Lipid Metabolism in the Human Fetus Development

12

Ornella Guardamagna and Paola Cagliero

Abbreviations

ABCA1	ATP-binding cassette A1
ABCG1	ATP-binding cassette G1
ApoA-1	Apoprotein A-1
ApoA-4	Apoprotein A-4
ApoE	Apoprotein E
CE	Cholesteryl ester
CETP	Colesteryl ester transfer protein
CHO	Cholesterol
HDL	High density lipoprotein
FA	Fatty acid
FFA	Free fatty acid
LCAT	Lecithin:cholesterol acyl transferase
LDL	Low density lipoprotein
LP	Lipoprotein
LRP-1	LDL-receptor related protein 1
LRP-2	LDL-receptor related protein 2
NPC1L1	Niemann-Pick C1-like1
PTP	Phospholipid transfer protein
SPC-X/2	Sterol carrier protein X and 2
SR-B1	Scavenger receptor class B
TG	Triglyceride
VLDL	Very low density lipoprotein

O. Guardamagna, MD (✉) • P. Cagliero, PhD
Department of Health Science and Pediatrics,
Turin University, Piazza Polonia, 94,
Torino 10126, Italy
e-mail: ornella.guardamagna@unito.it

Introduction

Lipids including cholesterol (CHO) and fatty acids (FAs) are main constituents of human body cells and actors in physiological functions thus representing a critical requirement for the embryonic and fetal development.

CHO and FAs attain multiples functions: CHO is a cellular membrane constituent, a steroid hormone, bile acids and oxysterol precursor and it is essential for activation of various signalling pathway [1, 2]. CHO plays an important role before implantation, as a precursor of progesterone synthesis, and helps in maintaining the early pregnancy [3–7]. When the embryo is implanted in the uterine wall, CHO is determinant for the embryogenesis and morphogenesis and patterning of the central nervous system [8]. As well FAs and triglycerides (TGs) are cellular membrane constituents, represent an energy source and take part in neuronal and visual development [9].

The embrio and fetus do not come in direct contact with the maternal circulation thus are dependent upon tissues surrounding them to receive the nutritional support. These tissues are represented by the yolk sac and trophoblasts, early in the first trimester, then the placenta since the end of the first trimester and the second trimester [5]. The placenta is an hemochorial villous organ with multiple functions: oxygen and CO_2 exchange, nutrient absorbption and immune

© Springer International Publishing Switzerland 2016

N. Bhattacharya, P.G. Stubblefield (eds.), *Human Fetal Growth and Development: First and Second Trimesters*, DOI 10.1007/978-3-319-14874-8_12

barrier. It represents a bridge connecting mother and fetus through the maternal-placental (uteroplacental) blood circulation and the fetal-placental (fetoplacental) blood circulation. The functional unit of the placenta is the chorionic villus which contains syncytiotrophoblast/cytotrophoblast, villous stroma and fetal vascular endothelium, layers that separate the maternal blood from the fetal circulation [10]. The yolk sac and the placenta provide an adequate nutrient supply by transporting a wide variety of maternal molecules to the embrio and fetus, including lipids, so promoting the intrauterine development. The transfer of some nutrients is regulated by the placenta itself through specific enzymes, receptors and transport proteins; others nutrients are directly metabolized by the placenta.

During gestation metabolic changes intervene with a shift from carbohydrates to lipids for maternal energy production in order to make nutrients available for the fetus [11]. Glucose is the main substrate that crosses the placenta but other factors may also contribute to the fetal growth. The fetus requires a substantial amount of lipids throughout its development, the lack of CHO affecting growth disorders [12]. To satisfy these needs maternal physiological hyperlipidemia is manifest in pregnancy; CHO, TGs and FAs concentrations increase in both maternal plasma and erythrocytes thus allowing the fetus to rapidly receive and store fat, which exceeds by far that of any other nutrient [13]. Maternal plasma CHO may increase through the 12th week of gestation while TGs reach the 150–300 % of increase in the third trimester of pregnancy [6, 14, 15]. The two lipoproteins (LPs) classes involved in supporting the placental CHO need are low density lipoprotein (LDL) and high density lipoprotein (HDL) [16–18]. A supply of CHO requirement as a precursor for the production of steroid hormones in the placenta is further critical [19]. Fetal steroid precursors of estrogens regulate the uptake of maternal LPs to promote the placental progesterone synthesis. Both estrogen and progesterone are thus key determinants in pregnancy maintenance and fetal growth so being evident the basic role of fetal and maternal LPs [20, 21] (Fig. 12.1).

Lipids Synthesis and Transport

The fetus has two potential sources of CHO and FAs that include the endogenous and exogenous metabolic supply. The endogenous pathway is represented by lipids synthesized by the embrio and fetus themself, the exogenous pathway concerns lipids provided by the maternal and placental circulation. Fetal CHO and FAs are thus either taken up from the maternal circulation or synthesized *"de novo"*.

In humans very low density LP (VLDL) carries CHO and TG from the liver where originates to peripheral cells, LDL carries mainly CHO. HDL represents the reverse CHO pathway deputed to carry out free CHO from

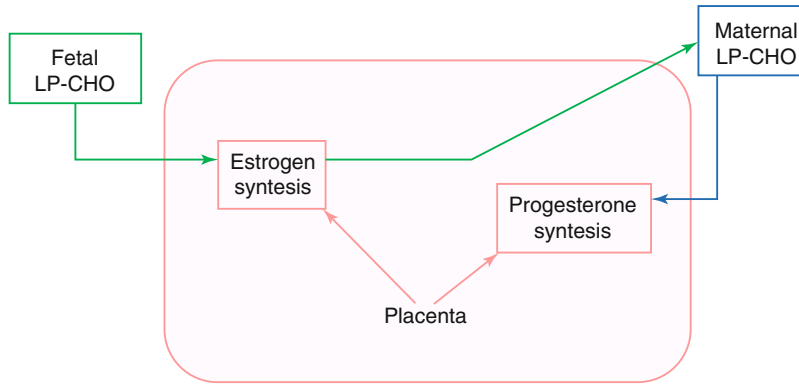

Fig. 12.1 Feto-maternal CHO intake and steroid hormonal synthesis regulation

peripheral cells, to promote CHO esterification to cholesteryl ester (CE), to provide exchange of CE and TG between circulating LPs and to bring up CE to the liver (Fig. 12.2). The delivery of lipids to the fetus is made available by the physiological maternal LPs increase which allow VLDL, LDL, HDL to be taken up by the placenta [6] (Fig. 12.3). Lipid metabolism undergoes particular changes during pregnancy, despite the fact that the placenta is practically impermeable to TGs, except for FAs. Through the early two third of pregnancy the mother

