Cholesterol in pregnancy: a review of knowns and unknowns

ÄAnne Bartels MB MSc and Keelin O'Donoghue PhD MRCOG

Department of Obstetrics and Gynaecology, Anu Research Centre, Cork University Maternity Hospital, University College Cork, Wilton, Cork, Republic of Ireland

Summary: Cholesterol forms part of every cell in the human body, and also helps make and metabolize hormones, bile acids and vitamin D. Human plasma cholesterol levels are determined by production in the liver and by dietary intake. Lipoproteins carry cholesterol around the body, and facilitate it crossing the placenta. Cholesterol is carefully monitored in the non-pregnant adult population, where its association with atherosclerosis and cardiovascular disease is well understood. Although it is known that cholesterol rises in pregnancy, at present it is not routinely measured or treated. The effects of maternal high cholesterol on pregnancy and on fetal development are not yet fully understood. However, a growing body of evidence from animal and human studies suggests adverse consequences of high cholesterol levels in pregnancy.

Keywords: cholesterol, pregnancy, low-density lipoprotein (LDL), high-density lipoprotein (HDL), atherosclerosis

WHAT IS CHOLESTEROL AND WHY IS IT IMPORTANT?

Cholesterol is an important part of the cell membrane, and works to decrease membrane fluidity while controlling cell membrane permeability. Bile and bile acids, which are essential for fat emulsification in the intestine, also contain cholesterol. Finally, cholesterol is a direct precursor of steroid hormones, including corticosteroids, androgens, oestrogens, progesterone and vitamin D, some of which are produced in the placenta.¹ Human plasma cholesterol levels are determined by endogenous synthesis and dietary intake. The liver is the main site of cholesterol synthesis and is dependent on acetyl-CoA, nicotinamide adenine dinucleotide phosphate (NADPH) and adenosine triphosphate (ATP) as an energy source for this process. The rate-limiting enzyme in cholesterol synthesis is HMG-CoA reductase, which is the enzyme targeted by HMG-CoA reductase inhibitors (statins).^{1,2}

Recommendations of the Irish Heart Foundation for healthy adults are levels of total cholesterol no greater than 5 mmol/L, high-density lipoprotein (HDL) of greater than 1 mmol/L, low-density lipoprotein (LDL) of no greater than 3 mmol/L and triglycerides of no greater than 2 mmol/L. The British Heart Foundation recommends levels for adults at high risk of cardiovascular disease as total cholesterol <4 mmol/L, HDL >1 mmol/L, LDL <2 mmol/L and triglycerides <1.7 mmol/L. In the USA, cholesterol is measured in mg/dL and the American Heart Association recommends total cholesterol <200 mg/dL (5.2 mmol/L), HDL >60 mg/dL (1.6 mmol/L), LDL <100 mg/dL (2.6 mmol/L) and triglycerides <150 mg/dL (1.7 mmol/L).

High cholesterol in the adult non-pregnant population is associated with an increased risk of atherosclerosis causing

cardiovascular disease. Endothelial damage caused by hypertension, diabetes, smoking, as well as excess of lipoproteins allows the deposition of lipoproteins (especially LDL) into the intima of arterial walls.¹ Therefore, LDL can become oxidized, causing further damage by inducing an inflammatory reaction. Monocytes are recruited and converted into macrophages,³ which take up oxidized LDL and change into foam cells. Accumulation of lipid-laden foam cells leads to arterial fatty streak formation, i.e. atherosclerosis.^{1,3-5} It has been suggested that LDL in pregnancy becomes a smaller lipoprotein and is therefore more atherogenic.⁶

Atherosclerosis is a chronic inflammatory condition, where fatty plaque deposition in the arterial wall causes arterial narrowing. If the plaque ruptures, a blood thrombus can form and cause complete occlusion of the vessel resulting in myocardial infarction or stroke. Oxidized LDL, unlike HDL, inhibits the release of nitric oxide, thereby reducing protective arterial vasodilation.³ A combination of elevated levels of LDL cholesterol and decreased levels of HDL cholesterol in the blood increase the risk of atherosclerosis.

