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REVIEW

The relevance of cholesterol and triglycerides in pregnancy

Milos Milincic [1], Stefan Dugalic [1, 2], Miroslava Gojnic [1,2]

[1] Department of Gynecology and Obstetrics, University Clinical Centre of Serbia, Belgrade, Serbia
[2] University of Belgrade, Faculty of Medicine, Belgrade, Serbia

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Correspondence to:
Miloš Milinčić, University of Belgrade, Faculty of Medicine, Belgrade, Serbia, 8, Dr Subotića Street, 11000 Belgrade, Serbia, +381658720461
milosmilincic@gmail.com

Summary

Cholesterol participates in the construction of all body cells, steroid hormones, and bile acids. Its role in pregnancy is of key importance in the form of the synthesis of hormones without which conception and pregnancy would not be possible, and later in developing the physiological functions of the fetus as well. Triglycerides as the main energy substrate serve in the normal growth and development of the fetus. Normal reference values for lipid status in pregnancy have not been established yet. It has been proven that elevated, as well as reduced values of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) participate in pathological conditions of pregnancy – gestational diabetes mellitus, preeclampsia, macrosomia, restricted fetal growth, etc. The treatment of dyslipidemia is limited due to the lack of pharmacological studies on pregnant women, as well as the teratogenic effect of anti-lipid drugs. This review article deals with the effect of cholesterol and triglycerides on pregnancy, pregnancy outcomes, prenatal and postnatal effects on the fetus, as well as current and future treatment options.

Keywords: Pregnancy; Hypercholesterolemia in pregnancy; Dyslipidemia in pregnancy; LDL-C in pregnancy, TG in pregnancy.

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INTRODUCTION

Cholesterol takes part in the development of all cells and serves as a starting compound for the synthesis of steroid hormones and bile acids (1). Tissues use exogenous cholesterol (intake from food) and endogenous cholesterol (synthesized in tissues, primarily in the liver). Cholesterol ingested with food is resorbed into the epithelial cells of the small intestine, where it is packaged together with other lipids and proteins into chylomicrons (1). The protein part of chylomicrons and other lipoproteins is called apolipoprotein (APO). Chylomicrons travel from the intestines through the thoracic lymphatic duct into the bloodstream and to the liver (1). Cholesterol stored in the body is transported from the liver in the composition of VLDL-C lipoproteins to peripheral tissues. In plasma, cholesterol, like other lipids, is found primarily in the composition of lipoproteins, and to a lesser extent as free cholesterol bound to plasma proteins (2). Cholesterol is monitored in a routine laboratory analysis together with triglycerides as a factor in many diseases, primarily cardiovascular, metabolic and endocrine. Cholesterol is a precursor to steroid hormones critical to pregnancy, including estrogens, progesterone, androgens, corticosteroids, and vitamin D (1,2). Many of these hormones are produced by the placenta (3).

Triglycerides are the most abundant fats in the human diet because they are the main form of fat storage in plants and animals (1,2). They consist of glycerol that is esterified with three fatty acids. They are broken down by a series of lipases in the intestinal tract and then absorbed in the small intestine, where they have condensed again into triacylglycerols, which combine into lipoprotein particles - chylomicrons (which contain both cholesterol and liposoluble vitamins (1,2). Chylomicrons in the peripheral blood are broken down by lipoprotein lipase stimulated by insulin. When the triglyceride level increases after a meal, insulin is released, which additionally activates LPL and accelerates the release of fatty acids from TG by hydrolysis which are then stored in adipose tissue. The rest of the chylomicrons are transported to the liver and absorbed into hepatocytes (4).