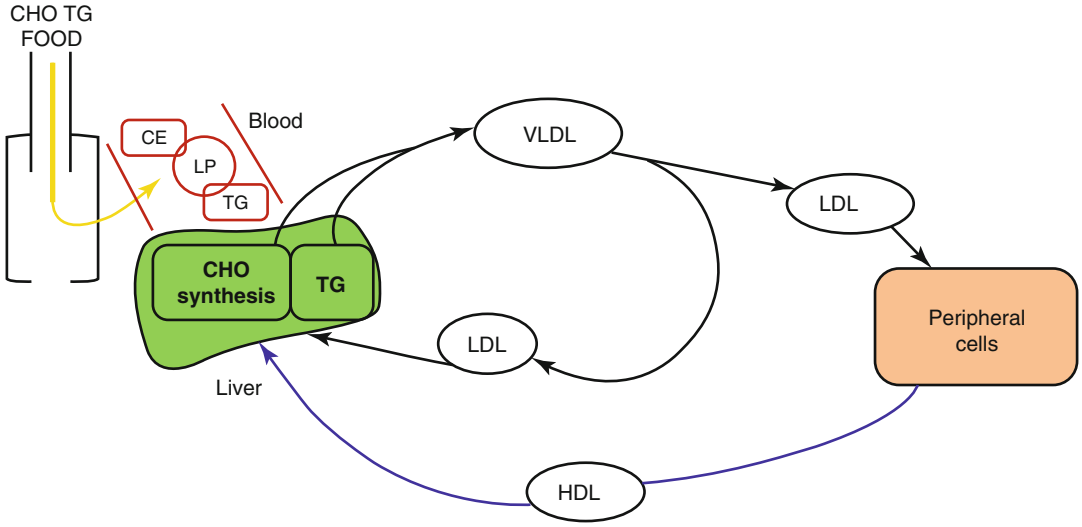

Fig. 12.2 Lipoprotein metabolism in unpregnant women

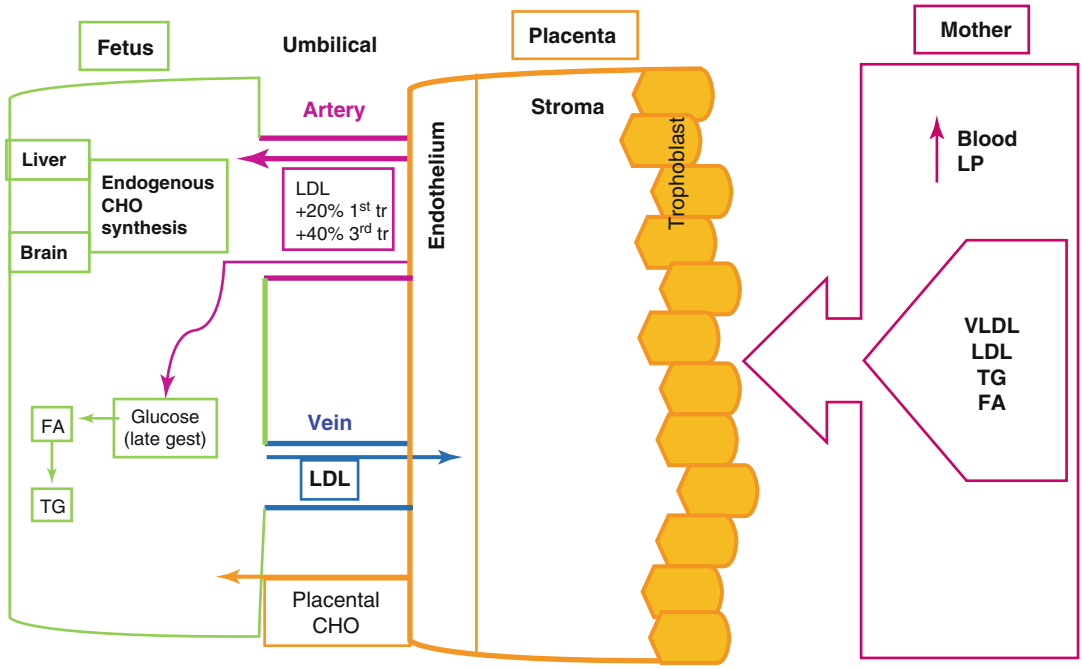

Fig. 12.3 Mother to fetus CHO and lipid exchange

accumulates fat stores thus providing nutrients sources to the fetus in the third part of pregnancy by the placenta transfer [22].

Fetal Cholesterol

Most of CHO required for the fetal growth is "*de novo*" synthesized by the fetus itself, thus making him autonomous from maternal or placental cholesterol supply [23]. The fetal CHO synthesis amount has been demonstrated to be higher than in adults and the endogenous production of CHO has been confirmed a mandatory need for fetal development [24]. The requirement of CHO is particularly high in brain and liver tissues, the synthesis by the liver being postulated to support other tissues requirement as demonstrated in animals [25]. Sterols markers of the CHO synthesis which include lanosterol, dihydrolanosterol, and lathosterol increase strongly since the 19th week of gestation while low till that period [26].

A maternal contribution to fetal CHO levels is anyway sustained by evidences supporting the postulate that up to 20 % of the sterol used by the fetus in the first trimester origins from maternal CHO and that an even greater percentage could be derived from the placenta with higher CHO concentrations [5]. More recently it was demonstrated that this figures grow up to around 22–40 % in the last trimester of pregnancy with a peak in the 2nd trimester [27] (Fig. 12.3).

Data, demonstrating that fetuses affected by CHO synthesis defect show at birth or later detectable CHO in tissues and plasma, support the hypothesis of a maternal supply to the fetal CHO pool [28, 29]. Furthermore comparing the LDL levels flux through the umbilical artery, which transports blood to the fetus via the placenta and that of the cord vein, which translates blood in the opposite direction (via the placenta to the fetus), it appears that LDL concentrations are higher in the umbilical artery [30]. CHO maternal LPs uptake can be also influenced by maternal, but not paternal, apolipoproteinE (APOE) phenotype thus adding a subject to exogenous CHO transfer to the fetus from maternal blood [31]. A further marker for maternal-fetal CHO transport consists of beta-sitosterol levels detectable in the amniotic fluid [26]. The maternal CHO availability in early pregnancy seems relevant to placental and embryonic development in humans [32–37] thus on the basis of the above demonstrations it has been hypothesized that the fetus can acquire maternal CHO whenever this hypothesis it is not definitively accepted and needs further confirmations.

CHO Transport

Maternal CHO has to cross the barriers between maternal and fetal tissues: the yolk sac in early pregnancy and, from approximately the fourth gestational week, the placenta (Fig. 12.4). Since the 10–12 weeks of gestational age the placental syncytiotrophoblast layer plug maternal blood on their apical side and fetal microvessels at its basolateral side. In-vitro studies suggest that the yolk sac is able to transfer externally derived CHO by receptor-independent processes such as aqueous diffusion [5, 38]. Most evidences come from studies conducted in animals that strongly suggest a transport over the yolk sac membrane during pregnancy [24].

