Chapter 6

Maternal Hypercholesterolemia in Gestational Diabetes and the Association with Placental Endothelial Dysfunction

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1. Introduction

Pregnancy is a physiological condition characterized by a progressive, weeks of gestation-dependent increase in maternal triglycerides (hypertriglyceridemia) and total cholesterol (hypercholesterolemia) [1-4]. In some cases a misadaptation occurs and these levels increase over a physiological range and dyslipidemia is recognized [5]. This condition occurs in some pregnancies coursing without associated pregnancy alterations [i.e., maternal supraphysiological hypercholesterolemia (MSPH)] and in pregnancies coursing with pathologies as preeclampsia and gestational diabetes mellitus (GDM) [3, 5].

GDM is widely associated with endothelial dysfunction of the placenta mainly triggered by hyperinsulinemia, hyperglycemia, and changes in nucleoside extracellular concentration and dyslipidemia associated with this pathology could play a role in this phenomenon since dyslipidemia is a risk factor to develop endothelial dysfunction and atherosclerosis [6]. Additionally, GDM predisposes to an accelerated development of cardiovascular disease (CVD) in adult life and as most of pregnancies with GDM course with elevated dyslipidemia, is feasible found a pathological link between dyslipidemia in GDM pregnancies and development of CVD later in life [6,7].

The hypertrygliceridemia described in GDM is directly related with the fetal macrosomia characteristic of this pathology, and a positive correlation between maternal triglycerides levels and neonatal body weight or fat mass has been found in GDM [7,8].

Even when hypercholesterolemia, described in GDM, is not related with the fetal macrosomia, could be related with fetal endothelial dysfunction and later development of cardiovascular diseases in the adulthood [6].

Although lipid traffic through the placenta is restrictive, a correlation between maternal and fetal blood cholesterol in the first and second trimesters of pregnancy has been established, suggesting that maternal cholesterol level could alter normal development of the fetus [9]. In fact it has been reported that due to altered lipid metabolism in the placenta as a result of high maternal blood cholesterol, atherogenesis, a clinical complication commonly appearing in adults, probably begins in fetal life with similar factors altered at the mother, the fetus and the placenta [9, 10].

In this regard, GDM correlates with placental macro and microvascular endothelial dysfunction, also considered as early marker of atherosclerosis, and neonates from GDM pregnancies have significant increase in the aortic intima-media thickness and higher lipid content, both considered as subclinical markers of atherosclerosis, conditions that will potentially increase the atherosclerotic process later in life [11,12].

Since the lack of information in the literature, nothing is yet available about the potential effect of hypercholesterolemia in GDM pregnancies regarding development of endothelial dysfunction and atherosclerosis in human fetoplacental vasculature [6], however cumulative evidence shows that high levels of blood cholesterol modify the endothelial function in different vascular beds, mostly associated with reduced vascular nitric oxide (NO) bioavailability (i.e. the L-arginine/NO pathway) and elevated oxidative stress leading to reduced vascular reactivity, and then vascular reactivity in children and adults [13].

Several changes caused by hypercholesterolemia could explain these alterations including post-transcriptional down-regulation of cationic amino acid transporters (hCATs)-mediated L-arginine transport [14], reduced NO synthase (NOS) expression [15], reduced expression of tetrahydrobiopterin (BH_4) an NOS cofactor [16], and increased expression and activity of arginases (enzymes that compete by L-arginine with NOS) [17] among others factors that finally leads to reduction of NO synthesis and endothelial dysfunction. Interestingly, these mechanisms have not been evaluated in GDM coursing with hypercholesterolemia [6].

2. Hypercholesterolemia in pregnancy

Several reports show that pregnancy is a physiological condition characterized by a progressive, weeks of gestation-dependent increase (reaching 40-50%) in the maternal blood level of cholesterol [1,2]. This phenomenon is known as maternal physiological hypercholesterolemia in pregnancy (MPH), and is considered to be an adaptive response of the mother to satisfy the high cholesterol demand by the growing fetus [3,4].

In the lack of a consensus and currently available information for general population, a mean value calculated from the reported data in the literature rising to ~247 mg/dl of blood cholesterol could represents a state of MPH (see table 1). When a maternal misadaptation to the

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cholesterol demand by the fetus occurs, a group of these women develop a pathological condition described as maternal supraphysiological hypercholesterolemia (MSPH) in pregnancy [5]. Unfortunately, the establishment of a cut-point value for this condition is difficult to define because the scare information in the literature regarding this condition. However, a review of the available information allows establish a MSPH condition when the maternal blood cholesterol at term of pregnancy level is over the 90th percentile or establishing a cut-point defined by different authors and based in their findings (Table 1).

With this global lack of information, the prevalence of MSPH in the pregnant population is unknown and could certainly be a consequence of the fact that maternal blood cholesterol level is not routinely evaluated during pregnancy. However, has been reported that the global prevalence for high blood cholesterol level (>200 mg/dl) in non-pregnant women is 40% with a range between 23% (Asia) and 53% (Europe) [18]. Based on this official information from WHO and assuming that pregnancy results in an increase of 40-50% in blood cholesterol [4], it is conceivable that a significant number of women that get pregnant will develop MSPH and who will potentially present an adverse intrauterine condition that could result in facilitating the developing of vascular alterations and atherosclerosis in the growing fetus.

