

*Chapter V*

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## **Hyperlipidemia and Vitamin E Metabolism in Pregnancy**

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### **Abstract**

Fat accumulation during pregnancy as result of both hyperphagia and increased lipid synthesis takes place during the first two-thirds of gestation, whereas it declines during the last third, as a consequence of enhanced adipose tissue lipolysis. This change together with a decrease in adipose tissue lipoprotein lipase (LPL) activity causes a net enhanced breakdown of fat stores, which is facilitated by the insulin-resistant condition that is normally present during late pregnancy. The main fate of the lipolytic products is maternal liver, where they are re-esterified for the synthesis of triacylglycerols (TG), which are released into the circulation as part of very low density lipoproteins (VLDL). The abundance of VLDL-TG in the presence of an increase in cholesteryl ester transfer protein activity taking place at mid gestation contribute to the accumulation of TG in the lipoprotein fractions of higher density, LDL and HDL. Maternal hyperlipidemia is associated with the predominance of small and dense LDL-particles, which are more susceptible to oxidation. The higher levels of lipid peroxides during late pregnancy are accompanied by higher levels of vitamin E, which values correlate with maternal hyperlipidemia. Although the lipolytic activity of LPL seems to play a significant role in the uptake of  $\alpha$ -tocopherol in certain tissues, like mammary gland around parturition, this is not the case in others, where LPL may function as a cell surface proteoglycan-anchored bridge for lipoproteins, facilitating the uptake of LDL  $\alpha$ -tocopherol. Other mechanisms exist for the tissue uptake of  $\alpha$ -tocopherol, including the receptor-mediated

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lipoprotein endocytosis, the LDL receptor pathway or the scavenger receptor class B type 1. The ATP-binding cassette transporter A1 has been also implicated in the supply of  $\alpha$ -tocopherol in the fetomaternal unit. Despite that the  $\alpha$ -tocopherol transfer protein seems to act in conjunction with lipoprotein receptors, lipolytic enzymes and fatty acid binding proteins in the placenta to facilitate the transfer of  $\alpha$ -tocopherol between maternal and fetal circulation, its rate is very low, justifying the low levels of vitamin E in fetal plasma. The induction of LPL activity in mammary gland around parturition contribute to both the disappearance of maternal hyperlipidemia and the efficient uptake by mammary gland of circulating  $\alpha$ -tocopherol, allowing its availability in the suckling newborn.

## Introduction

Uncomplicated pregnancy in women is associated to hyperlipidemia [4; 10; 75; 94] as well as an increase in serum levels of lipid peroxides [21; 96; 133; 149]. Also during normal pregnancy the higher levels of both lipoproteins and lipid peroxides are accompanied by enhanced levels of vitamin E ( $\alpha$ -tocopherol) [52; 96; 137; 140], which is a naturally occurring lipid-soluble antioxidant that participates in protecting membrane and blood lipoprotein particle lipids from autooxidation [17], being considered the most important lipid-soluble antioxidant in humans [65]. This protective effect of vitamin E results from both its preferential localization in lipid phases and its capacity at breaking the free radical-initiated lipoperoxidation chain reactions. Besides, several tocopherols have special properties that are unrelated to their antioxidant capacity. The first one may be considered its role in animal fertility initially proposed by Evans and Bishop [31], who discovered this essential factor for animal reproduction. Female rats fed on a vitamin E free diet are sterile or resorb their fetuses, whereas these phenomena can be reversed by administration of vitamin E to pregnant animals [32]. The mechanism by which  $\alpha$ -tocopherol allows pregnancy to proceed until term still remains unknown. Plasma levels of  $\alpha$ -tocopherol in human fetuses are normally lower than those in their mothers, although levels rise towards the end of pregnancy [8; 147]. Premature infants are at risk of "oxygen radical disease" due to their exposure to supplemental oxygen and/or to a decrease in their antioxidant defences systems [37; 114; 122].