Humans studies indicate that maternal CHO markedly contributes to the fetal CHO pool at early stages of gestation, both resulting significantly correlated [39]. The placental layer overcome by lipids could be more difficult. CHO uptake by syncytiotrophoblast cells is the result of receptor mediated as well as receptor-independent processes [24]. This step is allowed by means of different mechanisms, already demonstrated in animals, but still questionable in humans. These involve:

(a) LPs receptor mediated mechanisms involving LDL and VLDL receptors. LPs bound to the receptor undergo endocytosis to lysosomes/endosomes where CHO esters are degraded. The free CHO is transported across the cells via sterol carrier proteins, as Niemann-Pick C1-Like 1 (NPC1L1) and sterol carrier protein X and 2. The receptor is then recycled to the membrane [40].

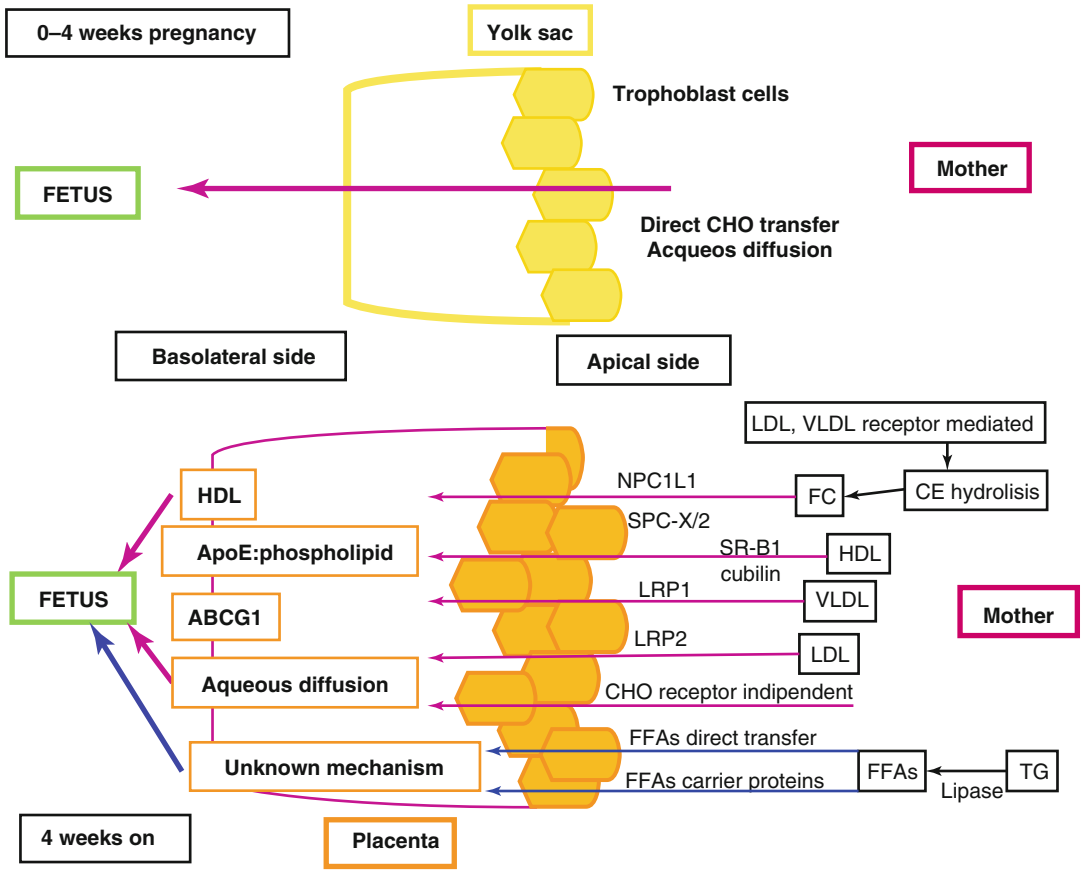

Fig. 12.4 Placental uptake and efflux of maternal LPs

(b) Receptors that transfer the CHO across the plasma membrane without internalization of the receptor. These include:
   1. The scavenger receptor class B (SR-B1) that transports CHO mainly from HDL and with less affinity from LDL;
   2. LDL receptor-related protein 1 (LRP-1) that binds apoE-containing particles such as VLDL. An increase in maternal blood CHO was demonstrated to reduce LDL receptor protein in trophoblasts and this result was considered a regulatory effect of maternal CHO on these receptor expression [41].
   3. LDL receptor-related protein 2 (LRP-2), also named megalin, binds LDL and apoB, while cubilin binds HDL, apoE and apoA-1.

The efflux of CHO across cellular membranes is promoted by HDL through the ATP-binding cassette (ABC) transporters ABCG1, but contrasting data are available about ABCA1 [27, 42]. Moreover the efflux can be sustained by aqueous diffusion or apoE and phospholipid complex [24].

The placenta contains several LP receptors supporting its ability in taking up CHO from maternal blood but this subject is still uncertain as are the procedures that need to be explained [30].

Fetal Fatty Acids and Triglycerides

FAs can be synthesized "*de novo*" by the fetus, including some satured FAs and monounsatured

FAs originating from glucose. This appears particularly in advanced gestation when there is a gradual shift from embryonic to fetal lipids maternally derived [43]. The relevance of FAs in the fetal development is suggested by their maternal circulation increase during gestation [44, 45] and were shown to correlate with fetal lipid concentrations and fetal growth [46–48].

Fetal Fatty Acids and Triglycerides Transport

The energy provided by FAs is available from the maternal circulation in two different forms: FAs in their free form bound to albumin, or TGs transported as LPs (Fig. 12.4).

FAs are hydrolized by lipase activity that produces free fatty acids (FFAs). FFAs can also be directly uptaken from the maternal circulation then enter the placenta and trophoblasts cells through passive diffusion or by membrane carrier proteins to reach the fetus [13, 49–51]. When taken up by trophoblast cells FFAs are either transported transcellulary to the basolateral membrane, via an undefined mechanism, or utilized by the placenta itself for energy or as membrane substrates [6, 52].

Whenever LPs cross the placenta with difficulty [53], TGs could anyway be available to the fetus [6]. Maternal TGs carried by plasma LPs can be taken up intact by the placenta or undergo enzymatic lipase activity as shown in the placenta. Two lipases achieve FFAs from maternal circulating LPs containing TGs: the lipoprotein lipase (LPL) and the endothelial lipase. LPL shows the main relevant TGs lipase activity, is abundant in the human placenta and ensures that TGs are hydrolyzed into FFAs; the endothelial lipase is a phospholipase with little triacylglycerol lipase activity. FAs are then re-esterified to synthesize glycerolipids thus providing an energy reservoir in the placenta [52]. Glycerolipids undergo a further hydrolysis to allow FAs to be released into the fetal blood bounded to the alfa–fetoprotein to be rapidly transported to the fetal liver.

