 1991; Lasunción *et al*, 1987; Palacin *et al*, 1984).

Maternal plasma is also the only source of amino acids for the fetus, but different from glucose, their concentration in fetal plasma is even higher than in the mother (Lasunción *et al*, 1987; Martin *et al*, 1990; Silver *et al*, 1994), because placental transfer of amino acids is carried out throughout an active process (Lasunción *et al*, 1987; Palacin *et al*, 1985). This warrants the appropriate availability of these essential metabolites to the fetus and justifies maternal tendencies to develop hypoaminoacidemia (Herrera *et al*, 1985).

Lipid metabolism

Adipose tissue lipolytic activity

During the last third of gestation there is an accelerated breakdown of fat depots (Chaves & Herrera, 1980; Freinkel *et al*, 1970a; Knopp *et al*, 1970). In fact, in white adipose

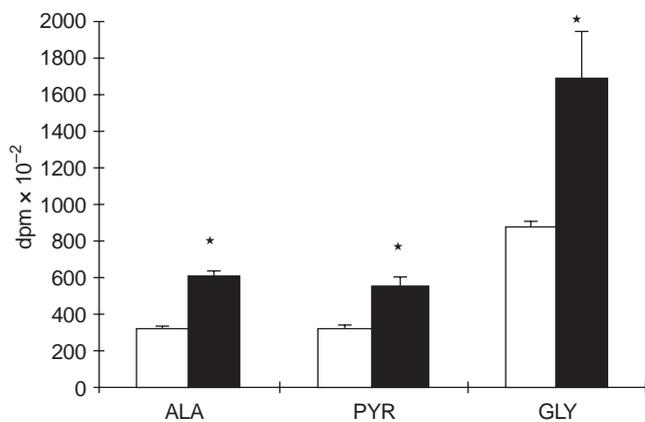


Figure 1 ¹⁴C-Glucose formation in 24h fasted 21-day pregnant (black bars) or virgin control rats (open bars) 5 min after 1 mmol of U-¹⁴C-alanine (ALA), 3-¹⁴C-pyruvate (PYR) or U-¹⁴C-glycerol (GLY). Unanesthetized rats were i.v. injected with the tracer, *n* = 6 rats/group. Values are means ± s.e.m. Statistical comparisons between pregnant and virgin animals are shown by an asterisk (**P* < 0.05). Other methodological details as in (Zorzano & Herrera, 1984).

tissue of late pregnant rats we previously found an enhanced activity and mRNA expression of the key lipolytic enzyme, hormone sensitive lipase (HSL), whereas lipoprotein lipase (LPL), an enzyme with an opposite effect on fat depots than HSL, shows reduced activity and mRNA expression (Martin-Hidalgo *et al*, 1994).

Despite the enhanced release of lipolytic products from adipose tissue into the circulation, their placental transfer is quantitatively low (Herrera *et al*, 1998). Under non-pregnant conditions, the main fate of these products is the liver (Carmaniu & Herrera, 1979; Mampel *et al*, 1981), and this is also the case during gestation (Mampel *et al*, 1985). In liver, after conversion of FFA into acyl-CoA and glycerol into glycerol-3-phosphate, these compounds are re-esterified for the synthesis of triglycerides and their subsequent release into the circulation in the form of very low density lipoproteins (VLDL) (Figure 2). Besides, under fasting conditions FFA may be used through the β -oxidation for acetyl-CoA and ketone bodies synthesis, whereas glycerol is used for glucose synthesis, and these pathways are enhanced during late pregnancy (Zorzano *et al*, 1986; Herrera *et al*, 1969; Scow *et al*, 1964). Ketone bodies easily cross the placenta through simple diffusion (Herrera *et al*, 1998), reaching in fetal plasma the same levels as in the mother (Herrera *et al*, 1987, 1990), despite that the fetus is not able to synthesize them. Besides, different to adults, ketone bodies may be used both as fuels (Shambaugh, 1985) and lipogenic substrates by the fetal brain (Patel *et al*, 1975). The high levels of glycerol in maternal plasma and its efficient conversion into glucose also benefit the fetus when the mother is under fasting conditions and the availability of other substrates, such as amino acids, become more limited (Herrera *et al*, 1992a; Zorzano & Herrera, 1986; Zorzano *et al*, 1986). These interactions are also summarized in Figure 2. Although few maternal tissues need glucose continuously, like the nervous tissue, under fasting conditions the use of ketone bodies by other maternal tissues, like the skeletal muscle, allows reduction of the consumption of glucose, which is preserved for placental transfer.

Enhanced fat depots in maternal tissues

In order to support the enhanced lipid catabolism during the last third of gestation, the mother had to store fat depots in earlier stages. It is well known that an enhanced accumulation of fat depots is one of the characteristic features during pregnancy both in women (Hyttén & Leitch, 1971; Villar *et al*, 1992) and rats (López-Luna *et al*, 1986, 1991). Studies in rats show that the increase in maternal fat depots takes place during the first two-thirds of gestation (López-Luna *et al*, 1986; Sohlström *et al*, 1994), and are a consequence of both hyperphagia, which is clearly present both in women (Murphy & Abrams, 1993; Piers *et al*, 1995) and in rats (Moore & Brassel, 1984; Lederman & Rosso, 1980), and enhanced adipose tissue lipogenesis (Herrera *et al*, 1991; Palacin *et al*, 1991).