2.1. Cholesterol traffic in pregnancy

Although lipids traffic through the placenta is restrictive and children born from MSPH generally have normal blood cholesterol level [19], a correlation between maternal and fetal blood cholesterol in the first and second trimesters of pregnancy has been established [9,20].

The sources of cholesterol for fetal metabolism along with endogenous production by fetal tissues include transplacental mother-to-fetus transport of cholesterol [9,19,21-26].

The maternal cholesterol must cross two layers of cells to enter in the fetal circulation, the first one are the trophoblast cells and the second one are the endothelial cells [19,27] (Figure 1).

In the maternal circulation the cholesterol is mainly transported in low density (LDL) and high density (HDL) lipoproteins which interacts with their membrane receptors, the LDL receptor (for native LDL (nLDL) and oxidized LDL (ox LDL)), the lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1, for oxLDL), and scavenger receptor class B type I (SR-BI, for HDL and oxLDL) to deliver the cholesterol content into the cell [28,29]. These lipoprotein receptors are expressed in placental cells including trophoblast and endothelial cells [23,30]. Once in the trophoblast cells, the cholesterol may exit cells secreted as lipoprotein or effluxed from the cellular membrane to extracellular acceptors precursors of mature lipoproteins (i.e., apolipoproteins or discoidal phospholipids) [19]. In the next step, this cholesterol is uptake by endothelial cells to be deliver in the fetal circulation, phenomenon where the expression of cholesterol transporters type ATP binding cassette transporter sub-family A member 1 (ABCA1) and sub-family G member 1 (ABCG1) is determinant since these transporters participate in the efflux of cholesterol to nascent fetal lipoproteins [26,31]. In this scenery the phospholipid transporter protein (PLTP) also participate in the formation of fetal HDL (fHDL) contributing with the efflux of phospholipids to nascent fHDL [26] (Figure 1).

Studied population (n)	Blood cholesterol (mg/dl)		Ref.
	MPH	Cut-point for MSPH	
USA (29)	251	318	[5]
USA (142)	260	300	[157]
USA (553)	250	300	[158]
Canada (59)	248	290	[24]
Mexico (130)	189	-	[159]
Argentina (101)	244	-	[160]
Chile (86)	263	280	[unpublished]
UK (8)	289	-	[161]
UK (40)	315	-	[162]
UK (114)	273	-	[163]
UK (118)	246	-	[163]
UK (178)	264	-	[164]
Italy (82)	-	281	[9]
Italy (156)	-	280	[21]
Italy (72)	205	280	[165]
Italy (22)	286	-	[1]
Norway (12.573)	211	-	[166]
France (73)	242	-	[167]
Germany (150)	253	-	[168]
Spain (45)	225	-	[143]
Spain (66)	259	-	[169]
Portugal (67)	285	-	[170]
Finland (22)	274	-	[171]
Japan (19)	280	-	[172]
China (20)	184	-	[173]
Pakistan (45)	209	-	[174]
Nigeria (222)	204	-	[175]
Tunisia (30)	222	-	[176]
Mean	247		

The values correspond to the third trimester of pregnancy. MPH: maternal physiological and hypercholesterolemia, MSPH: maternal supraphysiological hypercholesterolemia.

Table 1. Maternal total cholesterol in MPH and MSPH pregnancies.

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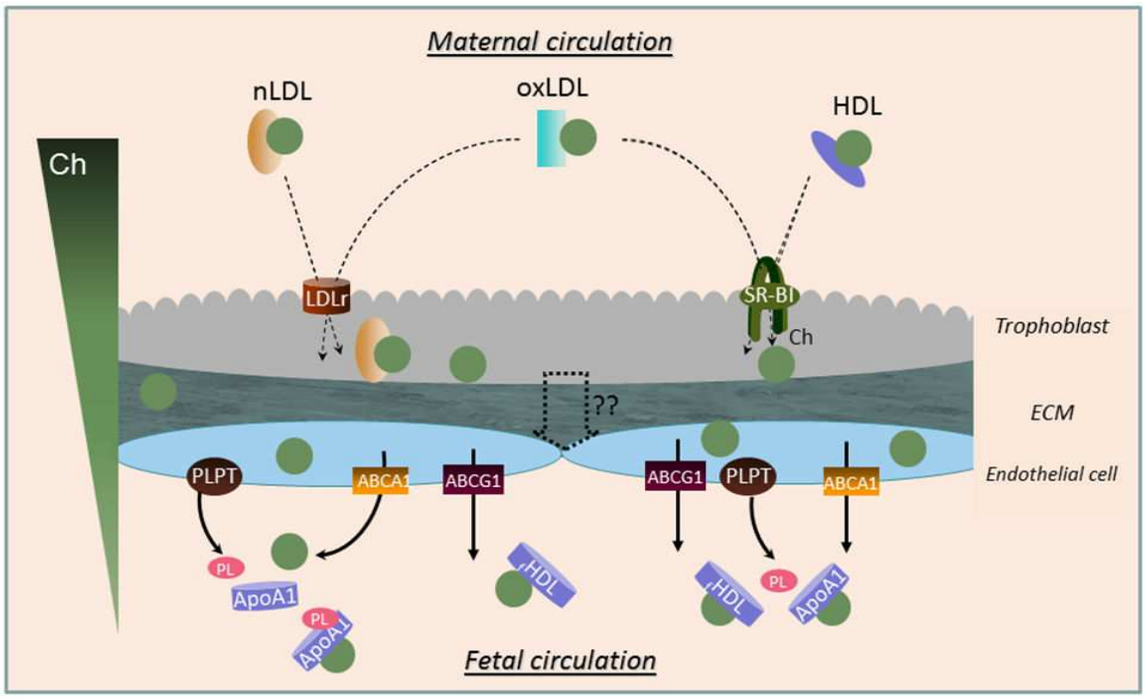

