

ROLE OF LIPID PROFILE IN CORD BLOOD AND ITS INFLUENCE ON NEONATAL HEALTH - A REVIEW

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ABSTRACT

Cord blood Lipid profiles play a crucial role in early development and can influence long-term health outcome of neonates and infants. The literature clearly shows that cord blood lipid profile may involve lifelong changes in the metabolic functions of individual. The adverse effects with high concentrations of cord blood lipid profile include stroke, kidney failure, coronary heart disease, atherosclerosis and leads to cardiovascular disease in the later life. This review article aims to identify potential links between lipid levels at birth and the likelihood of cardiovascular issues and other complications in neonatal life. This article explores the role of lipids, complications of cord lipids in association with different systems of the body of neonates across different gestational age's preterm, term, and late-term while investigating their correlation with birth weight.

INTRODUCTION

Babies born prematurely may have a higher chance of developing heart problems later in life because they have a lot of certain fats and proteins in their blood. Dyslipidemia can lead to serious health problems like stroke kidney failure heart disease and atherosclerosis.^[1] Fetal malnutrition and being born early can change the levels of different types of lipoproteins in cord blood.^[2] Infants born prematurely with high levels of certain fats and proteins in their blood as well as low birth weight may be more likely to develop heart problems later in life.^[3] In preterm babies the levels of certain enzymes like lipoprotein lipase hepatic lipase and lecithin-cholesterol acyltransferase may go down which could lead to higher levels of lipoproteins in their bodies.^[4] A research study in Spain discovered that babies born prematurely have less HDL-cholesterol in their cord blood compared to babies born full-term, On the other hand preterm babies have higher levels of VLDL in their blood.^[5] In Japan a study found that premature newborns have higher levels of certain types of cholesterol in their cord blood compared to full-term newborns.^[6] Another research conducted by donegá and colleagues. Preterm babies were found to have more total cholesterol LDL-C, HDL-C and apolipoprotein-B compared to full-term babies. However their triglyceride levels were lower.^[7] Moreover a study done in Iran found that baby girls had more total cholesterol and HDL-C than baby

boys.^[8] Moreover a new research found that babies with different weights at birth have different types of fats in their bodies when they are born. For example babies who are small for their age when they are born tend to have lower levels of certain types of cholesterol and higher levels of triglycerides in their blood compared to babies who are born at a normal weight for their age. However newborn babies who are bigger than usual for their age when they were born had slightly lower amounts of TG.^[9] The changes in fat levels in babies with different birth weights may affect how they grow and their chances of becoming overweight as children.

Sources of fetal cholesterol: During gestation, a significant amount of cholesterol is accumulated. A newborn weighing approximately 4.5 kg requires around 12 g of cholesterol. The concentrations of cholesterol in the liver and peripheral tissues are approximately 2.2 mg cholesterol/g, while in neuronal tissues; it is approximately 8 mg cholesterol/g.^[10] Cholesterol is important for maintaining structural integrity and also in various signaling events and for precursor of steroid hormone. Signaling processes rely on cholesterol are diverse, including its presence in special regions of the membranes called lipid rafts, which allow signaling proteins to aggregate and bind scaffold proteins, as well as the formation of endosomes.^[11,12] Additionally, cholesterol forms unique covalent bonds with Hedgehog (HH) and Smoothened,^[13] and can be converted into active oxysterols.^[14] The fetus

acquires cholesterol from two primary sources: de novo synthesis and maternal circulation. Similar to adults, the regulation of lipoprotein and cholesterol levels in the fetus is influenced by the equilibrium between cholesterol entering and exiting the circulation. However, in contrast to adults in a steady state, the influx and efflux of cholesterol in the fetal plasma are not balanced. The observed lower cholesterol levels in fetal plasma may indicate either a reduced influx of cholesterol or an increased efflux.

Low-Density Lipoprotein (LDL): The synthesis of LDL-C commences with liver producing, releasing VLDL that subsequently converts to LDL within the bloodstream. Given that the fetal liver is not fully matured,^[15] lipoprotein production and secretion may be restricted, which could account for the diminished levels of fetal LDL-C. Furthermore, the low cholesterol levels in fetal circulation result from increased uptake of lipoprotein and cholesterol by LDL receptors.

