Foetal growth can achieve its full potential only with an adequate and fine-tuned interaction between mother, placenta and foetus.
CHANGES IN PREGNANCY

Hyperlipidemia in pregnancy provides a functional reservoir for the foetus – allowing cholesterol to be used for building foetal cellular membranes, *steroid hormones*, and bile acids.

- Serum cholesterol levels can increase by as much as 25% to 50%, and triglyceride (TG) levels can double during the third trimester of pregnancy.
- The increased progesterone concentration contributes to the rise in LDL levels, and in return circulating LDL cholesterol is the chief substrate for placental progesterone synthesis.
- The elevated maternal oestrogen concentration in pregnancy causes an increase in total cholesterol, LDL cholesterol and triglycerides.

*Placenta* 34 (2013) 1142e1149  
*Journal of Clinical Lipidology* (2012) 6, 88–91
Defining Lipid levels

- TC is **not measured** in pregnancy in current obstetric practice
- **No reference ranges** defined for lipid parameters during normal pregnancy
- Still presently not known whether **optimal levels** of maternal serum cholesterol during pregnancy can be defined
- 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
- LDL found in maternal serum during pregnancy is atherogenic, small and dense, but these changes are felt to be generally non-atherogenic, and fall precipitously to pre-pregnancy levels following delivery
Lipid Parameters during pregnancy

- HDL, LDL, VLDL (Triglyceride) increase during pregnancy
- Triglycerides show the largest increase
- HDL shows the smallest increase
- 78% of women studied had total cholesterol levels greater than 5 mmol/L.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>169.1 ±32.6</td>
<td>182.9 ±31.4</td>
<td>223.4±34.7</td>
<td>259.8±44.6</td>
</tr>
<tr>
<td>TG</td>
<td>106.6 ±15.9</td>
<td>180 ±12.2</td>
<td>217.3±26.1</td>
<td>214.8±43.6</td>
</tr>
<tr>
<td>HDL-C</td>
<td>46.7±5.7</td>
<td>47.1±6.3</td>
<td>55.6±5.5</td>
<td>51.1±6.3</td>
</tr>
<tr>
<td>VLDL</td>
<td>16.2±3.1</td>
<td>16.8±5.8</td>
<td>28.2±8.3</td>
<td>45.3±9.7</td>
</tr>
<tr>
<td>LDL-C</td>
<td>103.2±19.2</td>
<td>114.1±20.2</td>
<td>132.6±21.6</td>
<td>154.3±25.2</td>
</tr>
</tbody>
</table>
Hypercholesterolemia was greatest in women with pre-existing hypercholesterolemia, and women in the third pregnancy showed higher plasma cholesterol concentrations than women in the first pregnancy.
Intermediate Metabolism in Pregnancy

- Adipose tissue expansion
- Peripheral insulin resistance
- Hepatic lipid synthesis increases

Lipolysis is increased as a result of insulin resistance, leading to increased flux of fatty acids.

Di Cianni CG et al., Diabetes Metab Res Rev 2003
Lipoprotein metabolism during late pregnancy
Maternal hypertriglyceridemia corresponds to an accumulation of triglycerides not only in VLDL lipoprotein but also in LDL and HDL lipoprotein.

Although triglycerides do not cross the placental barrier, the presence of lipoprotein receptors in the placenta, together with lipoprotein lipase, phospholipase A2, and intracellular lipase activities, allows the release to the foetus of polyunsaturated fatty acids transported as triglycerides in maternal plasma lipoproteins.
Early stages of pregnancy (i.e. before the 6th month) foetal LDL correlates to LDL levels of the mothers, while in third trimester this correlation is virtually absent.

Maternal physiological hyperlipidaemia allows the foetus to rapidly receive and store fat, which exceeds by far that of any other nutrient.

Maternal physiological hyperlipidaemia allows the foetus to rapidly receive and store fat, which exceeds by far that of any other nutrient.
The placenta is the central support organ for the developing foetus.
EFFECTS OF HYPERLIPIDEMIA ON PREGNANCY OUTCOME

- Pre-term delivery
- Increased gestational diabetes
- Pre-eclampsia
- Increased cholesterol deposition in the foetal aorta

Pre-eclampsia has an association with hypertriglyceridemia and elevated cholesterol level LDL and VLDL and decreased HDL level.