Figure 1. Mother-to-fetus transport of maternal cholesterol. In the maternal circulation (higher levels of plasma cholesterol) the cholesterol (Ch) is mainly transported in low density lipoproteins (LDL) (natives, nLDL and oxidized, oxLDL) and high density lipoproteins (HDL) lipoproteins and delivered into the trophoblast by LDL receptor (LDL-r) and scavenger receptor class B type I (SR-BI). The cholesterol deliver to extracellular matrix (ECM) and is uptake by endothelial cells through unknown mechanisms to finally, be delivered to the fetal circulation by the of cholesterol transporters type ATP binding cassette transporter sub-family A member 1 (ABCA1) and sub-family G member 1 (ABCG1), which together with phospholipid (PL)-transfer protein (PLPT) contribute with the assembly of fetal lipoproteins. In fetal circulation (lower levels of plasma cholesterol) cholesterol is deliver to acceptors as ApoAI and nascent fetal HDL (fHDL).

Thus the mother-*to*-fetus transport of cholesterol seems to be a controlled process that is crucial in fetal development; however the effect of a supraphysiological level of maternal cholesterol will modify the traffic of cholesterol increasing the risk of developing fetal vascular anomalies such as those seen in atherosclerosis [31].

2.2. Consequences of MSPH in the fetus

Studies in aortas from spontaneously aborted human fetuses and premature newborns (24-30 weeks of gestation) demonstrate that offspring from mothers with MSPH in pregnancy exhibit more and larger aortic lesion which were positive for almost one marker of atherosclerosis among the presence of macrophages and foam cell, LDL, oxLDL and oxidation-specific epitopes [9]. These data were additionally supported by another autopsy study that determined that children (1-13 years old) of mothers with MSPH in pregnancy exhibit faster progression of atherosclerotic lesions [21].

At present, the effect of MSPH have been evaluated as atherosclerosis in fetal arteries but the vascular effects of MSPH could be determined in placental vessels since its cells are indirectly exposed to maternal cholesterol (see section *Cholesterol traffic in pregnancy*). Interestingly, it has

been shown that MSPH is associated with increased expression of placental genes related to cholesterol metabolism (i.e. fatty acid synthase (FAS), sterol regulatory element-binding protein 2 (SREBP2)), thus exposing the fetus to an altered lipid environment and eventually promoting vascular alterations [24]. Additionally, increased level of maternal cholesterol and LDL leads to down-regulation of LDL receptor expression in whole placenta homogenized without changes in the expression of HDL receptor (SR-BI) [32], suggesting that the increase in the LDL concentration in the maternal blood induce the regulation of the LDL receptor expression. Interestingly these alterations are not related with changes in the newborn lipid levels, in fact normal levels of LDL and total cholesterol are determined at birth in the fetal blood of newborns from mothers with MSPH.

These data provide evidence for the potential effect of MSPH on the placenta and its consequences for the fetus where vascular lesion progression is triggered. However, even knowing this available information nothing is reported regarding whether abnormal maternal blood cholesterol level leads to placental vascular dysfunction [10,33].

3. Endothelial function in normal pregnancies

The placenta is a physical and metabolic barrier between the fetal and maternal circulation. The normal development and function of the placenta and the umbilical cord are crucial to sustain the adequate fetal development and growth [34]. The human fetoplacental circulation under physiological conditions exhibits a high blood flow and low vascular resistance [35]. Since it lacks of autonomic innervation [36] the equilibrium between the synthesis, release and bioavailability of vasoconstrictors and vasodilators circulating and locally released, such as NO and adenosine, are crucial to maintain the control of fetoplacental hemodynamics [37,38]. In a physiological context, different pathologies of pregnancy such as GDM [38,39], intrauterine growth restriction (IUGR) [40] or preeclampsia [41], exhibits altered synthesis and/or bioavailability of NO leading to changes in blood flow of the human placenta thus limiting fetal growth and development [37,38,42]. These conditions produce an imbalance or loss of essential endothelial functions leading to altered blood flow in the fetoplacental unit mainly associated with altered NO synthesis and membrane transport of the semi-essential cationic amino acid L-arginine, i.e., the 'endothelial L-arginine/NO pathway' (Figure 2) [35,42,43].

