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Intrauterine Effects of Impaired Lipid Homeostasis in Pregnancy Diseases

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Abstract: Lipids are crucial structural and bioactive components that sustain embryo, fetal and placental development and growth. Intrauterine development can be disturbed by several diseases that impair maternal lipid homeostasis and lead to abnormal lipid concentrations in the fetal circulation. Deficiency in essential fatty acids can lead to congenital malformations and visual and cognitive problems in the newborn. Either deficient mother-to-fetus lipid transfer or abnormal maternal-fetal lipid metabolism can cause fetal growth restriction. On the other hand, excessive mother-to-fetus fatty acid transfer can induce fetal overgrowth and lipid overacummulation in different fetal organs and tissues. The placenta plays a fundamental role in the transfer of lipid moieties to the fetal compartment and is affected by maternal diseases associated with impaired lipid homeostasis. Postnatal consequences may be evident in the neonatal period or later in life. Indeed, both defects and excess of different lipid species can lead to the intrauterine programming of metabolic and cardiovascular diseases in the offspring. This review summarizes the lipid impairments induced by different pathologies, including placental insufficiency, malnutrition, obesity and diabetes, and their consequent developmental defects.

Keywords: Pregnancy, lipids, intrauterine growth retardation, obesity, diabetes.

INTRODUCTION

During normal pregnancy, lipids are highly required in the intrauterine compartment and thus efficiently transported through the placenta from maternal circulation. Development implies the rapid generation of millions of new cells that will require lipids both as components and as bioactive molecules, crucial for proper developmental and growth patterns. As most lipid species can be synthesized by the mother and the fetus from other nutrients, caloric restriction can affect the formation of structural and bioactive lipids. Essential fatty acids (EFAs) are the n-3 and n-6 polyunsaturated fatty acids (PUFAs) that cannot be synthesized by either the mother or the fetus, and their deficiency has been largely known to be related to the induction of congenital malformations and visual and neurodevelopmental impairments in the newborn [1]. On the other hand, an excess of circulating free and esterified fatty acids during pregnancy in pathologies such as diabetes and obesity affects feto-placental development and leads to abnormal feto-placental growth through mechanisms that involve an excessive substrate transfer and oxidation, which is related to the induction of oxidative stress and a pro-inflammatory environment [2]. Increased oxidative stress induces loss of bioactive lipids through peroxidation. This includes the PUFAs that are ligands of the nuclear receptors PPARs, master regulators of metabolic and anti-inflammatory processes [3]. Importantly, pregnancy diseases related to both the excess and the deficiency of different lipid species in the intrauterine compartment can lead to the programming of diseases in the offspring [4-6]. This review summarizes the current knowledge of the damaging effects of impaired lipid homeostasis in intrauterine development and its postnatal consequences.

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LIPID IMPAIRMENTS AND THE INDUCTION OF CONGENITAL MALFORMATIONS

Congenital malformations arise during organogenesis and are mostly induced before the seventh week of human gestation [7]. Organogenesis is characterized by continuous and accelerated embryo growth and cell differentiation processes, and both embryo growth and development require lipids as structural components of cell membranes in formation, as oxidative fuels and also as signalling molecules [8]. The required lipids are both derived from the mother and synthesized by the embryo, which is capable of synthesizing both polar and neutral lipids from the early embryonic stages [9].

During the first stage of embryo development, lipids derived from the mother are absorbed by histotrophic mechanisms and the visceral yolk sac is involved in this process [10]. In a later stage, embryonic lipid uptake from maternal decidua or maternal blood requires a process of lipid hydrolysis and re-esterification to translocate across the yolk sac membrane. This involves a repackage mechanism of both maternal-derived lipids and endogenously synthesized lipids in the yolk sac that lead to the formation of apoB-containing lipoproteins, which are then secreted from yolk sac endoderm cells to viteline circulation or transported by diffusion to the growing embryo [11, 12].

Animal studies have shown that microsomal triglyceride transfer protein is involved in the secretion of apoB-containing lipoproteins, and embryo lethality occurs in null mice for either apoB or microsomal triglyceride transfer protein genes [13, 14]. Differently, in humans, apoB or micro-

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somal triglyceride transfer protein deficiency does not increase the incidence of early fetal loss, suggesting that in humans, these enzymes are not essential for early nutrient delivery. However, an impaired lipid absorption and peripheral delivery of vitamins A and E have been found in individuals with abetalipoproteinemia [15, 16]. Although no loss-of-function mutations have been reported for scavenger receptor class B member I (SR-BI) in humans, recent studies have shown induction of congenital malformations in SR-BI null mice, suggesting that this receptor is needed for uptake of cholesteryl esters and other lipids from high-density lipoproteins (HDL) during early organogenesis [17].