CHOLESTEROL METABOLISM AND TRANSPORT

Chylomicrons are formed to transport ingested cholesterol from the intestine to cells, and in the liver chylomicrons are metabolized to very low-density lipoprotein (VLDL). Lipoproteins transport triglycerides and cholesterol between organs and tissues by forming a hydrophilic surface around a hydrophobic core. Lipoprotein lipase hydrolyses VLDL in the peripheral tissue to yield VLDL remnants, which are hydrolysed further to form LDL. LDL has a specific apoprotein, apoB, which controls the metabolism of LDL by interacting with cellular receptors. In turn, LDL receptors are regulated by the intercellular cholesterol concentration.¹

Correspondence to: Dr Keelin O'Donoghue
Email: k.odonoghue@ucc.ie

The function of HDL in the blood is to transport cholesterol from the peripheral tissues to the liver for excretion and to promote the production of nitric oxide. Like LDL, HDL has specific membrane proteins, called ABCA and ABCG. These membrane proteins control the transfer of cholesterol from cells to HDL particles. Cholesterol cannot be metabolized by humans. When it reaches the liver as part of HDL it is excreted in bile and bile acids, most of which is reabsorbed in the terminal ileum.¹

In the placenta, cholesterol crosses two barriers to reach from the maternal to the fetal circulation. From the maternal lacunae, cholesterol travels across the syncytiotrophoblast, which expresses LDL receptors. ApoB in the trophoblast controls this uptake. ABCA and ABGA control the efflux of cholesterol into the fetal microcirculation as HDL particles.^{7,8} It has been stated that up to 20% of sterol in the embryo could be derived from maternal placental cholesterol and a possible greater percentage in placentas with hypercholesterolaemia.⁸ In Smith–Lemli–Opitz syndrome, a congenital defect in cholesterol biosynthesis, affected fetuses that cannot produce any cholesterol are born with small quantities of serum cholesterol, which confirms that some maternal cholesterol is passed onto the fetus.⁸

HYPERCHOLESTEROLAEMIA IN PREGNANCY

Cholesterol is not measured in pregnancy in current obstetric practice. There are no reference ranges defined for lipid parameters during normal pregnancy, although this is largely because of the lack of a good evidence base on the significance of elevated cholesterol levels. However lipid parameters, including total cholesterol, LDL, HDL and triglycerides, have been shown to be elevated in pregnancy, especially in the second and third trimesters (described in Table 1).

Most studies have divided women into three groups by trimester of pregnancy. Compared with healthy non-pregnant women, the rise in lipid parameters occurred from the second trimester in the majority of reports. In contrast, in an ongoing study Bartels *et al.* who examined lipid parameters in pregnant women divided into five groups by gestation found a progressive rise of total- and low-density lipoprotein throughout pregnancy (*unpublished data*). Mean cholesterol values were found to be raised from the first trimester, and 78% of women studied had total cholesterol levels greater than 5 mmol/L. HDL levels ranged from 0.9 to 3.69 mmol/L throughout pregnancy. In contrast, LDL levels ranged from 1.3 to 6.1 mmol/L, and were >3.0 mmol/L in 60% of women. Postnatally, cholesterol levels fell rapidly and were similar to levels in the first trimester by 72 hours after delivery.

Hypercholesterolaemia during pregnancy is due to changes in sex steroid hormones, hepatic and adipose metabolism.^{6,12,13} During pregnancy there is an increased production of sex steroids. The increased progesterone concentration contributes to the rise in LDL levels,¹² and in return circulating LDL cholesterol is the chief substrate for placental progesterone synthesis.¹⁴ The elevated maternal oestrogen concentration in pregnancy causes an increase in total cholesterol, LDL cholesterol and triglycerides. LDL found in maternal serum during pregnancy is atherogenic, small and dense.⁶ As well as LDL, apoB levels are elevated in pregnancy.¹² Hepatic lipase activity also increases during pregnancy, which causes surges of triglyceride synthesis

in the liver and is associated with raised LDL levels.⁶ VLDL metabolism is altered due to decreased lipoprotein lipase activity in the adipose tissue and increased activity in the placenta.¹³ The overall effects of altered lipid metabolism in pregnancy are accumulation of maternal fat stores in the first half and enhanced fat mobilization in the second half of pregnancy.¹³

During pregnancy there is a greater risk of thrombotic events due to hypercoagulability. Ischaemic heart disease is uncommon and is estimated to occur in one in 10,000 pregnancies, although with increasing numbers of women delaying childbearing until an older age, the incidence of coronary artery disease in pregnancy is likely to increase. Atherosclerosis appears to be the most common cause of acute myocardial infarction (MI) in pregnancy, although other causes such as coronary dissection and thrombus have also been reported. A 10-year retrospective review of cases of MI associated with pregnancy found that 24% had hyperlipidaemia, although it is unclear whether this was measured prepregnancy or found at presentation, and at which level hyperlipidaemia was defined.¹⁵ Published literature on ischaemic heart disease in pregnancy commonly makes no mention of the role of cholesterol on occurrence, presentation or progression of disease.