In this chapter, we first examine the mechanisms underlying the hyperlipidemia characteristic of normal pregnancy, so that maternal tendencies to have an oxidative stress condition may be understood. We also examine the changes of vitamin E metabolism during pregnancy, analyzing the mechanisms of its tissue uptake and its potential implications for the mother and her offspring, including its uptake by mammary gland around parturition, in preparation for lactation.

## Maternal Lipid Metabolism and Oxidative Stress

Two consistent manifestations of altered maternal lipid metabolism during normal gestation are the accumulation of lipids in early-pregnant maternal tissues [56; 135] as result

of major changes in adipose tissue metabolism and the development of maternal hyperlipidaemia [4; 10; 75; 94].

### **Adipose Tissue Metabolism**

Fat accumulation during pregnancy occurs in both women [56; 68; 135] and experimental animals [9; 81; 82; 95]. The accumulation of maternal fat depots takes place during the first two-thirds of gestation but stops or even declines during the last third [49; 56; 81; 121], as a consequence of enhanced adipose tissue lipolytic activity.

Body fat accumulation during early pregnancy seems to be the result of both hyperphagia [98; 106] and increased lipid synthesis [51; 104].

Changes in adipose tissue lipoprotein lipase (LPL) activity could be a means by which fat accumulation is controlled during early pregnancy. This enzyme, present in the capillary endothelium of extra-hepatic tissues, hydrolyzes triacylglycerols circulating in plasma in the form of triacylglycerol-rich lipoproteins [15], and the hydrolytic products, fatty acids and glycerol, are mostly taken up by the subjacent tissue [80]. In this way, LPL activity is a prerequisite for the uptake of circulating fat by adipose tissue. Whereas during mid gestation LPL activity in adipose tissue is either slightly increased [50; 73] or unchanged [4; 88], during late pregnancy, however, LPL activity in rat adipose tissue has consistently been found decreased [49] [43; 43; 102; 108]. Besides, postheparin LPL activity has also been found to decrease in pregnant women during the third trimester of gestation [4].

Thus, fat uptake by adipose tissue decreases during late pregnancy, and this change, together with the enhanced lipolytic activity (see below), results in the net accelerated breakdown of fat depots during the last trimester of pregnancy, actively contributing to the development of maternal hyperlipidemia.

An increased lipolysis of adipose tissue has been found both in women and in rats during the last third of gestation [30; 35; 74; 120; 143]. The products of adipose tissue lipolysis, non-esterified fatty acids (NEFA) and glycerol are released, in large part, into the circulation. Since the placental transfer of these products is quantitatively low [48], their main fate is maternal liver [86] where, after conversion into active forms, acyl-CoA and glycerol-3-phosphate respectively, they are re-esterified for the synthesis of triacylglycerols that are released into the circulation as part of very low density lipoproteins (VLDLs). The insulin-resistant condition of late pregnancy contributes to both the increased lipolysis of fat stores [109] and the increased VLDL production, although for the later, the enhanced estrogen concentration at late pregnancy seems to be its major activator [72].

### **Maternal Hyperlipemia**

The active lipolytic activity of maternal adipose tissue during late gestation is associated with the development of hyperlipidaemia, mainly corresponding to rises in triacylglycerols, with smaller rises in phospholipids and cholesterol in the circulation [72]. Although the greatest increase in plasma triacylglycerols corresponds to VLDL there is also an enrichment

of triacylglycerols in other lipoprotein fractions that normally do not transport them, like low density lipoproteins (LDL) and high density lipoproteins (HDL) [4]. This increase in plasma VLDL triacylglycerols during gestation results from enhanced production by the liver [141; 142] and decreased removal from the circulation as consequence of reduced adipose tissue LPL activity [4; 88].