Smith-Lemli-Opitz Syndrome

Relevant developmental anomalies caused by a deficiency in lipids are the result of impaired function of key enzymes in the cholesterol synthesis pathway. Smith-Lemli-Opitz syndrome (SLO) is a metabolic disorder that leads to a wide spectrum of congenital abnormalities [18]. Individuals with a severe phenotype have multiple major congenital anomalies and may die perinatally, whereas those with a mild phenotype may have learning disorders and minor dysmorphic characteristics [19, 20]. SLO is caused by a deficiency in the activity of 7-dehydrocholesterol reductase. This enzyme catalyzes the reduction of the Δ7 bond in sterols, reducing 7-dehydrocholesterol to yield cholesterol in the final step of cholesterol biosynthesis. Cholesterol is a major lipid component of cellular membranes and is an important structural component of lipid rafts, which play an essential role in signal transduction. Also, bile acids, steroid hormones, neuroactive steroids and oxysterols are synthesized from cholesterol. SLO impairments are caused at least in part by a deficiency in cholesterol and total sterols, by the toxic effects of the accumulation of 7-dehydrocholesterol or its derivatives, and by a combination of these factors [18].

Some of the malformations induced by SLO are similar to those seen in animals in which sonic hedgehog signalling is impaired [21], suggesting the involvement of this morphogen in SLO-induced malformations. It is important to note that in the pregnant woman, intrauterine identification of SLO syndrome may allow the initiation of maternal treatments with diets enriched in cholesterol that reach the embryo and the fetus and help preventing fetal dysmorphogenesis and cognitive impairments in the offspring later in life [20, 22].

Obesity

As lipid transport is highly facilitated to sustain embryo growth and development, the excess of lipid transfer affects the embryo and may cause congenital anomalies. Indeed, among the adverse fetal outcomes associated with pre-pregnancy obesity in women are neural tube defects (e.g. anencephaly, spina bifida, holoprosencephaly) and congenital heart defects (e.g. atrial septal defects, left and all right ventricular outflow tract obstruction defects, hypoplastic left heart syndrome, tetralogy of Fallot, aortic stenosis and pulmonary stenosis) [23, 24].

Obesity and pregnancy are independently associated with insulin resistance and pro-inflammatory changes, processes that may be enhanced when combined in obese gestations. In obese pregnant women, there is an earlier shift from an anabolic to a catabolic state and a predominance of lipolysis instead of the increase in adipose tissue lipid storage that normally occurs during early gestation, resulting in increased availability of lipids that reach the intrauterine compartment [25, 26]. Indeed, pre-pregnancy obesity in women leads to an increase in plasma triglyceride and very-low-density lipoprotein (VLDL) and a reduction in HDL [27]. Adipokines, including leptin, resistin and adiponectin, which modulate glucose homeostasis and lipid metabolism, influence insulin action and have an important role in reproductive tissues, are altered in obese women and animal models of obesity [25, 28]. Thus, they may potentially have a role linking obesity with alterations during embryo development.

Excessive oxidation of metabolic substrates is related to the generation of a pro-inflammatory environment and to the induction of congenital malformations, profoundly addressed in maternal diabetes during embryo organogenesis, as detailed later in this section [2, 29]. Similarly, an increase in systemic and local pro-inflammatory responses is found in women with pre-pregnancy obesity. In fact, there is an increase in adipocyte secretory products such as tumor necrosis factor α (TNF-α), interleukin-6 (IL-6) and also c-reactive protein, which play roles in lipid metabolism [27]. Moreover, in an animal model of obesity and pregnancy, nuclear factor κB (NFκB) and c-Jun N-terminal kinase signalling pathways are upregulated leading to the expression of pro-inflammatory genes and reducing the expression of antioxidant and mitochondrial genes in embryos from obese rats [30].

Recent studies performed in experimental models of obesity have shown alterations previous to organogenesis in the lipid content of the early embryo and the oocyte, which can be involved in the induction of congenital malformations [31, 32]. In obese ob/ob mice, ovaries show increased lipid content, and lipid droplets are observed in oocytes in which degenerated mitochondria are also evidenced [33]. In addition, several alterations in lipid metabolizing enzymes have been found in blastocysts from obese mice [34]. Importantly, human studies have shown that increased free fatty acid (FFA) concentrations in follicular fluid are correlated with poorer oocyte-cumulus complexes morphology [35].

Diabetes

Maternal diabetes increases two to eight fold the risk for congenital malformations. The malformations induced are central nervous system defects, cardiovascular defects, respiratory and skeletal anomalies, among many others [36, 37]. A common complication of obesity is diabetes, and both pathologies have additive effects on the risk of congenital central nervous system malformations [38].

In maternal diabetes, the maternal metabolic impairments resulting from the deficiency in insulin concentrations and/or signalling lead to an excess of metabolic substrates. The maternal lipid profile has been found altered during diabetic pregnancies both in humans and experimental animal models [39, 40]. In animal models of diabetes and pregnancy, an increase in circulating triglycerides and FFAs has been found during early organogenesis, and triglyceride accumulation is observed in developing embryos [41, 42].

Mechanisms involved in the induction of congenital malformations in diabetes have been mostly evaluated in animal models of diabetes and pregnancy [40]. In the embryo, the excess in metabolic substrates and their consequent oxidation leads to an increase in reactive oxygen species that exert embryo damage by themselves, by leading to the formation of peroxynitrites, and by inducing lipid peroxidation and the loss of the bioactive lipids needed during embryo organogenesis, including n-6 EFAs [2, 43, 44]. Besides, possibly as a compensatory mechanism for the increased transfer from maternal circulation, the *de novo* synthesis of cholesterol, cholesteryl esters, triglycerides, and phospholipids is reduced in embryos from diabetic rats during early organogenesis [42]. Due to the role of lipids as structural components of both plasma and nuclear cell membranes, as morphogens and as signalling molecules during organogenesis, the reduction in their synthesis in the appropriate location and time during organogenesis can impair developmental processes [45].