A relatively high placental transfer of lipids is related to the fetal requirement of some essential FAs to satisfy their increased request during gestation, as the fetus cannot synthesize them by itself. These are recognized as linoleic acid (LA), α-linolenic acid (ALA) and long chain polyunsatured fatty acids (LC-PUFA), in particular docosahexaeoic acid (DHA). LC-PUFA are mainly transported associated with plasma TG-rich lipoproteins as TGs rather than as FFAs, as demonstrated in humans [54]. DHA is particularly enriched in maternal plasma phospholipids (especially phosphatidylcholine) while ALA is present in TGs but not in phospholipids [55]. The correlation between maternal and late gestation fetal levels supports the mother to fetus transport of essential fatty acids with origins from the maternal diet and metabolism. An adequate availability of LC-PUFA to the fetus is clearly needed to preserve the normal fetal growth and this mechanism is preserved by the development of maternal hyperlipidaemia through pregnancy [6].

Fetal Lipoproteins and Molecular Mechanisms

Fetal LP levels in plasma were quantified during normal human gestation showing marked fluctuations (Table 12.1). The latter should be referred to the gestational age influence on fetal CHO levels with a strong inverse correlation. Early in the gestation Johnson [56] found that total plasma CHO levels were high thus suggesting a rapid biosynthesis rate of lipoprotein containing CHO occurring in the fetal liver (Table 12.2). As well CHO levels resulted significantly and directly correlated with maternal concentrations in fetuses younger than 6 months [6].

Table 12.1 Change in LP levels and gestational age

Week of gestation	CHO (mg/dl)	LDL CHO (mg/dl)	HDL CHO (mg/dl)
31–32	68.0 ± 7.0	44.0 ± 5.0	24.0 ± 2.0
33–34	73.0 ± 7.0	49.0 ± 6.0	24.0 ± 2.0
35–36	65.0 ± 7.0	35.0 ± 3.0	22.0 ± 4.0
37–38	64.0 ± 4.0	37.0 ± 3.0	23.0 ± 2.0
39–40	56.0 ± 2.0	30.0 ± 2.0	22.0 ± 1.0
41–42	53.0 ± 3.0	28.0 ± 2.0	22.0 ± 1.0

Human fetal adrenal glands make use of LPs containing CHO, and in particular LDL, as a substrate for steroid hormones production. Further LDL levels are inversely related to plasma concentrations of the major fetal adrenal secreted hormone: the dehydroepiandrosterone sulfate. The early CHO decrease in plasma fetal levels is concurrent with the adrenal gland size increase as happens through the 12–20 weeks of the gestation so providing a putative cause [57].

Some major variations characterize fetal and maternal LPs (Fig. 12.5). LDL and VLDL are poorly represented in fetal blood [58] while HDL represents the main lipoprotein class in cord blood [59, 60]. The fetal transport of CHO by HDL accounts at least the 50 % of the whole fetal pool, while LDL is the mainly transporter in the mother [61]. Fetal HDL differs from adult ones for physical-chemical properties. First the HDL_2 sub-fraction is mainly represented in fetal blood whereas HDL_3 sub-fraction is more prevalent in adults [62]. Second the fetal HDL apoprotein composition shows high apoE contents [62] and apoA-4 enrichment. ApoE is a relevant player in LP metabolism as interacts with cell surface receptors [63] and is mainly carried by HDL than TG rich LPs [61] so it is likely that the main role of apoE is to participate to the HDL metabolism. For instance apoE may facilitate the uptake of HDL by the fetal liver. ApoA-4 shows great structural similarities with apoA-1, which does not efflux CHO from the trophoblast [51], thus being postulated apoA-1 and apoA-4 to be exchangeable in the fetus [64]. The fetal HDL apoproteins profile gives an explanation for changes in their functions including an increased atheroprotective effect in the feto-placental vasculature. This effect could be explained by the role of apoA-4 and apoE in promoting lecithin:cholesterol acyl transferase (LCAT) activation [65]. To the antiatherogenic effect contributes the lower fetal colesteryl ester

Table 12.2 Fetal cholesterol levels through the gestational period

Week of gestation	CHO (mg/dl)
10–16 (n = 68)	85.4 ± 30.7
16.5–20 (n = 19)	39.9 ± 21.0
26.5–32 (n = 17)	67.8 ± 5.8
32.5–36 (n = 16)	58.8 ± 13.6
36.5–40 (n = 44)	51.4 ± 11.5

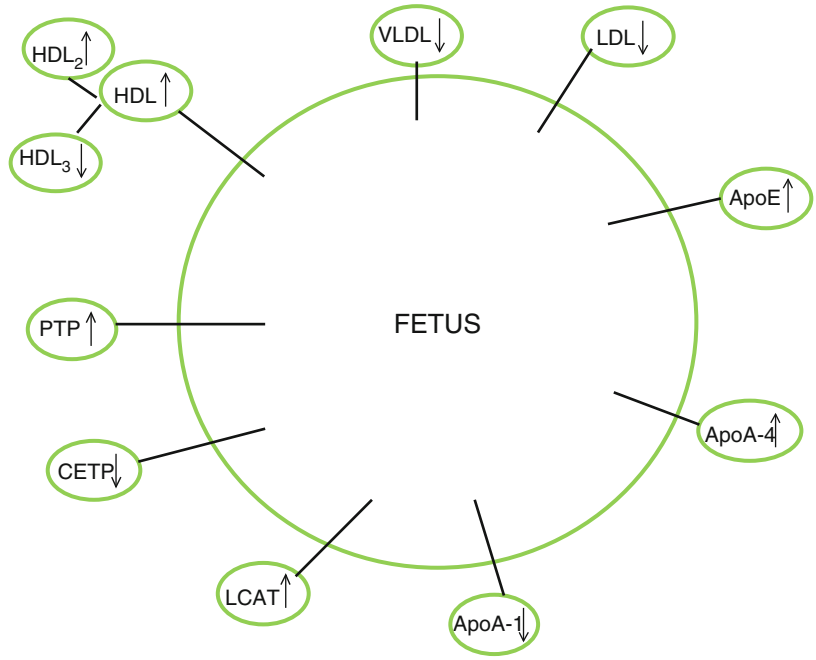

Fig. 12.5 LPs, apoprotein and enzyme activity variation in fetal plasma compared to maternal plasma

transfer protein (CETP) activity accounting for larger HDL subfraction [66] and the phospholipid transfer protein that increases particle's efflux capacity [67]. Fetuses exhibit major modifications of their HDL proteome in addition to the quantitative decrease of HDL-TGs and increase of HDL CHO levels [65].

FA transfer proteins expressed by the placenta include FA transport proteins (FATP1-4, FATP6), FA translocase protein (FAT/CD36), and plasma membrane fatty-acid-binding protein (FABPpm) [68, 69] which are devoted to secrete into the fetal blood the maternally derived FFAs [70]. FABPpm shows a selective action addressed to LC-PUFA transport to the fetus whenever in smaller quantity with respect to TGs.

