Changes in serum lipid levels during pregnancy in women with gestational diabetes. A narrative review

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We review current knowledge on lipid metabolism changes during pregnancy with special focus on changes in gestational diabetes. In physiological pregnancy, total plasma cholesterol, triglyceride and HDL-cholesterol level rises, the atherogenic index (LDL-cholesterol / HDL-cholesterol) remains unchanged. Compared with healthy women, women with GDM show more pronounced signs of mixed dyslipidaemia – increased levels of triglyceride, changes in cholesterol and lipoprotein concentrations with a shift towards greater small dense LDL subfractions, which is typical for insulin resistance states. Dyslipidaemia, particularly hypertriglyceridemia, is thought to be one of the key drivers of foetal macrosomia and that is why measurements of plasma lipids may be valuable in detecting the metabolic abnormality in GDM and in predicting foetal outcome. Dyslipidaemia in GDM is seen as proatherogenic and potentially harmful for the baby and therefore it should be monitored more carefully.

Key words: plasma lipids, gestational dyslipidaemia, triglycerides, pregnancy, gestational diabetes, insulin resistance

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INTRODUCTION

Insulin resistance in pregnancy leads to metabolic changes similar as can be to those found in type 2 diabetes mellitus. In type 2 diabetes, decreased HDL cholesterol, elevated triglyceride (TG) levels, and changes in LDL cholesterol are common. These changes represent an important atherogenic risk factor, and they are also present in gestational diabetes (GDM). GDM is an insulin resistance state, and post-partum women with GDM who keep their gestational weight gain do not have improvement in their insulin sensitivity¹.

Women with normal pregravid glucose tolerance who develop GDM in pregnancy likely have subclinical metabolic dysfunction prior to conception compared with those who do not develop GDM during pregnancy². These women are not able to adapt metabolically in pregnancy, and glucose intolerance ensues³. Even in normal pregnancy, there is a 60% decrease in insulin sensitivity (physiological insulin resistance); that is why women with subclinical metabolic dysfunction develop diabetes in pregnancy¹. Moreover, it has been shown that women who developed GDM had a smaller LDL peak diameter, lower mean HDL concentrations, and higher mean concentrations of small, dense LDL particles before pregnancy. These parameters were associated with the subsequent development of GDM, independently of other known risk factors (body mass index, weight gain before pregnancy, age, insulin resistance, and family history of diabetes) (ref.⁴).

Mild forms of hyperlipidaemia are common during normal pregnancy, but also extreme hyperlipoproteinaemia may occur in the gestational period. In these cases, there is usually an underlying genetic disorder (e.g. lipoprotein lipase deficiency, ApoE3/3 genotype, dysbetalipoproteinaemia). In these genetic disorders, hyperlipoproteinaemia develops when a secondary metabolic factor such as pregnancy occurs⁵.

Changes in the maternal metabolic milieu can play a key role in the baby's later life⁶. A positive association between maternal triglycerides and LGA (large-for-gestational-age) infants independently of long-term blood glucose control was found^{7,8}. Moreover, pregnant women with dyslipidaemia also have higher incidence rates of preeclampsia, cholestasis, and foetal growth retardation⁹.

LIPID CHANGES IN NORMAL PREGNANCY AND IN PREGNANCY WITH GDM

During pregnancy, lipoprotein metabolism in the liver and adipose tissue changes, altering the serum concentrations of fatty acids, triglycerides (TG), cholesterol, and phospholipids. After an initial decrease in the first eight weeks of pregnancy, there is a steady increase in lipoproteins and, especially, in TG levels^{3,10}.