MANAGEMENT OF HYPERCHOLESTEROLAEMIA

At present hypercholesterolaemia is not treated in pregnancy, partly due to the absence of established normal parameters for pregnancy, as well as clinicians' uncertainty as to the significance of elevated levels for a limited time period. HMG CoA-reductase inhibitors (statins), which are the most commonly used drugs to treat high cholesterol outside of pregnancy, are contraindicated. Statins inhibit the synthesis of mevalonic acid, which plays an important role in DNA replication and is essential for the synthesis of steroids and cell membranes in fetal development. Animal studies have demonstrated increased incidence of skeletal abnormalities with lovastatin as well as maternal, fetal and neonatal mortality with fluvastatin. There are reports of fetal neurological damage and central nervous system defects with lipophilic statins (such as simvastatin and atorvastatin), as well as impaired placental implantation and function with use of both lipophilic and hydrophilic types of statins.^{2,16,17} Specifically, simvastatin was found to impair migration and production of trophoblast cells and reduce the levels of progesterone.²

Omega-3 fatty acids naturally occur in fish and plant oils. Research showing that a diet rich in omega-3 fatty acids may help lower triglycerides and increase HDL cholesterol has led to dietary recommendations and supplementation with omega-3 in at-risk adults. The link between omega-3 supplementation during pregnancy and a positive effect on pregnancy outcome including length of gestation as well as a reduction in postpartum depression is being investigated. A direct association between increased omega-3 intake during pregnancy and a reduction in LDL with an increase in HDL is less clearly defined. However a cohort study looking at the fish consumption of 923 pregnant women found that increased fish intake was inversely related with plasma triglyceride (−11.5 mg/dL; *P* = NS) and positively related to HDL levels (+2.8 mg/dL; *P* = 0.04).¹⁸ Omega-3 supplementation has been used in pregnancy in women with pre-existing

Table 1 Lipid profile in pregnancy

Author	Study design	Subjects	Gestational groups	Findings	P values
Piechota <i>et al.</i> (1992) ⁹	Cross-sectional analysis	719 pregnant 65 controls	172 1st trimester 227 2nd trimester 320 3rd trimester	Lipids and apolipoproteins elevated in 2nd and 3rd trimester	$P < 0.001$ (compared with controls)
Brizzi <i>et al.</i> (1999) ⁶	Longitudinal case-control study	22 pregnant 24 controls	22 women (samples in 1st, 2nd and 3rd trimester)	Lipids and apolipoproteins elevated in 2nd and 3rd trimester	$P < 0.01$ (2nd, 3rd versus 1st, 3rd versus 2nd trimester)
Lippi <i>et al.</i> (2007) ¹⁰	Cross-sectional analysis	57 pregnant 21 controls	20 (1st trimester) 20 (2nd trimester) 17 (3rd trimester)	Lipids and apolipoprotein A elevated in 2nd and 3rd trimester	
Husain <i>et al.</i> ¹¹	Case-control study	50 pregnant 100 controls	50 (2nd trimester)	All lipids elevated in pregnancy	$P < 0.001$ (compared with controls)
Bartels <i>et al.</i> (2011) (Unpublished data)	Cross-sectional analysis	222 pregnant	48 (11–14 weeks) 50 (19–23 weeks) 32 (27–29 weeks) 45 (35–37 weeks) 47 (postnatal)	Lipids are progressively elevated throughout pregnancy but start to fall postpartum	$P < 0.001$ (2nd, 3rd trimester versus 1st trimester, postnatal)

hypercholesterolaemia or hypertriglyceridaemia, but is not yet routinely advised in normal pregnancy.

Familial hypercholesterolaemia (FH) is an autosomal dominant condition where individuals have LDL receptor deficiencies, and suffer from elevated total and LDL serum cholesterol concentrations.^{1,8} In one study, a similar relative increase in cholesterol was found in 22 women with FH compared with 149 healthy pregnant women ($P > 0.05$); however, the absolute plasma cholesterol was much higher in FH pregnancies (9.1 ± 1.1 mmol/L at 17–20 weeks gestation).¹⁹ Outside of pregnancy FH is treated with a cholesterol-lowering diet and statin drug therapy, whereas during pregnancy treatment relies on dietary control and fish oil supplementation. Plasma exchange is now largely replaced by LDL aphaeresis, which lowers LDL efficiently with limited impact on HDL cholesterol.²⁰ LDL aphaeresis has been successfully used in selected cases with high cardiovascular disease risk to reduce maternal cholesterol (pretreatment levels 381 mg/dL or 9.9 mmol/L versus post-treatment 247 mg/dL or 6.4 mmol/L) and has been combined with plasma exchange to treat acute pancreatitis in pregnant women with hypertriglyceridaemia.²¹ Human studies have yet to conclusively demonstrate safety or efficacy of these lipid-lowering interventions in pregnant women with FH.²²