The abundance of VLDL triacylglycerols in the presence of an increase in cholesteryl ester transfer protein (CETP) activity taking place at mid gestation [4; 57] contribute to the accumulation of triacylglycerols in the lipoprotein fractions of higher density, LDL and HDL [4; 94]. Another factor contributing to this same effect is the decrease in the hepatic lipase activity which also occurs during late pregnancy [4]. The decrease in this enzyme activity decreases the conversion of buoyant HDL<sub>2</sub> triacylglycerol-rich particles into small HDL<sub>3</sub> triacylglycerol-poor particles, allowing a proportional accumulation of the formers [4]. These interactions addressed to develop maternal hyperlipidemia during late pregnancy are schematically summarized in figure 1.

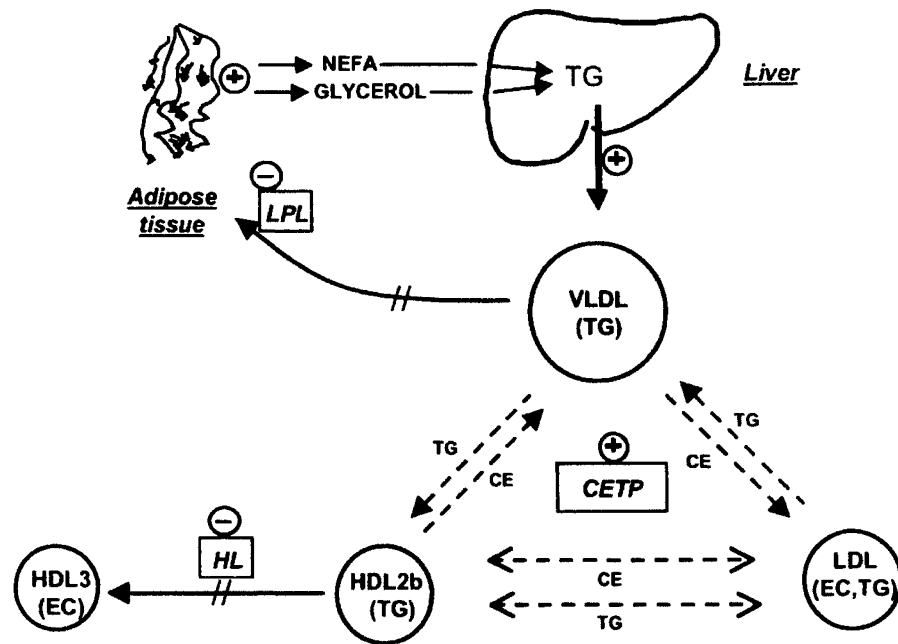


Figure 1. Schematic representation of lipoprotein metabolism during late pregnancy, indicating the mechanism for increased triacylglycerol (TG) content in all the lipoprotein fractions. + = enhanced pathway; - = inhibited reaction. NEFA = non-esterified fatty acids; CE = cholesteryl esterified; CETP = cholesteryl ester transfer protein; LPL = lipoprotein lipase; VLDL = very low density lipoproteins; LDL = low density lipoproteins; HDL = high density lipoproteins. Other details in text.

## Oxidative Stress

Maternal hyperlipidemia during late pregnancy is also associated with the predominance of small and dense LDL-particles [112; 119]. These small and dense LDL-particles have been shown to be more susceptible to oxidation [26]. Hyperlipidemia and the occurrence of small and dense LDL particles during late pregnancy might increase the oxidative damage, and an increase of serum lipoperoxides has been reported [21; 96; 133]. The higher levels of lipid peroxides during late pregnancy are accompanied by higher levels of vitamin E [52; 96; 137; 140]. The increased levels of vitamin E seems to be responsible for the increase in the oxidative stability of LDL with progressing gestation that has been reported [25].