The greater the severity of preeclampsia, the higher is the level of serum triglycerides cholesterol LDL and VLDL and the lower is the HDL.
Factors in foetal life can influence long-term adult health

Associated with later development of atherosclerosis in offspring.

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.
A systematic assessment of fatty streak formation was carried out in fetal aortas from normocholesterolemic mothers (22), hypercholesterolemic mothers (33), and mothers who were hypercholesterolemic only during pregnancy (27).

Fetal aortas from hypercholesterolemic mothers and mothers with temporary hypercholesterolemia contained significantly more and larger lesions than aortas from normocholesterolemic mothers.

LDL oxidation and formation of fatty streaks occurs already during fetal development, and that both phenomena are greatly enhanced by maternal hypercholesterolemia.
Maternal hypercholesterolemia during pregnancy may program lipid metabolism to a certain extent in the foetus.

- THE absolute serum TC/TG concentrations are usually much greater in mothers with FH.
- No difference in pregnancy outcomes between those with FH and normal patients.

Pregnancy may lead to a rapid progression of atherosclerosis, postulated to be driven by changes in sex steroids, insulin resistance, inflammation, oxidative stress, as well as acute elevations in lipids.
The guidelines do not recommend routinely checking cholesterol levels during pregnancy as cholesterol levels will increase and the use of most lipid-modifying agents are contraindicated.

<table>
<thead>
<tr>
<th>Lipid-lowering agents</th>
<th>Pregnancy class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>X Contraindicated in pregnancy</td>
</tr>
<tr>
<td>Fibrates</td>
<td>C Potential benefits may warrant use of the drug in pregnant women despite potential risks</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>C</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>C</td>
</tr>
<tr>
<td>Cholestryramine</td>
<td>C</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>B No risk in other studies/risk poss</td>
</tr>
</tbody>
</table>

Journal of Clinical Lipidology (2012) 6, 88–91
Lipoprotein apheresis

- LA is the recommended lipid lowering treatment for pregnant HoFH patients.
- The benefits of LA are well established and include the ability to lower total cholesterol and LDL-C levels significantly and to prevent progression of atherosclerotic disease.
- By down-regulating several cytokines, LA also has an anti-inflammatory response.
- LA is costly, time consuming and not available in all countries
HEART UK statement

- Lp apheresis during pregnancy is safe
- Drug treatment, other than BAS with folate supplementation should not be used as evidence of safety is lacking.

- Pregnancy is hazardous for patients with HoFH.
- Patients should be advised that pregnancy in HoFH is hazardous
- Pre-conception, women should be referred to a cardiologist. The pressure gradient across the aortic valve and root should be assessed by echocardiography
- Pre-conception, women with HoFH should be counselled that their children will have HeFH and if their partner has HeFH the risk of HoFH is 1 in 2
Statins: cohort study

- Statins have been considered contraindicated in pregnancy based on animal data showing teratogenic potential at high doses and concern that they might disrupt cholesterol biosynthesis in the developing foetus.

- Data on the effects of in utero exposure to statins are few.

- Women taking statins during the first trimester of pregnancy were at an increased risk of delivering an infant with malformations.

- The association was explained by underlying characteristics of users, mainly pre-existing diabetes.

- Statins themselves did not seem to have any meaningful teratogenic effect.
Because of teratogenicity, women with FH who are planning pregnancy must interrupt statin therapy at least 1 month before stopping contraception, and remain without therapy until breastfeeding is completed (Atorva and Rosuva found in breast milk).

Cholestyramine, colestipol, or colesevelam can be safely prescribed during pregnancy and breastfeeding, but these reduce LDL-C by approximately 15% at most and have tolerability issue.

For HoFH subjects and FH subjects with cardiovascular disease, LDL apheresis can decrease LDL-C and prevent complications.
Statins and other lipid-lowering therapy and pregnancy outcomes in homozygous familial hypercholesterolaemia: A retrospective review of 39 pregnancies

Cohort of 39 (18 exposed to statins) pregnancies, complications did not differ from those reported during pregnancies of healthy woman

- We recommend that, where LA is not feasible, patients should discontinue all lipid lowering therapy a month prior to planned conception and reinstate lipid lowering therapy, statin plus ezetimibe, during the second trimester
Severe Hypertriglyceridemia in Pregnancy

