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Literature Review

Signs of Predisposition to Atherosclerosis in Fetal Development

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Abstract: Atherosclerotic Cardiovascular Disease (ASCVD) remains a significant global health concern, contributing to a substantial number of deaths worldwide. The etiology of this condition is multifaceted, influenced by a plethora of genetic and environmental determinants. Notably, certain risk factors and predictive markers associated with ASCVD may already present or emerge during the prenatal or neonatal period. Early recognition of these markers is pivotal in identifying an individual's vulnerability to ASCVD, enabling timely interventions that can effectively mitigate risks or impede disease progression. This review paper endeavors to delve into the distinct markers of susceptibility to atherosclerosis specifically observed in human fetuses, shedding light on their diagnostic and prognostic significance. By scrutinizing these markers in the context of prenatal development, novel insights can be gleaned regarding the early origins and potential predictive value of atherosclerotic predisposition, thereby paving the way for innovative preventive strategies and personalized healthcare interventions.

Keywords: Fetal Development, Pregnancy, CVD, Atherosclerosis, Risk Factors

Introduction

Embryonic and fetal growth constitutes a highly intricate process governed by a myriad of signaling cascades operating at the molecular level. The precise orchestration of events, encompassing DNA transcription to RNA translation and subsequent protein synthesis, is paramount across various developmental stages. Perturbations within these intricate pathways can have profound repercussions on cellular functionality and organogenesis (Jukam *et al*., 2017). The genesis of hereditary disorders and the impact of teratogenic agents such as radiation, pharmaceuticals, and adverse environmental conditions can impede normal development, culminating in severe anomalies and potential embryonic demise. The seminal insights garnered in the 1970s prompted the global imposition of restrictions on irradiation and medication usage during gestation (Kumar and De Jesus, 2020).

The interplay between genetic predispositions and prenatal environmental influences during pregnancy and infancy significantly shapes fetal development. The prenatal milieu emerges as a pivotal determinant influencing the predisposition to chronic ailments in offspring. Building upon the pioneering work of Barker and Osmond, the concept of "fetal programming" posits that stimuli or insults during critical prenatal windows engender adaptive modifications in fetal structure, function, and metabolism with enduring repercussions throughout the individual's lifespan (Aris *et al*., 2018; Leduc *et al*., 2010). Figure 1 delineates the intricate web of interactions between fetal programming, maternal factors, and the enduring impacts on long-term health outcomes. The interconnection between maternal influences, environmental stimuli, and developmental adaptations during the prenatal period evokes a cascade of biological responses that permeate into adulthood, influencing health outcomes and disease susceptibility.

Cardiovascular Disease (CVD) represents the foremost cause of morbidity and mortality worldwide, prevailing in both economically developed and developing nations alike. Atherosclerosis, precipitated by hypercholesterolemia, stands as the primary etiological factor underlying CVD. The insidious progression of

atherosclerosis serves as the underlying pathogenic basis for debilitating cerebrovascular and myocardial infarctions (Olvera Lopez *et al*., 2022). Notably, the incipient stages of atherosclerotic vascular lesions commence during the prenatal period, characterized by the emergence of fatty streaks harboring distinct lipids, peroxidation by-products, and infiltrating macrophages within the fetal aorta. Concurrently, the coronary arteries exhibit augmented Intima-Media Thickness (IMT), setting the stage for future vascular pathology. As the individual matures, the evolution of fatty streaks escalates, with select lesions evolving into more advanced atherosclerotic lesions (Cantin *et al*., 2021). The confluence of conventional risk factors exacerbating vascular inflammation and plaque instability propels the relentless progression of atherosclerosis post-initiation (Boroń *et al*., 2022). To conduct a comprehensive review titled "Signs of predisposition to atherosclerosis in fetal development," a systematic search strategy was employed to identify relevant studies investigating markers of predisposition to atherosclerosis during fetal development. The following databases were searched for articles published from inception to September 2021: PubMed, Embase, Web of Science, and Scopus.

Keywords and Medical Subject Headings (MeSH) terms used in the search strategy included "fetal development," "atherosclerosis," "prenatal programming," "genetic factors," "maternal influences," "low birth weight," "cardiovascular risks," "endothelial dysfunction," "mitochondrial dysfunction," "oxidative stress," and "epigenetic modifications."

