DIABETES/METABOLISM RESEARCH AND REVIEWS
Diabetes Metab Res Rev 2000; **16**: 202–210.

REVIEW ARTICLE

Lipid metabolism in the fetus and the newborn

Emilio Herrera*
Encarnación Amusquivar

Facultad de Ciencias Experimentales y Técnicas, Universidad San Pablo-CEU, E-28668 Madrid, Spain

*Correspondence to: Dr. E. Herrera, Universidad San Pablo-CEU, Urb. Montepríncipe, Ctra. Boadilla del Monte km 5.3, E-28668 Madrid, Spain.
E-mail: eherrera@ceu.es

Received: 19 October 1999
Revised: 15 March 2000
Accepted: 30 March 2000

Summary

During late gestation, although maternal adipose tissue lipolytic activity becomes enhanced, lipolytic products cross the placenta with difficulty. Under fasting conditions, free fatty acids (FFA) are used for ketogenesis by the mother, and ketone bodies are used as fuels and lipogenic substrates by the fetus. Maternal glycerol is preferentially used for glucose synthesis, saving other gluconeogenic substrates, like amino acids, for fetal growth. Placental transfer of triglycerides is null, but essential fatty acids derived from maternal diet, which are transported as triglycerides in lipoproteins, become available to the fetus owing to the presence of both lipoprotein receptors and lipase activities in the placenta. Diabetes in pregnancy promotes lipid transfer to the fetus by increasing the maternal–fetal gradient, which may contribute to an increase in body fat mass in newborns of diabetic women. Deposition of fat stores in the fetus is very low in the rat but high in humans, where body fat accretion occurs essentially during the last trimester of intra-uterine life. This is sustained by the intense placental transfer of glucose and by its use as a lipogenic substrate, as well as by the placental transfer of fatty acids and to their low oxidation activity. During the perinatal period an active ketonemia develops, which is maintained in the suckling newborn by several factors: (i) the high-fat and low-carbohydrate content in milk, (ii) the enhanced lipolytic activity occurring during the first few hours of life, and (iii) both the uptake of circulating triglycerides by the liver due to the induction of lipoprotein lipase (LPL) activity in this organ, and the presence of ketogenic activity in the intestinal mucose. Changes in LPL activity, lipogenesis and lipolysis contribute to the sequential steps of adipocyte hyperplasia and hypertrophia occurring during the extra-uterine white adipose tissue development in rat, and this may be used as a model to extrapolate the intra-uterine adipose tissue development in other species, including humans.

Keywords fetal metabolism; adipose tissue; essential fatty acids; ketone bodies; suckling; diabetes

Metabolic changes occurring in the mother sustaining fetal lipidic metabolism

Fetal metabolism, and consequently fetal growth, directly depend on the nutrients crossing the placenta, and therefore the mother adapts her metabolism in order to support this continuous draining of substrates. The mother develops hyperphagia from early gestation which, together with endocrine changes, allow her net body weight to be increased (free of the conceptus), and such change mainly corresponds to the accumulation of fat depots which occurs during the first two-thirds of gestation both in women [1–3] and in rat [4–6]. During the last trimester of gestation, maternal lipid metabolism switches to a catabolic condition, as shown by an accelerated breakdown of fat depots. Adipose tissue lipolytic activity becomes enhanced

both in women [7,8] and in rat [9,10]] as a consequence of an increase in both mRNA expression and activity of the hormone sensitive lipase [11], the key enzyme for the lipolytic cascade.

In light of the above, one would expect an intense transfer of maternal adipose tissue lipolytic products to the fetus but this is not the case. As shown in Figure 1, the substrate crossing the placenta in the largest quantities is glucose, followed by amino acids [12–14], whereas both FFA and glycerol cross the placental barrier in smaller proportions [15]. In fact, when interspecies comparisons of fetal accretion are made, it emerges that in humans, which at birth have a high body fat content, the placenta is relatively permeable to free fatty acids. It has been suggested that during early gestation, embryonic and fetal lipids are derived from maternal FFA crossing the placenta, whereas in advanced gestation there is a gradual shift to *de novo* synthesis in fetal tissue [16]. As shown in Figure 2, plasma FFA level is higher in 24 h-fasted 20-day pregnant rats than in virgin rats, which agrees with the active adipose tissue lipolytic activity in the former and the limited capability of the placenta for FFA transfer, which may also be responsible for the low plasma level of FFA found in fetal plasma. Plasma FFA are mainly directed to the liver, where they can be used for either esterification in the synthesis of glycerides or oxidation and ketone body synthesis. Both of these pathways are enhanced in the fasted mother during late gestation as shown in the rat [17–19], and plasma ketone body level in 24 h-fasted 20-day pregnant rats is much higher than in virgin rats (Figure 2). Despite ketogenesis not being active in the fetus [20,21], ketone bodies in fetal plasma reach the same level as in the mother (Figure 2) since they are easily transferred through the placenta. The fetus therefore benefits from this product of maternal fatty acid metabolism since ketone bodies may be used not only as fuels [21] but also as lipogenic substrates [22,23].

Placental transfer of glycerol is also very limited (Figure 2), which together with the active adipose tissue lipolytic activity during late gestation described above, justifies the increase in plasma glycerol level seen

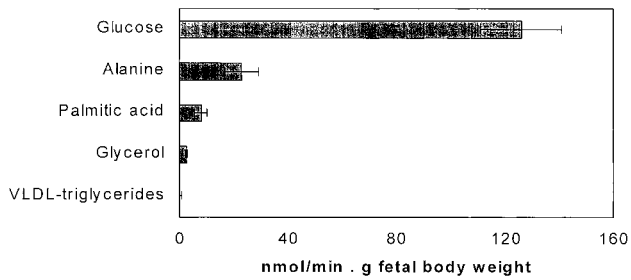

Figure 1. Transfer of D-glucose, L-alanine, palmitic acid, glycerol and very low density (VLDL) triglycerides in the 20-day pregnant rat placenta *in situ*. Placental transfer was measured as previously described [120], based on the infusion of ^{14}C-labeled substrates through the left uterine artery and making proper correction of data for specific activity dilution and uterine artery blood flow

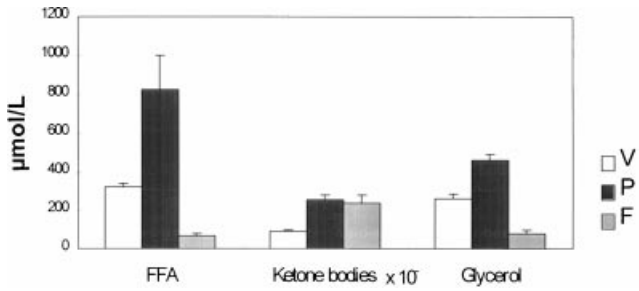

Figure 2. Plasma level of FFA, ketone bodies (β-hydroxybutyrate plus acetoacetate) and glycerol in 24 h-fasted virgin (V), 20-day pregnant rats (P) and their fetuses (F) measured by enzymatic procedures. Differences between values of pregnant vs virgin rats were always statistically significant ($p < 0.001$) whereas those between fetuses and their mothers were significant for both FFA and glycerol ($p < 0.001$) but not for ketone bodies

in the 24 h-fasted 20-day pregnant rat, and its low concentration in fetal plasma. Maternal glycerol is, however, being used as a preferential substrate for glucose synthesis, as reported in the rat [24–26], and this mechanism not only warrants the availability of glucose for placental transfer but saves the use of other gluconeogenic substrates like amino acids, which are less available in maternal circulation [27,28] but are essential for fetal growth.