- Pregnancy-related hypertriglyceridemia is rare, but it can be life threatening in some patients with genetic susceptibility.
- Complications can include acute pancreatitis, hyperviscosity syndrome, and possibly pre-eclampsia.
- Overall, our recommendations are to monitor for pregnancy-related hypertriglyceridemia in those with pre-pregnancy fasting triglyceride level greater than 4 mmol/liter and to institute therapy when triglyceride level increases to more than 10 mmol/liter.
<table>
<thead>
<tr>
<th>Knowns</th>
<th>Unknowns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol is elevated due to changes in sex steroid hormones, hepatic and adipose metabolism</td>
<td>Pregnancy-specific cholesterol reference ranges</td>
</tr>
<tr>
<td>Cholesterol is not routinely measured in pregnancy</td>
<td>Role of hypercholesterolaemia in pregnancy-related cardiovascular disease</td>
</tr>
<tr>
<td>LDL-cholesterol and triglycerides are elevated, especially in 2nd and 3rd trimesters</td>
<td>Risk of progression of maternal atherosclerosis due to hypercholesterolaemia</td>
</tr>
<tr>
<td>LDL in pregnancy becomes more atherogenic</td>
<td>Effect of a cholesterol-lowering diet</td>
</tr>
<tr>
<td>Statins are contraindicated</td>
<td>Role of statins in pregnancy</td>
</tr>
<tr>
<td>Increased risk of preterm delivery with hyperlipidaemia</td>
<td>Role of omega-3 supplementation during pregnancy</td>
</tr>
<tr>
<td>Association of hyperlipidaemia with development of preeclampsia and GDM</td>
<td>Reduction in incidence of preeclampsia, GDM and preterm delivery with reduction of cholesterol levels</td>
</tr>
<tr>
<td>Greater aortic fatty streak formation in offspring of mothers with hypercholesterolaemia*</td>
<td>Long-term outcome of children of mothers with high cholesterol levels in pregnancy</td>
</tr>
<tr>
<td>Faster progression of atherosclerotic lesions in offspring of mother with hypercholesterolaemia*</td>
<td>Effects of persistent maternal hypercholesterolaemia after pregnancy</td>
</tr>
</tbody>
</table>

GDM, gestational diabetes mellitus

*Data from animal studies
THANK YOU
Data from the OMEGA study reported that active women (early in pregnancy) had significantly lower mean TC and TG in comparison to those of women performing no recreational physical activity [29]. Other studies suggest a positive effect of physical activity on TG levels during pregnancy [15, 16], however results with other lipids are scarce. For example, data from NHANES (2003–2006) found that sedentary behaviour, assessed by accelerometry, was associated with higher LDL-c levels and moderate to vigorous physical activity with higher HDL-c levels in pregnant women [16].
Notably, animal and human studies suggest that there may be a critical window for fetal development where changes in the maternal condition can influence long-term cardiovascular risk in the offspring.

At one end of the spectrum, maternal nutrient deprivation is associated with a more atherogenic lipid profile and increased cardiovascular risk in the offspring in adult life.

Maternal hypercholesterolemia may increase the risk for CVD in the offspring.

In humans, fatty streak formation progressed strikingly faster in children of hypercholesterolaemic mothers than in those of normocholesterolaemic mothers.

Arterioscler Thromb Vasc Biol. 2010;30:2673-2677
Lipoprotein metabolism
Intermediate metabolism in pregnancy

Metabolic maternal changes through gestation: shift from carbohydrates to lipids for maternal energy production in order to make nutrients available for the foetus

Di Cianni CG et al., Diabetes Metab Res Rev 2003
Maternal lipoprotein metabolism in late pregnancy
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. During pregnancy there is an increased production of sex steroids. The increased progesterone concentration contributes to the rise in LDL levels, and in return circulating LDL cholesterol is the chief substrate for placental progesterone synthesis. 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. As well as LDL, apoB levels are elevated in pregnancy. Hepatic lipase activity also increases during pregnancy, which causes surges of triglyceride synthesis in the liver and is associated with raised LDL levels. VLDL metabolism is altered due to decreased lipoprotein lipase activity in the adipose tissue and increased activity in the placenta. 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.
- Maternal cholesterol is essential for both the hormonal and physical changes of early pregnancy.
- This physiologic hypercholesterolemia of later pregnancy suggests an adaptive function for pregnancy maintenance or foetal growth.
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.