Hyperlipidemia during pregnancy

Hyperlipidemia is constantly present during late gestation and mainly corresponds to an intense increase in plasma triglycerides, as reported in women (Alvarez *et al*, 1996; Herrera *et al*, 1988; Knopp *et al*, 1992; Montelongo *et al*, 1992) and in rats (Argiles & Herrera, 1981; Herrera & Munilla, 1997; Munilla & Herrera, 1997; Soria *et al*, 1996).

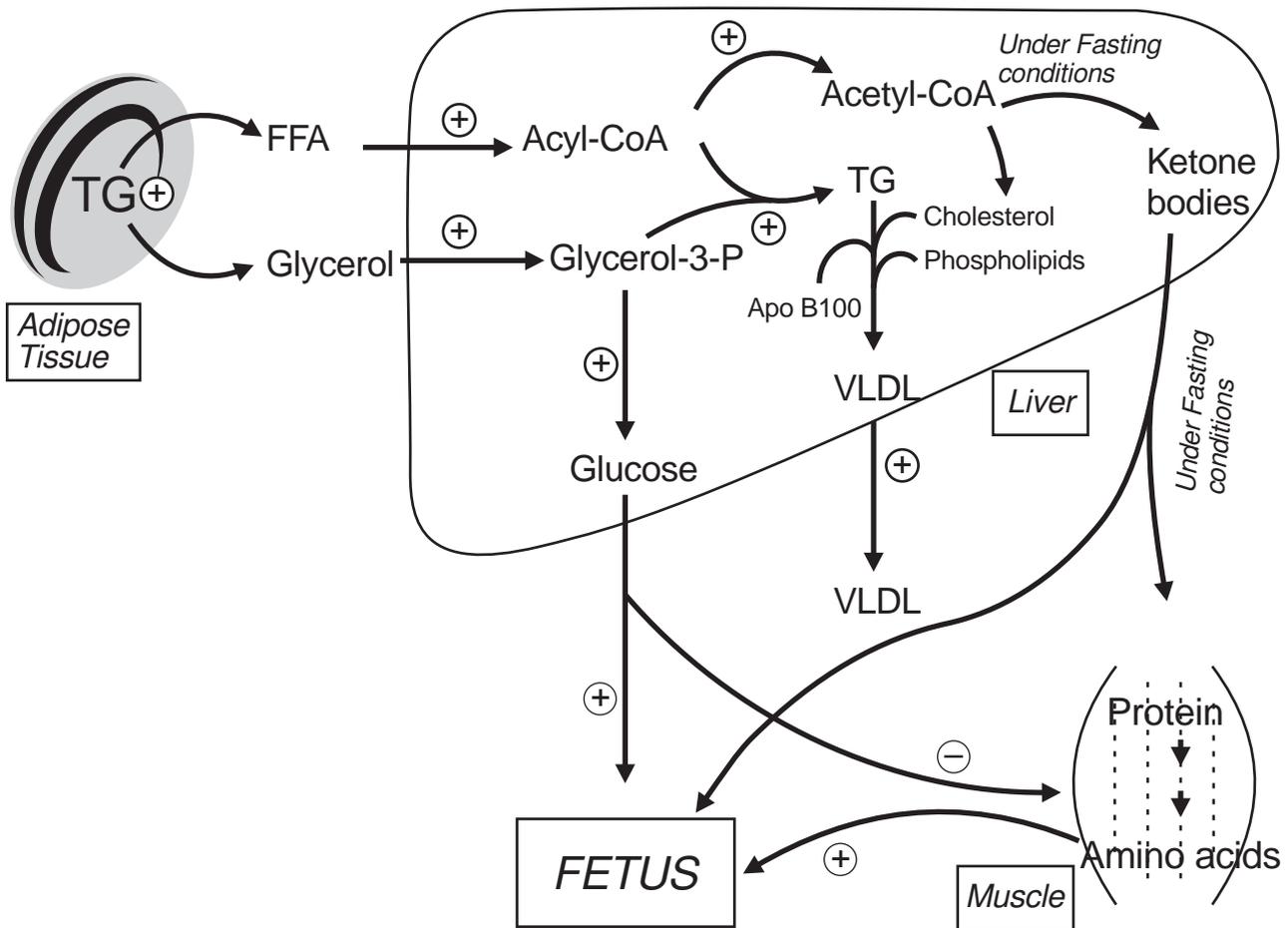


Figure 2 Schematic representation of the effect of pregnancy on adipose tissue lipolysis, the metabolic fate of the lipolytic products and liver production of glucose, very low density lipoproteins (VLDL) and ketone bodies, and the availability of substrates to the fetus. TG = Triglycerides; FFA = free fatty acids.