Another metabolic adaptation normally occurring during late gestation is the development of maternal hypertriglyceridemia. Such hypertriglyceridemia occurs in the mother resulting from an enhanced liver production of VLDL-triglycerides [29,30], together with an increase in the transfer of triglycerides among the different lipoprotein fractions [31,32], an increase in the intestinal absorption of dietary lipids [33] and a reduced clearance of triglyceride-rich lipoproteins due to decreased extrahepatic lipoprotein lipase (LPL) activity which occurs both in women [32] and in rats [11].

Maternal triglycerides do not directly cross the placenta (see Figure 1) but, besides being a source of essential fatty acids for the fetus (see below), they may be used by the fetus as a source of oxidative substrates, although in an indirect manner and under a metabolic emergency condition, such as starvation. Despite the fact that the adult liver lacks LPL expression, 24 h starvation causes a marked increase in liver LPL activity in pregnant rats, although not in nonpregnant rats [34,35], and such change is paralleled by a similar increase in both liver triglycerides and plasma ketone body concentrations [36]. It is believed that such LPL activity in the liver of the starved pregnant rat has an extrahepatic origin, but it is proposed that through this mechanism, the liver, which under normal conditions is a triglyceride-exporter organ, becomes a heightened acceptor of circulating triglycerides, thus allowing their increased consumption as ketogenic substrates, and therefore contributing to the enhanced maternal ketonemia commented above. This condition not only promotes ketone bodies availability to the fetus but must also contribute to a reduced utilization

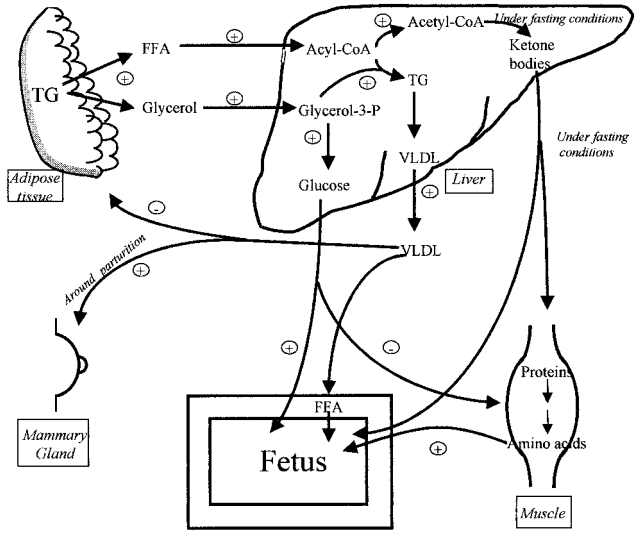

Figure 3. Schematic representation of major interactions of maternal lipid metabolism during the third trimester of gestation, with an indication of their consequences for the availability of substrates by the fetus. Activated steps (+) and inhibited steps (−). TG = triglycerides

of other substrates by maternal tissues. This appears to be the case for glucose and amino acids, whose levels in the fasting mother's plasma must be preserved for their placental transfer to the fetus, where they are essential. An integrated representation of these interactions of lipid metabolism during the last trimester of gestation is shown in Figure 3.

Maternal insulin resistance normally developed during the last third of gestation in both women [37,38] and rats [39,40] seems to play a key role in some of these metabolic adaptations of lipid metabolism during pregnancy. Studies in the rat have shown that insulin resistance during late pregnancy is responsible for the enhanced adipose tissue lipolysis [41] as well as for a decreased adipose tissue lipoprotein lipase activity [42]. These changes, together with the enhancement in plasma estrogen levels taking place during late pregnancy [32], which are known to decrease hepatic lipase activity [43], enhance liver VLDL production [44,45] and enrich HDL in triglycerides [46], have been proposed to be responsible for the major interactions occurring in lipoprotein metabolism during late gestation [32,47]. Plasma estrogen levels during gestation were found to be decreased in diabetic women [47], and this effect may restrain the development of an overtly hyperlipidemic condition in certain diabetic pregnant patients.

Availability of essential fatty acids to the fetus

In spite of the lack of direct placental transfer of triglycerides (Figure 1 and refs [15,48]), essential fatty acids derived from maternal diet, which are transported as triglycerides in triglyceride-rich lipoproteins in maternal plasma, have to become available to the fetus. Intrauterine requirements for $\omega 6$ and $\omega 3$ fatty acids in the human fetus during the last trimester of fetal development through the early weeks of life have been estimated to be 400 mg/kg/day and 50 mg/kg/day, respectively [16]. In tissues such as the brain, where lipid makes up nearly 50% of the dry weight, around half the total lipid content is composed of long-chain polyunsaturated fatty acids (LCPUFA) [49], of which, arachidonic acid ($20:4\omega 6$) and docosahexaenoic acid ($22:6\omega 3$) are metabolically the most important. The presence of a direct maternal/fetal relationship for essential fatty acids in the rat is shown in Figure 4. At day 20 of gestation, maternal plasma linoleic acid ($18:2\omega 6$), arachidonic acid ($20:4\omega 6$), eicosapentaenoic acid ($20:5\omega 3$) and docosahexaenoic acid ($22:6\omega 3$) in rats fed a semisynthetic diet containing 5% of either palm oil, sunflower oil, olive oil or fish oil as the only source of fat through gestation correlated linearly and significantly with those present in fetal liver (Figure 4).

Apart from their role in maintaining the membrane structure and functional properties, the LCPUFA also play a critical role in metabolic control as precursors of the prostacyclins, prostaglandins, thromboxanes and leukotrienes. Thus, the ability of the placenta to extract those fatty acids from maternal circulation and deliver them to the fetus becomes highly important. The availability of those fatty acids present in maternal plasma triglycerides to the fetus occurs thanks to the presence of lipoprotein receptors [50–52] and lipase activities [53–55] in the placenta. Through this mechanism, maternal plasma triglycerides are taken up by the placenta, where their intracellular hydrolysis facilitates the diffusion of released fatty acids to the fetus and their subsequent transport to the fetal liver. Besides, FFA in maternal circulation also cross the placenta [56,57], being an important FFA source to the fetus. There is now evidence that cellular uptake of FFA occurs via a facilitated membrane translocation process involving a plasma membrane fatty acid-binding protein ($FABP_{pm}$) [58,59]. It has been shown that $FABP_{pm}$ is present in both sheep [60] and human placental membranes [61], being also responsible for the preferential uptake of LCPUFA by the human placenta [62,63]. In fact, a selectivity by the human placenta for both uptake and intracellular metabolism and transport of individual fatty acids to the fetus has been reported [57,64,65], which may explain why the concentrations of some LCPUFAs are greater in the fetal than maternal circulation [64]. Through this mechanism, the placenta selectively transports arachidonic acid and docosahexaenoic acid from the maternal to the fetal compartment, resulting in an enrichment of these LCPUFAs in circulating lipids in the fetus. This occurs during the third trimester, when the fetal demands for neural and vascular growth are greater [66–68].