High Density Lipoprotein (HDL): On the other hand, levels of HDL-C are noticeably higher in fetuses. HDL is made in the blood unlike VLDL and LDL which need the fetal liver to be made. HDL is made by taking cholesterol out of cells using APOA1 or APOE which don't have a lot of fat. Then the cholesterol gets changed into a different form esterified by lecithin cholesterol acyl transferase by LCAT. These things all happen in the blood of a developing baby.^[16] In the US, babies are mostly fed with three types of food in their first few months: breast/Mother milk cow milk formula and soy milk formula. These different food choices have varying effects on cholesterol balance in the body. Factors like the amount of cholesterol the ratio of polyunsaturated to saturated fats protein content phytoestrogen levels and the special hormones found in breast milk can all play a role. Furthermore new parts of milk like miRNAs prebiotics and extracellular vesicles might also be involved in metabolic functions.^[17] The fetus acquires cholesterol from two primary sources: de novo synthesis and maternal circulation. During this critical growth period, neonates, much like fetuses, have a substantial demand for cholesterol to support growth, energy production, and normal cellular functions. Infants who are breastfed receive greater amounts of lipids/cholesterol than who consume commercial feeds. Mother/Breast milk typically contains around 10-15mg/dl of cholesterol, whereas cow milk formula provide only 1-4 mg/dl, and soy-based formulas contain no cholesterol. Nevertheless, soy-based formulas do include phytosterols, which are plant sterols that inhibit cholesterol absorption.^[18] Consequently, it is not unexpected that breastfed infants exhibit high cholesterol levels when compared with the formula-fed counterparts.^[19,20] In contrast to fetuses, rapidly growing neonates tend to suppress the rates of sterol synthesis.^[21] A condition exceeds an arbitrary normal limit of cholesterol, triglycerides and its lipoproteins in plasma called as

hyperlipidemia. Hyper lipidemia leads to several complications. [Figure 1]

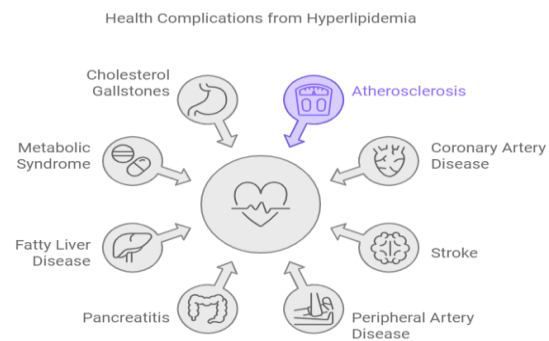


Figure 1: Complications of hyperlipidemia (HLP)

1. Cord blood lipid profiles and its role in cardiac diseases

Cardiovascular disease (CVD) is responsible for around 17.9 million deaths each year, ranking it as the leading cause of death globally. In recent years, extensive research has revealed numerous risk factors associated with CVD, encompassing lifestyle choices like smoking and obesity, as well as genetic predispositions such as familial hypercholesterolemia (FH) and elevated lipoprotein(a) (Lp (a)). Cardiovascular diseases include various disorders of the heart and blood vessels, such as coronary heart disease, cerebrovascular disease, and rheumatic heart disease, among others.^[22] Atherosclerosis starts in childhood when fatty streaks build up in the inner layer of the arteries. These streaks contain fat-filled cells called foam cells and T lymphocytes. These fatty streaks might get worse or they might get better. In some people fat buildup increases and can form a hard plaque when the fat is covered by a fibrous cap. There are stages of atherosclerosis between the fatty streak and fibrous plaque that can't be seen just by looking at them. Over time fibrous plaques get bigger and go through changes like calcification, hemorrhage, ulceration, rupture, and thrombosis. Thrombotic occlusion caused by these processes can lead to serious health conditions such as heart attack stroke or tissue death (gangrene) depending on which artery is affected. [Figure 2]

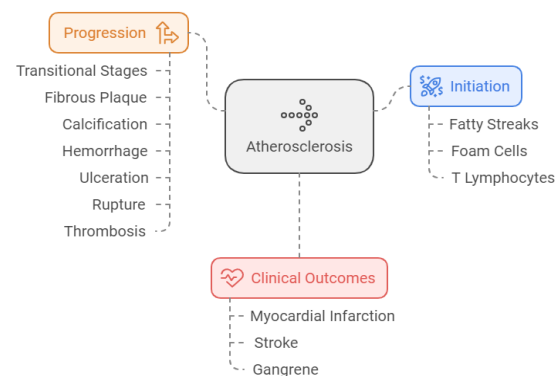


Figure 2: Natural history of atherosclerosis

Studies done on kids and young adults who passed away from non-heart-related reasons have shown that atherosclerosis starts early in life. Atherosclerosis-induced plaque can also impede blood flow to arteries supplying distant organs like the legs and feet, giving rise to peripheral artery disease. Initially, patients may experience symptoms such as limping and intermittent pain, requiring them to rest before resuming movement. Over time, the distance they can walk gradually decreases, their feet feel cold to the touch, sensation diminishes, and the pulse becomes undetectable. In severe cases, necrosis may occur due to insufficient blood supply, sometimes necessitating amputation.^[23,24]