EFFECTS OF HYPERCHOLESTEROLAEMIA ON PREGNANCY OUTCOME

Maternal hypercholesterolaemia is believed to have unfavourable effects on the fetus and on pregnancy outcome.^{7,12,23–26} The CARRDIP (Cardiovascular Risk Reduction Diet in Pregnancy) study randomized 141 women to a cholesterol-lowering diet during pregnancy and compared outcome to 149 controls. The diet achieved a beneficial effect on maternal LDL cholesterol levels ($P = 0.04$). In the interventional group the incidence of preterm delivery was significantly reduced (1 [0.7%] of 141 women in the intervention group versus 11 [7.4%] of 149 women in the control group delivered before 37 weeks [RR 0.10; 95% CI 0.01–0.77]); this was suggested to be due in part to the finding of reduced blood flow impedance in the umbilical artery in cases.^{25,26}

Edison *et al.*¹⁴ in a study of 118 women suggested that low maternal cholesterol had a negative effect on the pregnancy,

and contributed to an increased risk of preterm delivery ($P = 0.001$). Term infants of mothers with low total cholesterol weighed on average 150 g less than those who were born to control mothers and a trend of increased microcephaly risk among neonates of mothers with low total cholesterol was also found. The authors also suggested that the risk of preterm delivery existed for mothers with an elevated total cholesterol.¹⁴ As part of the PEPP (Pregnancy Exposures and Preeclampsia Prevention) study, 116 pregnancies that ended at less than 37 weeks were compared with 199 term pregnancies. The comparison showed that women with early pregnancy hyperlipidaemia were more likely to deliver before 34 weeks gestation (adjusted OR 2.8, 95% CI 1.0–7.9).²³

Links have now been established between abnormal maternal lipid profiles during pregnancy and gestational diabetes mellitus (GDM). A recent report found that women with a high cholesterol diet had an increased risk of developing GDM ($P = 0.024$, OR 1.88, CI 1.09–3.23).²⁴ Two other studies reported low levels of HDL ($P < 0.01$, OR 3.07, CI 1.62–5.84), as well as an elevated body mass index (BMI) ($P < 0.05$) as significant predictors of GDM.^{27,28} Women with GDM and gestational impaired glucose tolerance were found to have increased LDL and apoB levels at three months postpartum compared with controls ($P < 0.01$).²⁹ Further, it has been suggested that infants of diabetic mothers have a higher incidence of LDL hypercholesterolaemia.³⁰

Abnormal lipid parameters have also been suggested as a pathogenic factor in the development of preeclampsia (PET). This may partially be due to endothelial damage caused by oxidized LDL, which has been shown to be smaller and more atherogenic in pregnancies complicated by PET. Three studies have reported significantly increased levels of LDL and triglycerides in women with PET compared with controls ($P < 0.05$, OR 8.9–9.6),^{31–33} and these plasma changes persisted for one to three years after delivery.³³

Finally, parity is associated with the risk of coronary artery disease, stroke and the severity of preclinical atherosclerosis. One explanation is that pregnancy may lead to a rapid progression of atherosclerosis, postulated by some authors to be driven by changes in sex steroids, insulin resistance, inflammation, oxidative stress, as well as acute elevations in lipids. Independent of other risk factors, the reduction in HDL cholesterol levels ($P < 0.0001$) and the progression of carotid intima-media thickness (7.5 ± 3.2 $\mu\text{m}/\text{birth}$, $P = 0.02$) in women who

gave birth over a six-year time period in the 'Cardiovascular Risk in Young Finns' study provides some evidence to support this theory.³⁴

EFFECTS OF HYPERCHOLESTEROLAEMIA ON THE FETUS

It is now recognized that *in utero* environment has an effect on the fetus and its risk of developing disease in adulthood – atherosclerosis was among the first conditions for which a role of developmental programming was described. Barker described the link between low birth weight and the increased risk of cardiovascular disease in adult life in 1986, and it is since clear that many other factors in fetal life can influence long-term adult health.³⁵ A more recent study showed that the low birth weight of a female infant increased the probability of developing altered lipid metabolism during later pregnancy, although mechanisms underlying this are still not fully understood.³⁶