Diabetes in humans has been shown to have a profound impact on maternal circulating lipids in pregnancy, promoting their transfer to the fetus by increasing the maternal–fetal concentration gradient, especially of FFA

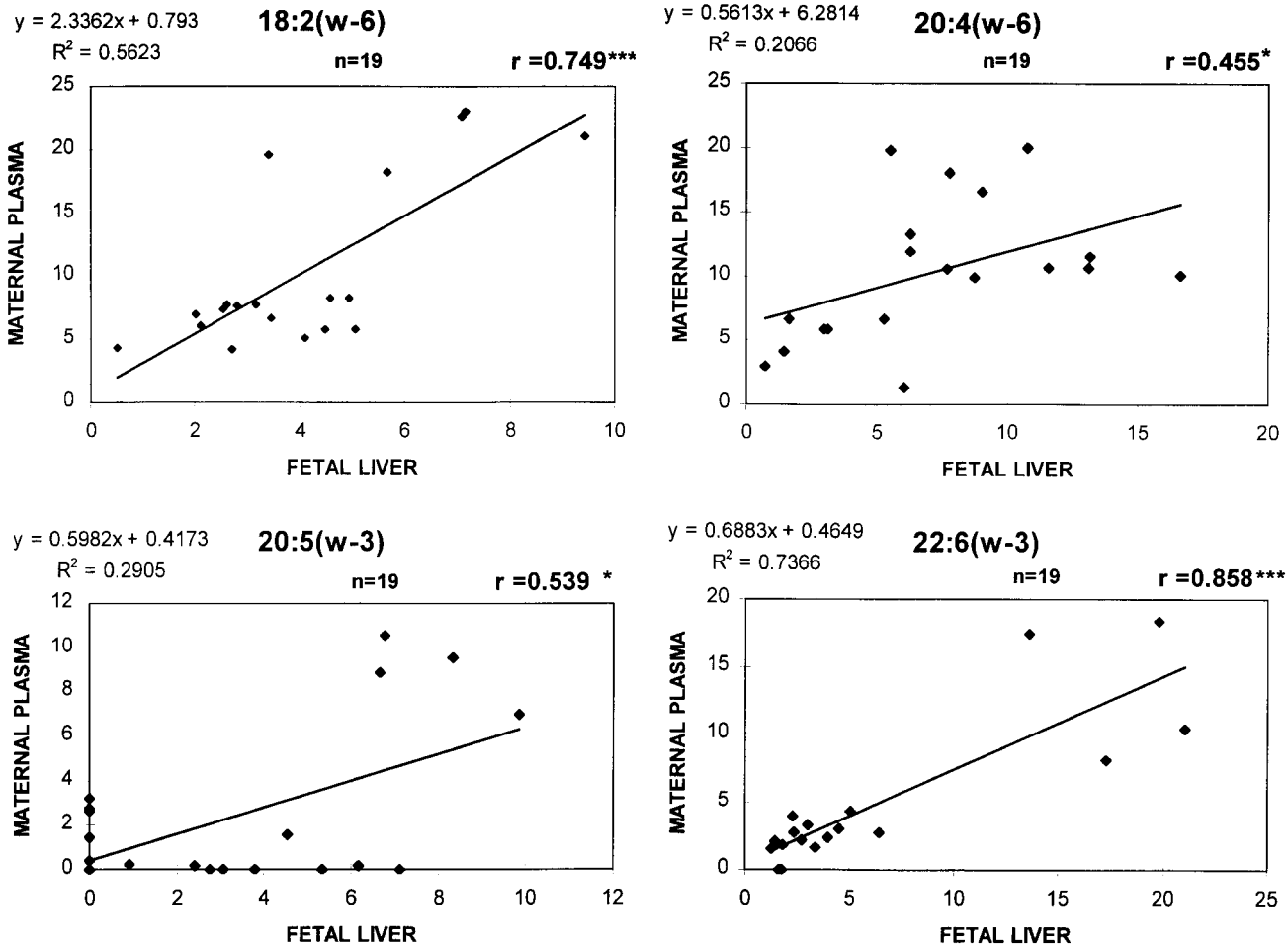

Figure 4. Linear correlation of essential fatty acids between maternal plasma and fetal liver in 20-day pregnant rats fed with a semisynthetic diet [121] containing 5% of either palm oil, sunflower oil, olive oil or fish oil as the only fat source from the day of mating. Asterisks indicate statistically significant correlation (*=$p<0.05$. ***=$p<0.001$)

and triglycerides [47,69]. It has been shown that the transfer of linoleic acid paralleled the increased transplacental passage of lipids in diabetes, but the uptake of arachidonic acid and its preferential incorporation into triglycerides rather than into phospholipids of the placental tissue and fetal effluent are increased in perfused human term placenta from women with Type 1 diabetes mellitus (DM) [70]. Thus, both the transfer and distribution of this essential LCPUFA is altered in Type 1 DM. An increased transport of linoleic and arachidonic acids was also noted in streptozotocin-induced diabetic rats [71].

Triglycerides and phospholipids are accumulated in the placenta in both human and rat diabetes [72], indicating an enhanced uptake, hydrolysis and re-esterification activity. In the diabetic late pregnant rat a correlation in plasma triglycerides and FFA between the mother and the fetus as well as an enhanced placental transfer of maternal fat to the fetus were found [73,74]. Since the higher birth weight in human diabetic pregnancy has been positively correlated with the extent of both maternal hyperlipoproteinemia [75] and maternal FFA levels [76], it is proposed that maternal hyperlipidemia and enhanced maternal–fetal fat transport may contribute to the fetal macrosomia frequently found in newborns of diabetic women.

Fat depots in the fetus

The continuous and active transfer of nutrients through the placenta fulfills the energetic demands, growth and fat storing deposition of the fetus. The latter is highly variable among mammalian species, lipid storage during fetal life being an exception rather than a rule, and in most species, body fat content at birth is very low and white adipose tissue is barely detectable, including in the rat [77,78]. However, in the human newborn, fat represents around 16% of body weight [79], and most of it is found in the form of white adipose tissue. In humans, body fat accretion occurs essentially during the last trimester of intra-uterine life. In fact, from week 30, fat accumulation exceeds that of nonfat components [80], and at week 36 of gestation, 1.9 g of fat accumulates for each gram of nonfat daily weight gain, and by term gestation, the deposition of fat accounts for more than 90% of the calories accumulated by the fetus [81], permitting the accumulation of 2.4 g of fat/kg/day [80,82].

Two main factors contribute to this rapid accumulation of lipids in the human fetus during late gestation: (i) besides being quantitatively the main substrate crossing the placenta, glucose is the main energy source for the fetus [83], and approximately 70% of fetal glucose uptake is converted to fat [16]. Both fetal liver and adipose tissue have been shown to have the capacity to synthesize fatty acids *de novo* [84,85]. The enlargement of body fat mass in newborns of diabetic women depends on the insulin-induced increase in triglyceride synthesis and storage as a result of the increased insulin production by the fetal pancreas which, in turn, is secondary to a larger glucose availability *in utero* [86]. (ii) As commented above, fetal essential fatty acids reflect those present in the mother's plasma, indicating that maternal fatty acids are available to the fetus throughout their placental transfer. In addition, fetal fatty acid oxidation is low [84] allowing the preferential channeling of fatty acids to adipose tissue for triglyceride synthesis.