Using ultrasound to measure the thickness of the carotid artery's inner lining can help predict the likelihood of having a heart attack or dying in the future. This means that cIMT can help show if someone has atherosclerosis even if they are young and don't show any signs of heart disease yet. In the newest *Circulation* magazine Koskinen and his team use information from the International Childhood Cardiovascular Cohort (i3C) group to find signs in childhood that are connected to high cIMT in adulthood. [Figure 3]

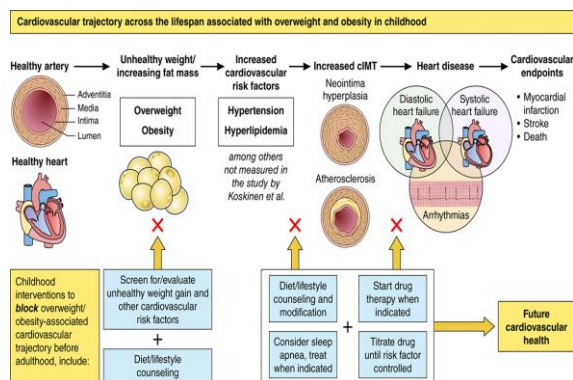


Figure 3^[25]: The relationship between childhood overweight and obesity and cardiovascular health throughout life

This complete set of data contains 23.4 years study where researchers studied 2893 young people aged twelve to eighteen in four different studies across three continents. The studies took place in various countries around the world. The information from i3C shows that being obese having high blood pressure and having unhealthy cholesterol levels during childhood can predict having a thickened carotid artery as an adult.^[25]

2. Cord blood lipid profiles and its role in endocrine system

Several endocrine glands release hormones that signal the body to utilize cholesterol, such as estrogen, testosterone, and cortisol.^[26] Therefore, hormone levels in the bloodstream also impact cholesterol levels. Maternal hormones are most important in supporting fetal growth and development. Dyslipidemia is a common problem in endocrine clinics and is frequently seen in people with type 2 diabetes and obesity.^[27] In people with

diabetes there is a specific pattern of lipid phenotype in the blood. This includes low levels of HDL-C high levels of triglycerides and small dense LDL-C.^[28] Lipid problems are found in both metabolic syndrome and polycystic ovary syndrome (PCOS). PCOS is connected to higher levels of bad cholesterol (LDL) triglycerides and Lp(a) and lower levels of good cholesterol (HDL). Obesity metabolic syndrome and diabetes can cause big changes in how fat is stored in the body especially leading to more visceral and ectopic fat. This condition called adiposopathy is very important because it changes how certain chemicals like adipokins are released in the body causing long-lasting swelling and harmful fat build-up leading to chronic inflammation and lipotoxicity.^[29]

3. Cord blood lipid profiles and its role in nervous system

Cholesterol is very important for the human brain, it makes up about 25% of the body's total cholesterol supply. It plays crucial for growth, protection of nerve cells and enabling the brain to function effectively and regulate various life activities. While the brain requires a certain amount of cholesterol for optimal functioning, excessive levels can have detrimental effects. Excess cholesterol can lead to the formation of plaque in the artery walls, increasing the risk of stroke and ischemic stroke. These conditions can result in memory loss, reduced mobility, difficulty swallowing, difficulty speaking, and other impairments. Furthermore, various studies have been established association between high blood cholesterol levels, memory loss as well as cognitive function decline. This association is attributed to the acceleration of beta-amyloid plaque formation, which causes brain damage in individuals with Alzheimer's disease. The unique nature of the brain presents challenges in sampling due to progressive changes, such as myelination, the aging process. Additionally, the rapid turnover rates of certain lipids and the presence of diverse cell types contribute to these sampling difficulties. Consequently, major lipid composition in the brain undergoes changes during the aging process. (Fig.4) For instance, At birth phosphatidylcholine (PC) is the most common lipid making up 50% of lipids. However as a person grows older the amount of PC decreases while sphingomyelin (SM) increases from 2% to 15% by age 8. This change is related to the role of sphingomyelin in the myelin sheath and mature membranes.^[30]

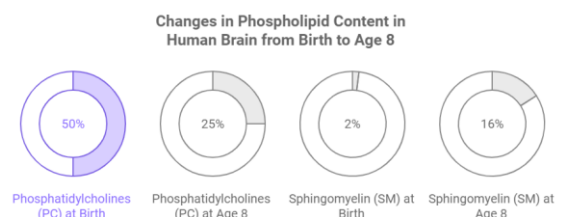


Figure 4: The phospholipids content of control human brain with age

4. Cord blood lipid profiles and its role in metabolic disorders

Umbilical cord blood metabolite concentrations serve as crucial markers that reflect the intrauterine metabolic condition of fetuses. New research has found that certain factors related to heart health and metabolism in the umbilical cord blood are connected to how a baby grows in the womb and their weight at birth. In the later stages of pregnancy there is a connection between how much a baby weighs and the levels of insulin in the body. Additionally the weight of the baby before birth is linked to lower levels of triglycerides (TG) and higher levels of good cholesterol (HDL-C) in the mother's blood in the last three months of pregnancy.^[31] Umbilical cord leptin a hormone that helps control lipid metabolism via negative feedback mechanism and has been linked to birth weight and body mass index in newborns.^[32]