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.
- During pregnancy, there is adipose tissue expansion, and hepatic lipid synthesis increases.
- Pregnant women experience peripheral insulin resistance, and levels of hormones such as leptin and insulin are higher in this period than in the non-pregnant state.
- Lipid metabolism plays a role in both healthy and complicated pregnancies.
- Although maternal cholesterol is an important source of cholesterol for the fetus during early gestation, its importance becomes minimal during late pregnancy, owing to the high capacity of fetal tissues to synthesize cholesterol.
- Maternal hypertriglyceridemia is a characteristic feature during pregnancy and corresponds to an accumulation of triglycerides not only in very low-density lipoprotein but also in low- and high-density lipoprotein.
Although triglycerides do not cross the placental barrier, the presence of lipoprotein receptors in the placenta, together with lipoprotein lipase, phospholipase A2, and intracellular lipase activities, allows the release to the foetus of polyunsaturated fatty acids transported as triglycerides in maternal plasma lipoproteins.
Lipid metabolism changes during pregnancy

The anabolic phase of early pregnancy encourages lipogenesis and fat storage in preparation for rapid foetal growth in late pregnancy.

Lipolysis is increased as a result of insulin resistance, leading to increased flux of fatty acids to the liver promoting the synthesis of very low-density lipoproteins (LDLs) and increased triglyceride (TG) concentrations.

Because of a decrease in the activity of lipoprotein lipase, very-LDL remains in the plasma for longer and leads to the accumulation of LDL.

During the course of normal pregnancy, plasma triglyceride and cholesterol concentrations rise and as pregnancy progresses both become normal.
Maternal lipoprotein metabolism in late pregnancy
The hormonal effects

- The endogenous female sex hormones have a significant effect on serum lipids.
- During pregnancy, there is an increase in the hepatic lipase activity and decrease in lipoprotein lipase activity.
- Hepatic lipase is responsible for the increased synthesis of the TGs at the hepatic level, whereas the decreased activity of lipoprotein lipase is responsible for the decreased catabolism at the adipose tissue level.
- Net effect of which will be an increase in circulating TGs and the second step of uptake of the remnant chylomicrons by the liver is delayed so it leads to accumulation of TGs in plasma.
Another hypothesis is that hypertriglyceridemia is probably a consequence of competition between chylomicrons and very LDL cholesterol for the lipoprotein lipase.

Classically, chylomicron clearance occurs in two sequential steps: (1) TG hydrolysis by lipoprotein lipase and (2) uptake of the remnants by the liver.

Delay in the second step leads to accumulation of remnants in plasma and is generally thought to represent the atherogenic risk of hypertriglyceridaemia.

The conclusion of another study also indicated that there exists a consistent positive association between elevated maternal TG and the risk of pre-eclampsia.
During early pregnancy, maternal metabolic environment is modified by a rise in serum estrogen and progesterone level, pancreatic beta-cell hyperplasia and raised serum insulin level. This hyperinsulinemia causes peripheral glucose utilization, increased tissue storage of glycogen, increased storage of fats and decreased lipolysis.
Metabolism in pregnancy

- Maternal metabolism is designed to provide adequate nutrition for foetal growth, in the form of glucose, ketones, lipids, and other fuels.
- Maternal insulin resistance increases in third trimester; this combined with lipolysis in peripheral adipose tissue results in increased maternal lipoprotein concentrations and elevated lipoprotein triglyceride content.
- TG content predominantly increases in late gestation by about two to four times but precipitously falls to pre-pregnancy levels following delivery.
- Normal pregnancy is marked by an increases in lipid concentration as gestation progresses.
- These elevations are non atherogenic.
Dependent on acetyl-CoA, NADPH and ATP as an energy source for this process
State of relative insulin resistance (thereby releasing free fatty acids from adipocytes)
Occurs from the second trimester
Hyperlipidemic third-trimester

LDL levels ranged from 1.3 to 6.1 mmol/L, and were > 3.0 mmol/L in 60%

Hepatic lipase activity also increases during pregnancy, which causes surges of triglyceride synthesis

Postnatally, cholesterol levels fell rapidly and were similar to levels in the first trimester by 72 hours after delivery
Changes in pregnancy

- Hypercholesterolaemia during pregnancy is due to changes in sex steroid hormones, hepatic and adipose metabolism.
- During pregnancy there is an increased production of sex steroids.
- As well as LDL, apoB levels are elevated in pregnancy.
- Hepatic lipase activity also increases during pregnancy, which causes surges of triglyceride synthesis in the liver and is associated with raised LDL levels.
- VLDL metabolism is altered due to decreased lipoprotein lipase activity in the adipose tissue and increased activity in the placenta.
- 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.
LIPOPROTEIN METABOLISM
Adipose metabolism in pregnancy
The placenta is the central support organ for the developing foetus, serving as the site of maternal–fetal exchange of ions and lipids.
Possible slide overview of placenta and chol
This is a composite structure that separating the fetal blood from the maternal blood.