Arachidonic acid is an n-6 EFA for the embryo required during early organogenesis and is a precursor of prostaglandins (PGs), important bioactive lipids needed for proper morphogenesis [45]. Experimental models of diabetes show reduced arachidonic acid concentrations in embryos from diabetic rats during organogenesis [46]. PGE_2 participates in the process of neural tube closure and its levels are reduced in embryos from diabetic rats during early organogenesis [47, 48]. Indeed, both PGE_2 and arachidonic acid supplementation reduce the embryonic malformations induced by the diabetic condition, both *in vivo* and *in vitro* [46, 49, 50]. It has been reported that PGI_2 can also prevent hyperglycemia-induced embryonic malformations [51]. Interestingly, PGI_2 is an endogenous agonist of the peroxisome proliferator activated receptor δ (PPARδ), and the PGI_2-PPARδ signalling pathway is a fundamental pathway for embryo implantation and decidualization [52, 53]. Certain unsaturated lipids, prostaglandins and leukotrienes are endogenous ligands of the nuclear receptor PPARs, transcription factors that regulate metabolic homeostasis, anti-inflammatory pathways and cell differentiation in different tissues [3]. PPARs have critical roles in metabolic diseases such as diabetes and are specifically involved in regulating maternal diabetes-induced reproductive impairments [54]. Both PPARδ and PGI_2 concentrations have been found reduced in embryos from diabetic rats [55]. PPARδ activation up-regulates PGI_2 and PGE_2 levels in embryos from diabetic rats and increases the synthesis of phospholipids, highly required to sustain the rapid growth of the neural folds during the process of closure of the neural tube [42, 55].

Thus, in maternal diabetes, impaired lipid homeostasis is involved in the etiology of congenital malformations in a complex way: damage is due to the excess of oxidable metabolic substrates in the intrauterine compartment that will increase oxidative stress, to the deficiency in n-6 EFAs that will lead to a deficiency in prostaglandins, and to the impaired PPAR-mediated signalling pathways required during embryogenesis.

In maternal diabetes, the malformation rate varies in different populations, as well as in different rat strains [56, 57]. The genetic background and the environment influence the incidence of diabetic rat embryopathy, partly related to the embryonic antioxidant defences [58, 59]. Accordingly, congenital malformations are reduced in experimental models of diabetes by moieties with antioxidant effects (e.g. vitamin E and C, folic acid) and with supplementation of diets enriched in mono- and polyunsaturated fatty acids capable of activating PPARs [41, 60-63]. Further work is still needed to address whether congenital malformations are ameliorated by these treatments in diabetic patients. Indeed, as a limitation, data addressing mechanisms of induction of congenital malformations have been mainly obtained through the evaluation of animal models of diabetes and pregnancy [40]. Besides, as congenital malformations can be originated before organogenesis [64], the involvement of oocyte and embryo lipid composition in diabetes-induced congenital malformations has not been clarified and thus deserves further research. Indeed, alterations in arachidonic acid-derived prostaglandins have been found both in oocyte-cumulus complexes and during implantation in experimental models of diabetes and pregnancy and related to alterations in the ovulatory and implantation processes [45].

Summarizing, in the reviewed diseases, congenital malformations can be induced both directly by the deficiency in structural and bioactive lipids, such as cholesterol and EFAs, or indirectly as a result of the generation of a pro-inflammatory environment generated either by the excess of metabolic substrates or by the deficiency in bioactive lipids that regulate both metabolic and anti-inflammatory processes. In contrast to fetal growth effects, the broad spectrum of malformations suggests that the insult occurs very early during embryo development, affecting different tissues and fetal organs.

LIPID IMPAIRMENTS AND FETO-PLACENTAL GROWTH AND DEVELOPMENT

With the establishment of the placenta, nutrition changes from histiotrophic to hemotrophic by the end of the first trimester of pregnancy and further remodelling will occur during the second trimester of pregnancy to allow an efficient exchange of substrates between the maternal and fetal blood according to fetal development [65, 66]. Placental transport of nutrients is exquisitely regulated through specific transporters for the different nutrients, and is especially complex for the transport of lipid moieties [26, 67, 68].

Lipids are provided by maternal circulation and available in increasing concentrations through pregnancy as a result of adaptations in maternal metabolism, which are crucial to provide the lipids to support appropriate fetal growth and development. They involve a first trimester depot of triglycerides in adipose tissue needed for providing sufficient circulating free fatty acids and lipoproteins after mid-pregnancy, when a catabolic and insulin-resistant state driven by pregnancy hormones, will allow providing sufficient energy substrates needed by the fetus and the placenta [26]. EFAs play a fundamental role in fetal development both as components that regulate signalling pathways and as substrates for the generation of other bioactive lipids in cell membranes, cytosolic and nuclear compartments. Their high requirement is fulfilled through an efficient transport of from mother-to-fetus through the placenta, which is assured in physiological conditions [26, 67].

Gestational pathologies either related to nutrient deficiencies or nutrient excesses that affect maternal fat deposition and circulating lipid concentrations have profound consequences in both placental function and fetal development.

