Maternal Hypercholesterolemia is a Significant Risk Factor for Atherogenesis – A Systematic Review

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Abstract

Background: Cardiovascular diseases, typically associated with older individuals, have been found to have risk factors that can develop during childhood and even fetal development. Maternal hypercholesterolemia, experienced during pregnancy, is one such factor that affects the fetus. This review aims to explore the mechanisms through which maternal hypercholesterolemia can contribute to the development of atherosclerosis and subsequent cardiovascular diseases and events. **Methods:** To conduct this review, we systematically analyzed existing literature and collected relevant information on the impact of maternal hypercholesterolemia on fetal development and subsequent cardiovascular health. We examined studies that investigated the pathways and mechanisms by which maternal hypercholesterolemia influences atherosclerosis and its related diseases. **Results:** Our review identified several mechanisms by which maternal hypercholesterolemia can stimulate the development of atherosclerosis and contribute to cardiovascular diseases and events. These mechanisms include alterations in lipid metabolism, oxidative stress, endothelial dysfunction, inflammation, and vascular remodeling. Maternal hypercholesterolemia during pregnancy can lead to lipid abnormalities in the fetus, triggering early atherosclerotic changes that persist into adulthood. These changes may increase the risk of cardiovascular diseases later in life. **Conclusion:** This review highlights the potential impact of maternal hypercholesterolemia on the development of atherosclerosis and subsequent cardiovascular diseases in offspring. Understanding the mechanisms involved is crucial for developing effective preventive strategies and interventions. By addressing maternal hypercholesterolemia and its effects during pregnancy, healthcare providers can contribute to reducing the burden of cardiovascular diseases in future generations. Further research is needed to elucidate the precise mechanisms and long-term effects, which will aid in developing targeted approaches for early intervention and risk mitigation.

Keywords: Maternal hypercholesterolemia; Hypercholesterolemia; Atherosclerosis; CVD; Pregnancy; Gestation.

Significance | Maternal hypercholesterolemia during pregnancy influences fetal development, leading to lasting atherosclerotic changes, emphasizing preventive strategies to reduce future cardiovascular disease burdens.

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1. Introduction

Maternal cholesterol levels can significantly affect the process of early fetal atherogenesis. This process is influenced by a number of factors, such as genetics, maternal nutrition, diseases carried, and so on. However, a number of studies show that the occurrence or acceleration of the natural processes of atherogenesis in normocholesterolemic children occurs even if the excess of a

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certain level of cholesterol in the mother (hypercholesterolemia) is temporary and in the absence of additional genetic complications and diseases (Palinski and Napoli, 2002). Recent research has provided a detailed description of the molecular mechanism responsible for the mother-child exchange of cholesterol during pregnancy. This has made it possible to select effective prevention and therapy of hypercholesterolemia in the period before and during pregnancy (Bartels and O'Donoghue, 2011).

In most countries, routine cholesterol tests during pregnancy are not common, which limits research on the effects of high maternal cholesterol during pregnancy on the health of the offspring in adulthood. However, a recent study conducted on patients from the Framingham Heart Study suggests that mothers who have high cholesterol before and after pregnancy are likely to have gestational hypercholesterolemia. Maternal dyslipidemia is a predictor of dyslipidemia in their offspring (Adank et al., 2022). The study found that adults who were exposed to high levels of maternal LDL-C had 3.8 times higher odds of having elevated LDL-C levels. This explained 13% of the variation in adult offspring LDL-C levels beyond genetic factors and traditional risk factors. The study also found a positive association between maternal cholesterol and newborn HDL cholesterol and subclasses. In addition, the study found that maternal cholesterol explained 61% of the variation of early lesion sizes in foetal aortas. Maternal total cholesterol and LDL-C levels were also positively associated with methylation of SREBP2 in foetal aortas, indicating that maternal cholesterol levels during pregnancy may have an impact on the epigenetic signature in offspring. While the study provides detailed mapping of SREBP2 methylation, it is still unknown whether maternal hypercholesterolemia affects the long-term progression of atherosclerosis and its clinical manifestations (Sletner et al., 2021). Establishing this is important because unlike inherited genetic risk, developmental programming-induced susceptibility to atherogenesis may be prevented by brief dietary or other interventions in mothers. Several cohort studies have shown that whole blood DNA methylation signatures of diet are associated with cardiovascular disease risk (Ma et al., 2020).