3.1. Endothelial L-arginine/NO signaling pathway

Synthesis of NO requires active NOS, a group of enzymes conformed by, at least, three isoforms, i.e., neuronal NOS (nNOS or type 1), inducible NOS (iNOS or type 2) and endothelial NOS (eNOS or type 3), of which mainly eNOS is expressed in endothelial cells [43,44]. The NO diffuses from endothelium to vascular smooth muscle cells leading to cyclic GMP (cGMP)-dependent vasodilatation [45].

Activity of NOS may depend on the ability of endothelial cells to take up its specific substrate L-arginine via a variety of membrane transport systems [42,43,46,47]. L-Arginine is taken up into the endothelial cells through the membrane transport systems y^+ (cationic amino acid

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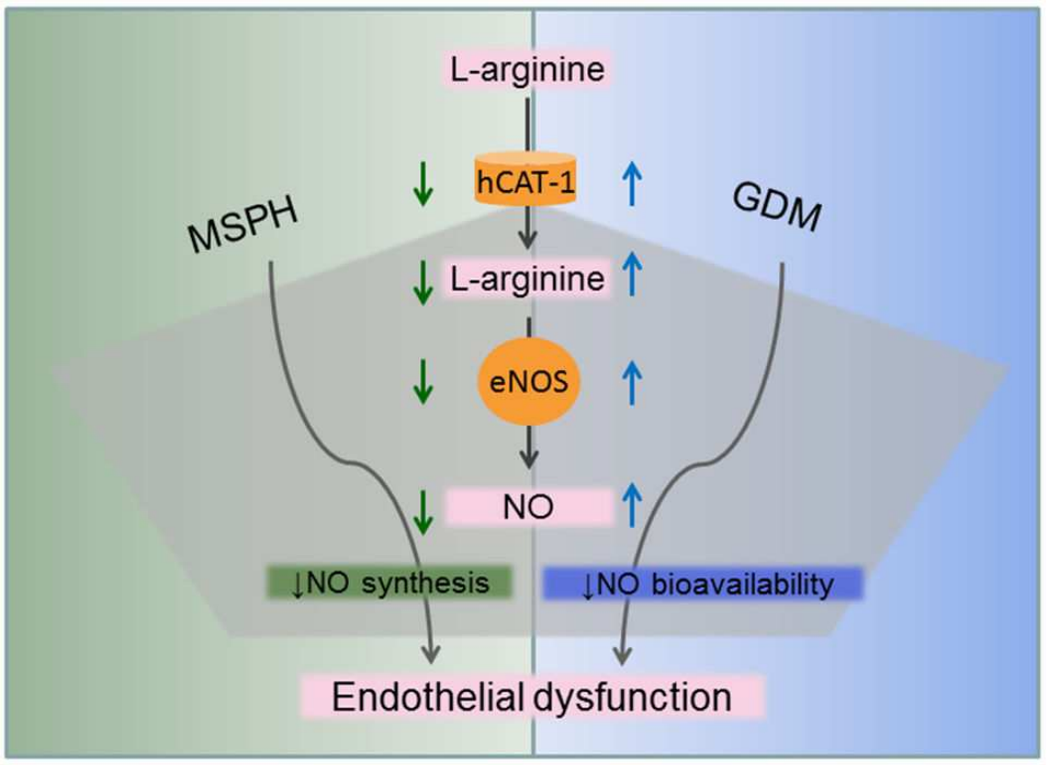

Figure 2. Endothelial L-Arginine/NO pathway regulation by GDM and MSPH. In human endothelial cells L-arginine is mainly taken up via cationic amino acid transporter 1 (hCAT-1). Then, L-arginine is metabolized in nitric oxide (NO) and L-citrulline by endothelial NO synthase (eNOS). In GDM is described an increase (blue up arrows) in the elements in L-Arginine/NO pathway, but with a decrease in NO bioavailability leading endothelial dysfunction. As seen in other vascular beds, MSPH leads to decreased (green down arrows) hCAT-1 and eNOS expression; and NO synthesis leading also to endothelial dysfunction.

transporters family, CATs), y^+L (very high affinity transporters), $b^{0,+}$ and $B^{0,+}$ (Na^+-independent and dependent, respectively) [48,49,50]. CATs is a family of membrane transporters with at least 5 isoforms identified in human tissues, i.e., human CAT-1 (hCAT-1), hCAT-2A, hCAT-2B, hCAT-3 and hCAT-4 [43,51]. In endothelial cells from the human placenta such as human umbilical vein endothelial cells (HUVEC) and human placental microvascular endothelial cells (hPMEC), only hCAT-1 and hCAT-2B isoforms like transport have been identified, the first exhibiting low-capacity and high-affinity, and the second exhibiting higher-capacity and lower-affinity [41,51]. Moreover, eNOS activity seems to depend on the ability of these cells to take up L-arginine mainly via hCAT-1 and/or hCAT-2B [40, 33, 52]. Interestingly in pathological conditions such as GDM the L-arginine/NO pathway is highly up-regulated in HUVEC [6, 39, 53, 54] (Figure 2).