Intrauterine Growth Restriction

In experimental models of maternal nutrient restriction, impaired fetal growth is related to the impaired formation of maternal fat depots [69]. In humans, intrauterine growth retardation (IUGR) is related to reduced maternal seric concentrations of lipoproteins (VLDL2, low density lipoprotein (LDL)), although no changes in VLDL1 and HDL and circulating triglycerides and free fatty acids (FFAs) have been reported in various studies [70, 71]. Cholesterol concentrations are reduced when the fetuses have defects in their synthesis, as described in the previous section for the SLO syndrome, but also reduction in maternal-derived cholesterol can affect fetal development [68]. Indeed, IUGR is related to maternal low cholesterol concentrations [72, 73]. Placental insufficiency is an established cause of impaired fetal nutrition and has been related to impairments in fetal lipid metabolism [71, 74]. Also related to placental insufficiency, hypoxia is an important factor involved in the induction of oxidative stress and placental vascular and lipid metabolism impairments [75]. Indeed, increased oxidized LDL, decreased lectin-like oxidized LDL receptor 1 (an oxidized LDL scavenger receptor), increased cholesterol ATP-binding cassette transporter, and increased lipid peroxidation (i.e. TBARS and isoprostanes) are related to hypoxia in preeclampsia and considered relevant in placental damage and dysfunction in this gestational disease [76-78].

Fetal growth and metabolism needs to be a balance of nutrients and oxygen. Indeed, in both human pregnancies and animal models of IUGR, despite the reduction in nutrient transfer, the small for gestational age fetuses have increased circulating triglycerides and even increased liver fat content [79-82]. Besides, studies performed in animal models of IUGR suggest that insulin action is impaired in the fetuses, an alteration that occurs together with reductions in β cell mass and increases in lipid concentrations in the circulation [4].

On the other hand, in fetal growth restriction, reduced concentrations of lipoprotein lipase (LPL) have been described in the human placenta [83], an alteration that may contribute to changes in the transport of lipids to the fetuses and is especially relevant for the transfer of EFAs being carried out in maternal circulation in their esterified form. The relationship of a deficiency in n-6 EFAs to the induction of congenital malformations has been already described in this review. In addition, it is largely known that deficient n-3 EFAs in the last trimester of gestation can affect neurodevelopment, lead to visual defects, and induce cognitive impairments later in life [1, 84]. Indeed, human studies have evidenced in IUGR increased incidence of neurodevelopmental defects, low seric EFAs concentrations in neonates, and reduced capacity to form n-3 PUFAs in infants [85-87]. Besides, in placental insufficiency caused by preeclampsia there are increased concentrations of maternal lipids, an alteration that has been related to the complications of this pathology [88].

Nutrient restriction and placental insufficiency are stressful for the fetus, and pro-inflammatory and pro-oxidant responses have been observed in animal models of these gestational diseases [89]. In placentas from human pregnancies complicated with IUGR, there is increased oxidative and nitrative stress [90]. Pro-inflammatory cytokines like IL-8, IL-12 and TNFα have been found increased in maternal serum, maternal lymphocytes, and cord blood serum in IUGR [91-93]. Therefore, a pro-oxidant and pro-inflammatory intrauterine environment challenges the intrauterine development when fetal nutrients are restricted, similar to that described in those diseases that provide an excess of nutrients, such as obesity and diabetes.

Obesity

In obese patients and obesity experimental models, the mother possesses increased adipose depots, circulating lipids, insulin resistance and a pro-inflammatory state from the pre-pregnancy state [25, 94]. The insulin-resistant state provides an excess of nutrients, including lipids, for transfer to the fetus throughout pregnancy, which is related to fetal overgrowth, and associated with an increase in fat mass rather than lean mass [95]. Besides, in humans and experimental models, not only the mother but also the fetus has been found to be insulin resistant in obese gestations [5, 96]. In part, the presence of insulin resistance in fetuses from obese mothers can be explained by the activation of IRS-1 serine phosphorylation (one of the mechanisms involved in insulin signalling inhibition) and by the increased blood concentrations of pro-inflammatory cytokines [96]. Studies performed in the placenta from obese sheep have shown increased cytokines (TNFα, IL-8, IL-18), NFκB activation and macrophage infiltration, which are related to an increase in toll-like receptor 4, a receptor which is activated by lipopolysaccharide (LPS) and FFAs [97]. Also in humans, the placenta from obese patients have shown increased pro-inflammatory cytokines, chemokines and macrophage infiltration [98, 99]. On the other hand, in animal models of obesity, changes such as increased placental infarctions, reduced blood flow in the fetal side of the placenta, and reduced fetal and placental junctional zone weights are induced [5]. In humans, impairments of nutrient exchange mechanisms, structural alterations and the pro-inflammatory environment can all be related to the frequent macrosomic phenotype but also to the restricted growth phenotype observed in maternal obesity [94].