The review emphasizes the possible influence of maternal hypercholesterolemia on atherosclerosis development and the resulting cardiovascular diseases in children. Gaining insight into the underlying mechanisms is essential for formulating effective prevention strategies and interventions. Addressing maternal hypercholesterolemia and its impact during pregnancy will enable healthcare providers to diminish the prevalence of cardiovascular diseases in future generations. Further research is necessary to unveil the exact mechanisms and long-term consequences, thus facilitating the development of targeted early intervention and risk reduction approaches.

2. Hypercholesterolemia

Atherosclerosis is a progressive disease characterized by the buildup of cholesterol and formation of atherosclerotic lesions, which is strongly associated with hypercholesterolemia. This condition is the most significant risk factor for cardiovascular disease (CVD), the leading cause of death worldwide (Pahwa and Jialal, 2023). While the recommended blood cholesterol levels vary depending on the population and associated risk factors, a total cholesterol (TC) level of less than 200 mg/dL and a low-density lipoprotein (LDL)-cholesterol level of less than 100 mg/dL are generally recommended (Lee and Siddiqui, 2023).

Hypercholesterolemia can induce endothelial dysfunction, which is an early occurrence in the development of atherosclerosis. This condition results from an imbalance between vasoconstrictor and vasodilator molecules produced or acting on endothelial cells. High cholesterol levels in the blood are also associated with the formation of foam cells from macrophages, which serves as an early indicator of atherosclerosis (Gimbrone and García-Cardeña, 2016). Although CVDs are typically diagnosed in adulthood, there is evidence that endothelial dysfunction and foam cell formation, indicative of early atherosclerotic lesions, can start during fetal development in the blood vessels of the fetus. This condition arises from elevated maternal cholesterol levels during pregnancy, but the mechanisms behind these changes are not yet fully understood (Benagiano et al., 2021).

3. Maternal hypercholesterolemia

Gestation, also known as pregnancy, is the state in which a woman carries one or more fetuses inside the uterus. During gestation, lipid concentrations increase to meet the growing fetus's lipid demands, resulting in a physiological increase in cholesterol levels, which is considered normal. This increase is primarily due to elevated levels of total cholesterol (TC) by 40-50% and triglycerides (TG) that may reach 2-4 times pre-pregnancy levels in late gestation (Wild and Feingold, 2023). This adaptive response is considered non-atherogenic and usually returns to normal levels post-delivery, although there is an increase in the proportion of small, dense LDL particles. However, in mid-pregnancy, high levels of HDL-c and apolipoprotein A (ApoA) provide protection against the increase in atherogenic LDL-c and TG levels. Although levels of atherogenic Lp(a) increase with each trimester, there is no conclusive evidence of adverse pregnancy outcomes due to its elevated levels throughout gestation. This is distinct from inherited lipid disorders such as FH and currently considered clinically irrelevant (Ogura et al., 2002). Thus, there is a lack of information on its global prevalence in pregnant women to establish a diagnostic cut-off value for cholesterol levels. However, some studies suggest that women with TC levels exceeding 280-290 mg/dL at the end of gestation or above the 75th percentile for all three trimesters of pregnancy are hypercholesterolemic and have maternal supraphysiological hypercholesterolemia (MSPH).

In recent decades, the placenta has been recognized as a dynamic organ that plays a crucial role in fetal connections with the maternal immune system, undergoes structural and functional changes during gestation, and regulates the fetal environment (Jayalekshmi and Ramachandran, 2021).

In the early stage of pregnancy, the fetus is nourished by substances secreted by the glands of the uterus as well as by the yolk sac. In the next stage, at the end of early pregnancy, the placenta fully develops, which becomes the main source of nutrients for the fetus and establishes a mechanism of metabolism between mother and fetus that persists throughout pregnancy (Herrick and Bordoni, 2023). Maternal blood fills the intervillous spaces about ten weeks from conception, which is considered the starting point for a fully developed placenta (Wang and Zhao, 2010).