4. Hypercholesterolemia and endothelial L-arginine/NO pathway

Endothelial dysfunction and reduced NO seems are considered early markers in the development of cardiovascular disease [55-58]. Thus, studies designed to evaluate the impact of

hypercholesterolemia (in non-placental vessels) have determined that this pathological condition induces endothelial dysfunction in vessels of the macro and microcirculation, but the biological effects may differ between both vascular beds [59-60]. It has been shown that high levels of total cholesterol and oxLDL impair endothelial function increasing the production of the vasoconstrictor endothelin-1 [61-62] and reducing NO bioavailability [13,63-67], alterations that have been associated with impaired endothelium-dependent relaxation [68-73]. Therefore, alterations in cholesterol levels leading to endothelial dysfunction in different vascular beds have been associated with molecular changes in the expression and activity of different component of the L-arginine/NO pathway, thus decreasing the production or bioavailability of NO (Table 2). However, no studies have addressed whether elevated maternal blood cholesterol modulate L-arginine/NO pathway and endothelial function in placental endothelial cells form pregnancies coursing with MSPH or pregnancy diseases associated with increased levels of cholesterol as GDM or preeclampsia [12,35].

4.1. eNOS expression and activity in hypercholesterolemia

Hypercholesterolemia is associated with decreased expression of eNOS in aortic rings of hypercholesterolemic rabbits [58] and in human saphenous vein endothelial cell, porcine aortic endothelial cells and HUVEC expose to high concentration of nLDL or ox-LDL [15,75,76], an effect that is reversed by restitution of normal blood cholesterol level (e.g., with the use of statins). The mechanism behind this effect of hypercholesterolemia on eNOS expression is not well understood and few studies have proposed a time- and concentration-dependent decrease in eNOS mRNA level involving transcriptional inhibition and reduced mRNA stability (i.e., reducing eNOS mRNA half-life) [15,75,76].

Additionally to down regulation of eNOS expression, high levels of cholesterol are also associated with changes in eNOS cellular localization and function, a phenomenon related with up-regulation of the protein caveolin [77-83]. In the endothelial cell eNOS targets to caveolae [70,71] where it is functionally inhibited by binding to caveolin [84-87]. Optimal eNOS activity occurs when the eNOS-caveolin complex interaction is disrupted by calcium-calmodulin binding to eNOS-caveolin [87]. It has been shown that caveolin expression is regulated by cholesterol increasing eNOS-caveolin complex formation, and diminishing NO production [88-90].

4.2. Asymmetrical dimethylarginine (ADMA) availability in hypercholesterolemia

ADMA, an arginine metabolite proposed as endogenous inhibitor of eNOS [91-95], is increased in hypercholesterolemic monkeys [92] and in human endothelial cells incubated with high concentration of nLDL and oxLDL [96]. The mechanisms involved in this phenomenon are the up-regulation of the expression of protein arginine N-methyl transferases (PRMTs), which are involved in the synthesis of ADMA and decreased activity of dimethylarginine dimethylaminohydrolase (DDAH), an enzyme responsible of ADMA degradation [78,82,83]. Moreover, the regulation of ADMA is relevant in the atherogenic process and extensive data have shown a good correlation between plasmatic levels of ADMA and the presence of atherosclerosis [92].

Element	Gestational Diabetes Mellitus			Non-pregnancy		
				Hypercholesterolemia		
	Cell type	Effect	References	Cell type	Effect	References
hCATs expression	HUVEC	Increased	[43]	EAhy926	Increased	[113]
				rAR	Increased	[114]
hCATs activity	HUVEC	Increased	[43]	EAhy926	Increased	[113]
				rAR	Reduced	[14]
				bAEC	Reduced	[111]
				pAEC	Reduced	[74]
				HUVEC	Unaltered	[109]
				HUVEC	Unaltered	[110]
eNOS expression	HUVEC	Increased	[28,43]	hSVEC	Reduced	[15]
	hPT	Increased	[177]	rbAS	Increased	[75]
				rbAS	Reduced	[152]
				HUVEC	Reduced	[76]
				pAEC	Reduced	[180]
eNOS activity	HUVEC	Increased	[28,29,43]	hSVEC	Reduced	[15]
	hVT	Unaltered	[178]	rbAS	Reduced	[152]
				HUVEC	Reduced	[76]
				pAEC	Reduced	[74]
				rAC	Reduced	[181]
NO level	HUVEC	Increased	[179]	hSVEC	Reduced	[15]
Arginase I				hPBMC	Increased	[182]
Arginase II				hAEC	Increased	[17,114,115]
				mAEC	Increased	[114,115]

hCATs, human cationic amino acid transporters; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; HUVEC, human umbilical vein endothelial cell; hPT, human placental tissue; hVT, human villous tissue; EAhy 926, human endothelial cell line EAhy 926; rAR, rat aortic ring; bAEC, bovine aortic endothelial cell; pAEC, porcine aortic endothelial cell; hSVEC, human saphenous vein endothelial cell; rbAS, rabbit aortic segment; rAC, rat aortic cell; hPBMC, peripheral blood mononuclear cells; hAEC, human aortic endothelial cell; mAEC, mouse aortic endothelial cell. Table modified from reference 6.