Studies performed in obese pregnant women and in experimental models of obesity show that a pro-inflammatory environment in maternal obesity is found not only in the mother and the placenta, but also in the fetuses. Indeed, maternal high fat diets trigger lipotoxicity in the fetal liver of non-human primates [100]. In sheep, maternal obesity is related to a low grade inflammation in the fetus that impairs skeletal muscle development and induces intestine inflammation [101, 102]. In humans, sera obtained from large for gestational age fetuses induce increased matrix metalloproteinase 9 overactivity in cultured human umbilical cord blood endothelial cells (HUVEC) [103]. In overweight patients, amniotic fluid shows increased concentrations of TNFα and C-reactive protein [104]. Both maternal and fetal deficiency of the n-3 PUFA docosahexaenoic acid (DHA) has been

found in both maternal and fetal circulation in non-primates fed high-fat diets, despite normal content of dietary DHA [105]. Moreover, maternal hypercholesterolemia is related to an increase in aortic fatty streaks in the human fetuses from spontaneous abortions/dead preterm newborns [106].

Therefore, maternal obesity leads to metabolic and pro-inflammatory derangements in the intrauterine compartment, similar to that occurring in diabetic gestations.

Diabetes

In both pregestational and gestational diabetes, increased circulating glucose concentrations and increased lipid concentrations resulting from insulin deficiency and/or insulin resistance provide an excess of oxidative substrates related to the generation of a pro-inflammatory state that will affect placental and fetal development [2, 29].

In placentas from both patients and experimental models of diabetes, there are increased markers of oxidative and nitrative stress, increased lipid peroxidation, matrix metalloproteinases overactivity and increased pro-inflammatory cytokines concentrations [29, 40, 90]. Overaccumulation of triglycerides is evident in diabetic placentas, possibly related to increases in placental lipases (LPL, endothelial lipase), lipid moieties transfer proteins (phospholipid transfer protein, fatty acid binding protein) and multiple changes in placental lipid metabolism gene expression that sustain the placental lipid accretion and increased transfer to the fetuses [83, 107-111]. In agreement, FFAs have been directly related to the generation of pro-inflammatory cytokines and lipid droplets in cultured human trophoblasts [112]. Synthesis of different lipid species is reduced in the placenta from diabetic rats, possibly to compensate the increased lipid transport [113]. On the other hand, human studies have shown that concentrations of n-6 and n-3 PUFAs are reduced in maternal circulation in diabetes, although an increased uptake of arachidonic acid in the placenta from diabetic patients has been described [114, 115].

The high susceptibility of long chain PUFAs to oxidation affects their role as bioactive lipids [116]. Indeed, deficiency in certain eicosanoids, bioactive lipids derived from arachidonic acid, is observed in placentas and fetuses in maternal diabetes [2]. This could also be due to the reduction in delta5 and delta6 desaturases, insulin-dependent enzymes needed to form arachidonic acid from linoleic acid [117]. Indeed, it has been largely known that the PGI_2/TXA_2 ratio is reduced, and thus that the vasodilatory/vasoconstrictive balance is directed towards vasoconstriction in the diabetic placenta in humans and experimental models [2]. This, together with defects in the production of bioactive nitric oxide, challenges the placental and umbilical circulation in maternal diabetes [45, 118]. On the other hand, arachidonic acid derivatives that activate the nuclear receptors PPARs are involved in metabolic and anti-inflammatory pathways in the placenta [54]. In the placenta from diabetic patients and from experimental models of diabetes and pregnancy, there are reduced concentrations of $15deoxy\Delta^{12,14}PGJ_2$(15dPGJ$_2$), a prostaglandin that can activate the nuclear receptor PPARγ and regulate pro-inflammatory pathways such as reduction of excessive nitric oxide and matrix metalloproteinases overproduction [113, 119]. In experimental models of diabetes, PPARα, the PPAR isotype mostly involved in lipid catabolism, is reduced in the placenta from diabetic rats, and its activation by leukotriene B_4 (an arachidonic acid metabolite) and fibrates (their pharmacological activators) can regulate both placental lipid content and peroxidation [120]. In addition, PGI_2, an arachidonic acid derivative with potent vasodilator effects in the placenta and capable of activating the nuclear receptor PPARδ, is also reduced in the placenta from diabetic rats, and has the capacity to negatively regulate excessive nitric oxide production and lipid overaccumulation and peroxidation [121].

In maternal diabetes, fetal overgrowth is the result of the increased glucose transferred to the fetus and the consequent increased insulin secretion which lead to anabolic pathways that are sustained by the increase in nutrients provided through the placenta. However, as evidenced in experimental models of diabetes and pregnancy, fetal hyperglycemia can also lead to degranulation of the fetal β cells, resulting in this case in fetal hypoinsulinemia and fetal growth retardation [40].

In the fetuses from diabetic rats, excessive accumulation both of structural lipids such as phospholipids at mid-gestation and of triglycerides and cholesteryl esters in the fetal liver at term provides evidence of the excess of the metabolic substrates [122, 123]. In circulation, increases in triglyceride and cholesterol concentrations are observed in fetuses from diabetic rats [124, 125]. Indeed, fat mass and circulating LDL are increased in infants born to diabetic mothers [126, 127]. Besides, in cord blood from newborns from diabetic patients, FFAs and/or triglycerides have been found increased, although cholesterol concentrations have been found either increased or decreased in newborns from diabetic mothers [39, 128, 129].