A study conducted by Koukkou¹¹ showed that, during the third trimester of pregnancy, women with GDM had higher serum TG, but lower LDL cholesterol concentrations than controls. Total cholesterol, HDL cholesterol,

mesters) whereas HDL cholesterol levels were lower (in the second and third trimesters of pregnancy) in women with GDM compared with those without GDM (ref.²). There were no differences in aggregate total cholesterol or LDL cholesterol levels between women with GDM and those without insulin resistance². Different results of the above-mentioned studies might be elucidated by O'Malley et al. who suggest that the association between GDM and dyslipidaemia is mediated through maternal obesity. They found that, after adjustment for BMI (obesity), the trend towards higher triglycerides was seen only in obese women¹⁴.

LIPID METABOLISM DURING PREGNANCY

The reason for the change

Changes in lipid metabolism during pregnancy are important for accumulation of maternal fat stores in early and mid-pregnancy and accelerate fat mobilization in late pregnancy³. The anabolic phase of early pregnancy promotes lipogenesis and fat storage in preparation for the rapid foetal growth in late pregnancy¹⁹. Lipid deposition and lipolysis inhibition are favoured by increased oestrogen, progesterone, and insulin³. The placenta uses cholesterol for steroid synthesis, and fatty acids are used for placental oxidation and membrane formation³. In late pregnancy, the increase in plasma fatty acid and glycerol concentrations are consistent with the mobilization of lipid stores. This shift from an anabolic to a catabolic state enables the use of lipids as a maternal energy source while preserving glucose and amino acids for the foetus³.

Changes in VLDL and TG concentrations

As mentioned above, plasma concentrations of TG in particular, but also of cholesterol and apolipoprotein B increase during pregnancy²⁰. Plasma TG levels rise markedly whereas the increase in phospholipids and cholesterol is less pronounced – plasma cholesterol levels increase by 50% while TG levels rise between 2- and 4-fold in normal pregnancies⁵. Changes in plasma lipid levels are summarized in Table 1, and lipid metabolism is presented in Fig. 1. The rising levels of TG observed even during normal pregnancies are a result of high serum oestrogen concentrations and increasing insulin resistance. Oestrogens increase the synthesis of VLDL and decrease hepatic TG lipase activity²². This leads to more extensive lipolysis and increased flux of fatty acids to the liver, promoting the synthesis of large VLDL particles and higher TG concentrations⁵. TG and oestrogen levels show a strong correlation and it seems that oestrogens are primarily responsible for hyperlipidaemia²⁰. In women with GDM, increased insulin resistance leads to an even more pronounced increase in TG concentrations^{12,16}.

Because of decreased activity of lipoprotein lipase (LPL) (ref.⁵) and hepatic lipase²³, VLDL remains in plasma for a longer time. LPL is present in the vascular bed of extrahepatic tissues and catalyses the hydrolysis of TG in VLDL particles and their subsequent conversion into intermediate-density lipoproteins and LDL; thus, LPL is

a key enzyme for the VLDL-IDL-LDL cascade²³. Both LPL and hepatic lipase activities are decreased in pregnancy, with the change being more prominent for hepatic lipase than for LPL (ref.²³). Alvares showed that LPL was significantly decreased only in the third trimester of pregnancy whereas hepatic lipase activity had already been decreased in the first trimester and decreased further in the second and the third trimesters when compared with values either postpartum or postlactation²³. The production of VLDL is also augmented due to enhanced activity of hormone-sensitive lipase in the adipose tissue, which in turn reinforces VLDL production in the liver⁵.

The triglyceride/cholesterol ratio remains stable in VLDL despite a significant increase in the triglyceride/cholesterol ratio in both low-density lipoproteins (LDL; 358% change between postpartum and third trimester values) and high-density lipoproteins (HDL; 241% change between postpartum and third trimester values) as pregnancy advances²³. The specific enrichment of triglycerides in VLDL would require the cholesteryl ester transfer protein (CETP)-mediated transfer of triglycerides from triglyceride-rich lipoproteins to lipoproteins of higher density. CETP activity has been demonstrated to be enhanced in pregnant women, especially in the second trimester²³. This corresponds with the greatest increase in LDL and HDL triglyceride content.