Table 2. Effect of GDM and hypercholesterolemia on endothelial L-Arginine/NO pathway.

Thus, this is a different way by which increased levels of cholesterol leads to a reduction in NO synthesis.

4.3. Tetrahydrobiopterin (BH_4) availability in hypercholesterolemia

A reduced expression of the eNOS cofactor BH_4 leads to deficient activation (or even uncoupling) of eNOS, a phenomenon characterized by eNOS-reduction of molecular oxygen by a no longer coupled L-arginine oxidative mechanism resulting in generation of superoxide anion rather than NO [98]. This phenomenon contributes to vascular oxidative stress and endothelial damage and dysfunction [16]. Hypercholesterolemic mice and rabbit exhibit reduced level of BH_4 in the aorta and myocardium [99,100], a phenomenon related with endothelial dysfunction and major progression of atherosclerosis. Additionally, it has been demonstrated that BH_4 supplementation improves the endothelial function in hypercholesterolemic patients [101,102], suggesting that this cofactor is reduced in this pathological condition. Endothelial cells from the human placenta vasculature express functional BH_4 which is reduced with the progress of pregnancy by a mechanism involving lower activity of guanosine triphosphate cyclohydrolase I (GTPCH) and 6-pyruvoyl tetrahydropterin synthase (PTPS), key enzymes involved in BH_4 synthesis [103,104]. Alternatively, in other cell types, a reduced level of BH_4 dependent of down-regulation of GTPCH expression has been associated with hypercholesterolemia in rat macrophages and smooth muscle cells [105,106].

4.4. L-Arginine transport in hypercholesterolemia

Decreased bioavailability of L-arginine could result from reduced expression and/or altered cellular localization of hCATs, as reported for hCAT-1 and potentially hCAT-2B in HUVEC [53,54,107,108]. Interestingly, it was initially shown that hCAT-1–like transport was unaltered by oxLDL in HUVEC cultures [109,110]. However, no kinetic parameters were addressed in these studies opening the possibility that L-arginine transport at a unique fixed concentration of this amino acid (100 μM) [109] could be insensible to oxLDL, or that a long period of incubation for L-arginine uptake (1-24 hours) [110] will not be a condition close to initial velocity for transport, something required for this type of analysis [49,51]. Additional studies in other types of endothelial cells show that LDL (native or oxLDL) reduces L-arginine transport in aortic endothelium from hypercholesterolemic rats, involving protein kinase C [14]; and bovine aortic endothelium where a maximal transport capacity (V_{max}/K_m) [49] is reduced [111,112]. Interestingly, human aortic endothelial cells exposed to nLDL/oXLDL exhibit decreased intracellular content of L-arginine, a phenomenon explained as resulting from post-translational down-regulation of CAT1 and increased CAT1 internalization [102]. In addition, and highlighting the involvement of L-arginine transport in placental vascular reactivity, recent studies suggest that L-arginine transport mediated by hCAT-1 will be a mechanism limiting human placental vascular reactivity since reduced transport (by the use of *N*-ethylmaleimide) or cross-inhibition (by L-lysine) of hCATs leads to reduced insulin-induced dilatation of human umbilical vein rings from normal pregnancies [54].

4.5. Arginases expression in hypercholesterolemia

Up-regulation of arginases (isoforms I and II) is another mechanism by which NO synthesis is proposed to be reduced leading to placental endothelial dysfunction. Arginases are enzyme competing by L-arginine with eNOS [17,114,115], favoring conversion of L-

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arginine into L-ornithine and urea. Therefore, an increase in arginases activity will limit the availability of L-arginine to be metabolized by eNOS for NO synthesis. Interestingly, a link between hypercholesterolemia and arginase I and II expression has been demonstrated in mice [115] and in human aortic endothelial cells [116] where oxLDL induces an overexpression of arginases and a reduction of total eNOS protein abundance associated with lower NO production [114], mostly by the interaction with LOX-1 receptor and the activation of the small GTPase RhoA and Rho A kinase (ROCK) signaling pathway [17]. Interestingly, the reduction of arginases activity caused by statins in hypercholesterolemic subjects improves the endothelial function [117]. These findings show that arginases could play a role in the modulation of endothelial function, most likely regarding NO synthesis by competing for L-arginine with eNOS.