Lipid metabolism during the perinatal period

Source of lipids in maternal milk around parturition

Fat constitutes about 50% of the total caloric value of human milk [87], triglycerides corresponding to the major lipidic component in both colostrum and mature milk [88–91]. The induction of lipogenic activity in mammary glands does not occur until after parturition as reported in the rat [92] and, therefore, lipids in colostrum must come from maternal circulation. In fact, as shown in Figure 5, around parturition in the rat, LPL activity in mammary glands increases whereas in adipose tissue it decreases. Through this mechanism, plasma triglycerides are driven to be taken up by mammary glands for milk synthesis instead of being accumulated in adipose tissue [33,93] (see Figure 3). Besides the induction effect of prolactin on mammary glands LPL [94,95], these changes are mediated by the opposite responsiveness to insulin seen around parturition between mammary glands and adipose tissue, which is enhanced in the former [42,96] and decreased in the latter [41,42,97]. These changes allow essential fatty acids from maternal diet circulating as triglyceride-rich lipoproteins in maternal plasma to become available to the suckling newborn.

Ketonemia in the neonatal period

Since nonesterified fatty acids (long and medium chain length) are the major precursors for ketone bodies synthesis, the relative high-fat and low-carbohydrate diet present in milk contributes to the marked hyperketonemia normally present in both humans and rats during the suckling period [98]. In adults, adipose tissue lipolysis determines the main supply of long chain fatty acid to the liver, and immediately after birth [99] and during suckling, although less intensely, the rate of lipolysis has been shown to be enhanced both in humans [100] and in rats [101]. The enhanced lipolysis occurring in the first few hours of life appears to be regulated by catecholamine release, resulting in cAMP production and increased protein kinase C activity [99,102]. During the suckling phase, the enhanced lipolysis seems to be caused by an enhanced sensitivity to lipolytic hormones, like thyrotropin [100], and a decreased plasma insulin/glucagon ratio, which also favors lipolysis [103,104].

Although the liver in the adult is considered to be the sole tissue capable of synthesis and release of ketone bodies to the circulation, intestinal mucose has been shown to synthesize ketone bodies in neonatal rats due to the expression of the key enzyme hydroxymethylglutaryl-

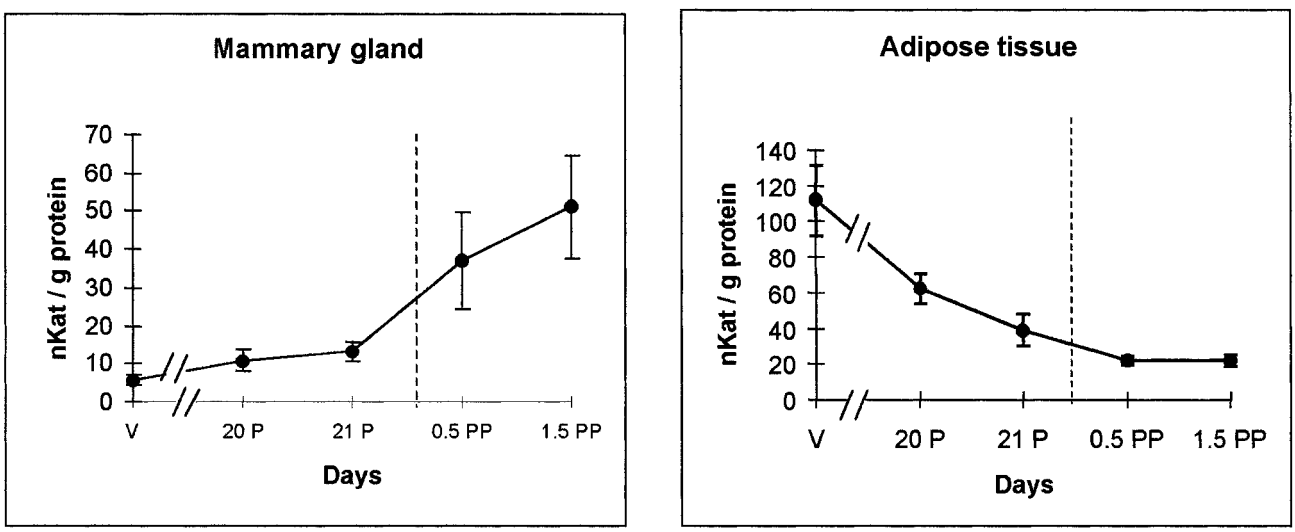

Figure 5. Changes in mammary gland and adipose tissue lipoprotein lipase activity in virgin (V), pregnant (P) and postpartum (PP) rats. Values of LPL activity in both P and PP rats vs virgin rats were statistically significant ($p < 0.05$) at all the time points studied. Experimental details are as previous described [93]

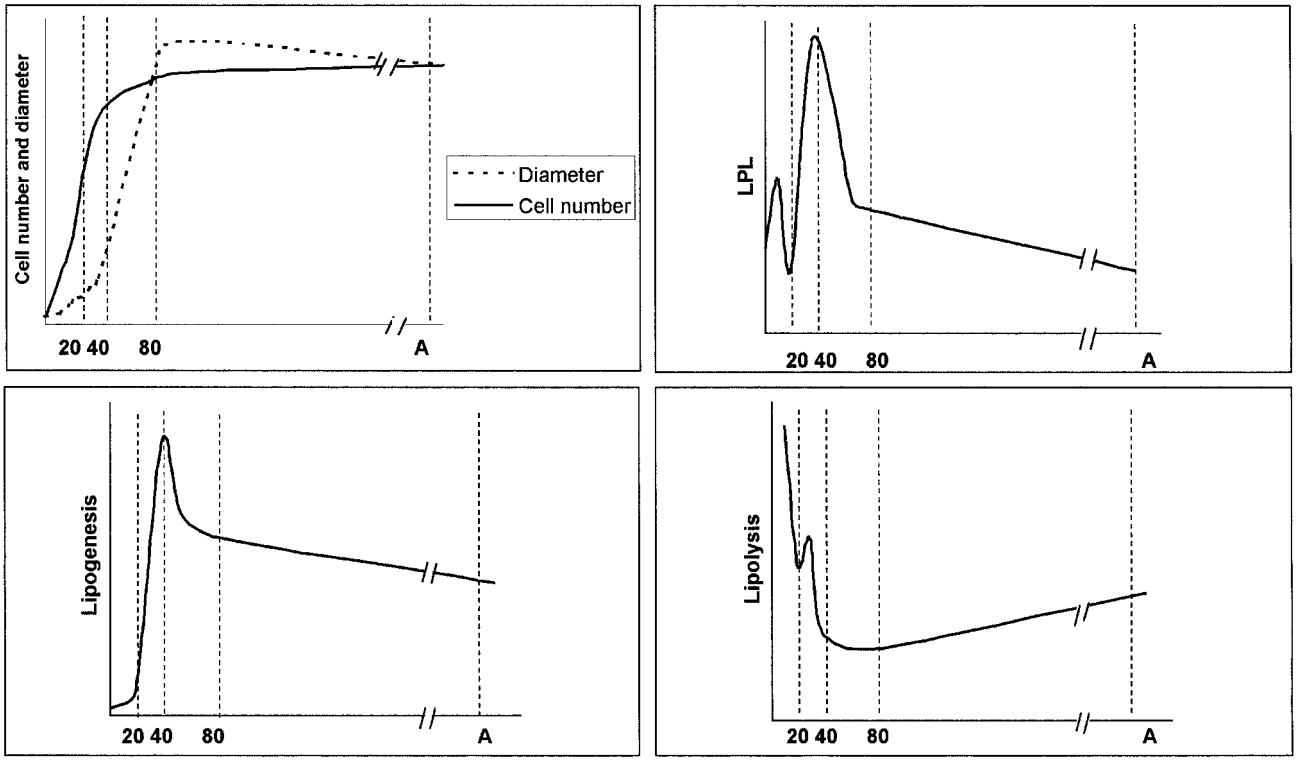

Figure 6. Qualitative morphologic and biochemical changes taking place during the development of white adipose tissue in the rat, based on the references mentioned in the text. The numbers in abscissae correspond to days after birth whereas A represents adults

CoA synthase [105], which is suppressed on weaning suckling rats [105,106]. Although the rate of intestinal ketogenesis does not exceed 10% of that in the suckling liver, it represents an additional strategy to provide ketone bodies to developing tissues [107].