The inclusion criteria encompassed original research articles, systematic reviews, meta-analyses, and observational studies investigating the association between fetal developmental factors and predisposition to atherosclerosis. Studies focusing on genetic and epigenetic determinants of cardiovascular health, maternal influences on fetal programming, and the impact of prenatal environment on cardiovascular outcomes were considered for review.

Interconnections between different mechanisms in the context of fetal predisposition to atherosclerosis are intricate and involve a complex interplay of genetic, epigenetic, and environmental factors. Genetic predispositions significantly influence an individual's susceptibility to atherosclerosis by impacting processes like lipid metabolism, inflammation, and vascular health. These genetic variations can interact with epigenetic modifications, which can regulate gene expression without altering DNA sequences, to influence the expression of genes involved in atherosclerosis development.

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNAs, can be influenced by environmental exposures during fetal development, shaping the expression of genes crucial for atherosclerosis pathways. For instance, maternal undernourishment or exposure to oxidative stress during pregnancy can induce epigenetic changes that enhance the risk of cardiovascular disease in offspring.

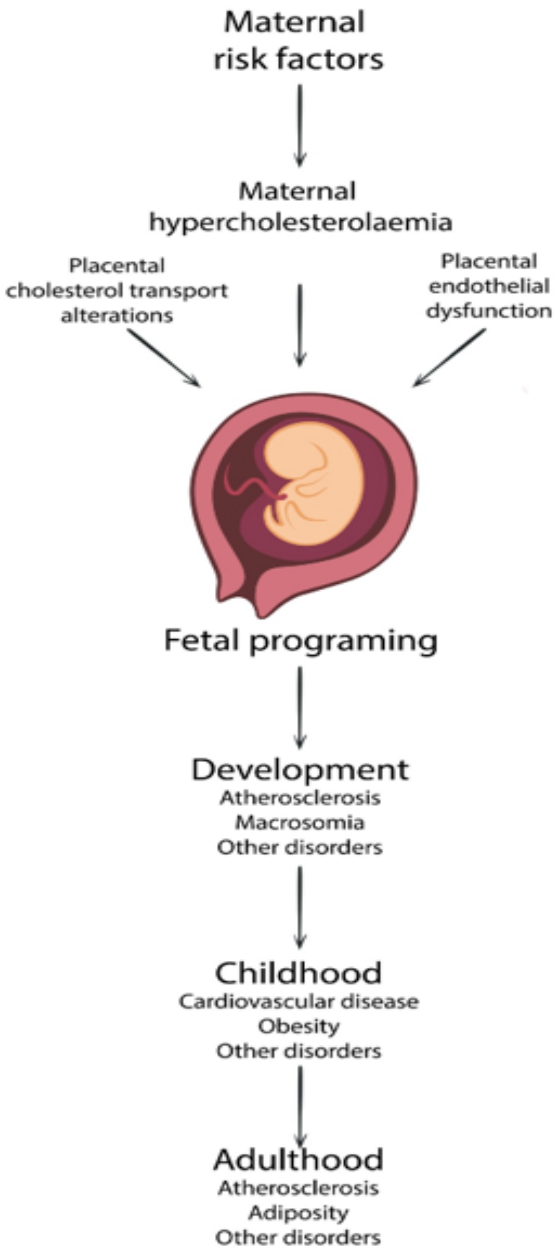

Fig. 1: Fetal programming and its consequences through the lifetime

Environmental factors, such as maternal diet, exposure to toxins, and socio-economic conditions, play pivotal roles in fetal programming and subsequent cardiovascular

health outcomes. Conditions such as high maternal cholesterol or obesity can expose the developing fetus to atherogenic environments, potentially amplifying the risk of metabolic dysfunction and atherosclerosis in later life. These environmental factors work in concert with genetic and epigenetic pathways to modulate the risk of atherosclerotic cardiovascular disease.

Intrauterine Growth Restriction (IUGR), characterized by low birth weight, is associated with impaired fetal development and an increased risk of cardiovascular disease in adulthood. IUGR can result from a mix of genetic, epigenetic, and environmental factors that disrupt normal fetal growth processes. This interplay can lead to altered vascular development and function, laying the groundwork for cardiovascular complications later in life.