Lipids in pregnancy

There is indisputable evidence that changes in lipid status occur during pregnancy. These changes are necessary for the normal growth and development of the fetus (5). During pregnancy, there is a physiological increase of 30-50% in triglycerides and total cholesterol in the plasma, especially in the second and third trimester. The reason for such a significant change in lipid status during pregnancy is found in changes in hormones such as estrogens, progesterone, HPL, and insulin, as well as altered general metabolism of the liver and fat tissue (5). In the first trimester, under the influence of insulin, cholesterol, and triglycerides increase based on increased lipid synthesis (lipogenesis) and inhibition of lipid degradation (lipolysis) (6). As pregnancy progresses and the fetus develops, more and more energy is needed to perform normal metabolic functions. For this reason, there is a shift of the mother's lipid metabolism towards increased lipolysis, compared to its inhibition during early pregnancy (7). The consequences of these changes lead to an increased deposition of lipids in adipose tissue during the first trimester, and in the second and third trimesters to a marked mobilization of lipids in the form of an increased level of free fatty acids, triglycerides and cholesterol, which will be delivered to the fetus via the placenta and serve it for general metabolic functions, and the synthesis of necessary steroid hormones (5,7).

Recommended reference values by WHO (World Health Organization) lipid profile in the normal population are as follows: total cholesterol <5.20, HDL-C >1.53, LDL-C <2.6, Triglycerides <1.69. When it comes to pregnant women, there are still no recommended values. The reason for this practice is the insufficiently researched influence of hyperlipidemia and hypercholesterolemia during normal pregnancy. Although the reference values of the lipid profile in pregnant women are not established, we can see the values obtained in the latest research. Wang et al. showed the values of TC, LDL-C, HDL-C, TG, and the TG/HDL-C ratio in a large population of pregnant women of Asian origin, as well as the changes in these values through the trimesters of pregnancy. The values of TC (from 4.04 to 6.16 mmol/L), HDL-C (from 1.42 to 1.71 mmol/L), LDL-C (from 2.15 to 3.30 mmol/L), TG (from 0.94 to 3.14 mmol/L), TG/HDL-C (from 0.70 to 1.96) (8). Given the physiological differences in lipid status between different ethnic populations (9), in a similar study by Bever AM et al., the following values were obtained from the Caucasian population – TC 6.28 mmol/L, LDL-C 3.38 mmol/L, HDL-C 1.67 mmol/L, TG 2.51 mmol/l (10). What is of particular importance is that molecularly smaller LDL-C particles are created during pregnancy, which have been proven to be more atherogenic than those outside of pregnancy (5). As there has been a general epidemic of metabolic syndrome, heart disease, high blood pressure, atherosclerosis, and diabetes, more attention has been paid to the lipid status of pregnant women. Pregnancies burdened with gestational diabetes, gestational hypertension, and preeclampsia showed higher than normal lipid values. These changes have also shown an impact on the growth and development of the fetus, as well as on the outcome of the pregnancy. This created a wide and unexplored field for further research (5,6).

Role of the placenta in lipid synthesis and transport

The placenta is the link between the mother and the fetus. Through it, elevated lipid concentrations can affect the

growth and development of the fetus (11). The placenta participates in the biosynthesis, regulation, and transport of cholesterol between mother and fetus. Approximately 20% of the total cholesterol requirement of the fetus is transported across the placenta and this percentage increases in states of maternal hypercholesterolemia (12). Evidence for this transport can be found in Smith-Lemli-Opitz syndrome, a congenital defect in cholesterol synthesis (13). Given that there is no synthesis by the fetus, and fetuses are born with a certain amount of cholesterol, this confirms the transfer pathways between the placenta and the fetus (13). The placenta is also equipped with the necessary enzymes for the production of many steroid hormones for the maintenance of pregnancy and the development of the fetus - estrogens, progesterone, androgens, and glucocorticoids. Given that all cells require cholesterol, it is clear why large amounts of this lipid are needed in a fast-growing organism. In the syncytiotrophoblast, there are receptors for uptaking cholesterol from the mother's bloodstream through receptors similar to those in hepatocytes - low-density lipoprotein receptor (LDL-CR) and scavenger receptor class B type I (SRB1) (14). ApoB in the trophoblast controls lipoprotein uptake. Also, VLDL-C metabolism is changed in pregnancy due to reduced activity of lipoprotein lipase in the liver and adipose tissue, and increased activity in the placenta. In this way, degraded lipoproteins, i.e., products of enzymatic degradation, can effectively reach the fetus and fulfill its increased metabolic requirements (10).