The adult liver does not express LPL, but the fetal liver contains a high level of LPL activity, as initially shown in the rat [108] and later in other species [109], although in human fetal or neonatal liver it has not been documented. This activity increases after birth and further increases under starving conditions in the newborn [110], and although it declines progressively with age, it remains higher in the liver of the suckling rat than after weaning, when this activity declines to the undetectable level seen in adults [111]. Liver LPL activity in newborn rats parallels changes in liver content of triglycerides as well as those of circulating triglycerides and ketone bodies [110]. It is therefore proposed that in the suckling neonate, long chain fatty acids derived from milk lipids, which are transported as chylomicron triglycerides, are channeled to the liver courtesy of its LPL, and such a change may also contribute to the high ketogenic capacity of that organ during the suckling period.

Changes in the metabolism of adipose tissue during development

As described earlier, great interspecies differences exist in the time course of the development of adipose tissue. In contrast to the active intra-uterine development of adipose tissue occurring in humans, it occurs after birth in rat and this characteristic provides an appropriate model to study adipose tissue development. Figure 6 summarizes in a qualitative manner the major changes known to take place in rat adipose tissue development along the time, differentiating the end of the suckling period which occurs 20 days after birth, the phase of highest hyperplasia, between birth and 40 days after birth, and the phase of highest cell hypertrophia occurring between 40 and 80 days after birth. Changes in adipose tissue LPL activity gives an index of tissue capability to take up circulating triglycerides, and as shown in Figure 6, it peaks at mid-suckling to decline around weaning but increasing again at 30–40 days of age to decline thereafter [111–114]. The lipogenic activity is very low through the suckling period [115,116] coinciding with the enhanced availability of fatty acids from milk lipids, whereas it rapidly increases during weaning, when diet composition switches from high fat to high carbohydrate. The rate of lipolysis is high after birth, partially declines as the suckling period advances [101,117], shows a small peak just after weaning, and declines afterwards.

In summary, when adipose tissue hyperplasia predominates, corresponding to the suckling period in the rat, lipogenesis is not very active, but the uptake of fatty acids from circulating triglycerides mainly coming from those in milk, appears enhanced. At the same time, adipose tissue lipolytic activity is enhanced, allowing a

rapid turnover of triglycerides within the adipocytes and therefore contributing to the enhanced rate of cell proliferation. From weaning up to around 40 days after birth, the number of adipocytes is still progressively increasing but they start to be filled up with fat (resulting in a rapid increase in cell size) owing to the intense increase in both LPL activity and lipogenesis, which compensates for the reduction of plasma triglycerides caused by the decreased lipid content of the diet during weaning as compared to suckling. The slight increase in cell size occurring around 80 days after birth (Figure 6) could be explained by the intense decline in adipose tissue lipolysis, and the peak of lipogenic activity at a time when new adipocytes are no longer formed. From then on, until adulthood, which in the rat corresponds to the age of 150–180 days, both adipocyte size and number remain constant and the activities of both LPL and lipogenesis progressively decline, whereas the lipolytic activity remains low with a tendency to recover. A similar metabolic process to that occurring in the development of rat adipose tissue after birth takes place in other species during the intra-uterine life, as shown in sheep [118,119], although it is not yet known whether this is also the case in the human fetus, where adipose tissue is, however, known to have lipolytic activity, but with a low sensitivity to hormones [117].

Acknowledgements

The present study was supported by grants from the Comisión Interministerial de Ciencia y Tecnología of Spain (grant # PM96-0022), Fondo de Investigación Sanitaria, Ministerio de Sanidad y Consumo (grant # 99/0205) and Universidad San Pablo-CEU (grant # 21/98). We acknowledge the excellent technical assistance of Milagros Morante and thank Beatriz Ramos for her editorial help.