**It has four layers:**
- Syncytiotrophoblast
- Cytotrophoblast
- Connective tissue of villus
- Endothelium of fetal capillaries

After the 20th week, the cytotrophoblastic cells disappear and the placental membrane consists only of three layers.
**Placental (membranes) barrier:**
- These are layers separating the fetal blood in the villi from maternal blood in the intervillous space.
- These layers prevent mixing of the fetal and maternal blood but they allow passage of certain substances throw it.
- It is not a true barrier because only few substances are unable to cross it. Most drugs in the maternal blood can pass through it to the fetal circulation and cause major fetal congenital anomalies.
POSIBLE SLIDE OF AN OVERVIEW OF CHOLESTEROL
Lipid metabolism in pregnancy

- Free fatty acids, fatty acids and cholesterol are important for foetal growth and development which are provided via maternal lipoproteins.
- Very low density lipoprotein (VLDL), high density lipoprotein (HDL) and low density lipoprotein (LDL) content increase in pregnancy.
- VLDL levels are increased due to high oestrogen levels and also due to decreased lipoprotein lipase activity.
- Elevation in LDL in mid and late gestation occurs due to enhanced conversion of VLDL with increase in proportion of smaller dense LDL particles.
- Because of reduced hepatic lipase activity, there is reduced conversion of HDL2 to HDL3.
- It is HDL2 that is responsible for elevated HDL in pregnancy with peak levels during second trimester.
Maternal-Foetal interaction

- Maternal lipoproteins cannot cross placenta directly
- Although maternal cholesterol is an important source of cholesterol for the fetus during early gestation, its importance becomes minimal during late pregnancy, owing to the high capacity of fetal tissues to synthesize cholesterol
- They are transported to the foetus via specific lipoprotein receptors, lipases, and fatty acid binding transport proteins on the placenta
- Elevated TG and low levels of HDL-C are associated with adverse pregnancy outcomes in a non-diabetic pregnancy
alterations in lipogenesis have been linked to perinatal morbidity and mortality by recent studies which are ushering in the field of dyslipidemia in pregnancy as a hot area for outcomes research
CHO and TG INCREASE IN PREGNANT WOMEN

Maternal plasma CHO may increase through the 12th week of gestation while TGs reach the 150-300% of increase in the third trimester of pregnancy.

Amundsen AL, Atherosclerosis 2006
EFFECTS OF HYPERCHOLESTEROLAEMIA ON PREGNANCY OUTCOME

■ Unfavourable effects on the foetus and on pregnancy outcome
■ Risk of preterm delivery existed for mothers with an elevated total cholesterol
■ Women with a high cholesterol diet had an increased risk of developing GDM
■ Abnormal lipid parameters have also been suggested as a pathogenic factor in the development of pre-eclampsia
Maternal hypercholesterolemia is also suspected to be injurious, because concentrations >300 mg/dL have been linked to increased cholesterol deposition in the foetal aorta.

It is also reasoned that this elevated maternal cholesterol may have a disproportionate impact during critical periods for placentation and early neuro-epithelial expansion.
The guidelines do not recommend routinely checking cholesterol levels during pregnancy as cholesterol levels will increase and the use of most lipid-modifying agents are contraindicated.

Women should not resume statin therapy until after they have completed lactation.
NORMAL PREGNANCY

- Serum cholesterol levels can increase by as much as 25% to 50%,
- Triglyceride (TG) levels can double during the third trimester of pregnancy
- there is a link between pre-eclampsia and hypercholesterolemia
Pre-eclampsia

- hypertension,
- systemic chronic inflammation,
- oxidative stress OR antioxidant deficiency,
- diffuse endothelial activation,
- and dyslipidemia, particularly hypertriglyceridemia and reductions in plasma high density lipoprotein-cholesterol (HDL-cholesterol)
Maternal Exposure to Statins and Risk for Birth Defects: A Case-Series Approach

- based on a limited number of cases, we did not observe the distribution of defects previously described among cases born to mothers exposed to statins in pregnancy

Management

- 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.