The exchange of nutrients and gases between the growing fetus and the mother is initiated by the direct flow of maternal blood to syncytialized trophoblasts (STBs) at a rate of 3-4 times per minute. STBs are single, multinucleated trophoblast cells formed by the syncytial fusion of underlying progenitor villous cyto-trophoblasts (STBs). They are characterized by a basal membrane facing the fetal circulation and a brush border membrane facing the maternal circulation (Bačenková et al., 2022). It was previously thought that maternal cholesterol might not pass through the placental barrier, but this idea was refuted by the detection of cholesterol in the cells and plasma of offspring with Smith-Lemley-Opitz syndrome (SLOS), which had a mutation in both alleles of the 7-dehydrocholesterol gene (DHCR7). The presence of the mutated DHCR7 gene led to impaired cholesterol biosynthesis and suggested that the fetus has an exogenous source of cholesterol, indicating that maternal-fetal cholesterol transport occurs at some stages of pregnancy. The mechanism of cholesterol transport through the placenta has been shown to contribute significantly to the fetal cholesterol pool (Porter and Herman, 2011).

Cholesterol transport to the fetus occurs in two ways: through the secondary yolk sac during the early stages of pregnancy, and via the fully developed placenta later on. During the early stages of pregnancy, cholesterol molecules from the maternal circulation seep out into the exocoelomic cavity where the secondary yolk sac absorbs them and expels them to the fetal circulation (Baardman et al., 2013). Receptors such as scavenger receptor-B1, intrinsic factor-cobalamine receptor, LDLR-related protein-2, and LDLR expressed on the visceral endoderm of the secondary yolk sac transport various apolipoproteins such as apoA1, apoE, and apoB in the form of HDL, LDL, and VLDL to the fetal blood. Moreover, a novel transporter called microsomal triglyceride transfer protein in the yolk sac is involved in the transport of cholesteryl esters (Baardman et al., 2013).

As gestation progresses, the placental villi establish vascularization, and the secondary yolk sac regresses, leaving the placenta to take over its nutrition role. At this stage, maternal cholesterol has to cross syncytialized trophoblasts (STBs) and endothelial cells (ECs) to reach the fetal circulation (Bergmann et al., 2004). The apical (maternal) side of STBs has receptors such as scavenger receptor-B1, intrinsic factor-cobalamine receptor, LDLR-related protein-2, LRP-8, LRP-1, LDLR, scavenger receptor-A1/A2, and VLDL receptor. These receptors facilitate the entry of HDL with apoA, LDL with apoB, and VLDL with apoB and apoE into the trophoblasts, which are then carried to the lysosomes (Yang et al., 2013; Krieger, 2001).

Further, free cholesterols are released from cholesteryl esters of lipoproteins, and sterol carrier proteins shift them to the basal side of the STBs. The SR-B1, ATP binding cassette transporter subfamily A member 1, and ATP binding cassette transporter subfamily G member 1 expressed on the basal side of STBs are thought to efflux these cholesterols to the stroma (Yañez and Leiva, 2022). ABCA1 is expressed on both apical and basal sides of STBs, which can contribute to bidirectional transport of cholesterol, while ABCG1 is reported to express only on the basal side of STBs. Hence, cholesterol is carried to fetal ECs through an unknown mechanism to the LDLR and SR-B1 expressed on the apical side, thereby activating the ABCA1 and ABCG1 transporters (Aye et al., 2022).

Finally, in the basal side of STBs, transporters such as ABCA1 and ABCG1 perform cholesterol efflux to APOA1, APOE, and APOB in the fetal circulation. It was also reported that Phospholipid Transfer Protein, another transporter in ECs, also participates in this mechanism by enhancing the cholesterol efflux from STB by the interaction with ABCA (Stefulj et al., 2009). This complex process of cholesterol transport through both the secondary yolk sac and placenta is essential for fetal growth and development, and further research is needed to fully understand the mechanisms involved (Burke et al., 2009).

The placenta can undergo changes due to abnormal maternal nutrition or high cholesterol levels, which can affect its physiology through epigenetic regulation or gene expression. However, the mechanisms underlying these changes and cholesterol transport across the placenta are not well understood. A small study of pregnant women with high cholesterol levels found a correlation between the expression of PCSK9, LDLR, and VLDLR genes in the placenta. Studies in mice suggest that PCSK9 negatively regulates LDLR to reduce cholesterol in circulation. High levels of total cholesterol and oxidized LDL can increase endothelin-1 production and decrease NO availability, leading to endothelial dysfunction and atherosclerosis in both placental and non-placental vessels (Zhang et al., 2017; Roubtsova et al., 2022). Furthermore, oxidative stress caused by an imbalance between

ROS, such as superoxide anion and hydrogen peroxide, can occur in the placenta. In normal placental physiology, ROS is involved in cellular pathways for trophoblast invasion and vascular development (Hussain et al., 2021).