Fetal genome and in particular APOE and LPL genes were demonstrated to modulate the maternal LP phenotype when particular polymorphisms change related are considered. In the presence of APOE2 isoforms the fetal liver uptake of HDL may be reduced [71]. Following metabolic changes include the depletion of intrahepatic CHO content and the reduction of LDL CHO concentration as occurs in postnatal life. Otherwise fetal genetic polymorphisms produce lipid phenotypes that are contrary to those observed in adults as the case of APOC3 (APOC3*S2 lowers LDL in fetus while increase LDL in adults). Furthermore the effects of fetal polymorphisms are strongly modulated by maternal polymorphisms suggesting that LP effects of these polymorphisms may differ before and after birth [33]. These data confirm a fetal contribution to maternal LP metabolism through the pregnancy [72]. Furthermore maternal genetic polymorphisms seems to impact on fetal LP levels, independently of maternal LPs and of fetal genome.

Fetal Consequences of Maternal and Fetal Disorders

The altered feto-maternal LP metabolism and exchanges exit in different degree disorders ranging from inability to the embrio implantation, leading to heavy malformations and abortion or minor disorders which impact on the future life. Disorders related are both of maternal or fetal origin (Table 12.3): the former include the Familial Hypercholesterolemia (FH), Pre-eclampsia and Diabetes; the latter the Intrauterine Growth Restriction (IUGR) and defects of CHO biosynthetic pathway.

Table 12.3 Fetal outcome related to fetal and/or maternal lipoprotein metabolism disorders

Maternal disorders	**Fetal consequences**
Familial hypercholesterolemia	High LDL CHO
	Preterm birth
Pre-eclampsia	Altered placental transfer of lipids
	High TGs
Gestational diabetes mellitus	LGA
	High FFAs
	Low TGs
Diabetes	Malformation and macrosomia
	High VLDL and LDL
Fetal disorder	
IUGR	Low CHO, LDL CHO, HDL CHO
	High TGs
SLOS	Central nervous system anomalies
	Deficient CHO

Maternal Disorders

Familial Hypercholesterolemia

Pregnant women affected by FH show higher CHO levels [73] than non-FH pregnant women whenever both show a similar percentage rise [15]. As well LDL CHO levels in the cord blood of FH newborns are higher if compared with non-FH newborn ones. On the contrary cord blood TGs and HDL CHO levels were similar to those of controls [74]. FH women gave birth to normal weight infants so indicating the good nutritional status of mothers and no impact on the fetal growth [75]. Furthermore epidemiological data indicate that maternal hyperlipidemia in pregnant FH women is associated with a more procoagulant profile and changes in fetal-uteroplacental

circulation, suggesting the fetus being at risk of preterm birth [76]. A study on over 2000 individuals showed that FH patients born from an FH mother present with higher LDL CHO levels than those who inherited FH from their father [77]. This observation open the discussion toward the atherogenic LPs profile of FH pregnant women, on deleterious effects on their offspring considering the risk of CVD later in life, and on the need of a treatment while on pregnancy of FH woman.

Pre-eclampsia

Pre-eclampsia (PE) is a multiple system disorder that affects the mother and can adversely influence the feto-placental unit. PE is associated with placental dysfunction, oxidative stress [78], endothelial cell activation [79], and it is a cause of maternal and fetal morbidity. PE affected women demonstrate marked dyslipidaemia, hypertension and an increased systemic inflammatory condition potentially triggered by widespread endothelial dysfunction.

PE pregnancy is characterized by a pro-atherogenic lipid profile with increased TGs levels, HDL reduction and increased small dense LDL particles [80]. This altered LP metabolism is involved in the pathogenesis playing a role in the development of the disorder. The placental vascular bed of PE pregnant women shows acute atherosis and atherosclerotic placental lesions characterized by the accumulation of foam cells and perivascular cell infiltration. These abnormalities reduce the placental perfusion and placental/fetal hypoxia may develop [78]. Fetal lipid metabolism can be affected due to an altered placental lipid transfer but contrasting data are described. Rodie et al. [81] observed that CHO levels were higher in the umbilical cord blood from pre-eclamptic pregnant women (with respect to controls) while HDL values were unchanged, supposing that placental transport mechanisms could be up-regulated. These results were not confirmed by Catarino et al. [50] who showed lower CHO and HDL values in the umbilical cord blood of PE pregnant women. This hypothesis is sustained by the evidence that LP receptor expression is decreased in the placenta of women with PE [82]. Moreover higher values of fetal TGs were observed in the umbilical cord blood associated with a significant increase in maternal blood TGs as a compensatory way to face the utero-placental hypoperfusion [83].

Diabetes

Gestational diabetes mellitus (GDM) and maternal diabetes mellitus type 1 or 2 are characterized by high incidence of fetal macrosomia and neonates that are large for gestational age (LGA) [84]. Poor metabolic control of diabetes early in pregnancy is associated with an increased risk of fetal malformations [85]. Poorly controlled diabetes in the second half of pregnancy could exit in neonatal macrosomia. Fetus from mother under poor metabolic control shows an LP cord blood level increase when compared with fetuses from non-diabetic mothers. This case frequently occurs in diabetic mothers.

Maternal hypertriglyceridaemia and hyperglycaemia are a consequence of the augmented insulin resistant condition, these changes enhancing the substrate availability to the fetus. In GDM pregnancies, maternal lipids correlate with fetal lipids and fetal growth; the increase of mother LP concentrations could have effects on lipids transferred to the fetus by their intensified passage [85]. This process enhances the risk for oxidative stress and lipid peroxidation [86]. Also in pregnancies under well-controlled GDM, both maternal TGs and FFAs levels have been shown to correlate positively with neonatal weight and fat mass, indicating that maternal hyperlipidaemia in GDM actively enhances the availability of lipids to the fetus, contributing to his fat depot accumulation. Maternal FFAs and TGs levels predict also LGA birth weight and these values are linked with those measured in cord blood serum [48].

Fetal Disorders

Intrauterine Growth Restriction (IUGR)

Small for gestational age (SGA) newborns could be divided into two groups, depending on the causes of low birth weight. SGA neonates include those who are genetically small and IUGR. In this

latter pathologic condition the fetus does not reach its genetically growth potential, with a growth velocity reduction and related fetal disorders. The current hypothesis about pathogenesis include the insufficient trophoblast development that may lead to atherosclerotic placental lesions. Thus IUGR has similar placental pathology as PE [87].

Authors evidenced lower maternal LDL and CHO concentrations in pregnancies complicated by IUGR but few data are available about fetal LPs in IUGR condition. Pecks et al. [88] showed a significant decrease of HDL and LDL CHO levels in the umbilical cord blood of IUGR pregnant women. Furthermore authors underlined the current increase of oxLDL/LDL ratio which was negatively correlated to HDL concentrations. On the contrary TG levels were significantly increased.

IUGR fetuses show a proatherogenic profile. Based on Baker's hypothesis, change in lipid concentrations may represent one of the pathogenic links between low birth weight for gestational age and subsequent cardiovascular events in adulthood. This suggests a metabolic programming in intrauterine environment resulting from placental insufficiency [88].