- 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 foetal development.
Statins in pregnancy

- Animal data showing teratogenic potential at high doses and concern that they might disrupt cholesterol biosynthesis in the developing foetus.
- About half of all pregnancies in the United States are unintended.
- Women taking statins during the first trimester of pregnancy were at an increased risk of delivering an infant with malformations.
- The association was explained by underlying characteristics of users, mainly pre-existing diabetes.
- Statins themselves did not seem to have any meaningful teratogenic effect.
- The absolute risk of teratogenicity of statins, if any, appears relatively small. A large-scale study is needed to further characterize the teratogenic potential.

cohort of 886,996 pregnancies

BMJ 2015;350:h1035

Reproductive Toxicology 26 (2008) 175–177
Lipoprotein (a)

- is comprised of a LDL covalently bound to apolipoprotein (a) along the B100 portion
- studies have suggested a proatherogenic and prothrombotic effects
- a gender predilection where similar Lp(a) carry greater atherosclerotic risk in women versus age-matched men.
- During pregnancy, Lp(a) levels increase with gestational age and similar to other lipid fractions, fall to pre-pregnancy levels within six months postpartum
- Preeclamptic women tend to have increased levels of Lp(a), however no studies to date have demonstrated adverse pregnancy outcomes with elevations in Lp(a) concentration
Pre-Conception Dyslipidemia Is Associated with Development of Preeclampsia and Gestational Diabetes Mellitus

- To conclude, there was an increased rate of preeclampsia and gestational diabetes in women with low HDLc and high triglycerides values measured prior to conception. In view of high severity of the two pregnancy complications—the finding may warrant routine screening for the abnormal lipid profile, especially among women planning pregnancy and having an elevated risk of gestational diabetes and/or hypertensive disease of pregnancy.
Fig 1. Outcome rates in patients with triglyceride level above and below 150 mg/dL.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0139164
Fig 2. Outcome rates in patients with HDL level above and below 50 mg/dL.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0139164
Table 4. General estimating equation (GEE) for the prediction of the composite outcome (preeclampsia/GDM).

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.08</td>
<td>1.06–1.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>1.02</td>
<td>1.01–1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>1.04</td>
<td>1.03–1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fertility treatments</td>
<td>1.60</td>
<td>1.12–2.28</td>
<td>0.01</td>
</tr>
<tr>
<td>History of repeated abortions</td>
<td>1.80</td>
<td>1.32–2.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parity</td>
<td>0.91</td>
<td>0.88–0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose by 10 mg/dL</td>
<td>1.05</td>
<td>1.02–1.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Compared to triglycerides&lt;150 and HDLc&gt;50 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL</td>
<td>1.61</td>
<td>1.29–2.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDLc, mg/dL ≤50</td>
<td>1.33</td>
<td>1.09–1.63</td>
<td>0.01</td>
</tr>
<tr>
<td>TGL≥150 and HDLc≤50 mg/dL</td>
<td>2.32</td>
<td>1.80–2.99</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0139164
These derangements of elevated LDL-C fractions with lower HDL-C levels appear to be more pronounced in women with gestational hypertension and diabetes, and preeclampsia.

Women who have higher concentrations of small dense LDL fractions during pregnancy tend to have increased risk of cardiovascular disease later in life.
Pregnancy is also associated with alterations in the composition and size of LDL particles.

Previous studies have demonstrated that as TG levels increase, there is a decrease in overall LDL size with an increased proportion of smaller, denser LDL particles that are thought to be more atherogenic.

HDL-C levels and apolipoprotein A-I levels also increase during normal gestation, with peak levels during the second trimester.

Studies have suggested a potential protective effect to the mother to offset elevations in atherogenic LDL-C and TG levels.

Multiparous women tend to have relative decrease in HDL-C levels in comparison to their primiparous counterparts.
The current status of lipoprotein (a) in pregnancy

- The production of Lp(a) occurs at the hepatocyte surface and clearance is via the kidney
- Lp(a) accumulation in atherosclerotic lesions
- Pro-thrombotic effect
- Thought to predispose those with high levels to CHD
- Increased levels of Lp(a) compared to non-pregnant controls AND Lp(a) levels increase during the course of pregnancy
- No clear role of Lp(a) in either normal or complicated pregnancies: no consensus
IHD in pregnancy

- 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.
- cardiovascular disease that precedes gestation
- unmasked cardiovascular disease during pregnancy
- subset populations of gravid women with gestation hypertension and diabetes have more marked derangement of atherogenic lipid profiles
Lipid changes throughout pregnancy according to pre-pregnancy BMI: results from a prospective cohort

- Pre-pregnancy BMI was the main factor associated with the rate of change in TC and LDL-c throughout pregnancy, and OW and OB women presented lower rates of change compared with NW controls.
Material lipid profile during early pregnancy and pregnancy complications and outcomes: the ABCD study.