When there is an imbalance between the production of reactive oxygen species (ROS) and the antioxidative mechanism to scavenge them, it can cause lipid peroxidation and damage to DNA and proteins. Such conditions can lead to pregnancy complications like preeclampsia and fetal growth restriction. Preeclampsia is characterized by elevated levels of markers of oxidative DNA repair and damage and hypoxia, indicating reduced blood flow to the fetus, which may ultimately lead to fetal abnormalities (Joo et al., 2021). These markers of oxidative stress are also associated with hypercholesterolemia and atherogenesis, where they are linked to the pathophysiology of ASCVDs. Similarly, in MH, free lipids in the placenta may be oxidized by ROS and other free radicals, resulting in the formation of modified lipids like ox-LDLs. The transport of these modified lipoproteins to the fetus may lead to the development of MH-induced atherogenesis in offspring. However, to date, no studies have been conducted to confirm these hypotheses experimentally (Panda et al., 2022).

Over the past few decades, numerous studies have attempted to elucidate the potential methods of maternal-fetal cholesterol transportation across the placenta. However, a better comprehension of how cholesterol efflux occurs in the basal side of syncytiotrophoblasts (STBs) and the mechanism of cholesterol molecule entry from the stroma or extracellular matrix (ECM) to the apical side of endothelial cells (ECs) is required (Horne et al., 2019). The participation and individual contributions of receptors and transporters in cholesterol efflux across STBs and fetal ECs remain unclear as there are no conclusive findings. There may be additional receptors and transporters involved in this process. Additionally, there is a dearth of knowledge on how this mechanism operates during hypercholesterolemic pregnancies and other pathological situations. Furthermore, there is a severe scarcity of data regarding the potential role of underlying progenitor cytotrophoblasts (CTB). Furthermore, MH and other metabolic syndromes may contribute to altered cholesterol transport mechanisms across the placenta (Yvan-Charvet et al., 2010; Rodrigues et al., 2009). We summarized the metabolic maternal-fetal lipid transport in Figure 1.

4. Effects of lipoproteins on cells relevant to atherosclerosis

Various types of cells are involved in the development of atherosclerosis, with endothelial cells and monocytes/macrophages being the primary cells responsible for the early stages of this disease. The initial events that trigger atherosclerosis are endothelial activation and dysfunction, characterized by the expression of glycoproteins such as VCAM-1 and ICAM-1 on the endothelial surface, as well as an imbalance in the production or activity of nitric oxide (NO) by eNOS (Xu et al., 2019). These events contribute to the disruption of the endothelium and increased permeability, leading to the recruitment and migration of monocytes to the subendothelial space of the intima, where they differentiate into macrophages and take up oxidized lipoproteins, mainly LDL, to form foam cells. Macrophages can polarize to either a pro-inflammatory M1-phenotype or an anti-inflammatory M2-phenotype. Lipoproteins are thought to play a crucial role in the prevention or progression of CVD by modulating the functions of EC and monocytes/macrophages in the early stages of atherosclerosis (Kloc et al., 2020). Despite this knowledge and the fact that neonates from MSPH pregnancies show early atherosclerotic lesions, the contribution of fetal lipoproteins to the disease and their potential effects on EC or monocyte/macrophage functions, as well as any changes in their lipid or protein composition, have not been fully explored (Stadler et al., 2021).

4.1. Effects of lipoproteins on endothelial cell function

HDL has anti-inflammatory effects on early atherogenesis by preventing TNF-α-induced expression of endothelial adhesion molecules, such as VCAM-1 and ICAM-1. The composition of HDL, including apolipoprotein composition, phospholipid content, and eicosapentaenoic acid concentration, affects its ability to inhibit VCAM-1 expression in human umbilical vein EC. The shape of the HDL particles also plays a role, with spherical particles being more effective than discoidal ones, and HDL3 being more effective than HDL2 (Muñoz-Vega et al., 2018). In human EC lines, sphingomyelin and reconstituted HDL can inhibit ICAM-1 and VCAM-1 expression, respectively. HDL's protective mechanisms against TNF-α-induced endothelial activation involve inhibiting the translocation and transactivation of transcription factors NF-κβ and activator protein-1, as well as interrupting the sphingosine kinase signaling pathway. In contrast, oxidized HDL (oxHDL) induces endothelial dysfunction by activating NF-κβ in HUVEC. Unlike native LDL (nLDL), oxidized LDL (oxLDL) induces the expression of ICAM-1 and VCAM-1 in human venous EC, human aortic EC (HAEC), and HUVEC (Chen et al., 2002). However, the effects of oxLDL on the expression of these adhesion molecules vary between studies, with some showing upregulation of only ICAM-1 or VCAM-1. Lyso-PC, a component of oxLDL, induces both VCAM-1 and ICAM-1 expression in human iliac artery EC and only upregulates ICAM-1 expression in HUVEC (Zhu et al., 2005).