Defects in the Cholesterol Biosynthetic Pathway

Seven known disorders involving enzyme defects in post-squalene cholesterol biosynthesis have been identified: desmosterolosis, X-linked dominant chondrodysplasia punctata, CHILD syndrome, lathosterolosis, hydrops-ectopic calcification-moth-eaten skeletal dysplasia, Antley–Bixler syndrome, Smith–Lemli–Opitz syndrome. The most common is the Smith-Leimli-Opitz syndrome (SLOS), while the other six syndrome are extremely rare and often lethal.

SLOS is a congenital multiple anomaly/intellectual disability syndrome caused by a deficiency of CHO synthesis resulting from an inherited deficiency of 7-dehydrocholesterol (7DHC)-reductase, encoded by DHCR7 gene. The enzyme catalyses the last step of CHO biosynthesis, the conversion of 7DHC to CHO. As a result deficient CHO levels are produced while the precursor 7DHC and derivatives accumulate both during embryonic development and after birth. Tissues (especially brain) deprived of CHO, or because of sterol precursors and derivatives deposit, develop abnormally and function poorly. Substitution of 7DHC for CHO alters the lipid raft stability, protein compositions and decreases membrane bending rigidity. The precocious altered sterol composition in SLOS affects the physical and chemical properties as well as the function of cellular membranes. These changes are causative of signal transduction [89]. IUGR is the most frequent ultrasound finding, detected in 67–100 % of affected fetuses [90, 91]. SLOS affected newborns have a distinctive appearance with specific facial dysmorphism and suffer from multiple congenital anomalies including cleft palate, congenital heart disease, genitourinary abnormalities, and malformed limbs. They often manifest mentally retardation with significant central nervous system anomalies [92, 93].

Conclusion

Lipoprotein metabolism in human fetus is uncompletely understood but it is finally clear that a strict relationship between mother and fetus LP phenotypes effect pregnancy outcome and mother and fetus well-being. This correlation is related to the genetic fetal and maternal background and LP polymorphisms associated, besides environmental conditions.

Main key points concern the relevance of fetus CHO pool and FAs that are critical to the growth rate, the fetus as auxotrophic human being for CHO and lipid synthesis and the LP transport as feasible from maternal blood through the placenta. CHO transport in the fetus is mainly supported by HDL subclass and among FAs LC-PUFA uptake by the placenta is preferential. The transport is made available by transporters or by acqueous diffusion including both CHO and FAs. Considering the CHO efflux from the placenta to the fetus this is mainly provided by HDL or by simple diffusion while mechanisms regarding FFAs efflux are not finally established. Further studies aimed to ascertain actually unrecognized physio-pathological mechanisms are requested whenever ethical issues should not be neglected.