In experimental models of diabetes and pregnancy, despite increased fetal fat content, increased lipid synthesis remain increased in fetuses from diabetic rats, an alteration that is regulated by the activation of the nuclear receptor PPARα [123]. At term gestation, fetal treatments with the PPARα activator LTB_4 have been found to regulate lipid metabolism and pro-inflammatory pathways in the fetal liver and fetal lung from diabetic rats [122, 124]. Besides, fetal activation of PPARα has been found to reduce overgrowth of the placenta, the fetus, and fetal organs such as the liver and the lung in experimental models of diabetes and pregnancy [120, 122, 124].

Similar to that occurring in IUGR and in maternal obesity, deficiency of PUFAs occurs in diabetic gestations. This deficiency can be observed in cord blood from type 1, type 2 and gestational diabetic patients [115, 130, 131]. Indeed, EFAs deficiency is related to the induction of congenital malformations, as described earlier in this review, and is possibly related to the induction of neurodevelopmental defects, which are enhanced in the offspring of diabetic mothers [84, 132].

Therefore, fetuses and placentas are affected by pathologies that change maternal lipid concentrations, not only directly due to the altered transfer of lipids to the fetus, but also indirectly as a result of the damage caused by the pro-inflammatory environment and the loss of bioactive lipids that regulate metabolic and anti-inflammatory processes during development.

INTRAUTERINE LIPID IMPAIRMENTS AND POSTNATAL CONSEQUENCES

Postnatal consequences arise both at the perinatal period and in the long term in pregnancy diseases associated with intrauterine lipid impairments. IUGR as well as diabetes and obesity are causes of increased infant morbidity and mortality in the infancy and childhood, and also have long-term impact on adult life [95, 133-135]. Growing evidence relates both small and large for gestational age newborns with the programming of metabolic and cardiovascular diseases [4, 5]. Due to its role in nutrient transport and as a determinant of fetal weight, the placenta has a relevant role in the intrauterine programming of these diseases [74, 136, 137]. The concept of intrauterine programming is supported by epidemiological evidence that shows that the *in utero* environment influences the onset of diseases later in life. The mechanisms involved in programming the susceptibility of diseases in the offspring are a current focus of research and remain to be fully elucidated.

Programming of Type 2 Diabetes

Human studies have established an association between intrauterine growth retardation and increased risk of glucose intolerance and type 2 diabetes in later life [138, 139]. In experimental models of IUGR, impaired insulin action and increased catch-up growth in the offspring occur in parallel with enhanced fat deposition in the early postnatal life and are related to the later development of glucose intolerance [140].

Pre-pregnancy obesity and excessive gestational weight gain are implicated in the offspring´s increased risk of multiple metabolic abnormalities, including an increase in plasma levels of insulin, FFAs and triglycerides, insulin resistance, an increase in hepatic gluconeogenic pathways, accelerated neonatal catch-up growth, glucose intolerance and obesity, as observed in both humans and animal models [100, 141-143]. Besides, in different species (rodents, lambs and non-human primates) experimental models of obesity have shown hepatic steatosis, fatty pancreas disease and nonalcoholic fatty liver disease in the offspring [100, 144, 145].

Experimental studies in diabetes and pregnancy have clearly established the increase in mother-to-fetus glucose transfer and the hypertrophy and hyperplasia of insulin-producing β cells in fetuses from diabetic mothers, as well as the resulting impaired glucose tolerance when the offspring become adult [146]. This abnormal glucose homeostasis in the offspring of diabetic mothers has also been reported in epidemiological studies [147-149]. Impaired adaptative responses of β cell mass are implicated in the increased risk for diabetes in later life not only in maternal diabetes, but also in maternal overnutrition, intrauterine growth restriction and uteroplacental insufficiency [150, 151].

Other factors related to the intrauterine programming of adulthood diseases in maternal obesity, diabetes and intrauterine growth restriction and to the impaired lipid metabolism is the adipokine leptin [5, 151]. The intrauterine and perinatal changes in leptin concentrations and/or leptin resistance in these pathologies program an altered brain appetite regulation and energy balance in the offspring. In IUGR, low levels of fetal leptin have been shown to be followed by increases in leptin in the infants, children and adults, affecting satiety, adiposity and weight gain [152]. In the offspring from animals fed high-fat diets, hyperphagia and increased energy intake are observed, and these changes are associated with increases in serum lipid concentrations and increases in the expression of orexigenic peptides, which result from the proliferation and differentiation of neurons that express orexigenic peptides during development [153-155]. Experimental and human studies have shown altered leptin concentrations and altered programming of orexigenic and anorexigenic hypothalamic neurons function in the offspring from diabetic mothers [156, 157].

It is important that in both humans and animal models, programming of type 2 diabetes often shows gender-specific effects on the type and degree of metabolic alterations [158-160]. In experimental IUGR models, this is partly related to gender-dependent impairments in hepatic fatty acid metabolism and triglyceride concentrations that specifically affect the male offspring [161, 162].

Programming of Cardiovascular Diseases

Pregnancy diseases that lead to lipid metabolism impairments are clearly related to the programming of cardiovascular diseases. Indeed, human and experimental studies have shown that fetal nutrient restriction or excess can induce cardiac and vascular impairments in the offspring [163, 164]. In rats fed a saturated fatty acid diet, the offspring shows an abnormal fatty acid composition of the aorta [165], whereas in obese mice, the offspring show hypertension and resistance artery endothelial dysfunction [166]. Besides, in humans, maternal hypercholesterolemia induces early markers of cardiovascular disease such as endothelial dysfunction, vascular reactivity and atherosclerosis in the offspring [167]. The risk of developing cardiovascular disease is increased for both the mother and the offspring in diabetic patients [168]. Interestingly, in rats, not only excessive lipid concentrations but also n-3 PUFAs deficiency during fetal development are found related to an increased blood pressure in the offspring [169].