The mechanisms by which oxLDL affects endothelial adhesion molecules involve several signaling pathways, including toll-like receptor 4-mediated NF-κβ, FAK-dependent RSK, LOX-1-mediated peroxisome proliferator-activated receptor gamma signaling, TGF-β1, and ROCK1 and ROCK2. Therefore, the

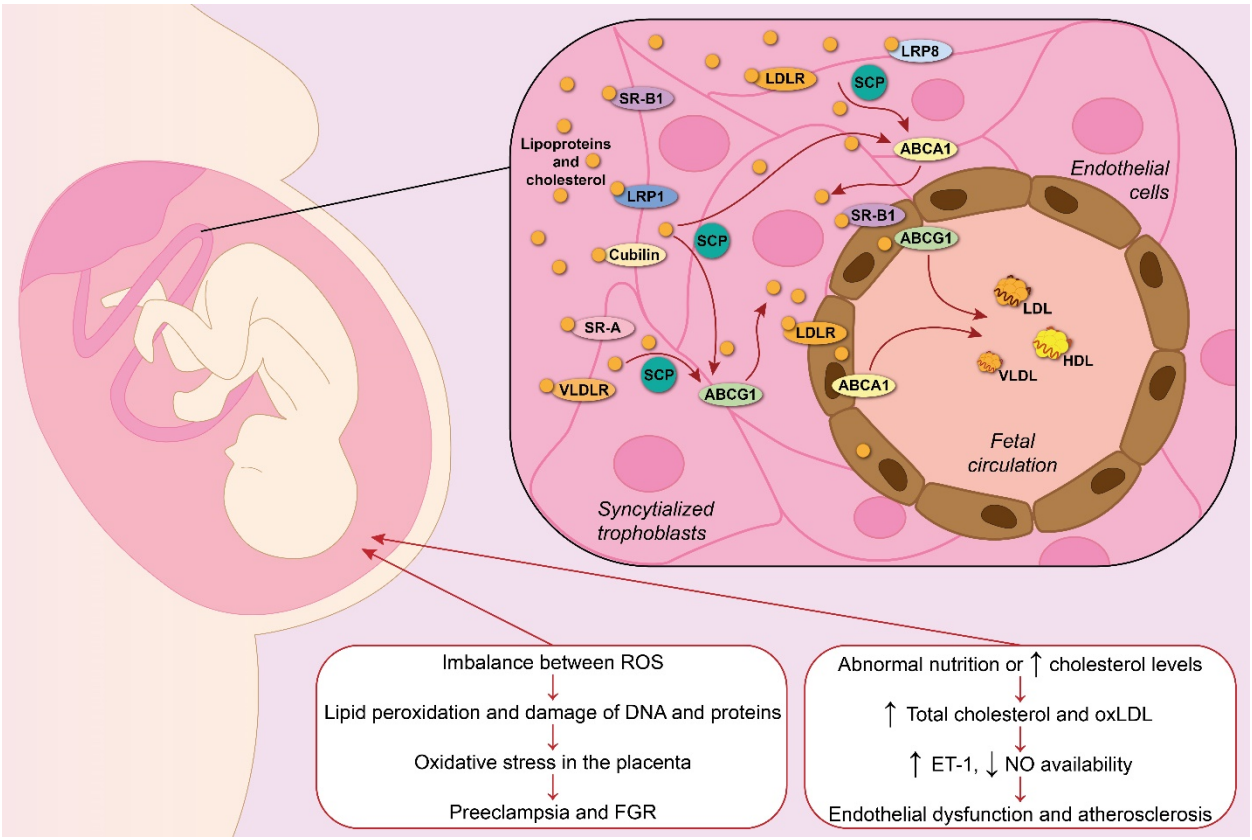

Figure 1. Metabolic maternal-fetal lipid transport: implications of maternal hypercholesterolemia.
Abbreviations: ABCA1 – ATP-binding cassette sub-family A member 1; ABCG1 – ATP-binding cassette sub-family G member 1; ET-1 – endothelin-1; FGR – fetal growth restriction; HDL – high-density lipoprotein; LDL – low-density lipoprotein; LDLR – low-density lipoprotein receptor; LRP1 – low density lipoprotein receptor-related protein 1; LRP8 – low density lipoprotein receptor-related protein 8; NO – nitric oxide; oxLDL – oxidized low-density lipoprotein; ROS – reactive oxygen species; SCP – sterol carrier protein; SR-A – scavenger receptor-A1/A2; SR-B1 – scavenger receptor-B1; VLDL – very low-density lipoprotein; VLDLR – very low-density lipoprotein receptor.

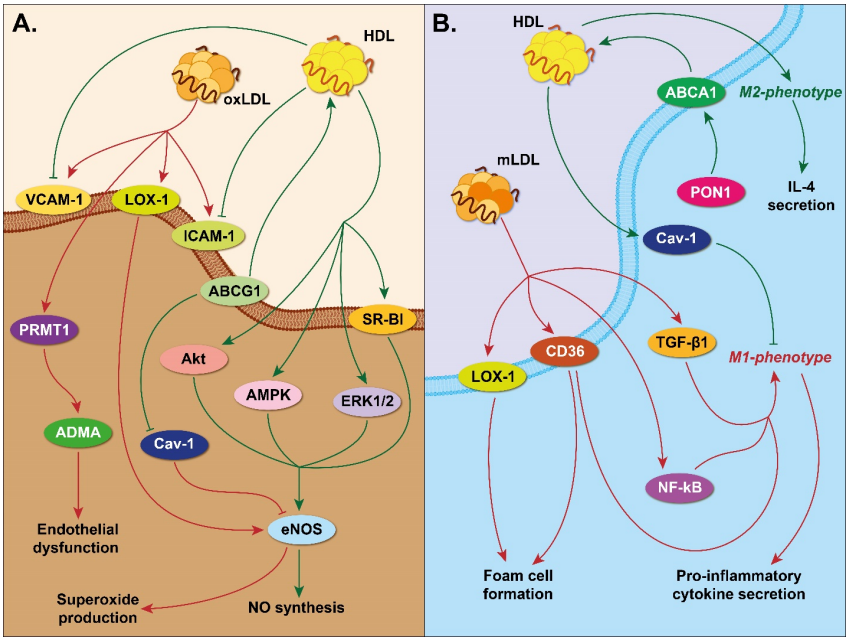

Figure 2. Effects of lipoproteins on cells relevant to atherosclerosis. **(A)** Endothelial cells. **(B)** Macrophages.

impact of lipoproteins, both native and modified, on endothelial activation is dependent on the type of cell exposed to them. However, it is noteworthy that the influence of neonatal HDL or LDL derived from MSPH on endothelial activation remains uncertain (Feng et al., 2014).

4.1.1. Effects of lipoproteins on NO bioavailability and eNOS function