References

1. Fielding CJ, Fielding PE. Membrane cholesterol and the regulation of signal transduction. Biochem Soc Trans. 2004;32:65–9.
2. Cooper MK, Wassif CA, Krakowiak PA, et al. A defective response to Hedgehog signaling in disorders of cholesterol biosynthesis. Nat Genet. 2003;33: 508–13.
3. Baardman ME, Kerstjens-Frederikse WS, Berger RMF, et al. The role of maternal-fetal cholesterol transport in early fetal life: current insights. Biol Reprod. 2013;88:1–9.
4. Murphy CR. The plasma membrane transformation of uterine epithelial cells during pregnancy. J Reprod Fertil Suppl. 2000;55:23–8.
5. Woollett LA. Maternal cholesterol in fetal development: transport of cholesterol from the maternal to the fetal circulation. Am J Clin Nutr. 2005;82:1155–61.
6. Herrera E, Amusquivar E, Lopez-Soldado I, Ortega H. Maternal lipid metabolism and placental lipid transfer. Horm Res. 2006;65:59–64.
7. Weissgerber TL, Wolfe LA. Physiological adaptation in early human pregnancy: adaptation to balance maternal-fetal demands. Appl Physiol Nutr Metab. 2006;31:1–11.
8. Bertrand N, Dahmane N. Sonic Hedgehog signaling in forebrain development and its interactions with pathways that modify its effects. Trends Cell Biol. 2006;16:597–605.
9. Innis SM. Dietary omega 3 fatty acids and the developing brain. Brain Res. 2008;1237:35–43.
10. Wang Y, Zhao S. Vascular biology of the placenta. San Rafael: Morgan & Claypool Life Sciences; 2010.
11. Di Cianni CG, Miccoli R, Volpe L, et al. Intermediate metabolism in normal pregnancy and in gestational diabetes. Diabetes Metab Res Rev. 2003;19(4):259–70.
12. Tint GS, Salen G, Batta AK, et al. Correlation of severity and outcome with plasma sterol levels in variants of the Smith-Lemli-Opitz syndrome. J Pediatr. 1995;127:82–7.
13. Gil-Sánchez A, Koletzko B, Larqué E. Current understanding of placental fatty acid transport. Curr Opin Clin Nutr Metab Care. 2012;15:265–72.
14. Martin U, Davies C, Hayavi S, et al. Is normal pregnancy atherogenic? Clin Sci. 1999;96:421–5.
15. Amundsen AL, Khoury J, Iversen PO, et al. Marked changes in plasma lipids and lipoproteins during pregnancy in women with familial hypercholesterolemia. Atherosclerosis. 2006;189:451–7.
16. Tuckey RC. Progesterone synthesis by the human placenta. Placenta. 2005;26:273–81.
17. Henson MC, Shi W, Greene SJ, Reggio BC. Effects of pregnant human, nonpregnant human, and fetal bovine sera on human chorionic gonadotropin, estradiol, and progesterone release by cultured human trophoblast cells. Endocrinology. 1996;137:2067–74.
18. Knopp RH, Warth MR, Charles D, et al. Lipoprotein metabolism in pregnancy, fat transport to the fetus, and the effects of diabetes. Biol Neonate. 1986;50:297–317.
19. Saarelainen H, Laitinen T, Raitakari OT, et al. Pregnancy-related hyperlipidemia and endothelial function in healthy women. Circ J. 2006;70:768–77.
20. Pepe GJ, Albrecht E. Actions of placental and fetal adrenal steroid hormones in primate pregnancy. Endocr Rev. 1995;16:608–49.
21. Desoye G, Schwenditisch MO, Pfeiffer KP, Zechner R, Kostner GM. Correlation of hormones with lipid and lipoprotein levels during normal pregnancy and postpartum. J Clin Endocrinol Metab. 1987;64:704–12.
22. Herrera E, Lasunción MA, Gomez-Coronado D, et al. Role of lipoprotein lipase activity on lipoprotein metabolism and the fate of circulating triglycerides in pregnancy. Am J Obstet Gynecol. 1988;158:1575–83.
23. Jurevics HA, Kidwai FZ, Morell P. Sources of cholesterol during development of the rat fetus and fetal organs. J Lipid Res. 1997;38:723–33.
24. Avis HJ, Hutten BA, Twickler MT, et al. Pregnancy in women suffering from familial hypercholesterolemia: a harmful period for both mother and newborn? Curr Opin Lipidol. 2009;20:484–90.
25. Haave NC, Innis SM. Cholesterol synthesis and accretion within various tissues of the fetal and neonatal rat. Metabolism. 2001;50:12–8.
26. Baardman ME, Erwich JJHM, Berger RMF, et al. The origin of fetal sterols in second-trimester amniotic fluid: endogenous synthesis or maternal-fetal transport? Am J Obstet Gynecol. 2012;207:19–25.
27. Larque E, Ruiz-Palacios M, Koletzko B. Placental regulation of fetal nutrient supply. Curr Opin Clin Nutr Metab Care. 2013;16:292–7.
28. Linck LM, Hayflick SJ, Lin DS, et al. Fetal demise with Smith–Lemli–Opitz syndrome confirmed by tissue sterol analysis and the absence of measurable 7-dehydrocholesterol delta(7)-reductase activity in chorionic villi. Prenat Diagn. 2000;20:238–40.
29. Nowaczyk MJM, Farrell SA, Sirkin WL, et al. Smith–Lemli–Opitz (RHS)syndrome: holoprosencephaly and homozygous IVS8-1G C genotype. Am J Med Genet. 2001;103:75–80.
30. Parker Jr CR, Deahl T, Drewry P, Hankins G. Analysis of the potential for transfer of lipoprotein-cholesterol across the human placenta. Early Hum Dev. 1983;8:289–95.
31. Witsch-Baumgartner M, Gruber M, Kraft HG, et al. Maternal apo E genotype is a modifier of the Smith–Lemli–Opitz syndrome. J Med Genet. 2004;41:577–84.
32. Wadsack C, Hammer A, Levak-Frank S, et al. Selective cholesteryl ester uptake from high density lipoprotein by human first trimester and term villous trophoblast cells. Placenta. 2003;24:131–43.
33. Descamps OS, Bruniaux M, Guilmot PF, et al. Lipoprotein concentrations in newborns are associated with allelic variations in their mothers. Atherosclerosis. 2004;172:287–98.
34. Madsen EM, Lindegaard ML, Andersen CB, et al. Human placenta secretes apolipoprotein B-100-containing lipoproteins. J Biol Chem. 2004;279:55271–6.
35. Wittmaack FM, Gafvels 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;136:340–8.
36. Rindler MJ, Traber MG, Esterman AL, et al. Synthesis and secretion of apolipoprotein E by human placenta and choriocarcinoma cell lines. Placenta. 1991;12:615–24.
37. Lopez D, McLean MP. Estrogen regulation of the scavenger receptor class B gene: anti-atherogenic or steroidogenic, is there a priority? Mol Cell Endocrinol. 2006;247:22–33.
38. Woollett LA. The origins and roles of cholesterol and fatty acids in the fetus. Curr Opin Lipidol. 2001;12:305–12.
39. Napoli C, D'Armiento FP, Mancini FP, et al. Fatty streak formation occurs in human fetal aortas and is greatly enhanced by maternal hypercholesterolemia. Intimal accumulation of low density lipoprotein and its oxidation precede monocyte recruitment into early atherosclerotic lesions. J Clin Invest. 1997;100:2680–90.
40. Woollett LA. Review: transport of maternal cholesterol to the fetal circulation. Placenta. 2011;32 Suppl 2:S218–21.
41. Ethier-Chiasson M, Duchesne A, Forest JC, et al. Influence of maternal lipid profile on placental protein expression of LDLr and SR-BI. Biochem Biophys Res Commun. 2007;359:8–14.
42. Lindegaard ML, Wassif CA, Vaisman B, et al. Characterization of placental cholesterol transport: ABCA1 is a potential target for in utero therapy of Smith–Lemli–Opitz syndrome. Hum Mol Genet. 2008;17:3806–13.
43. Van Aerde JE, Feldman M, Clandinin MT. Accretion of lipid in the fetus and newborn. In: Polin RA, Fox WW, editors. Fetal and neonatal physiology. 2nd ed. Philadelphia: W. B. Saunders Co; 1998. p. 458–77.
44. Burt RL, Leake NH, Pulliam RP. Regulation of plasma NEFA in pregnancy and the puerperium. Preliminary observations. Obstet Gynecol. 1961;17:215–21.
45. Herrera E, Ortega H, Alvino G, et al. Relationship between plasma fatty acid profile and antioxidant vitamins during normal pregnancy. Eur J Clin Nutr. 2004;58:1231–8.
46. Kitajima M, Oka S, Yasuhi I, et al. Maternal serum triglyceride at 24–32 weeks' gestation and newborn weight in nondiabetic women with positive diabetic screens. Obstet Gynecol. 2001;97:776–80.
47. Nolan CJ, Riley SF, Sheedy MT, et al. Maternal serum triglyceride, glucose tolerance, and neonatal birth weight ratio in pregnancy. Diabetes Care. 1995;18:1550–6.
48. Schaefer-Graf UM, Graf K, Kulbacka I, et al. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care. 2008;31:1858–63.
49. Haggarty P. Fatty acid supply to the human fetus. Annu Rev Nutr. 2010;30:237–55.
50. Catarino C, Rebelo I, Belo L, et al. Fetal lipoprotein changes in pre-eclampsia. Acta Obstet Gynecol Scand. 2008;87:628–34.
51. Schmid K, Davidson W, Myatt L, Woollett A. Transport of cholesterol across a BeWo cell monolayer: implications for net transport of sterol from maternal to fetal circulation. J Lipid Res. 2003;44:1909–18.
52. Coleman RA, Haynes EB. Synthesis and release of fatty acids by human trophoblast cells in culture. J Lipid Res. 1987;28:1335–41.
53. Herrera E, Lasunción MA. Maternal–fetal transfer of lipid metabolites. In: Polin RA, Fox WW, Abman SH, editors. Fetal and neonatal physiology. 3rd ed. Philadelphia: W.B. Saunders Co; 2004. p. 375–88.
54. Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. Endocrine. 2002;19:43–55.
55. Otto SJ, Houwelingen AC, Antal M, Manninen A, et al. Maternal and neonatal essential fatty acid status in phospholipids: an international comparative study. Eur J Clin Nutr. 1997;51:232–42.
56. Johnsonh Jr J, Simpsonb ER, Carr P, et al. The levels of plasma cholesterol in the human fetus throughout gestation. Pediatr Res. 1982;16:682–3.
57. Carr BR, Porter JC, Masnald PC, et al. Metabolism of low-density lipoprotein by human fetal adrenal tissue. Endocrinology. 1980;107:1034–340.
58. Dolphin PJ, Breckenridge WC, Dolphin MA, Tan MH. The lipoproteins of human umbilical cord blood apolipoprotein and lipid levels. Atherosclerosis. 1984;51:109–22.
59. Averna MR, Barbagallo CM, Di Paola G, et al. Lipids, lipoproteins and apolipoproteins AI, AII, B, CII, CIII and E in newborns. Biol Neonate. 1991;60: 187–92.
60. Parker Jr CR, Carr BR, Simpson ER, MacDonald PC. Decline in the concentration of low-density lipoprotein-cholesterol in human fetal plasma near term. Metabolism. 1983;32:919–23.
61. Nagasaka H, Chiba H, Kikuta H, et al. Unique character and metabolism of high density lipoprotein (HDL) in fetus. Atherosclerosis. 2002;161:215–23.
62. Augsten M, Hackl H, Ebner B, et al. Fetal HDL/apoE: a novel regulator of gene expression in human placental endothelial cells. Physiol Genomics. 2011;43:1255–62.
63. Herz J, Hamann U, Rogne S, et al. Surface location and high affinity for calcium of a 500-kd liver membrane protein closely related to the LDL-receptor suggest a physiological role as lipoprotein receptor. EMBO J. 1998;7:4119–27.
64. Sreckovic I, Birner-Gruenberger R, Obrist B, et al. Distinct composition of human fetal HDL attenuates its anti-oxidative capacity. Biochim Biophys Acta. 2013;1831:737–46.
65. Zhao Y, Thorngate FE, Weisgraber KH, et al. Apolipoprotein E is the major physiological activator of lecithin-cholesterol acyltransferase (LCAT) on apolipoprotein B lipoproteins. Biochemistry. 2005;44:1013–25.
66. Schaefer EJ, Asztalos BF. Increasing high-density lipoprotein cholesterol, inhibition of cholesteryl ester transfer protein, and heart disease risk reduction. Am J Cardiol. 2007;100:25–31.