The impact of dyslipidemia on pregnancy

Dyslipidemia in pregnancy is associated with gestational diabetes mellitus (GDM), preeclampsia, macrosomia, preterm birth, and other pregnancy complications. Women with a rich-in-cholesterol diet have a higher incidence of developing gestational diabetes (15). A low level of HDL-C and an elevated BMI have a particular impact on the development of GDM (13). On the other hand, women with gestational diabetes show elevated levels of LDL-C and apoB in their laboratory lipid values. A peculiarity in pregnancy is that LDL-C particles are smaller in size than those outside pregnancy (5). It has been proven that these LDL-C particles are more atherogenic and can lead to faster clogging of blood vessels, especially coronary arteries. A protective factor, if we can say so, is the length of pregnancy of 40 weeks, during which so many extensive changes in the myocardium cannot occur. Whether any reversible changes occur remains to be seen (5).

Elevated LDL-C is associated with preeclampsia due to its endothelial damaging properties via its oxidized form. In pregnant women with preeclampsia, there were elevated LDL-C values in laboratory values, which were maintained up to three years after delivery. In a large study by Jin, Wy et al. it has been proven that an increase in each unit of triglycerides and total cholesterol, especially LDL-C, during pregnancy leads to an increased risk of developing gestational diabetes, preeclampsia, macrosomia, and premature birth. On the other hand, with an increase in HDL-C concentration in the total ratio with LDL-C, the percentage of occurrence of pathological conditions and poor pregnancy outcomes was lower (16).

On the other hand, reduced cholesterol values have a negative impact on pregnancy and may contribute to the risk of premature birth ($p=0.001$) (17). Newborns of mothers with lower total cholesterol values had 150g lower body weight at birth than healthy controls. The authors also suggested that the risk was somewhat increased in mothers with hypercholesterolemia.

In a study conducted by Sharami S. et al. pregnant women with dyslipidemia in the form of elevated triglycerides, cholesterol, and LDL-C had increased incidences of gestational diabetes ($p<0.001$), preeclampsia ($p<0.001$), cholestasis ($p=0.041$) and macrosomia ($p<0.001$) (18).

The effect of dyslipidemia on the fetus

Disturbed maternal lipid values during pregnancy have a negative outcome for the fetus. The consequences are visible in all parts of fetal development and later in adulthood. The influence of elevated lipid values in utero leads to LGA (large for gestational age) and fetal macrosomia. It affects the term of delivery in the form of preterm birth, as well as the impact on postpartum life in the form of metabolic syndrome later in life. Recent studies have shown the influence of reduced triglyceride values on intrauterine fetal growth (17).

This raises the question of the importance of lipid control in pregnancy and it focuses on the aspect of fetal programming that can prevent these metabolic changes later in adult life.

A meta-analysis by Wang Y. et al. investigated the relationship between maternal dyslipidemia and intrauterine growth retardation. They monitored the values of total cholesterol, triglycerides, LDL-C, and HDL-C. A total of eight studies (over 14,000 pregnant women) were included in the analysis. The result of the research indicated that reduced values of total cholesterol, triglycerides, and LDL-C were risk factors for SGA (small for gestational age) fetuses (20).

The results so far show that the lipid status of the mother during pregnancy has a direct effect on the growth of the fetus and its metabolism later in life. In a physiological pregnancy, there is an increase in the level of lipids in the mother's blood and fat tissue, but if malnutrition occurs, or a pathologically high accumulation of total cholesterol and triglycerides, then there are consequences for the fetus in the form of decreased or increased body weight at birth (21). When in question, otherwise protective in the cardiovascular sense, HDL-C in the study by Kramer et al. showed that higher mean

HDL-C values in the second trimester of pregnancy were found in fetuses with a lower than average body weight, while elevated triglyceride values were protective and associated with a lower risk of SGA (22).