The function of endothelial cells can be influenced by lipoproteins through various mechanisms. One such mechanism is the regulation of the availability of nitric oxide (NO) and the function of endothelial nitric oxide synthase (eNOS). In human vascular endothelial cells, high-density lipoprotein (HDL) can activate extracellular signal-regulated kinase 1/2 (ERK1/2) and Akt, which leads to an increase in eNOS abundance by modifying its half-life (Riwanto and Landmesser, 2013). Apolipoprotein A-I (ApoAI) can also associate with eNOS and promote its phosphorylation by activating 5' adenosine monophosphate-activated protein kinase (AMPK) or its receptor F1-ATPase/P2Y1, thereby increasing eNOS activity. However, the activation of eNOS is reduced after exposure to oxidized HDL (oxHDL) or human free ApoAI (Drew et al., 2004).

HDL-induced stimulation of eNOS occurs through the HDL receptor, scavenger receptor class B type I (SR-BI), in a ceramide-dependent manner. The increase in eNOS may also be related to HDL's ability to deliver estrogens. SR-BI mediates HDL's ability to protect caveolae from the depletion of cholesterol induced by oxidized low-density lipoprotein (oxLDL) and the redistribution of eNOS. HDL also counters oxLDL by reducing the formation of oxygen-free radicals and preserving NO bioactivity (Gong et al., 2003). ATP binding cassette sub-family G member 1 (ABCG1) mediates cholesterol efflux to HDL and decreases eNOS interaction with caveolin-1 (Cav-1), which promotes NO synthesis. The activity of HDL-associated PON1 has also been suggested to play a role in eNOS activation and NO production. However, when PON1 activity is inhibited, HDL does not stimulate eNOS activation and NO production (Gu et al., 2014).