67. Scholler M, Wadsack C, Metso J, et al. Phospholipid transfer protein is differentially expressed in human arterial and venous placental endothelial cells and enhances cholesterol efflux to fetal HDL. J Clin Endocrinol Metab. 2012;97:2466–74.
68. Duttaroy AK. Transport of fatty acids across the human placenta: a review. Prog Lipid Res. 2009;48:52–61.
69. Haggarty P. Placental regulation of fatty acid delivery and its effect on fetal growth-a review. Placenta. 2002;23:S28–38.
70. Hanebutt FL, Demmeimair H, Schiessl B, et al. Long-chain polyunsaturated fatty acid (LC-PUFA) transfer across the placenta. Clin Nutr. 2008;27:685–93.
71. Mahley RW, Huang Y. Apolipoprotein E: from atherosclerosis to Alzheimer's disease and beyond. Curr Opin Lipidol. 1999;10:207–17.
72. Descamps OS, Bruniaux M, Guilmot PF, et al. Lipoprotein metabolism of pregnant women is associated with both their genetic polymorphisms and those of their newborn children. J Lipid Res. 2005;46:2405–14.
73. Potter JM, Nestel PJ. The hyperlipidemia of pregnancy in normal and complicated pregnancies. Am J Obstet Gynecol. 1979;133:165–70.
74. Vuorio AF, Miettinen TA, Turtola H, et al. Cholesterol metabolism in normal and heterozygous familial hypercholesterolemic newborns. J Lab Clin Med. 2002;140:35–42.
75. Toleikyte I, Retterstøl K, Leren TP, et al. Pregnancy outcomes in familial hypercholesterolemia: a registry-based study. Circulation. 2011;124:1606–14.
76. Khoury J, Amundsen AL, Tonstad S, et al. Evidence for impaired physiological decrease in the uteroplacental vascular resistance in pregnant women with familial hypercholesterolemia. Acta Obstet Gynecol Scand. 2008;29:1–5.
77. van der Graaf A, Vissers MN, Gaudet D, et al. The dyslipidemia of mothers with familial hypercholesterolemia deteriorates lipid levels in their adult offspring. Boston: Oral presentation at the International Atherosclerosis Society Conference; 2010.
78. Serdar Z, Gur E, Colakodullary' M, et al. Lipid and protein oxidation and antioxidant function in women with mild and severe preeclampsia. Arch Gynecol Obstet. 2003;268:19–25.
79. Var A, Kuscu N, Koyuncu F, et al. Atherogenic profile in preeclampsia. Arch Gynecol Obstet. 2003;268:45–7.
80. Belo L, Caslake M, Gaffney D, et al. Changes in LDL size and HDL concentration in normal and preeclamptic pregnancies. Atherosclerosis. 2002;162:425–32.
81. Rodie V, Caslake M, Stewart F, et al. Fetal cord plasma lipoprotein status in uncomplicated human pregnancies complicated. Atherosclerosis. 2004;176:181–7.
82. Murata M, Kodama H, Goto K, et al. Decreased very-low-density lipoprotein and low-density lipoprotein receptor messenger ribonucleic acid expression in placentas from preeclamptic pregnancies. Am J Obstet Gynecol. 1996;175:1551–6.
83. Tabano S, Alvino G, Antonazzo P. Placental LPL gene expression is increased in severe intrauterine growth-restricted pregnancies. Pediatr Res. 2006;59:250–3.
84. DeRuiter MC, Alkemade FE, Gittenberger-de Groot AC, et al. Maternal transmission of risk for atherosclerosis. Curr Opin Lipidol. 2008;19:333–7.
85. Herrera E, Ortega-Senovilla H. Disturbances in lipid metabolism in diabetic pregnancy – are these the cause of the problem? Best Pract Res Clin Endocrinol Metab. 2010;24:515–25.
86. Herrera E, Ortega-Senovilla H. Lipid metabolism during pregnancy and its implications for fetal growth. Curr Pharm Biotechnol. 2014;15:24–31.
87. Sattar N, Greer IA, Galloway PJ, et al. Lipid and lipoprotein concentrations in pregnancies complicated by intrauterine growth restriction. J Clin Endocrinol Metab. 1999;84:128–30.
88. Pecks U, Brieger M, Schiessl B, et al. Maternal and fetal cord blood lipids in intrauterine growth restriction. J Perinat Med. 2012;40:287–96.
89. Porter FD. Smith–Lemli–Opitz syndrome: pathogenesis, diagnosis and management. Eur J Hum Genet. 2008;16:535–54.
90. Goldenberg A, Wolf A, Chevy F, et al. Antenatal manifestations of Smith-Lemli-Opitz (RSH) syndrome: a retrospective survey of 30 cases. Am J Med Genet A. 2004;124:423–6.
91. Quelin C, Loget P, Verloes A, et al. Phenotypic spectrum of fetal Smith-Lemli-Opitz syndrome. Eur J Med Genet. 2012;55:81–90.
92. Irons M, Elias ER, Salen G, et al. Defective cholesterol biosynthesis in Smith-Lemli-Opitz syndrome. Lancet. 1993;341:1414.
93. Nowaczyk MJ, Irons MB. Smith-Lemli-Opitz syndrome: phenotype, natural history, and epidemiology. Am J Med Genet C: Semin Med Genet. 2012;15:250–62.