Treatment

Since reference values for lipids in pregnant women have not been established yet, it is difficult to talk about specific treatment of hyperlipidemia. Statins (HMG CoA-reductase inhibitors) that are widely used in the treatment of hypercholesterolemia are not used in pregnancies (23). In animal studies, statin use resulted in various skeletal abnormalities and increased fetal morbidity and mortality. The impact of statins that cross the blood-brain barrier in the form of neurological damage has also been confirmed. In addition, in the majority of studies dealing with the treatment of dyslipidemia, pregnant women were excluded from research. The result is a huge gap in the control and treatment of this condition in pregnancy.

Omega-3 fatty acids are used as a supplement to regulate elevated lipid levels. They have been proven to reduce triglyceride levels. They have a direct impact on increasing "good" HDL-C and reducing "bad" LDL-C (24). Williams M. et al. showed that supplementation with fish oil led to a decrease in triglycerides and an increase in HDL-C cholesterol in maternal plasma (22).

For now, a successful type of therapy for both reduced and elevated maternal plasma lipid values is performed through a dietary hygiene regimen. One of the drastic types of therapy in pregnancy is used in the treatment of the rare condition of acute pancreatitis and familial hypercholesterolemia. Due to extremely elevated cholesterol values in this condition, the process of LDL-C aphaeresis is used, which reduces the concentration of LDL-C cholesterol in a targeted manner, while HDL-C cholesterol remains unchanged (25).

CONCLUSION

The influence of cholesterol and triglycerides on the mother and fetus is complex. Dyslipidemia contributes to the development of cardiovascular diseases, gestational diabetes, hypertension in pregnancy, preeclampsia, and other pathological conditions. Elevated lipid levels contribute to premature birth, macrosomia, and the development of metabolic syndrome later in life. The lack of cholesterol and triglycerides during pregnancy negatively affects the growth and development of the fetus. Further studies are necessary to define lipid reference values in pregnancy, as well as numerous scientific contributions and pharmacological studies for establishing adequate therapy.

Conflict of interest

None to declare

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RELEVANTNOST HOLESTEROLA I TRIGLICERIDA U TRUDNOĆI

Milos Milincic[1], Stefan Dugalic[1, 2], Miroslava Gojnic[1,2]

Sažetak

Holesterol učestvuje u izgradnji svih ćelija organizma, steroidnih hormona i žučnih kiselina. Njegova uloga u trudnoći je od ključnog značaja u vidu sinteze hormona bez kojih začeće i trudnoća ne bi bili mogući, a kasnije i u razvijanju fizioloških funkcija fetusa. Trigliceridi kao glavni energetski supstrat služe normalnom rastu i razvoju ploda. Normalne referentne vrednosti lipidnog statusa u trudnoći još uvek nisu uspostavljene. Dokazano je da povišene, kao i smanjene vrednosti ukupnog holesterola, holesterola lipoproteina velike gustine (HDL-C), holesterola lipoproteina male gustine (LDL-C) i triglicerida (TCG) učestvuju u patološkim stanjima trudnoće – gestacioni dijabetes melitus, preeklampsija, makrozomija, restrikcija rasta, itd. Lečenje dislipidemije je ograničeno zbog nedostatka farmakoloških studija na trudnicama, kao i teratogenog efekta antilipidnih lekova. Ovaj pregledni rad se bavi uticajem holesterola i triglicerida na trudnoću, ishod trudnoće, prenatalnim i postnatalnim uticajem na plod, kao i mogućnostima trenutnog i budućeg lečenja.

Ključne reči: Trudnoća; Hiperholesterolemija u trudnoći; Dislipidemija u trudnoći; LDL holesterol u trudnoći, Trigliceridi u trudnoći.

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