PPARs

Nuclear receptors PPARs, master regulators of metabolic homeostasis and inflammatory processes that are activated by PUFAs and their derived eicosanoids, have also been related to the intrauterine programming of metabolic diseases. Indeed, experimental models of both intrauterine growth restriction and maternal obesity induced by high-fat diet lead to an enhanced activity of PPARγ in adipose tissue of offspring due to two different mechanisms: upregulation of PPAR coactivators in IUGR and downregulation of PPAR corepressors in obese pregnancies, leading in both cases to a subsequent increase in fat mass [170]. Low intramuscular expression of PPARγ and high expression of fatty acid transporters, which correlate with intramuscular triglycerides, are found in lambs born to obese mothers [171]. On the other hand, adult offspring from high-fat fed rats show increased hepatic PPARα expression, an alteration associated with an increased expression of key genes that regulate fatty acid oxidation, with the expression of insulin growth factor-2 (IGF-2) and with changes in the expression of several microRNAs that could be involved in the impaired regulation of the gene expression observed [172].

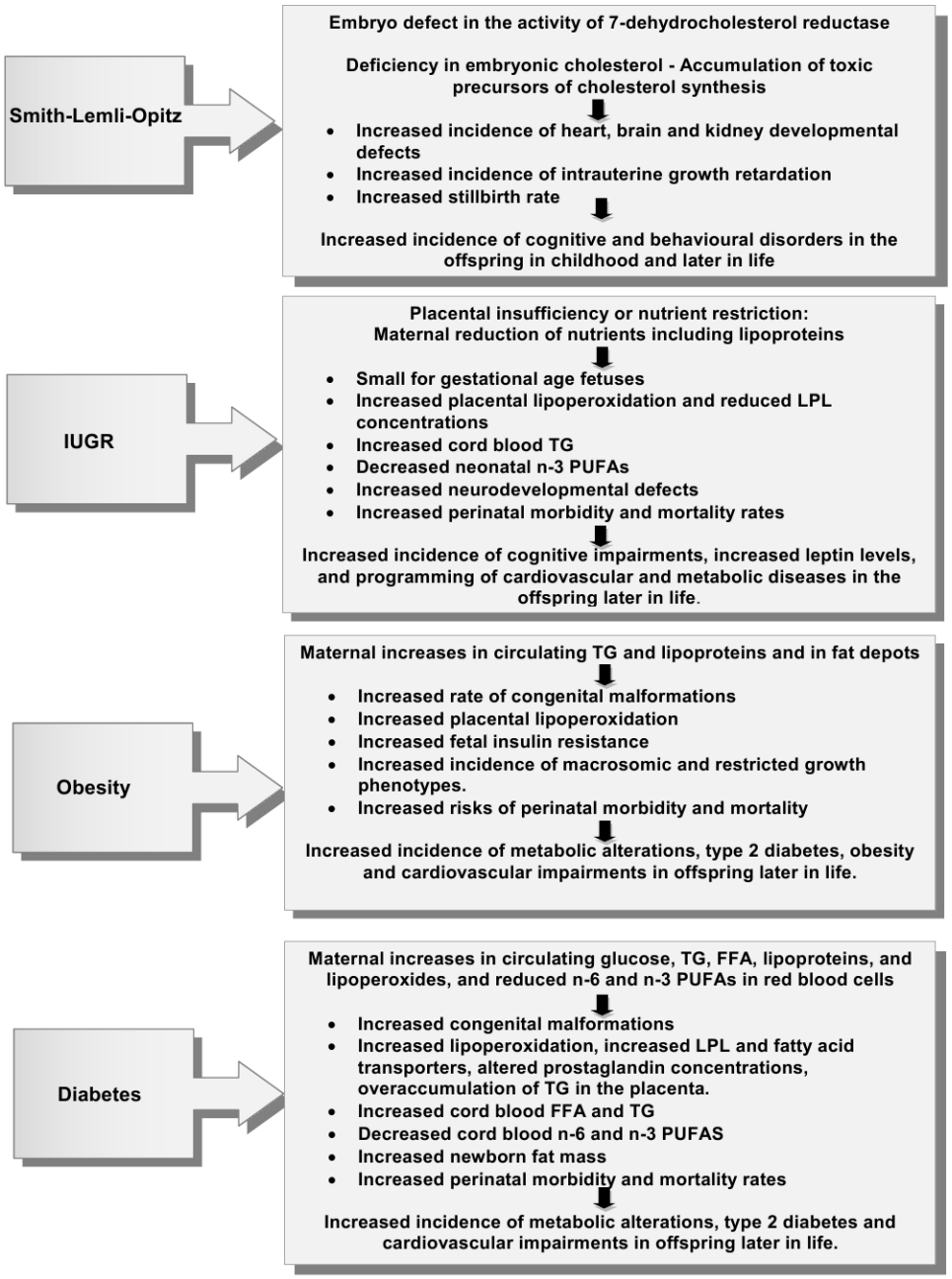

Fig. (1). Main clinical features related to lipid impairments in Smith-Lemli-Opitz and gestational diseases.