References

1. Hytten FE, Leitch I. *The Physiology of Human Pregnancy* (2nd edn), Blackwell Scientific Publisher: Oxford, 1971; 286–369.
2. King JC, Butte NF, Bronstein MN, Kopp LE, Lindquist SA. Energy metabolism during pregnancy: influence of maternal energy status. *Am J Clin Nutr* 1994; **59**(Suppl.): 439S–445S.
3. Villar J, Cogswell M, Kestler E, Castillo P, Menendez R, Repke JT. Effect of fat and fat-free mass deposition during pregnancy on birth weight. *Am J Obstet Gynecol* 1992; **167**: 1344–1352.
4. López-Luna P, Muñoz T, Herrera E. Body fat in pregnant rats at mid- and late-gestation. *Life Sci* 1986; **39**: 1389–1393.
5. Lopez Luna P, Maier I, Herrera E. Carcass and tissue fat content in the pregnant rat. *Biol Neonate* 1991; **60**: 29–38.
6. Herrera E, Muñoz C, Lopez-Luna P, Ramos P. Carbohydrate-lipid interactions during gestation and their control by insulin. *Braz J Med Biol Res* 1994; **27**: 2499–2519.
7. Williams C, Coltart TM. Adipose tissue metabolism in pregnancy: the lipolytic effect of human placental lactogen. *Br J Obstet Gynaecol* 1978; **85**: 43–46.
8. Elliott JA. The effect of pregnancy on the control of lipolysis in fat cells isolated from human adipose tissue. *Eur J Clin Invest* 1975; **5**: 159–163.
9. Knopp RH, Herrera E, Freinkel N. Carbohydrate metabolism in pregnancy.VIII. Metabolism of adipose tissue isolated from fed and fasted pregnant rats during late gestation. *J Clin Invest* 1970; **49**: 1438–1446.
10. Chaves JM, Herrera E. *In vitro* glycerol metabolism in adipose tissue from fasted pregnant rats. *Biochem Biophys Res Commun* 1978; **85**: 1299–1306.
11. Martin-Hidalgo A, Holm C, Belfrage P, Schotz MC, Herrera E. Lipoprotein lipase and hormone-sensitive lipase activity and mRNA in rat adipose tissue during pregnancy. *Am J Physiol* 1994; **266**: E930–E935.
12. Lasunción MA, Lorenzo J, Palacín M, Herrera E. Maternal factors modulating nutrient transfer to fetus. *Biol Neonate* 1987; **51**: 86–93.
13. Aldoretta PW, Hay WW Jr. Fetal nutrition. *Nutr Res* 1994; **14**: 929–965.
14. Hay WW Jr. Placental transport of nutrients to the fetus. *Horm Res* 1994; **42**: 215–222.
15. Herrera E, Bonet B, Lasunción MA. Maternal–fetal transfer of lipid metabolites. In *Fetal and Neonatal Physiology* (2nd edn), Polin RA, Fox WW (eds). W. B. Saunders Co.: Philadelphia, 1998; 447–458.
16. Van Aerde JE, Feldman M, Clandinin MT. Accretion of lipid in the fetus and newborn. In: *Fetal and Neonatal Physiology*, (2nd edn), Polin RA, Fox WW (eds). W. B. Saunders Co.: Philadelphia 1998; 458–477.
17. Scow RO, Chernick SS, Brinley MS. Hyperlipemia and ketosis in the pregnant rat. *Am J Physiol* 1964; **206**: 796–804.
18. Herrera E, Knopp RH, Freinkel N. Carbohydrate metabolism in pregnancy VI. Plasma fuels, insulin, liver composition, gluconeogenesis and nitrogen metabolism during gestation in the fed and fasted rat. *J Clin Invest* 1969; **48**: 2260–2272.
19. Zorzano A, Herrera E. Pregnancy and pentobarbital anaesthesia modify hepatic synthesis of acylglycerol glycerol and glycogen from gluconeogenic precursors during fasting in rats. *Biochem J* 1988; **256**: 487–491.
20. Scow RO, Chernick SS, Smith BB. Ketosis in the rat fetus. *Proc Soc Exp Biol Med* 1958; **98**: 833–835.
21. Shambaugh GE. Ketone body metabolism in the mother and fetus. *FASEB J* 1985; **44**: 2347–2351.
22. Edmond J. Ketone bodies as precursors of sterols and fatty acids in the developing rat. *J Biol Chem* 1974; **249**: 72–80.
23. Patel MS, Johnson CA, Ratan R, Owen DE. The metabolism of ketone bodies in developing human brain: development of ketone-body utilizing enzymes and ketone bodies as precursors for lipid synthesis. *J Neurochem* 1975; **25**: 905–908.
24. Zorzano A, Lasunción MA, Herrera E. Role of the availability of substrates on hepatic and renal gluconeogenesis in the fasted late pregnant rat. *Metabolism* 1986; **35**: 297–303.
25. Zorzano A, Herrera E. Comparative utilization of glycerol and alanine as liver gluconeogenic substrates in the fed late pregnant rat. *Int J Biochem* 1986; **18**: 583–587.
26. Herrera E, Lasunción MA, Martín A, Zorzano A. Carbohydrate–lipid interactions in pregnancy. In *Perinatal Biochemistry*, Herrera E, Knopp RH (eds). CRC Press: Boca Raton, 1992; 1–18.
27. Cetin I, Ronzoni S, Marconi AM, *et al*. Maternal concentrations and fetal–maternal concentration differences of plasma amino acids in normal and intrauterine growth-restricted pregnancies. *Am J Obstet Gynecol* 1996; **174**: 1575–1583.
28. Metzger BE, Unger RH, Freinkel N. Carbohydrate metabolism in pregnancy. XIV. Relationships between circulating glucagon, insulin, glucose and amino acids in response to a "mixed meal" in late pregnancy. *Metabolism* 1977; **26**: 151–156.
29. Wasfi I, Weinstein I, Heimberg M. Increased formation of triglyceride from oleate in perfused livers from pregnant rats. *Endocrinology* 1980; **107**: 584–596.
30. Knopp RH, Bonet B, Lasunción MA, Montelongo A, Herrera E. Lipoprotein metabolism in pregnancy. In *Perinatal Biochemistry*, Herrera E, Knopp RH (eds). CRC Press: Boca Raton, 1992; 19–51.
31. Iglesias A, Montelongo A, Herrera E, Lasunción MA. Changes in cholesteryl ester transfer protein activity during normal gestation and postpartum. *Clin Biochem* 1994; **27**: 63–68.
32. Alvarez JJ, Montelongo A, Iglesias A, Lasunción MA, Herrera E. Longitudinal study on lipoprotein profile, high density lipoprotein subclass, and postheparin lipases during gestation in women. *J Lipid Res* 1996; **37**: 299–308.
33. Argiles J, Herrera E. Appearance of circulating and tissue 14C-lipids after oral 14C- tripalmitate administration in the late pregnant rat. *Metabolism* 1989; **38**: 104–108.