In contrast, native low-density lipoprotein (LDL) also increases the production of NO and the expression of both eNOS and inducible nitric oxide synthase (iNOS) in human umbilical vein endothelial cells (HUVEC). oxLDL reduces eNOS mRNA levels through a combination of early transcriptional inhibition and post-transcriptional destabilization. oxLDL also induces endothelial dysfunction through eNOS uncoupling, in which eNOS generates superoxide instead of NO (Yoon et al., 2019). After interacting with lectin-like oxidized LDL receptor-1 (LOX-1), oxLDL activates a G protein-dependent signaling pathway that results in the activation of endothelial Ca(2+)-activated K(+) channels and reduces acetylcholine-induced NO synthesis by increasing superoxide production. Furthermore, oxLDL increases the levels of ADMA by enhancing the gene expression of protein arginine N-methyltransferases, which catalyze ADMA synthesis, leading to endothelial dysfunction (Mentrup et al., 2021).

4.1.2. Possible implications of lipoproteins effects on endothelial cells function in MSPH pregnancies

Neonates show lower concentrations of ApoAI and larger content of very large HDL, leading to decreased capacity to inhibit VCAM-1 and ICAM-1 expression when endothelial activation occurs. The anti-inflammatory activity of neonatal HDL could be even more diminished in MSPH, as differences in lipidomic profiles have been reported compared to neonates from MPH mothers, which can potentially lead to reduced HDL's ability to inhibit endothelial adhesion molecule expression (Parker et al., 1998; Contreras-Duarte et al., 2023). Additionally, sdLDL predominates in neonates and is more susceptible to oxidation, contributing to VCAM-1 and/or ICAM-1 expression induction and reduced NO synthesis and eNOS activity. Although fetal HDL have a reduced antioxidant capacity, they are a major carrier of S1P and promote vasoprotective effects, favoring NO production and eNOS function. However, preliminary results show that neonatal HDL from MSPH have a reduced capacity to induce eNOS activity compared to lipoproteins from the MPH group, which could be related to a less interaction between HDL and S1P or between this complex with its receptor. The implications of maternal hypercholesterolemia on neonatal LDL susceptibility to oxidation and potential effects on NO production remain to be studied. Therefore, neonatal HDL and LDL could be important factors behind the endothelial dysfunction and early atherosclerotic lesions in MSPH pregnancies (Del Gaudio et al., 2020). We illustrated the impact of lipoproteins on endothelial cells in Figure 2 (A).

4.2 Effects of lipoproteins on macrophages function

The ability of high-density lipoprotein (HDL) to transport cholesterol out of macrophages prevents the formation of foam cells and protects against the development of atherosclerosis. This cholesterol efflux process is stimulated by liver X receptor agonists in foam cells and is mediated by the ATP-binding cassette sub-family A member 1 (ABCA1), which is independent of ABCG1 expression. The process is most efficient with HDL3 particles, which are enriched in negatively charged phospholipids like phosphatidylserine. HDL also upregulates the expression of genes that stimulate cholesterol efflux; however, oxidized HDL has been shown to reduce free cholesterol and oxysterol efflux, leading to increased intracellular cholesterol accumulation (Franceschelli et al., 2023).

The protein composition of HDL particles is also important in cholesterol efflux. Native or synthetic apolipoprotein A-I (ApoAI) promotes reverse cholesterol transport, while dysfunctional ApoAI has reduced ability to induce cholesterol efflux. Apolipoprotein E

(ApoE) is involved in the cholesterol efflux process via ABCA1, and HDL particles containing ApoM are more efficient than those lacking this protein (Valanti et al., 2018). The presence of Apo-SAA on HDL has little impact on cholesterol efflux, but HDL3 containing SAA is less effective at transporting cholesterol out of cells. Additionally, paraoxonase 1 (PON1) promotes cholesterol efflux in ABCA1-enriched macrophages, and reduced PON1 activity impairs this process (Trakaki and Marsche, 2021).