By comprehensively understanding the connections between genetic, epigenetic, and environmental factors in fetal programming for atherosclerosis, researchers and healthcare providers can gain valuable insights into the mechanisms driving ASCVD susceptibility. This holistic approach sets the stage for targeted interventions that address multiple facets of atherosclerosis development, from early genetic screening to lifestyle modifications aimed at reducing environmental risk factors. Embracing this interconnected perspective enhances our capacity to prevent and manage cardiovascular disease from the earliest stages of life.

The Role of Programming in Vascular Development

Several researchers have proposed that developmental programming may play a part in atherogenesis. Humans demonstrate a connection between cholesterol levels in the mother and the fetus in the first 26 weeks of pregnancy. Napoli *et al*. (1997) additionally showed that hyperlipidemic mothers' offspring had reduced regression of fatty streak lesions, compared to control groups. In a rabbit model of developmental atherosclerosis programming, administering vitamin E and cholestyramine to pregnant mothers was found to lower the prevalence of atherosclerosis in the grown litters, resulting in levels similar to those in animals born to mothers with normal cholesterol levels. Introducing a mouse model could greatly aid in studying the impacts of fetal programming, along with its main mechanisms and potential prevention methods (Fan *et al*., 2015).

Cheung *et al*. (2004) found evidence that young people whose Weight at Birth (BW) was below the tenth percentile for their gestational stage and who were born prematurely, are more susceptible to Cardiovascular (CV) risks such as hypertension and elevated systemic arterial stiffness compared to those with normal BW (Cheung *et al*., 2004). Brodszki *et al*. described dissimilarities in endothelial function and blood pressure in twins of eight years of age born in pregnancy with twin growth discordance (Brodszki *et al*., 2008). Oren *et al*. (2003) reported that young people born in the lowest BW quartile had the highest BMI and carotid IMT when they were between the ages of 27 and 30, raising their risk of atherosclerosis (Oren *et al*., 2003).

These investigations deduce that the development of atherosclerosis is already in babyhood, several decades before symptomatic cardiovascular disease. CIMT increase wall thickness is presumably one of the initial changes that lead to atherosclerosis since it emerges in the coronary arteries of neonates. This thickening is frequently observed at the start of the left main coronary artery and left anterior descending artery, which is the same location where atherosclerosis becomes noticeable later in life (Hong, 2010). The arterial media beneath substantial intimal thickening is meager, comparable to the thin media beneath atherosclerotic plaques. These alterations are more conspicuous in boys than in girls and the genetic factors behind Coronary Heart Disease (CHD) in high-risk groups are likely to forecast the level of IMT in infants. Recent studies demonstrated that newborns with intrauterine growth restriction have an amplified aortic wall thickness in contrast to infants with normal BW (Bucciarelli *et al*., 2002).

There is proof of endothelial dysfunction of arteries in full-term newborns, children, and young people with low BW. In the late teens, decreased arterial compliance has been recorded with considerably smaller diameters of end-diastolic vessels. Consequently, inadequate vascular growth appears to continue in adolescence. This occurrence might be the cause of the elevated arterial stiffness detected in infants with Intrauterine Growth Restriction (IUGR). Increased arterial stiffness could potentially initiate the development of hypertension later in life (Kwon and Kim, 2017).

The Barker Hypothesis

During the 1980s, David J.P. Barker released a significant study that linked maternal undernourishment during pregnancy with a higher likelihood of their children developing atherosclerosis and ischemic cardiomyopathy as adults (Robinson, 2001). Barker's hypothesis was established on epidemiological information regarding the incidence of Coronary Heart Disease (CHD) in individuals whose BW had been documented. A statistically relevant association was observed between mortality rates from CHD and weight at birth. Individuals with low BW demonstrated increased rates of heart attack than those with normal BW (Argeri *et al*., 2020; Skilton, 2018). Research in numerous human diseases has verified Barker's hypothesis over time. Intrauterine growth restriction has been related to

vulnerability to terminal kidney disease in adult life. The scenario looks as follows:

(1) Undernourishment during pregnancy
(2) Adverse impact on kidney development
(3) Low glomerular number at birth
(4) Vascular impairments in middle and small renal arteries
(5) Glomerulosclerosis
(6) End-stage renal disease

Remarkably, recent years have seen various studies providing a better comprehension of the fundamental pathways that associate Low Birth Weight (LBW) with an increased risk of CVD (Wissler and Strong, 1998; Nasioudis *et al*., 2018).