## Metabolism of Vitamin E in Pregnancy

### $\alpha$ -Tocopherol in Plasma

Plasma concentrations of  $\alpha$ -tocopherol are well known to increase in normal pregnancy with advancing gestation [25; 52; 96; 137; 140]. This change correlates with maternal hyperlipidemia [52] and is also accompanied by the increase of lipid peroxides, although the increase in  $\alpha$ -tocopherol is more pronounced in such a way that  $\alpha$ -tocopherol/lipid peroxide ratio increases with progressing gestation [25].

The increase in vitamin E levels during pregnancy does not seem to be due to changes in dietary intake. Analysis of food frequency questionnaires has not reported enhanced dietary vitamin E intake during the course of pregnancy [14; 14; 101; 116]. Indeed, it has been proposed that the increases of vitamin E in pregnancy is a consequence of the increase of substrate available for lipid peroxidation [25], which agrees with the disappearance of increments when pregnant women plasma vitamin E levels are adjusted by lipid values [52].

The lipophilic nature of  $\alpha$ -tocopherol and the absence of a specific binding protein in blood forces that its intertissue traffic occurs via plasma lipoproteins. In fact, as summarized in figure 2, the metabolism of  $\alpha$ -tocopherol is closely linked to the metabolism of lipoproteins [67; 127; 131], and therefore it would be expected that changes in lipoprotein metabolism taking place during pregnancy would also affect in the same direction the metabolism of  $\alpha$ -tocopherol. However, although vitamin E in plasma may parallel lipoprotein metabolism [47] and could be affected by the changes of lipoprotein metabolism taking place during pregnancy [46; 72], its tissue uptake and intracellular metabolism seems to have specific characteristics.  $\alpha$ -Tocopherol circulates in the amphipathic outer layer of lipoproteins, which allows the spontaneous exchange or transfer of  $\alpha$ -tocopherol between lipoproteins and cells [41; 91; 129]. However, protein-facilitated transfer appears to play an important role in controlling its distribution between lipoprotein classes *in vivo* [87].

Rapid exchange of  $\alpha$ -tocopherol between HDL and apoB-containing lipoproteins is facilitated by the plasma phospholipids transfer protein (PLTP) [77] (figure 2) which also facilitates the exchange of  $\alpha$ -tocopherol between different lipoproteins and cells, including its net transfer to endothelial cells [27]. To our knowledge no reports on PLTP levels in pregnancy has been reported, but this protein is related to the cholesterol ester transfer

protein (CETP)[55], which activity is enhanced in pregnant women at the second trimester of gestation [57]. Besides, PLTP is known to play a major role in the remodelling of HDL by facilitating their enrichment in triacylglycerols [117], and such enrichment is a specific characteristic in HDLs of late pregnant women [4], which further would indicate its enhancement during late pregnancy.