Epigenetics

There are exciting advances in the involvement of epigenetic regulation in intrauterine programming of metabolic diseases. Several studies in experimental models and some human studies have shown that an excess or restriction of nutrients can epigenetically modify expression of certain genes by altering the methylation status of gene promoter regions or by the post-translational modification of histone tail residues through methylation, acetylation, phosphorylation, sumoylation and/or ubiquitination, resulting in changes in chromatin condensation and gene expression [25, 151, 173]. Undernutrition in rats during pregnancy induces hypomethylation of the PPARα promoter and increases the expression of this key regulator of lipid metabolism in the liver and heart of the offspring [174, 175]. Besides, intrauterine growth retardation in rats is related to an epigenetic modification in the PDX-1 gene that codifies for pancreatic and duodenal homeobox 1 (PDX-1) transcription factor, critical for β cell development and plasticity and function after birth [176]. Interestingly, intervention studies in IUGR rat neonates provide reversal of epigenetic changes in the PDX-1 gene with postnatal treatments with exendin-4, treatments also associated with a reduction in lipid peroxidation in the liver [177].

On the other hand, in primates, maternal high-fat diets lead to an increase in histone H3 acetylation and a decrease in histone deacetylase activity in the liver, in correlation with an altered lipid metabolism in the fetus [173]. In a recent human

study performed in umbilical cord tissue, methylation of the promoter of retinoid X receptor (RXR), an obligate heterodimer of PPAR nuclear receptors, has been found associated with children later adiposity [178]. Interestingly, in rats, high fat fed fathers have been shown to program β cell dysfunction by altering the expression of multiple genes in the β cell of female offspring, at least in part through epigenetic modifications [179]. Besides, recently, in an experimental model of diabetes in pregnancy, glucose intolerance in both F1 and F2 has been associated with an abnormal expression and hypermethylation of IGF-2/H19, a paternal imprinted growth factor and its regulator, which are involved in β cell development and function [180, 181]. Besides, epigenetic changes in histone acetylation in embryos from diabetic rats during embryo organogenesis suggest a possible epigenetic role in diabetic embryopathy, and these changes are different from those found in embryos from rats fed a high-fat diet [182].

Overall, lipid homeostasis is highly relevant in fetal and perinatal stages to sustain growth and development, to regulate metabolic and signalling pathways and to lead to a proper gene transcription that will be relevant in the infant and adult offspring. Therefore, impaired lipid homeostasis during pregnancy diseases is a relevant component in the mechanisms of programming of intrauterine diseases that warrants further evaluation.

CONCLUSIONS

The clinical relevance of impaired lipid homeostasis in pregnancy diseases is summarized in (Fig. **1**). It is interesting to note that common pathways related to impaired maternal lipid homeostasis have been associated with different gestational pathologies and with two extreme phenotypes, the IUGR and the overweight offspring. Although the mechanisms that relate the fetal growth-related disturbances to lipid derangements are far to be completely understood, it is clear that there are roles for the mother, the placenta and the fetus, which differentially lead to the altered lipid concentrations and metabolism here reviewed. Indeed, relevant roles of the abnormal formation of adipose depots, the generation of a pro-inflammatory state, the insulin-resistant state, the deficiency in EFAs and alterations in the placental transfer and utilization of lipids by the fetus have been here described and related to the alterations in fetal growth and the programming of intrauterine diseases. Also, congenital malformations are related to impaired lipid homeostasis, and the availability of EFAs and cholesterol play a fundamental role. Although experimental studies have shown that supplementation with antioxidants and PUFAs has beneficial effects in some of these pregnancy pathologies, there are still no clear beneficial results in clinical studies [6, 29, 54, 84, 132, 183]. Thus, to what extent essential fatty acids deficiency may lead to abnormalities of embryonic, fetal or post-natal development still remains unresolved. Overall, further research is needed for a better understanding of the mechanisms involved in abnormal lipid moieties-induced damage during gestation and for further translation of this knowledge to clinical assays.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

15dPGJ2	=	15deoxy$\Delta^{12,14}$PGJ$_2$
DHA	=	Docosahexaenoic Acid
EFAs	=	Essential Fatty Acids
FFAs	=	Free Fatty Acids
HDL	=	High-Density Lipoprotein
HUVEC	=	Human Umbilical Cord Blood Endothelial Cells
IGF-2	=	Insulin Growth Factor-2
IL	=	Interleukin
IUGR	=	Intrauterine Growth Retardation
LDL	=	Low Density Lipoprotein
LPL	=	Lipoprotein Lipase
LPS	=	Lipopolysaccharide
NFκB	=	Nuclear Factor Kappa B
PDX-1	=	Pancreatic and Duodenal Homeobox-1
PGs	=	Prostaglandins
PPAR	=	Peroxisome Proliferator Activated Receptor
PUFAs	=	Polyunsaturated Fatty Acids
RXR	=	Retinoid X Receptor
SLO	=	Smith-Lemli-Opitz Syndrome
TNFα	=	Tumor Necrosis Factor α
VLDL	=	Very-Low-Density Lipoprotein

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