Changes in HDL cholesterol

As already mentioned, HDL cholesterol concentrations increase significantly throughout pregnancy¹⁰, peaking in mid-gestation²², whereas women with GDM have lower HDL cholesterol levels in comparison with those without GDM (ref.¹³⁻¹⁵). More importantly (and similarly to the case of LDL cholesterol), HDL subfractions change; there is a significant rise in serum total HDL cholesterol and HDL2 mass²⁰. HDL receives some surface components from VLDL lipolysis, resulting in the conversion of lipid-poor HDL3 particles to the less dense, lipid-enriched HDL2 particles. HDL2 particles are degraded by hepatic lipase which catalyses the hydrolysis of HDL phospholipids and TG; thus, HDL2 is again converted to lipid-poor HDL3 (ref.²³). The proportional distribution of HDL subfractions showed that it was only the HDL2b fraction which increased with pregnancy whereas both HDL3a and HDL3b decreased most. An additional factor that could participate in the shift in HDL subclasses distribution to large HDL2b particles could be the lecithin:cholesterol acyltransferase (LCAT) activity which rises during pregnancy²³. The increase in apoAI concentration already seen in the second trimester of pregnancy could also facilitate increased LCAT activity. This mechanism enhances conversion of HDL2a into HDL2b, which, in turn, may increase the availability of substrate for CETP involvement in the interchange of TG and esterified cholesterol for the generation of triglyceride-enriched HDL2b (ref.²³).

The increase in HDL cholesterol levels in the first half of pregnancy may be due to the effects of oestrogens²² which are known to elevate HDL cholesterol and stimulate the synthesis of apoA1 in the liver²⁰. In the second

half of pregnancy, HDL cholesterol concentrations may be primarily controlled by insulin, the concentration of which rises²², and progesterone²⁰. Progesterone showed a negative correlation with HDL cholesterol, and this suggests that large amounts of progesterone are responsible for some decrease in HDL cholesterol in late pregnancy²⁰.

Changes in LDL profile

Gestational increase in TG is associated with a change in LDL cholesterol concentrations although the exact type of this change remains controversial. Accumulation of VLDL can lead to accumulation of LDL (ref.¹⁹) due to accelerated conversion of VLDL to lipoproteins of higher density²³. However, not all studies have confirmed higher serum LDL cholesterol levels, with some reporting even lower LDL cholesterol concentrations in women with GDM. Howard et al. hypothesized that increased direct removal of triglyceride-enriched VLDL may lead to a decreased production of LDL (ref.²⁴). The total pool of LDL may be further decreased by the effect of hyperoestrogenaemia on LDL catabolism²⁵. Although it is still unclear whether the LDL cholesterol is increased or decreased during pregnancy, the most important fact is that the subclasses of LDL are changed²⁰. In a study by Belo with healthy pregnant women, a change in the LDL profile towards smaller particles was already evident early in pregnancy¹⁰. During late pregnancy, LDL categorized as LDL subclass patterns B or I indicate that small, dense LDL particles predominate. This predominance is associated with plasma TG concentration with a significant inverse relationship between the LDL peak particle diameter and plasma TG concentration^{10,20}. Changes in LDL particles were confirmed by Belo et al. who found a significant decrease in LDL peak and mean particle diameter during pregnancy¹⁰. An increase in VLDL promotes TG enrichment of LDL particles; the subsequent hydrolysis of TG in LDL even with a low gestational hepatic lipase activity may result in the remodelling of LDL subclasses into smaller, denser species¹⁰. In addition, small LDL particles formed during pregnancy have a reduced clearance, thus contributing to their accumulation in plasma during late gestation²⁰. The changes in LDL particles are very similar to those described in type 2 diabetes mellitus where small, dense LDL particles and decreased numbers of cholesterol ester molecules per particle have been reported²⁶. Women with diabetes prior to conception have higher LDL levels already in the first trimester, and LDL levels rise progressively throughout pregnancy more than in women without diabetes at all time points¹⁹. This implies that adverse modification of LDL is a characteristic of diabetes since the LDL score is elevated¹⁹.