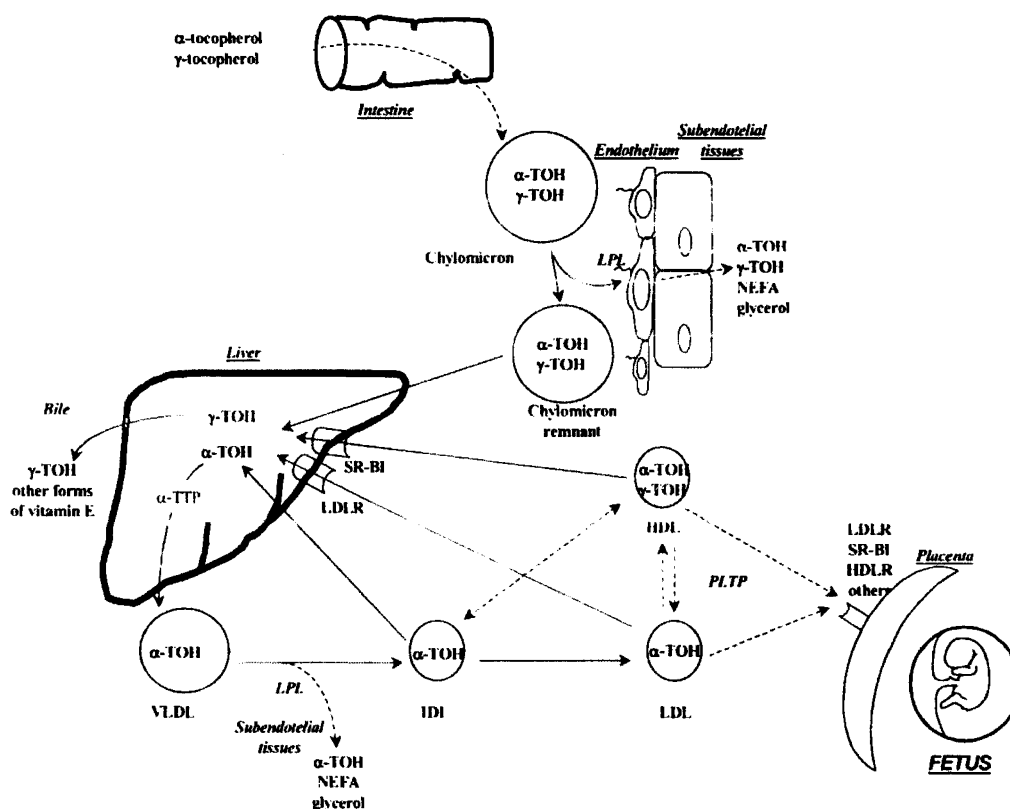


Figure 2. Schematic representation of vitamin E metabolism in late pregnancy.  $\alpha$ -TOH =  $\alpha$ -tocopherol;  $\gamma$ -TOH =  $\gamma$ -tocopherol; NEFA = non-esterified fatty acids; PLTP = phospholipid transfer protein; LPL = lipoprotein lipase; VLDL = very low density lipoproteins; IDL = intermediate density lipoproteins; LDL = low density lipoproteins; HDL = high density lipoproteins; SR-BI = scavenger receptor class B type I; LDLR = LDL receptor; HDLR = HDL receptor. Other details in text.

## Tissue Uptake

LPL attached to the surface of capillary endothelium has been proposed to play a role in the delivery of  $\alpha$ -tocopherol to extrahepatic tissues, carried in triacylglycerol-rich lipoproteins, chylomicrons, and very-low density lipoproteins (VLDL) [130]. However, LPL activity does not play a major role in the uptake of  $\alpha$ -tocopherol in white adipose tissue during pregnancy by two main reasons: i) During late pregnancy, LPL activity in adipose

tissue is consistently decreased [4; 43; 69; 88; 102; 108] and ii) it has been directly shown in the rat that the uptake of  $\alpha$ -tocopherol in adipose tissue is independent of changes in LPL activity [90]. Other mechanisms besides its role hydrolyzing triacylglycerols in chylomicrons and VLDL could make LPL to contribute to the tissue uptake of  $\alpha$ -tocopherol and cannot be discarded. LPL can function as a cell surface proteoglycan-anchored bridge for lipoproteins, and this action seems to play a major role in the delivery of  $\alpha$ -tocopherol to different tissues. In fact, tissue specific overexpression of LPL in skeletal muscle of transgenic mice led to increased muscle  $\alpha$ -tocopherol concentration [113], and selective uptake of LDL  $\alpha$ -tocopherol is enhanced in the presence of LPL requiring the presence of intact heparin-sulfate proteoglycans, but not the lipolytic activity of the enzyme [38]. No information concerning how this mechanism of tissue  $\alpha$ -tocopherol uptake during pregnancy exists, but the low pre- and post-heparin LPL mass or activity consistently found during pregnancy in women [69; 70] would point to an overall deficiency of LPL that hardly could facilitate tissue uptake of  $\alpha$ -tocopherol.