Low Birth Weight and Atherosclerosis

As per Barker's theory, understanding low BW can assist in identifying a subset of young/adult individuals who seem healthy but are at a greater risk of developing serious atherosclerosis. Nonetheless, an unanswered question is: What is the connection between decreased BW and the serious progression of atherosclerosis? The initial response pertains to the biological implications of low birth weight. 2.5 kg Low (BW) in full-term newborns has been identified as a strong surrogate marker for intrauterine growth restriction and a powerful predictor of pathologic manifestations in the future (Li *et al*., 2017). LBW may also be linked to preterm birth, which is closely related to the deficient development of multiple organs, particularly the brain, kidneys, and lungs. According to the Developmental Origins of Health and Disease (DOHaD) theory, LBW may be considered the "first hit" (Ducsay *et al*., 2018). LBW may result from epigenetic factors arising during pregnancy and may predispose an individual to develop CVD at a later age. Deleterious effects of various environmental factors after birth, such as a high-in-cholesterol diet, maybe the "second hit." The latter is necessary for the disease's clinical manifestation, resulting in an additive model in which a combination of predisposition and external factors leads to a disease (Goodfellow *et al*., 1998). Goodfellow *et al*. (1998) research may elucidate the connection between intrauterine growth restriction and LBW newborns' predisposition to develop arterial atherosclerosis at a later age (Franco *et al*., 2006). Recognizing that low birth weight is linked with high blood pressure and ischemic cardiomyopathy, a condition known as the "small baby syndrome", the authors hypothesized that in LBW individuals' atherosclerotic plaque formation may result from endothelial dysfunction (Martin *et al*., 2000). To test this theory, Goodfellow and colleagues utilized ultrasound "wall-tracking" to measure Flow-Mediated brachial artery Dilation (FMD) in low (<2.5 kg) and normal (3.0-3.8 kg) BW individuals. Low BW children demonstrated impaired FMD compared to the normal BW group, which suggests that endothelial dysfunction is the main implication of fetal undernourishment, leading to the development of small baby syndrome at a later age (Engan *et al*., 2021). Later research on the low BW impact on CVD risk in later life confirmed the connection of reduced BW with endothelial dysfunction and decreased FMD in young people. The authors argue that low birth weight needs to be taken into account as an essential component in the emergence and development of atherosclerosis at a later age (Stamerra *et al*., 2022).

Mitochondrial Dysfunction and Impaired Fetal Growth

Increased production of Reactive Oxygen Species (ROS) by mitochondria and their dysfunction are linked with cardiovascular disease. The overproduction of ROS causes damage to proteins, lipids, nucleic acids, and mtDNA, leading to alterations in mitochondrial function. Common atherogenic risk factors, like smoking, elevated cholesterol levels, and obesity, are correlated with enhanced mtDNA impairment. Increased ROS production by mitochondria is related to the dysfunction and apoptosis of endothelial cells and proliferation-apoptosis of Vascular Smooth Muscle Cells (VSMCs) leading to the progression of atherosclerosis. Consequently, impaired mitochondrial function appears to be associated with conventional proatherogenic risk factors (Aouache *et al*., 2018).

Gestation is characterized by Oxidative Stress (OS). Rapid production of ROS by various placental cells might be caused by elevated metabolism in the placenta and decreased scavenging ability of antioxidants. Patients with preeclampsia demonstrated increased levels of OS markers in the placenta (Vaka *et al*., 2018). The overproduction of ROS by placental mitochondria might be discharged into the fetal blood, damaging vascular mtDNA. Considerable accumulation of ROS increases vulnerability to the opening of the mitochondrial Permeability Transition Pore (PTP) in the vasculature, which has been demonstrated to promote ROS formation in cardiomyocytes. Therefore, mitochondrial PTP opening and excessive ROS release may be involved in a vicious cycle and constitute a pathway leading to vessel damage by affecting mitochondria in the endothelium. At the same time, atherogenic PTP properties have not yet been definitely established (Ganu *et al*., 2012).