IMPLICATIONS OF GESTATIONAL DYSLIPIDAEMIA

A pregnancy with GDM is associated with mixed dyslipidaemia with predominantly elevated TG concentrations with a shift towards small, dense LDL particles¹⁹, as can also be found in other insulin resistance states,

such as type 2 diabetes mellitus. Women who develop GDM have significantly increased TG concentrations and decreased HDL concentrations in early pregnancy²⁷. Both lean and obese women with higher TG concentrations are at an increased risk for developing GDM (a 1.8-fold increase in risk in the lean group vs. a 2.7-fold increase in the obese group) while lean women with high HDL are protected²⁷. O'Malley even showed that the epidemiological association between GDM and dyslipidaemia was mediated through maternal obesity. Women with obesity alone or GDM alone did not have an elevated odds ratio for dyslipidaemia¹⁴. Animal studies observed that foetal metabolic abnormalities were mediated not only by maternal obesity, but also by a high-fat diet²⁸.

On the other hand, women with physiological pregnancy (without GDM) have plasma total cholesterol concentrations about 50% higher in comparison with pre-pregnancy, while TG concentrations are approximately twice as high. However, total cholesterol concentrations should not exceed 6.5 mmol/L. Physiological pregnancy dyslipidaemia differs from the pathological dyslipidaemia seen in GDM also by a parallel increase in HDL-C levels with total cholesterol and the atherogenic index (LDL-C / HDL-C) remains principally unchanged during pregnancy.

In GDM, higher plasma insulin may suppress fatty acid oxidation. Lower oxidation of exogenous TG in GDM may allow greater availability of TG to the foetoplacental unit. Fatty acids derived from maternal TG cross the placenta and contribute to foetal macrosomia³ providing additional substrates for foetal lipid synthesis¹. According to a robust meta-analysis done by Wang et al., maternal high TG and low HDL cholesterol levels in pregnancy are associated not only with foetal macrosomia, but also with increased birth weight and a higher risk of large-for-gestational-age infants²⁸. These findings were consistent across the studied populations; however, stronger associations were observed in women who were overweight or obese prior to pregnancy²⁸. Interestingly, in pregnant women with GDM, neither neonatal birth weight nor fat mass were associated with maternal glucose levels, but they correlated with maternal TG (ref.²⁹). This finding explains why mothers with GDM – even those with good blood glucose control – have a risk of macrosomia²⁹.

These results support the evaluation of lipid profile during pregnancy, which may be valuable in identifying and quantifying the metabolic abnormality in GDM and in predicting foetal outcome¹². This approach correlates well with a secondary analysis of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) data showing an independent effect of maternal obesity and glucose levels on excessive foetal growth³⁰. In view of the studies mentioned above, it is important not only to measure glucose, but also to evaluate the lipid profile during pregnancy, with a particular emphasis on TG levels. Both have an impact on foetal growth and outcome. It is especially relevant to advise women to avoid being obese before pregnancy because the presence of a subclinical metabolic dysfunction prior to conception subsequently leads to the development of GDM during pregnancy, and thus to adverse outcomes.

CONCLUSION

Dyslipidaemia in GDM is seen as proatherogenic (increased levels of triglyceride, changes in cholesterol and lipoprotein concentrations with a shift towards greater small dense LDL subfractions). Dyslipidaemia in GDM is potentially harmful for the baby and therefore it should be monitored more carefully.

Search strategy and selection criteria

The aim of our research strategy was to evaluate well documented studies on lipid metabolism changes in pregnancy with focus on gestational diabetes. The articles from 1980 to 2019 were searched using the PubMed databas. All searches were up-to-date since May 2020. The search terms used included “lipids”, “gestational diabetes”, “dyslipidaemia”. Only articles in English were reviewed.

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