The receptor-mediated lipoprotein endocytosis and/or the selective lipoprotein  $\alpha$ -tocopherol uptake could actively contribute to the availability of  $\alpha$ -tocopherol in maternal tissues.

The LDL receptor (LDLR) pathway has been involved in cellular  $\alpha$ -tocopherol uptake from LDL [125; 128], although it has been considered not essential for maintenance of normal tissue vitamin E levels due to the redundant function of other lipoprotein receptors [87].

Another mechanism for tissue  $\alpha$ -tocopherol uptake from circulating lipoproteins has been proposed to be its selective uptake without the net uptake of lipoprotein holoparticles. This is carried out together with other lipoprotein-associated lipids via the scavenger receptor class B type I (SR-BI), which is a cell surface glycoprotein that was described as a HDL receptor for cellular selective cholesteryl ester uptake [1]. By working with HepG2 hepatoma cells, it was initially shown that radiolabeled  $\alpha$ -tocopherol is incorporated into the cells through selective uptake from HDL [39], and by working with type II pneumocytes it was latterly demonstrated that HDL is the most potent lipoprotein-associated vitamin E donor, followed by VLDL and LDL [76]. It was also found in rat liver and HepG2 cells that the expression of SR-BI is down-regulated by the vitamin E status, in the sense that depletion of vitamin E causes its induction, that is partially reversed by vitamin E enrichment [144]. Concerning reproductive physiology, SR-BI deficiency in mice is associated to female infertility and decreased development of pre-implantational embryos [93; 132], probably as result of impaired delivery of  $\alpha$ -tocopherol to ovaries causing a pro-oxidative stress condition.  $\alpha$ -Tocopherol supplementation in SR-BI knockout female mouse does not restore their fertility [124] suggesting that this receptor is an essential component in facilitating the delivery of  $\alpha$ -tocopherol to the key reproductive tissues. This receptor seems to play a critical role in the post-implantational embryonic development by controlling the transfer of lipoprotein  $\alpha$ -tocopherol from maternal circulation into the growing embryo. It is expressed in both maternal (e.g., decidual and trophoblast cells) and embryonic (yolk sac visceral endoderm and placental chorionic labyrinth) sides of the maternal-fetal interface [44; 146], contributing to the efficient antioxidant defense required for normal intrauterine fetal development.

The ATP-binding cassette transporter A1 (ABCA1) is a protein that belongs to a large family of conserved transmembrane proteins that use ATP as an energy source that drives the transport of a wide variety of molecules across the plasma membrane of living cells [53]. This transporter interacts preferentially with lipid-poor apoA-I, allowing its lipidation by thereby forming nascent HDL [139]. In addition to apoA-I, ABCA1 interacts with other apolipoproteins with amphipathic helical motifs and induce lipid efflux by the same mechanism [134]. It has been also proposed that ABCA1 is an apoA-I receptor that upon binding induces the transfer of cholesterol and phospholipids [34; 99; 138]. Besides, recently it has been demonstrated the role of ABCA1 in cellular apolipoprotein A-I-mediated  $\alpha$ -tocopherol secretion [100]. ABCA1 is ubiquitously expressed, with high expression levels in placenta and fetal tissues [78]. Besides, it has been reported that in ABCA1 knockout mice, severe placental malformation occurred [23], and it has been proposed that these placental abnormalities are due to inadequate  $\alpha$ -tocopherol supply in the fetomaternal unit [65].