Animal studies have demonstrated that high maternal cholesterol levels promote fetal atherosclerosis.^{37–39} Murine models used to examine the effect of a high cholesterol *in utero* environment on hepatic cholesterol metabolism found that maternal hypercholesterolaemia during pregnancy changed hepatic cholesterol homeostasis in the offspring, and suggested this as the basis for the increased tendency to atherosclerosis in later life.³⁷ A study on maternal hypercholesterolaemia and treatment in rabbits showed that lesion progression was greatest in the offspring of mothers with high cholesterol. Further, vitamin E ingestion by the mothers had positive effects on lesion prevention in the offspring.^{4,38}

The FELIC (Fate of Early Lesions In Children) study showed that children born to mothers with a high cholesterol had faster progression of aortic fatty streak formation than those born to mothers with normal cholesterol ($P < 0.0001$).⁴⁰ Napoli *et al.*⁵ demonstrated that fetal cholesterol levels had an inverse correlation to fetal age, and showed that fetal to maternal cholesterol levels were closely related up to 28 weeks gestation, suggesting that this is the timeframe of maternal influence on fetal arterial fatty streak formation. In mid-pregnancy another study of 108 women and babies found that fasting maternal triglyceride levels had a direct correlation with neonatal birth weight, even when variables such as elevated BMI, greater pregnancy weight gain and hyperglycaemia were accounted for. These authors concluded that women with fasting hypertriglyceridaemia had a higher risk of delivering heavier babies (RR 2.6, 95% CI 0.78–8.4).⁴¹

CONCLUSION

It has been assumed for decades that hyperlipidaemia in pregnancy is physiological and not atherogenic. While cholesterol is carefully monitored in the non-pregnant adult population, cholesterol levels are not routinely measured in pregnancy and there are no accepted normal ranges across gestation. However, high maternal cholesterol levels during pregnancy are now linked with increased risks of preterm delivery, gestational diabetes and preeclampsia, as well as the later development of atherosclerosis in offspring. Animal studies demonstrate adverse consequences of maternal hypercholesterolaemia, and new human studies suggest maternal cholesterol levels are significantly elevated from the first trimester (see Table 2).

Table 2 Cholesterol in pregnancy – knowns and unknowns

Knowns	Unknowns
Cholesterol is elevated due to changes in sex steroid hormones, hepatic and adipose metabolism	Pregnancy-specific cholesterol reference ranges
Cholesterol is not routinely measured in pregnancy	Role of hypercholesterolaemia in pregnancy-related cardiovascular disease
LDL-cholesterol and triglycerides are elevated, especially in 2nd and 3rd trimesters	Risk of progression of maternal atherosclerosis due to hypercholesterolaemia
LDL in pregnancy becomes more atherogenic	Effect of a cholesterol-lowering diet
Statins are contraindicated	Role of statins in pregnancy
Increased risk of preterm delivery with hyperlipidaemia	Role of omega-3 supplementation during pregnancy
Association of hyperlipidaemia with development of preeclampsia and GDM	Reduction in incidence of preeclampsia, GDM and preterm delivery with reduction of cholesterol levels
Greater aortic fatty streak formation in offspring of mothers with hypercholesterolaemia*	Long-term outcome of children of mothers with high cholesterol levels in pregnancy
Faster progression of atherosclerotic lesions in offspring of mother with hypercholesterolaemia*	Effects of persistent maternal hypercholesterolaemia after pregnancy

GDM, gestational diabetes mellitus

*Data from animal studies

International pregnancy-specific normal cholesterol reference ranges need to be agreed in order to classify high maternal cholesterol levels and to determine their significance. Further, in order to investigate the clinical implications of maternal hypercholesterolaemia, a large international multicentre trial could investigate maternal cholesterol levels throughout pregnancy and relate these to specific pregnancy outcomes such as gestational diabetes, PET, preterm delivery and infant birth weight.

With established pregnancy-specific reference values, extreme maternal hypercholesterolaemia can be identified and monitored. Due to recognized adverse effects of high cholesterol on pregnancy and the fetus, intervention with a cholesterol-lowering diet may be necessary and prove beneficial, and other lipid lowering interventions should be investigated. Women identified with high cholesterol levels during pregnancy will need follow-up postnatally as persistent hypercholesterolaemia substantially increases the risk of atherosclerosis. Parity is also an important cardiovascular risk factor for women and should not be forgotten when risk prediction and prevention strategies are discussed. Finally, the long-term implications of hypercholesterolaemia in pregnancy for both fetus and mother need to be further explored.

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