These data imply potential harm and alterations to fetal vascular mitochondria that could happen in the uterus as a result of the intrauterine milieu. The passing down of traits across generations can be attributed to either the genetic makeup or the influence of the placental environment on the genome, causing epigenetic modifications. The precise extent of each factor's contribution is not yet well comprehended and is extremely challenging to investigate (Steven *et al*., 2019).

MtDNA and Atherosclerosis

Oxidative pressure and persistent inflammation are currently acknowledged as risk factors and both play a vital role in the development of endothelial cell malfunction and, eventually, atherosclerosis. Circulating indicators of endothelial cell stress can be quickly, in a few weeks, restored to normal levels by drugs that reduce blood pressure, lower glucose levels, and decrease lipid concentrations, presumably in the neonatal phase, though this has not yet been verified (White *et al*., 2022). Remedial treatments do not lessen arterial harm. Mitochondrial DNA impairments may serve as the connection between early-life poor nutrition and illness in adult life and could lead to the "thrifty" phenotype as a result of the programming effect. Additional research is required to gain a better comprehension of mitochondrial dysfunction processes. Both epigenetic and genomic techniques are required to assess the gene-specific consequences of antenatal malnourishment in regulating mtDNA (Pusukuru *et al*., 2016; Pitz Jacobsen and Fjeldstad, 2021).

The Materno/Fetal Cholesterol Hypothesis

Based on human autopsy research and findings in animal models, it is evident that maternal hyperlipidemia and the resulting OS can be atherogenic for the fetus and after birth. Nevertheless, it has yet to be determined whether a lipid disorder in the mother actually leads to hyperlipidemia in the fetus and what cholesterol figures in the fetus should be considered atherogenic (Woollett, 2011). The results of animal studies demonstrate that in spite of the fact that the placenta is impenetrable to large-size lipoprotein particles and cholesterol required by the fetus is chiefly generated by the placenta or the fetus, during the 2nd pregnancy trimester cholesterol in the fetus is regulated by the levels of sterols in the mother. In humans, cholesterol levels in 5-6-month-old fetuses correspond to maternal levels (Maymunah *et al*., 2014). It is thus probable that in the case of high cholesterol concentrations in the mother, the fetus will have higher cholesterol figures than the fetus of a mother with normal cholesterol. The limited number of very premature fetuses studied so far is insufficient to either prove or contradict this hypothesis. Additionally, it is difficult to compare fetuses of different ages because there is a linear reduction of fetal cholesterol with increasing age and, besides, after the sixth month, fetal cholesterol is no longer associated with maternal cholesterol (Jayalekshmi and Ramachandran, 2021; Cantin *et al*., 2021).

It is also difficult to define fetal hypercholesterolemia. Cholesterol figures for all 5-6 months old human fetuses were notably elevated, including fetuses of mothers with normal cholesterol levels. This suggests that the elevated levels may be a physiological response to the rapidly developing fetus's greater demand for cholesterol (Napoli *et al*., 1997). However, it is possible that further increases in cholesterol levels could lead to lipid retention in the vessel intima, potentially promoting plaque formation. The presence of fatty streaks in fetuses of non-cholesterolemic mothers supports this cholesterol. However, it is also possible that further increases in cholesterol levels could lead to a buildup of lipids in the arterial wall, potentially promoting lesion development. The occurrence of fatty streaks in fetuses of mothers with normal cholesterol levels supports this supposition (Napoli *et al*., 2000).

When maternal hypercholesterolemia occurs during gestation, elevated maternal lipid peroxidation is often seen. This, in turn, can cause the direct or indirect rise of oxidative end products in the fetus and lead to the accumulation of lipids in the aorta of the fetus (Palinski and Napoli, 2002). While the causal relationship between maternal hyperlipidemia and the outset of atherosclerosis in the fetus has been proved, as well as the connection between cholesterol metabolism in the mother and the fetus during part of pregnancy, the mechanism mediating this effect is unknown. The process may be enhanced by unmediated maternal-fetal transit of oxidized fatty acids and the harmful effects of growing OS on functions of the placenta (Marchio *et al*., 2019).

According to *in vitro* studies, the oxidized LDL buildup in and increased oxidative stress in plasma afflict various signaling pathways susceptible to oxidation in the fetal artery wall. Consequently, these pathways moderate regulatory gene expression influencing the functioning of the endothelium and promoting plaque formation (Bartels *et al*., 2012). In this way, they may impact the molecular memory in the artery wall so that in the future, atherosclerosis may develop as a reaction to traditional risk factors.