34. Testar X, Llobera M, Herrera E. Increase with starvation in the pregnant rat of the liver lipoprotein lipase. *Biochem Soc Trans* 1985; **13**: 134.
35. Vilaró S, Testar X, Ramirez I, Llobera M. Lipoprotein lipase activity in the liver of starved pregnant rats. *Biol Neonate* 1990; **57**: 37–45.
36. Herrera E, Lasunción MA, Gomez Coronado D, Aranda P, Lopez Luna P, Maier I. Role of lipoprotein lipase activity on lipoprotein metabolism and the fate of circulating triglycerides in pregnancy. *Am J Obstet Gynecol* 1988; **158**: 1575–1583.
37. Ciaraldi TP, Kettel M, El-Roeiy A, *et al*. Mechanisms of cellular insulin resistance in human pregnancy. *Am J Obstet Gynecol* 1994; **170**: 635–641.
38. Stanley K, Fraser R, Bruce C. Physiological changes in insulin resistance in human pregnancy: longitudinal study with the hyperinsulinaemic euglycaemic clamp technique. *Br J Obstet Gynaecol* 1998; **105**: 756–759.
39. Leturque A, Burnol A-F, Ferré P, Girard J. Pregnancy-induced insulin resistance in the rat: assessment by glucose clamp technique. *Am J Physiol* 1984; **246**: E25–E31.
40. Camps M, Gumà A, Testar X, Palacín M, Zorzano A. Insulin resistance of skeletal muscle during pregnancy is not a consequence of intrinsic modifications of insulin receptor binding or kinase activities. *Endocrinology* 1990; **127**: 2561–2570.
41. Ramos P, Herrera E. Reversion of insulin resistance in the rat during late pregnancy by 72-h glucose infusion. *Am J Physiol Endocrinol Metab* 1995; **269**: E858–E863.
42. Ramos P, Herrera E. Comparative responsiveness to prolonged hyperinsulinemia between adipose-tissue and mammary-gland lipoprotein lipase activities in pregnant rats. *Early Pregnancy: Biol and Med* 1996; **2**: 29–35.
43. Applebaum DM, Goldberg AP, Pykalisto OJ, Brunzell JD, Hazzard WR. Effect of estrogen on post-heparin lipolytic activity. Selective decline in hepatic triglyceride lipase. *J Clin Invest* 1977; **59**: 601–608.
44. Ginci G, Arezzini L, Terzuoli L, Pizzichini M, Marinello E. Effect of estradiol on serum triglyceride lipoprotein levels and fatty acid composition in castrated rats. *Horm Metab Res* 1997; **29**: 504–506.
45. Knopp RH, Zhu X, Bonet B. Effects of estrogens on lipoprotein metabolism and cardiovascular disease in women. *Atherosclerosis* 1994; **110** (Suppl): S83–S91.
46. Applebaum-Bowden D, McLean P, Steinmetz A, *et al*. Lipoprotein, apolipoprotein, and lipolytic enzyme changes following estrogen administration in postmenopausal women. *J Lipid Res* 1989; **30**: 1895–1906.
47. Montelongo A, Lasunción MA, Pallardo LF, Herrera E. Longitudinal study of plasma lipoproteins and hormones during pregnancy in normal and diabetic women. *Diabetes* 1992; **41**: 1651–1659.
48. Shand JH, Noble RC. The role of maternal triglycerides in the supply of lipids to the ovine fetus. *Res Vet Sci* 1979; **26**: 117–123.
49. Gurr M. Fats. In *Human Nutrition and Dietetics*, Garrow JS, James WPT (eds). Churchill Livingstone: Edinburgh, 1993; 77–102.
50. Albrecht ED, Babischkin JS, Koos RD, Pepe GJ. Developmental increase in low density lipoprotein receptor messenger ribonucleic acid levels in placental syncytiotrophoblasts during baboon pregnancy. *Endocrinology* 1995; **136**: 5540–5546.
51. Overbergh L, Lorent K, Torrekens S, Van Leuven F, van den Berghe H. Expression of mouse alpha-macroglobulins, lipoprotein receptor- related protein, LDL receptor, apolipoprotein E, and lipoprotein lipase in pregnancy. *J Lipid Res* 1995; **36**: 1774–1786.
52. Wittmaack FM, Gåfvels ME, Bronner M, *et al*. Localization and regulation of the human very low density lipoprotein/apolipoprotein-E receptor: Trophoblast expression predicts a role for the receptor in placental lipid transport. *Endocrinology* 1995; **136**: 340–348.
53. Elphick MC, Hull D. Rabbit placental clearing-factor lipase and transfer to the foetus of fatty acids derived from triglycerides injected into the mother. *J Physiol (Lond)* 1977; **273**: 475–487.
54. Rotherwell JE, Elphick MC. Lipoprotein lipase activity in human and guinea pig placenta. *J Dev Physiol* 1982; **4**: 153–159.
55. Bonet B, Brunzell JD, Gown AM, Knopp RH. Metabolism of very-low-density lipoprotein triglyceride by human placental cells: the role of lipoprotein lipase. *Metabolism* 1992; **41**: 596–603.
56. Coleman RA. The role of the placenta in lipid metabolism and transport. *Semin Perina* 1989; **13**: 180–191.
57. Kuhn H, Crawford M. Placental essential fatty acid transport and prostaglandin synthesis. *Prog Lipid Res* 1986; **25**: 345–353.
58. Abumrad NA, Park JH, Park CR. Permeation of long-chain fatty acids into adipocytes. *J Biol Chem* 1984; **259**: 8945–8953.
59. Goresky CA, Stremmel W, Rose CP, *et al*. The capillary transport system for free fatty acids in the heart. *Circ Res* 1994; **74**: 1015–1026.
60. Campbell FM, Gordon MJ, Dutta-Roy AK. Plasma membrane fatty acid binding protein ($FABP_{pm}$) from sheep placenta. *Biochim Biophys Acta* 1994; **1214**: 187–192.
61. Campbell FM, Gordon MJ, Dutta-Roy AK. Plasma membrane fatty acid binding protein from human placenta: identification and characterization. *Biochem Biophys Res Commun* 2000; **209**: 1011–1017.
62. Campbell FM, Gordon MJ, Dutta-Roy AK. Preferential uptake of long chain polyunsaturated fatty acids by isolated human placental membranes. *Mol Cell Biochem* 1996; **155**: 77–83.
63. Campbell FM, Clohessy AM, Gordon MJ, Page KR, Dutta-Roy AK. Uptake of long chain fatty acids by human placental choriocarcinoma (BeWo) cells: role of plasma membrane fatty acid binding protein. *J Lipid Res* 1997; **38**: 2558–2568.
64. Crawford MA, Hassam AG, Williams G, Whitehouse WL. Essential fatty acids and fetal brain growth. *Lancet* 1976; **i**: 452–453.
65. Haggarty P, Page K, Abramovich DR, Ashton J, Brown D. Long-chain polyunsaturated fatty acid transport across the perfused human placenta. *Placenta* 1997; **18**: 635–642.
66. Innis SM. Essential fatty acids in growth and development. *Prog Lipid Res* 1991; **30**: 39–103.
67. Simopoulos AP. Ω-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr* 1991; **54**: 438–463.
68. Uauy R, Mena P, Wegher B, Nieto S, Salem N Jr. Long chain polyunsaturated fatty acid formation in neonates: Effect of gestational age and intrauterine growth. *Pediatr Res* 2000; **47**: 127–135.
69. Hollingsworth DR, Grundy SM. Pregnancy-associated hypertriglyceridemia in normal and diabetic women. Differences in insulin-dependent, non-insulin-dependent, and gestational diabetes. *Diabetes* 1982; **31**: 1092–1097.
70. Kuhn DC, Crawford MA, Stuart MJ, Botti JJ, Demers LM. Alterations in transfer and lipid distribution of arachidonic acid in placentas of diabetic pregnancies. *Diabetes* 1990; **39**: 914–918.
71. Goldstein R, Levy E, Shafrir E. Increased maternal–fetal transport of fat in diabetes assesed by polyunsaturated fatty acid content in fetal lipids. *Biol Neonate* 1985; **47**: 343–349.
72. Diamant YZ, Metzger BE, Freinkel N, Shafrir E. Placental lipid and glycogen content in human and experimental diabetes mellitus. *Am J Obstet Gynecol* 1982; **144**: 5–11.
73. Shafrir E, Khassis S. Maternal–fetal fat transport versus new fat synthesis in the pregnant diabetic rat. *Diabetologia* 1982; **22**: 111–117.
74. Shafrir E, Barash V. Placental function in maternal-fetal fat transport in diabetes. *Biol Neonate* 1987; **51**: 102–112.
75. Knopp RH, Bergelin RO, Wahl PW, Walden CE. Relationships of infant birth size to maternal lipoproteins, apoproteins, fuels, hormones, clinical chemistries, and body weight at 36 weeks gestation. *Diabetes* 1985; **34**(Suppl. 2): 71–77.
76. Szabo AJ, Szabo O. Placental free fatty acid transfer and fetal adipose tissue development: an explanation of fetal adiposity in infants of diabetic mothers. *Lancet* 1974; **ii**: 498–499.
77. Greenwood MR, Hirsch J. Postnatal development of adipocyte cellularity in the normal rat. *J Lipid Res* 1974; **15**: 474–483.
78. Cryer A, Jones HM. The early development of white adipose tissue. Effects of litter size on the lipoprotein lipase activity of four adipose-tissue depots, serum immunoreactive insulin and tissue cellularity during the first four weeks of life in the rat. *Biochem J* 1979; **178**: 711–724.
79. Noble RC, Shand JH. The placenta: its role in the relationship between lipids of mother and fetus. *IRCS Med Sci* 1981; **9**: 174–177.