### Placental Transfer

$\alpha$ -Tocopherol transfer protein ( $\alpha$ -TTP) was first described by Catignani et al. [22] as a hepatic intracellular protein that transports cytosolic  $\alpha$ -tocopherol. This protein selectively recognizes  $\alpha$ -tocopherol, with lower affinities of various tocopherol analogs [54]. Although  $\alpha$ -TTP was first described as being solely present in the liver, it is now accepted that is expressed in several tissues, including in pregnant mouse uterus and human placenta [60; 63; 64]. The fact that RRR- $\alpha$ -tocopherol, which is the  $\alpha$ -tocopherol stereoisomer that is preferentially transported by  $\alpha$ -TTP, is preferentially transported to cord blood [2] and that impaired fertility is observed in animals lacking the  $\alpha$ -TTP [45] highly indicate that  $\alpha$ -TTP is important for the transport of  $\alpha$ -tocopherol in the fetomaternal unit.  $\alpha$ -Tocopherol concentration in plasma of human fetuses are lower than in their mothers, but rises towards the end of pregnancy [8; 147]. It was also found that RRR- $\alpha$ -tocopherol is enriched by a factor of 3.42 at its passage through the human placenta [2]. These antecedents were followed by the recent findings of  $\alpha$ -TTP in the trophoblastic cells [63] as well as in various other compartments of the human placenta at term, including the interface between the maternal and fetal circulation, which is composed of the trophoblast and the fetal capillaries' endothelium [97]. It has been therefore proposed that in these cells  $\alpha$ -TTP might be in charge of the stereo-selective transfer of maternal VLDL-bound RRR- $\alpha$ -tocopherol to the fetal plasma [2]. VLDL from maternal plasma does not directly cross the placenta [48]. It is taken up by a very low-density lipoprotein-receptor (VLDLR) at the syncytiotrophoblast, which mRNA expression in the chorionic villi parallels that of  $\alpha$ -TTP [145]. RRR- $\alpha$ -tocopherol may also reach the placenta associated to other lipoproteins besides VLDL, since the placenta expresses receptors for all them: e.g. LDL-receptor related protein and LDL- and scavenger-receptors [3; 13; 103; 118; 146] and HDL-receptors [79; 136; 146]. Besides, the placenta has lipolytic activities to partially breakdown the lipid moieties of the lipoproteins that have been taken up: e.g. LPL [12; 40; 111], phospholipase A<sub>2</sub> [16; 33] and triacylglycerol lipase [11; 66; 85]. The placenta also contains different fatty acid binding proteins: e.g. plasma membrane



fatty acid binding protein (p-FABPm) [19; 20], heart and liver fatty-acid binding proteins (H-FABP and L-FABP) [24] and fatty acid translocase (FAT) and fatty acid transport protein (FATP) [28; 29; 42; 71]. These binding proteins handle the long-chain fatty acids that are released by those lipolytic enzymes, and the fatty acids are finally diffused to the fetal size. Since it has been suggested that  $\alpha$ -TTP in the placenta is a transport- rather than a storage-protein [97], it is proposed that it acts in conjunction with those lipoprotein receptors, enzymes and binding proteins to facilitate the transfer of  $\alpha$ -tocopherol between the maternal and fetal circulation.

Despite the existence of these processes, efforts to investigate the actual kinetics of the transfer of vitamin E by isolated human placental systems has found that although it is specific for natural RRR- $\alpha$ -tocopherol rather than any other form of vitamin E, its rate is very low, being only 10% of passively transferred L-glucose [115]. This justifies the consistent finding of much lower  $\alpha$ -tocopherol levels in fetal plasma and red blood cells than in maternal [18; 52; 59; 89; 107], indicating an insufficient vitamin E supply for the fetus throughout gestation.

### **Antioxidant Status in Fetus and Newborn**

Besides the need for fatty acid protection against autoxidation in the fetus and the low vitamin E level in fetal plasma, the situation is more critical in the early extrauterine life, when defence systems against reactive oxygen species are less well developed [6; 126; 148; 150] and the newborn is submitted to an increased oxygen concentration. This interpretation agrees with the double thiobarbituric acid reactivity found in neonatal red blood cells as compared to adults [58], suggesting a greater peroxidation damage in the formers. The situation is further aggravated in premature infants even without major clinical symptoms, that are born with adequate vitamin E levels to respect to their gestational ages which are rapidly depleted, if no vitamin E supplement is applied [61; 62; 92]. Chronic lung disease, intraventricular hemorrhage, necrotizing enterocolitis and retinopathy of prematurity are important complications of premature infants, which etiology has been associated to the oxidative stress [37; 114; 122].