The above-mentioned indexes are assumed to differ considerably throughout pregnancy. Cholesterol levels rise during the last trimester, in women with normal cholesterol as well and research shows that this rise is significantly higher in women with elevated cholesterol levels. Functions and penetrability of the placenta may also vary over time, which can also be due to quick growth (Quehenberger *et al*., 2011). Moreover, it has been

verified that cholesterol in the fetus is elevated in the second trimester and drops progressively during the third trimester. As a result, it is possible that the pathogenic impact of the mother's hypercholesterolemia is not stable throughout gestation, but rather that there may be a window of susceptibility during which elevated fetal and maternal cholesterol and oxidative stress co-occur with the vulnerability of the artery wall, still immature at this time (Keverne, 2015).

Predisposition to hypercholesterolemia and potentially to other atherogenic factors after birth is increased by lesions in the fetal artery triggered by maternal hyperlipidemia or the subsequent formation of fatty streaks. This may be partly influenced by in utero programming, which is the continuous interaction of fetal genetics and environment. For the purposes of this analysis, the terms 'in utero programming' and 'imprinting' are used broadly and refer to mechanisms that happen throughout the prenatal period and permanently modify gene regulation or otherwise change the cellular activities stimulating the onset and development of atherosclerosis (Milutinović *et al*., 2020). It is in no way suggested that these mechanisms are similar to maternal imprinting. Since arteries and their affections are much smaller in fetuses than those in children and grown-ups, from a quantitative standpoint it is dubious that fetal affections decisively contribute to atherosclerosis at older ages. Nevertheless, subtle alterations in the artery wall structure, like cellular and extracellular matrix components, may be sustained throughout growth and promote atherogenesis after birth. In humans, it has not yet been determined whether in utero programming is adequate to stimulate atherogenesis without atherogenic risk factors after birth (Lee *et al*., 2017).

While animal models have unambiguously demonstrated that elevated cholesterol levels in the mother trigger plaque development in the fetus and accelerate atherosclerosis after birth, it is unclear to what extent they stimulate these occurrences in humans. Certainly, fetuses and children of mothers with chronic or temporally occurring hypercholesterolemia are genetically to a greater extent predisposed to develop atherosclerotic plaques (Poznyak *et al*., 2020).

Another element proposed to impact subsequent atherosclerosis is neonatal gene imprinting. Research suggests that even short-term exposure in the neonatal phase has a long-term effect. Specifically, cholestyramine treatment in animal models to promote cholesterol degradation resulted in considerable protection against diet-induced cholesterol excess in adult life. In the pre-treated animals, stimulation with a high in cholesterol diet raised the expression and activity of cholesterol 7 alpha-hydroxylase (Giammanco *et al*., 2020; Wang *et al*., 2020). Evidence has been reported of hormonal imprinting in newly-born rats treated with thyroid-stimulating hormone. As demonstrated for the Mas proto-oncogene, parental imprinting also takes place during certain phases of fetus development. There is multiple but contentious evidence concerning the impact of diet during lactation and early childhood. While not directly relevant here, the probability that dietary differences affect later atherogenesis highlights the importance of not confusing the design of studies in experimental models of hypercholesterolemic diets to mothers or newborns during the administration of lactation (Schipper and de Ferranti, 2022).

During puberty and in adult life, atherogenesis is primarily influenced by traditional risk factors and develops into an exceedingly intricate process. Currently, the rapid development of atherosclerosis in the human progeny of mothers with hypercholesterolemia has been proven only for children and teenagers (Goharkhay *et al*., 2008). Given the dramatic difference seen throughout childhood and the fact that lesion sizes diverged linearly with increasing age, it is tempting to extrapolate results to adulthood. However, as argued previously, it cannot be excluded that the presence of marked hypercholesterolemia and other risk factors attenuate the effect of fetal programming. Obviously, it is necessary to assess adult and elderly people to find out whether the progeny of mothers with hyperlipidemia demonstrate an increased frequency of clinical signs and symptoms of atherosclerotic conditions, or higher mortality associated with atherosclerosis (Sharami *et al*., 2019).