80. Hahn P, Novak M. Development of brown and white adipose tissue. *J Lipid Res* 1975; **16**: 79–91.
81. Heim T. Energy and lipid requirements of the fetus and the preterm infant. *J Pediatr Gastroenterol Nutr* 1983; **2**(Suppl. 1): S16–S41.
82. Hytten FE, Leitch I. The gross composition of the components of weight gain. In *The Physiology of Human Pregnancy*, (2nd edn), Hytten FE, Leitch I (eds). Blackwell: Oxford, 1971; 370–387.
83. Hay WW Jr. Metabolic interrelationships of placenta and fetus. *Placenta* 1995; **16**: 19–30.
84. Jones CT. The development of the metabolism in the fetal liver. In *Biochemical Development of the Fetus and Neonate*, Jones CT (eds). Elsevier: Amsterdam, 1982; 249.
85. Hausman DB, Hausman GJ, Martin RJ. Influence of the pituitary on lipolysis and lipogenesis in fetal pig adipose tissue. *Horm Metabol Res* 1993; **25**: 17–20.
86. Enzi G, Inelmen EM, Caretta F, Villani F, Zanardo V, Debiasi F. Development of adipose tissue in newborns of gestational-diabetic and insulin-dependent diabetic mothers. *Diabetes* 1980; **29**: 100–104.
87. Hambraeus L. Propietary milk versus human milk in infant feeding. *Pediatr Clin North Am* 1978; **24**: 17–36.
88. Bracco U, Hidalgo J, Bohren H. Lipid composition of the fat globule membrane of human and bovine milk. *J Dairy Sci* 1972; **55**: 165–172.
89. Bitman J, Wood DL, Hamosh M, Hamosh P, Mehta NR. Comparison of the lipid composition of breast milk from mothers of term and preterm infants. *Am J Clin Nutr* 1983; **38**: 300–312.
90. Harzer G, Haug M, Dieterich I, Gentner PR. Changing patterns of human milk lipids in the course of the lactation and during the day. *Am J Clin Nutr* 1983; **37**: 612–621.
91. Barbas C, Herrera E. Lipid composition and vitamin E content in human colostrum and mature milk. *J Physiol Biochem* 1998; **54**: 167–174.
92. Martin P, Hansen IA. Initiation of fatty acid synthesis in rat mammary gland. *Biochem J* 1980; **190**: 171–175.
93. Ramirez I, Llobera M, Herrera E. Circulating triacylglycerols, lipoproteins, and tissue lipoprotein lipase activities in rat mothers and offspring during the perinatal period: effect of postmaturity. *Metabolism* 1983; **32**: 333–341.
94. Scow RO, Chernick SS. Role of lipoprotein lipase during lactation. In *Lipoprotein Lipase*, Borensztajn J (ed.). Evener Publishers Inc.: Chicago, 1987; 149–186.
95. Da Costa THM, Williamson DH. Regulation of rat mammary-gland uptake of orally administered [1-^{14}C]triolein by insulin and prolactin: evidence for bihormonal control of lipoprotein lipase activity. *Biochem J* 1994; **300**: 257–262.
96. Carrascosa JM, Ramos P, Molero JC, Herrera E. Changes in the kinase activity of the insulin receptor account for an increased insulin sensitivity of mammary gland in late pregnancy. *Endocrinology* 1998; **139**: 520–526.
97. Herrera E, Ramos P, Martín A. Control by insulin of adipose tissue lipoprotein lipase activity during late pregnancy in the rat. In *Frontiers in Diabetes Research. Lessons From Animal Diabetes III*, Shafrir E (ed.). Smith-Gordon: London, 1990; 551–554.
98. Williamson DH. Ketone body production and metabolism in the fetus and newborn. In *Fetal and Neonatal Physiology*, (2nd edn), Polin RA, Fox WW (eds). W. B. Saunders Co.: Philadelphia, 1998; 493–504.
99. Kimura RE, Warshaw JB. Metabolic adaptations of the fetus and newborn. *J Pediatr Gastroenterol Nutr* 1983; **2**(Suppl. 1): S12–S15.
100. Marcus C, Ehren H, Bolme P, Arner P. Regulation of lipolysis during the neonatal period: importance of thyrotropin. *J Clin Invest* 1988; **82**: 1793–1797.
101. Gruen R, Kava R, Greenwood MR. Development of basal lipolysis and fat cell size in the epididymal fat pad of normal rats. *Metabolism* 1980; **29**: 246–253.
102. Bahnsen M, Burrin JM, Johnston DC, Pernet A, Walker M, Alberti KG. Mechanisms of catecholamine effects on ketogenesis. *Am J Physiol* 1984; **247**: E173–E180.
103. Girard JR, Cuendet GS, Marliss EB, Kervran A, Rieutort M, Assan R. Fuels, hormones and liver metabolism at term and during the early postnatal period in the rat. *J Clin Invest* 1973; **52**: 3190–3200.
104. Issad T, Coupe C, Ferré P, Girard J. Insulin resistance during suckling period in rats. *Am J Physiol* 1987; **253**: E142–E148.
105. Serra D, Asins G, Hegardt FG. Ketogenic mitochondrial 3-hydroxy 3-methylglutaryl-CoA synthase gene expression in intestine and liver of suckling rats. *Arch Biochem Biophys* 1993; **301**: 445–448.
106. Thumelin S, Forestier M, Girard J, Pegorier JP. Developmental changes in mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase gene expression in rat liver, intestine and kidney. *Biochem J* 1993; **292**: 493–496.
107. Williamson DH, Lund P. Strategies for the supply of lipid substrates during post-natal brain development: a tale of two tissues. *Dev Neurosci* 1993; **15**: 156–164.
108. Llobera M, Montes A, Herrera E. Lipoprotein lipase activity in liver of the rat fetus. *Biochem Biophys Res Commun* 1979; **91**: 272–277.
109. Olivecrona T, Bengtsson-Olivecrona G, Chernick SS, Scow RO. Effect of combined lipase deficiency (cld/cld) on hepatic lipase and lipoprotein lipase activities in liver and plasma of newborn mice. *Biochim Biophys Acta* 1986; **876**: 243–248.
110. Grinberg DR, Ramirez I, Vilaró S, Reina M, Llobera M, Herrera E. Starvation enhances lipoprotein lipase activity in the liver of the newborn rat. *Biochim Biophys Acta* 1985; **833**: 217–222.
111. Ramírez I, Galan X, Peinado-Onsurbe J, Llobera M. Lipoprotein lipase. In *Fetal and Neonatal Physiology*, (2nd edn), Polin RA, Fox WW (eds). W. B. Saunders Co.: Philadelphia, 1998; 535–541.
112. Chajek T, Stein O, Stein Y. Pre- and post-natal development of lipoprotein lipase and hepatic triglyceride hydrolase activity in rat tissues. *Atherosclerosis* 1977; **26**: 549–561.
113. Hietanen E, Greenwood MRC. A comparison of lipoprotein lipase activity and adipocyte differentiation in growing male rats. *J Lipid Res* 1977; **18**: 480–490.
114. Cryer A, Jones HM. Changes in the lipoprotein lipase (clearing-factor lipase) activity of white adipose tissue during development of the rat. *Biochem J* 1978; **172**: 319–325.
115. Smith PA, Kaplan ML. Development of hepatic and adipose tissue lipogenesis in the fa/fa rat. *Int J Biochem* 1980; **11**: 217–228.
116. Tsujikawa M, Kimura S. Changes in lipid synthesis in rat adipose tissue during development. *J Nutr Sci Vitaminol (Tokyo)* 1980; **26**: 367–374.
117. Cryer A. The postnatal development of white adipose tissue metabolism. *Biochem Soc Trans* 1981; **9**: 373–375.
118. Vernon RG, Robertson JP, Clegg RA, Flint DJ. Aspects of adipose tissue metabolism in foetal lambs. *Biochem J* 1981; **196**: 819–824.
119. Christie WW, Noble RC. Fatty acid biosynthesis in sheep placenta and maternal and fetal adipose tissue. *Biol Neonate* 1982; **42**: 79–86.
120. Lasunción MA, Testar X, Palacín M, Chieri R, Herrera E. Method for the study of metabolite transfer from rat mother to fetus. *Biol Neonate* 1983; **44**: 85–92.
121. Munilla MA, Herrera E. A cholesterol-rich diet causes a greater hypercholesterolemic response in pregnant than in nonpregnant rats and does not modify fetal lipoprotein profile. *J Nutr* 1997; **127**: 2239–2245.