DISCUSSION

Many studies have shown that high cholesterol levels in umbilical cord blood can indicate a risk for heart disease. In 1980 a British doctor and scientist named David James Purslove Barker suggested the Barker Hypothesis while working at the University of Southampton. This idea says that the health of a baby before and after birth can affect how their body works and may lead to long-term health issues as they grow older.^[33,34] Barker and his team suggested that being born small could make people more likely to have heart problems when they grow up.^[35] An expert studied data from Hertfordshire and found that people who were born heavier had lower chances of dying from heart diseases over a period of 60 years. This discovery supports the idea that health problems in adulthood can be linked back to poor conditions in the womb like not getting enough nutrients. These conditions can change how the body works and

increase the risk of heart disease later in life.^[36] Studies have shown that men and women who were born with low birth weights are more likely to develop heart disease. Furthermore babies born prematurely may not have had enough time to build up energy reserves before birth. As a result they often need to use their own stored endogenous reserves energy and activating lipid metabolism for processing fats to create energy and promote gluconeogenesis to support their growth. The lasting effects of these changes in metabolism lead to more people having heart diseases high blood pressure and type 2 diabetes. This is also influenced by factors from the mother like being overweight having high blood pressure and having diabetes.^[37] According to research atherosclerosis begins slowly at a young age and progresses into adulthood. It could be helpful to check a baby's blood fats when they are born.^[38] A research study showed a strong connection between the types of food pregnant women eat and the substances found in their baby's cord blood. Eating lots of fish shellfish meat and potatoes during pregnancy can affect the health of the baby in both the short and long term.^[39] Some research has suggested that when pregnant mothers consume n-3 LC-PUFAs it could affect the baby's lipid profile and leptin signal while they are still developing in the womb.^[40] Maternal physical activity and exercise can help increase the levels of a beneficial substance called HDL-c in a newborn baby's cord blood.^[41] Exercising lightly in the early stages of pregnancy can help increase blood flow in the umbilical cord and improve how blood flows in the placenta. This can also help the baby's heart adjust better to the surroundings.^[42] Eating healthy foods like fruits vegetables dairy and eggs during pregnancy can help lower the chance of babies having heart problems. (Table-1) On the other hand following a vegetarian diet while pregnant may increase the risk of babies having heart issues.^[43]

Table 1^[43]: Dietary Patterns and Food Groups

Dietary Pattern	Food Groups
Prudent pattern	Red meats, White meats, Legumes, Vegetables, Snacks*, Dairy.
Vegetarian pattern	Cereals and tubers, Fruits, Vegetables, Nuts, snacks*, Legumes
Dairy and egg pattern	Dairy, eggs, nuts, beverages

Snacks* - include Chinese cold noodle, Chinese dessert, cake, instant noodles, dumpling, bread, rice crust, and biscuits

CONCLUSION

As per the review of the different articles we conclude that there is a clear association between the maternal dietary patterns, maternal physical activities and exercises. [Figure 5]

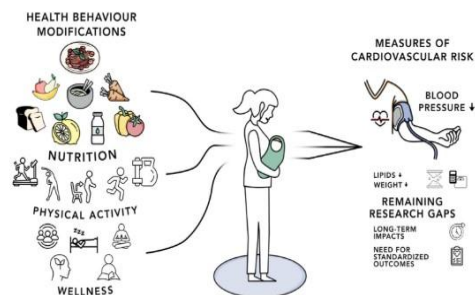


Figure 5^[45]: Healthy behavior modifications during pregnancy

During pregnancy that effects cord blood metabolites/lipids and likelihood of cardiovascular issues and other complications in neonatal life. Our information can assist researchers in designing new studies with more participants and for longer periods of time. More research is needed to understand how a mother's blood fats affect the growth and development of the baby. It is important to determine the ideal levels of healthy fats in the blood for pregnant women [The cord blood lipid profile data on 3157 newborns collected and is yet to be published]. The food that a pregnant woman eats can affect her blood fat levels which could in turn change the baby's body composition. Physical activity includes - Yoga: Physical postures (asana), breathing techniques and meditation, walking 30 minutes twice a day.^[44] It is already recommended for pregnant mothers. Finally we conclude that maintaining the healthy cord blood lipid profile of pregnant mothers throughout pregnancy is more important in decreasing the risk of cardiovascular diseases in the future and other diseases like coronary heart disease, stroke, kidney failure, and atherosclerosis of newborn babies.

Conflict of Interest: The authors have no conflicts of interest to declare.

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