Research exploring the impact of maternal hyperlipidemia, prenatal or postnatal imprinting, and future risk factors on the development of atherosclerosis from prenatal period to elderly age faces challenges in determining the optimal method for evaluating the progression rate of this disease. A linear development of the disease has been reported. In children, there was indeed a linear rise observed in both the size of individual lesion sites and the collective area of all lesions, adjusted for the aortic size (Humphrey and Taylor, 2008). This adjustment was necessary to distinguish between lesion growth proportionate to aorta enlargement and hastened atherogenesis, which is helpful when contrasting arteries of varying diameters. However, it is essential to take into account that absolute lesion sites grow exponentially with time (De Nigris *et al*., 2018).

Following the prior observation that in humans, the mother's hypercholesterolemia during gestation is linked with early atherosclerotic lesions in the fetus's aortas, an investigation measured the impact of total cholesterol and LDL cholesterol levels in maternal plasma on the size of aortic lesions in the fetus. Furthermore, since there is a growing understanding that epigenetics are a central mechanism in fetal programming with likely linked health outcomes in adult life, the aim of the study was to

comprehend whether increasing levels of maternal plasma cholesterol caused epigenetic alterations in the aortas of the fetus (Schiano *et al*., 2022). Besides, it was discovered that only SREBP2 methylation was correlated with the mother's total cholesterol and LDL-cholesterol levels and the size of the fetal aortic lesions in fetal aortas. At the same time, regression analysis showed that SREBP2 methylation is independently linked with maternal cholesterolemia, but its association with fetal lesion site is not significant when maternal cholesterol level is considered as a confounding factor (Soler-Botija *et al*., 2019). In terms of other epigenetic changes, a correlation was noticed between raised $H3K27m^3$ and an increase in the size of fetal lesion areas. Thus, these results support the idea that maternal cholesterol levels cause epigenetic changes in the fetus and suggest that the initiation of atherosclerotic lesions in fetal aortas may be linked to these epigenetic changes. Furthermore, elevated maternal cholesterol is connected not only with higher SREBP2 methylation but also with a decrease of its mRNA in fetal aortas. Therefore, the epigenetic changes noticed in fetal aortas may have a functional role. Besides, the alterations in methylation and the decreased SREBP2 expression in cholesterol-treated HAECs make it possible to conclude that extracellular cholesterol can impact the SREBP2 epigenetic and transcriptional regulation in fetal aortas (Leduc *et al*., 2010).

Conclusion

In this study, we have explored key markers that indicate a heightened risk of cardiovascular disease in individuals with a fetal predisposition to atherosclerosis. From genetic and epigenetic factors to influences such as maternal undernourishment, hyperlipidemia, and exposure to oxidative stress during prenatal and neonatal stages, we have gained valuable insights into the intricate pathways that contribute to Atherosclerotic Cardiovascular Disease (ASCVD) susceptibility.

These identified markers provide a basis for proactive risk assessment and enhanced diagnostic precision in predicting ASCVD. They offer a foundation for tailored interventions aimed at at-risk populations, potentially revolutionizing early screening and prevention strategies. By leveraging these markers, we can move towards personalized medicine and preemptive measures to combat the onset and progression of atherosclerosis-related cardiovascular conditions.

Furthermore, an expert viewpoint on the most significant or promising findings suggests that early identification of markers such as low birth weight and maternal influences can significantly impact the future cardiovascular health of individuals. These findings underscore the importance of early screening and intervention to mitigate the long-term risks associated with fetal atherosclerosis predisposition.

Despite the strengths of this study, including its comprehensive exploration of genetic, epigenetic, and environmental factors, there are notable limitations to consider. These include the potential for publication bias leading to an overrepresentation of positive findings, as well as the risk of selection bias due to reliance on existing literature. Additionally, the study's timeframe limitation and potential lack of generalizability to broader populations may impact the overall applicability of the findings.

By integrating these identified markers into clinical practice, healthcare providers can enhance early screening efforts and implement targeted interventions for individuals at heightened risk. This proactive approach not only improves risk assessment accuracy but also empowers healthcare professionals to intervene early in the trajectory of cardiovascular disease development, ultimately benefiting the cardiovascular well-being of individuals from a young age.

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Author's Contributions

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Alexander Nikolaevich Orekhov: Conceptualization.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

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