During atherosclerosis, macrophages can take up modified low-density lipoprotein (LDL) through scavenger receptors, leading to the accumulation of lipids and the formation of foam cells. Research has shown that electronegative LDL and small dense LDL induce inflammation and the differentiation of monocytes, promoting the accumulation of triglycerides and enhancing scavenger receptor expression on THP-1 macrophages (Puig et al., 2020).

Also, the formation of atherosclerosis is closely associated with the accumulation of oxLDL in macrophages, which results in the buildup of cholesterol and lysosomal entrapment of free and esterified cholesterol. This process leads to significant changes in macrophage gene expression related to cellular metabolism, cytoskeletal function, and cellular signaling (Mushenkova et al., 2021). Enhanced oxLDL loading leads to the expression of CD36 clusters and the formation of foam cells. Furthermore, oxLDL loading also inhibits lysosomal activity, which decreases the hydrolysis of cholesteryl esters and free cholesterol. Notably, macrophages exposed to oxLDL can oxidize cholesterol, producing oxysterols that can be released through HDL efflux (Wallner et al., 2016).

4.2.1 Effects of lipoproteins on macrophage phenotype

In the development of atherosclerosis, monocytes move from the blood vessels into the arterial wall, where they accumulate and become macrophages or dendritic cells. Macrophages can take on different phenotypes based on their surroundings, and studies have shown that HDL and LDL play a critical role in determining macrophage polarization. HDL inhibits macrophage differentiation into the pro-inflammatory M1-phenotype by redistributing Cav-1 (Ley et al., 2011). The impact of HDL on macrophage polarization into the alternative anti-inflammatory M2-phenotype is still controversial. Some studies have shown that S1P-carrying HDL induces M2 polarization through interleukin-4 secretion, while others have found no effect. ApoAI has also been associated with the inhibition of DC differentiation and maturation, suggesting that the major protein in HDL affects both macrophage polarization and monocyte differentiation (Lee et al., 2016).

nLDL causes macrophages to differentiate into the M1 phenotype, resulting in increased production of inflammatory cytokines. oxLDL uptake affects the functions of M1 macrophages mediated by TGF-β1 and NF-kB, but it does not affect those of M2 macrophages. However, a study has shown that oxLDL activates CD36 and the platelet activating factor receptor, inducing and enhancing the responses of M2 macrophages. LDL(−) induces the differentiation of M1 macrophages through a LOX-1-dependent pathway (Wu et al., 2022). We illustrated the impact of lipoproteins on macrophages in Figure 2 (B).

4.2.2 Possible implications of lipoproteins effects on macrophages function in MSPH pregnancies

Although our knowledge of how neonatal lipoproteins affect macrophage function and phenotype is limited, we hypothesize that differences in protein and lipid composition in neonatal HDL and LDL may affect these cells. This could result in changes to cholesterol efflux capacity, foam cell formation, and macrophage phenotype. We have preliminary results indicating that neonatal HDL from mothers with MSPH have a higher cholesterol efflux capacity compared to those from MPH mothers, which may counteract the potential pro-oxidative capacity described for neonatal LDL (Cantin et al., 2021). Additionally, since inflammation plays a crucial role in atherosclerosis and MSPH, we are interested in determining whether neonatal lipoproteins may promote a pro-inflammatory environment by modulating macrophage phenotype. Therefore, we suggest that neonatal lipoproteins not only influence EC modulation but also regulate macrophage function, which may differ in hypercholesterolemic pregnancies. Furthermore, our findings highlight the importance of investigating the composition and function of neonatal lipoproteins to understand the MSPH condition and its negative effects on the fetoplacental vasculature (Liu et al., 2022).

5. Conclusion

Maternal hypercholesterolemia has a significant impact on the accelerated formation of atherosclerosis. The effect is both on lipid metabolism and on the inflammatory component. The functions of all cell types that are significantly involved in the pathogenesis of atherosclerosis are influenced by Maternal hypercholesterolemia. The main mediators in the effects that this condition has on cells involved in atherogenesis are lipoproteins. Today we can say that Maternal hypercholesterolemia is one of the risk factors for the early development of atherosclerosis.

Author contribution

A.V.P. wrote, drafted; V.N.S., V.A.K., A.Y.P., N.K.S., A.N.O. wrote, reviewed and edited the paper.

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Competing financial interests

The authors have no conflict of interest.

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