5. Gestational diabetes mellitus

GDM is a syndrome characterized by glucose intolerance with onset or first recognition during pregnancy [118-120]. Clinical manifestations of GDM have been attributed mainly to the condition of hyperglycemia, hyperlipidemia, hyperinsulinemia, and fetoplacental endothelial dysfunction [34,37,119,121,123]. GDM is also associated with abnormal fetal development and perinatal complications, such as macrosomia, neonatal hypoglycemia, and neurological disorders [121]. This syndrome occurs with a high incidence, depending on diagnostic criteria used, ranging between 5 and 15% of pregnant women in developing [124,125] and developed countries [120,126-128].

Altered vascular reactivity is a characteristic of GDM and is due to endothelial dysfunction at the micro and macro fetoplacental vasculature [34,37,129-134].

Even when hyperglycaemia is the principal factor leading to endothelial dysfunction, other factors are involved including hyperinsulinemia and the extracellular nucleoside adenosine level [39,133,134]. Since GDM is associated with MSPH, this factor could also contribute with this phenomenon although the effect is actually unknown.

5.1. Endothelial function in GDM and L-arginine/NO pathway

It has been reported that the NO level in the human umbilical vein blood is increased in GDM [127] and that in HUVEC from GDM the synthesis of NO is increased [39,53, 135, 136]. These findings were associated with a constitutive increase in the number of copies for eNOS mRNA, as well as increased eNOS protein level and activity. Other studies show that in HUVEC isolated from GDM the L-arginine transport is increased due to higher maximal velocity (V_{max}) for transport, most likely resulting from increased expression of hCAT-1 [53,133]. Even when the synthesis of NO is increased in GDM cells, the bioavailability of this vasodilator is reduced leading to an state of endothelial dysfunction [6,34,39, 123] (Figure 2). Thus, the vascular reactivity of umbilical vein rings from GDM is lower compare with rings from normal pregnancies [39]. This phenomenon has been suggested to result from a less reactive umbilical vein due to a tonic and basal increased state of

vasodilation by over-release and/or accumulation of adenosine, a nucleoside that induce vascular relaxation, in the umbilical vein blood [39].

6. Dyslipidemia in GDM

GDM is a pathological condition also characterized by maternal dyslipidemia, alterations that affect directly the fetal development and growth [123].

Dyslipidemia is defined as elevated levels of triglycerides (hypertriglyceridemia) and total blood cholesterol (hypercholesterolemia) including increased LDL and reduced HDL cholesterol [137]. Dyslipidemia is recognized as the main risk factor for development of CVD [137,139]. Additionally, GDM has also been established as a significant risk factor to fetal programming of metabolic syndrome [140-142] and thus predisposing to accelerate the development of CVD in the adult life [141-146].

Interestingly, most of pregnancies that develop GDM course with dyslipidemia [7,24,147] (Table 3) and thus could be feasible to found a pathologic link between dyslipidemia in pregnancies with GDM and the development of CVD later in life.

GDM is related with fetal macrosomia and endothelial dysfunction and interestingly both characteristic could be related with the associated dyslipidemia. The association between dyslipidemia and macrosomia regards hypertriglyceridemia more than hypercholesterolemia; in fact, a positive correlation between maternal triglycerides and neonatal body weight or fat mass has been found in GDM [7,141,142]. In the other hand, hypercholesterolemia could contribute with the endothelial dysfunction described in the pathology [6,142,149]. Thus GDM could play a role in the fetal programming of adult CVD not only by the classical alterations mainly triggered by hyperinsulinemia, hyperglycaemia and changes in nucleoside extracellular concentration, but also by hypercholesterolemia associated with this pathology [6,142,149]. However, no studies have addressed whether elevated maternal blood cholesterol in GDM modulate endothelial function in placental endothelial cells [33].

6.1. Cholesterol metabolism in GDM

The increased levels of maternal cholesterol in GDM (Table 3) are related with alterations in the expression of proteins involved in lipid and cholesterol homeostasis [24,150,151].

Although MSPH is associated with decreased expression of LDL receptor in the placenta, the effect of GDM-associated dyslipidemia on lipoprotein receptors expression is unknown [24,32]. A study of microarray profile determined changes in the expression of multiple genes involved in lipid and cholesterol metabolism in placental tissue of pregnancies coursing with GDM. These genes include the fatty acid coenzyme A ligase, long chain 2, 3 and 4 (FACL2,3,4) that catalyze the conversion of fatty acids into fatty acyl-CoA esters (precursors for the synthesis of triglycerides, cholesterol, and membrane phospholipids), additionally 3-hydroxy-3-methylglutaryl-Coenzyme A reductase (HMGCR), 3-hydroxy-3-methylglutaryl-

	1°trimester	2°trimester	3°trimester	Reference
TG	101*	142*	187*	[147]
(mg/dl)		286*	271*	[183]
			226*	[184]
			260*	[185]
			268	[24]
			220	[158]
			203	[186]
		214		[187]
Ch	203*	226*	281*	[147]
(mg/dl)		241	224	[183]
			242	[184]
			267	[24]
			197	[158]
			243	[185]
		246		[187]
LDL		145	130	[183]
(mg/dl)		129		[187]
			130	[184]
			148†	[185]
			143	[24]
			197	[158]

Values of cholesterol (Ch) and triglycerides (TG) in GDM pregnancies were compared with those of normal pregnancy. *: level increased compared with a control group without GDM. †: level decreases compared with a control group without GDM. LDL: low-density lipoprotein.