Although under non-pregnant conditions the content of triglycerides in low density lipoproteins (LDL) and high density lipoproteins (HDL) is normally low as compared to very low density lipoproteins (VLDL), during late gestation

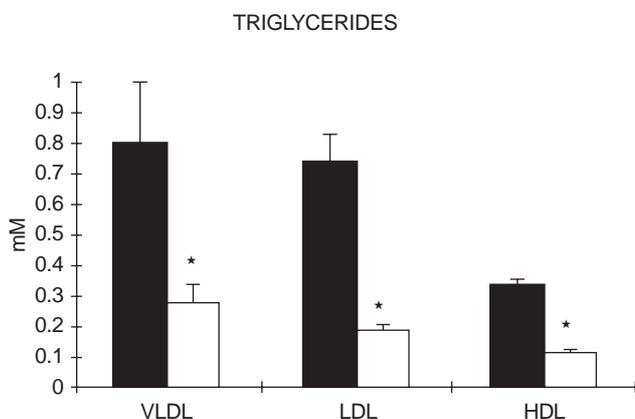


Figure 3 Plasma lipoprotein triglycerides in women at the third trimester of pregnancy (black bars) and at post-lactation (open bars). Values are means \pm s.e.m. Statistical comparisons between pregnant and post-lactating women are shown by asterisks (* $P < 0.05$). Other details as in Montelongo *et al* (1992).

in women there is a significant increase in plasma level of triglycerides in all these lipoprotein fractions (Figure 3).

Besides the enhanced lipolytic activity of adipose tissue commented on above, which enhances liver VLDL-triglycerides production, a decrease in adipose tissue LPL activity may also contribute to the augmented plasma level of VLDL-triglycerides during gestation. This enzyme is anchored to the vascular endothelium through heparan sulfate molecules in its active form, controlling the catabolism of VLDL-triglycerides (Braun and Severson, 1992), and its activity has been found to be decreased during late pregnancy, not only in adipose tissue (Herrera *et al*, 1988; López-Luna *et al*, 1994; Ramirez *et al* 1983) but in total body, as shown after the intravenous heparin administration (Alvarez *et al*, 1996).

Besides its physiological implications, the abundance of VLDL-triglycerides in maternal plasma may contribute to enrich lipoproteins of higher density, LDL and HDL with triglycerides. In healthy pregnant women an increase in the activity of the cholesterol ester transfer protein (CETP) has been found at mid gestation (Alvarez *et al*, 1996; Iglesias *et al*, 1996). This protein controls triglycerides and cholesterol exchange between VLDL, LDL and HDL. Thus, the increase in the level of VLDL-triglycerides in the presence of an enhanced CETP activity during pregnancy facilitates a proportional enrichment of triglycerides in LDL and HDL.

Benefits of maternal hypertriglyceridemia to the fetus and the newborn

Despite that triglycerides do not directly cross the placental barrier (Herrera *et al*, 1998), we think that maternal hypertriglyceridemia may benefit the fetus and the newborn in various manners. It represents a floating energetic deposit, which can be easily and rapidly used under fasting conditions for ketone body synthesis in the liver. Although the adult liver normally does not have LPL, in the liver of the fasting pregnant rat an intense increase in LPL activity has been detected (Herrera *et al*, 1988; Testar *et al*, 1985). Through this mechanism the liver of the fasting pregnant rat becomes an importer rather than an exporter organ for circulating triglycerides, which may be used as substrates for ketogenesis. This increases plasma ketone bodies in the fasted pregnant mother more than under nonpregnant conditions (Herrera *et al*, 1969, 1988), allowing not only glucose saving by maternal tissues but also an increase in the availability of ketone bodies to the fetus for their metabolism.

Another mechanism by which the fetus benefits from maternal hypertriglyceridemia is the availability of essential fatty acids from maternal diet. These fatty acids are normally carried in maternal plasma in the form of chylomicron-triglycerides, and efficient intestinal absorption of dietary triglycerides during late pregnancy is known (Argiles & Herrera, 1989). The placenta takes up maternal circulating triglycerides as a function of their concentration (Herrera *et al*, 1992b), where LPL and other lipases hydrolyze them, releasing free fatty acids to the fetal side (Herrera *et al*, 1998).

A third mechanism by which maternal hypertriglyceridemia may benefit the offspring development is its contribution to milk synthesis in preparation to lactation (Herrera *et al*, 1994b). Around parturition there is a rapid increase in LPL expression and activity in mammary gland (López-Luna *et al*, 1994, Ramirez *et al*, 1983; Ramos & Herrera, 1996), as a consequence of both increased prolactin and insulin levels and a specific enhancement in mammary gland insulin sensitivity (Carrascosa *et al*, 1998; Ramos *et al*, 1999), which together with its decrease in adipose tissue drives circulating triglycerides to the former tissue (Argiles & Herrera, 1989). The induction of LPL in mammary gland during late gestation therefore facilitates the clearance of circulating triglycerides for milk synthesis and, through this mechanism, essential fatty acids coming from maternal diet become available to the suckling newborn, actively contributing to his normal development.

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