### **Vitamin E in Mammary Gland**

Under normal conditions, a significant increase in plasma vitamin E levels occurs after commencement of oral feeding, which confirms that a substantial amount of vitamin E is supplied from breast milk [36; 105]. Vitamin E concentration in breast milk is high, being even higher in colostrum than in mature milk [7]. The way how this vitamin E is taken up by mammary gland around parturition deserves attention, because it occurs in parallel with the disappearance of the maternal hyperlipidemia present during late pregnancy [4; 94]. Throughout this same process polyunsaturated fatty acids mainly circulating in late pregnant maternal plasma in the form of lipoprotein-triacylglycerols are also taken up by mammary gland for milk synthesis.

The rapid decline of maternal hypertriacylglyceridemia around parturition coincides with a rapid increase in the mammary gland LPL activity and mRNA expression, whereas LPL activity in adipose tissue remains low [108; 110]. These combined changes facilitate an enhanced uptake of circulating triacylglycerols by the mammary gland instead of being stored in adipose tissue [5]. A similar fate has been proposed for  $\alpha$ -tocopherol, because adipose tissue constitutes its main store in the body [83], shows the highest LPL activity under nonpregnant conditions [15], and  $\alpha$ -tocopherol becomes highly enhanced in mammary gland around parturition, as suggested by its increased concentration in colostrum as compared with mature milk [7; 84; 101]. Direct studies in rats under basal conditions and after oral  $\alpha$ -tocopherol load in late pregnant rats and at mid lactation with or without litter removed have shown that contrary to what occurs in adipose tissue, where LPL activity does not seem to play a role in the uptake of circulating  $\alpha$ -tocopherol, during late pregnancy and lactation, changes in LPL activity in the mammary gland greatly modulate the uptake of  $\alpha$ -tocopherol by the gland [90].

## Concluding Considerations

Vitamin E metabolism plays a key role in the metabolic adaptations taking place during pregnancy. In the mother, plasma levels of  $\alpha$ -tocopherol parallel the development of her hyperlipidemia, which is mainly due to increments in triacylglycerols associated to all the lipoprotein particles. In fact, since under non pregnant conditions  $\alpha$ -tocopherol in plasma is carried in all the lipoprotein particles [123], it is expected that a similar distribution occurs in pregnancy. We do know that polyunsaturated fatty acids in plasma are mainly associated to these lipoproteins [46], and therefore the increase in plasma levels of  $\alpha$ -tocopherol protect from their peroxidation. Such protection is only partially attained, since an increase in maternal serum lipoperoxides has been consistently detected during late pregnancy [21: 96; 133]. Tissue  $\alpha$ -tocopherol uptake is facilitated by LPL, LDLR and/or SR-B1, which expression varies in different directions during pregnancy in specific different tissues, and therefore would determine the fate of circulating  $\alpha$ -tocopherol. Special attention deserves the placenta, which besides needing the ABCA1 protein for its normal development, contains  $\alpha$ -TTP, which in conjunction with lipoprotein receptors, lipolytic enzyme activities and fatty acid binding proteins, facilitates the maternal-fetal transfer of  $\alpha$ -tocopherol. Such transfer is carried out at a very low rate, causing that fetal plasma  $\alpha$ -tocopherol levels are much lower than in maternal plasma, a condition that is aggravated in the early extrauterine life. This situation is compensated during suckling by the high amounts of  $\alpha$ -tocopherol in colostrums and mature milk. In mammary gland, the induction of LPL around parturition contributes to both the disappearance of maternal hyperlipidemia and the efficient uptake of circulating  $\alpha$ -tocopherol, which by this way warrants its availability in the suckling newborn.

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