Table 3. Maternal lipids levels GDM pregnancies.

Coenzyme A synthase (HMGCS 1) among other genes involved in the novo synthesis of cholesterol were also regulated [150] and even when in this study the level of cholesterol were not determined among normal and GDM pregnancies, these data suggest that GDM leads to changes in genes related with cholesterol metabolism in the placenta. Previously was described that MSPH associates with increased expression of FAS and SREBP2 in the placenta, while the effect in FAS was observed also in placental cells from GDM without changes in SREBP2 expression [24].

These data suggest that both MSPH and GDM associates with changes in key element in the lipids metabolism, however, if MSPH potentiate the effect of GDM over theses parameters is unknown [6].

Another lipid modulator modified by GDM in placental cells is PLTP, a key protein involved in the metabolism of fetal HDL. PLTP is expressed in endothelial cells of the placental vasculature and is regulated as ABCA1 and ABCG1 by liver X receptor (LXR) nuclear receptors [26,152,153]. Interestingly diabetes leads to increased levels of the principal ligand of LXR, the oxysterols [154] and GDM associates with up-regulation of PLTP in endothelial cells of the placenta [151] mainly due to the hyperinsulinemia and hyperglycaemia related with GDM. The increased expression of PLTP could be a key phenomenon associated with the increased concentration of HDL described in newborns from GDM [11,151]. Additionally, the increased expression of PLTP in placental endothelial cells could affect the maternal to fetal cholesterol transport, a phenomenon not yet evaluated and potential worsen by conditions as MSPH where the mother-*to*-fetus cholesterol transport may be altered almost in the first months of pregnancies when the levels maternal cholesterol correlates with the fetal ones [9].

6.2. Hypercholesterolemia in GDM and endothelial dysfunction

As was previously discussed, physiological increase in the levels of maternal cholesterol is considered to be an adaptive response of the mother to satisfy the high lipids demand by the growing fetus. The misadaptation to this condition leads to develop MSPH a phenomenon associated with the earlier development of fetal atherosclerosis and with reduced endothelial function of the umbilical vein [6].

Additionally and regarding with the development of atherosclerosis, it is recognized that GDM correlates with endothelial dysfunction [34,39] and neonates of pregnancies coursing with GDM have significant increase in aortic and umbilical artery intima-media thickness (IMT) and higher lipid content, both markers of subclinical atherosclerosis that could increase the atherosclerotic process later in life [12,155,156].

The effect of GDM in the aortic IMT of newborns was assayed and an increased intimal-medial ratio was determined. Interestingly the IMT was evaluated in newborns of pregnancies coursing with GDM and increased levels of total cholesterol and LDL compared with the control group [12]. Thereby may be possible to found a potential effect of MSPH in this phenomenon. Similar findings were found in fetus in the lasts weeks of gestation where the IMT was evaluated in umbilical artery, where umbilical IMT was increased in arteries from GDM pregnancies, however the potential effect of maternal cholesterol was not evaluated [156].

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Unfortunately, nothing is yet available regarding the potential effects of MSPH in pregnancies coursing with GDM on the development of endothelial dysfunction and atherosclerosis in placental and eventually in fetal vessels at birth, a phenomenon that could leads to a potentiation of GDM-associated fetoplacental endothelial dysfunction.

7. Concluding remarks

MSPH is a risk factor promoting the development of atherosclerosis in the growing fetus and in the children, however the effects of this condition in fetoplacental endothelium is unknown even when increased levels of maternal cholesterol could lead to alterations in the hCAT-mediated L-arginine transport and eNOS-synthesis of NO (i.e., the endothelial L-arginine/NO signaling pathway) such as occurs in other vascular beds exposed to high cholesterol levels.

GDM is a condition that course with alterations of the L-arginine/NO signaling pathway in the human fetoplacental vasculature, phenomenon resulting in abnormal bioavailability of NO leading to altered vascular reactivity and changes in umbilical vessels blood flow with consequences in the fetal growth and development.

Interestingly, some pregnancies coursing with GDM associates with MSPH and the possibility that the observed fetoplacental endothelial dysfunction results from a potentiation of the classical factor associated with GDM and the increased levels of cholesterol is likely.

Further studies are required to elucidate whether pregnancies coursing with GDM and MSPH have different effect in placental endothelial function compare with those coursing with GDM and normal levels of maternal cholesterol because it could be possible find a different mechanism involved in both cases.

This may contribute to understand the mechanisms related with the vascular dysfunction associated with GDM and allow establishing a better knowledge based- management of the mother and the newborn.

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