Vrijkotte TG, Krukziener N, Hutten BA, Vollebregt KC, van Eijsden M, Twisk JR.

CONTEXT: Elevated lipid levels during late pregnancy are associated with complications and adverse outcome for both mother and newborn. However, it is inconclusive whether a disturbed lipid profile during early pregnancy has similar negative associations.

OBJECTIVE: Our objective was to investigate whether nonfasting maternal total cholesterol and triglyceride levels during early pregnancy are associated with six major adverse pregnancy outcomes.

METHODS: Data were derived from the Amsterdam Born Children and Their Development (ABCD) cohort study. Random blood samples of nonfasting total cholesterol and triglyceride levels were determined during early gestation (median = 13, interquartile range = 12-14 wk). Outcome measures were pregnancy-induced hypertension (PIH), preeclampsia, preterm birth, small/large for gestational age (SGA/LGA), and child loss. Only nondiabetic women with singleton deliveries were included; the baseline sample consisted of 4008 women. Analysis for PIH and preeclampsia were performed in nulliparous women only (n = 2037).

RESULTS: Mean (sd) triglyceride and total cholesterol levels were 1.33 (0.55) and 4.98 (0.87) mmol/liter, respectively. The incidence of pregnancy complications and perinatal outcomes were as follows: PIH, 4.9%; preeclampsia, 3.7%; preterm birth, 5.3%; SGA, 9.3%; LGA, 9.3%; and child loss, 1.4%. After adjustments, every unit increase in triglyceride was linearly associated with an increased risk of PIH (odds ratio (OR) = 1.60, P = 0.021), preeclampsia (OR = 1.69, P = 0.018), LGA (OR = 1.48, P < 0.001), and induced preterm delivery (OR = 1.69, P = 0.006). No associations were found for SGA or child loss. Total cholesterol was not associated with any of the outcome measures.

CONCLUSIONS: Elevated maternal triglyceride levels measured during early pregnancy are associated with pregnancy complications and adverse pregnancy outcomes. These results suggest that future lifestyle programs in women of reproductive age with a focus on lowering triglyceride levels (i.e., diet, weight reduction, and physical activity) may help to prevent hypertensive complications during pregnancy and adverse birth outcomes.
Prenatal exposure to HMG-CoA reductase inhibitors: Effects on fetal and neonatal outcomes

- The absolute risk of teratogenicity of statins, if any, appears relatively small.
- A large-scale study is needed to further characterize the teratogenic potential
Maternal Erythrocyte Omega-3 and Omega-6 Fatty Acids, and Plasma Lipid Concentrations, are Associated with Habitual Dietary Fish Consumption in Early Pregnancy

- Women who consumed fish > twice/week had lower plasma triglyceride (−11.5 mg/dl) and higher HDL-cholesterol (+2.8 mg/dl) concentrations than women consuming fish < once/week.
<table>
<thead>
<tr>
<th>MATERNAL DISORDERS</th>
<th>FETAL CONSEQUENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial hypercholesterolemia</td>
<td>High LDL CHO</td>
</tr>
<tr>
<td></td>
<td>Preterm birth</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>Altered placental transfer of lipids</td>
</tr>
<tr>
<td></td>
<td>High TGs</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Malformation and macrosomia</td>
</tr>
<tr>
<td></td>
<td>High VLDL and LDL</td>
</tr>
<tr>
<td>Intrauterine Growth Restriction</td>
<td>Low CHO, LDL CHO, HDL CHO</td>
</tr>
<tr>
<td></td>
<td>High TGs</td>
</tr>
<tr>
<td><strong>FETAL DISORDER</strong></td>
<td></td>
</tr>
<tr>
<td>Smith-Lemli-Opitz syndrome</td>
<td>Central nervous system anomalies</td>
</tr>
<tr>
<td></td>
<td>Deficient CHO</td>
</tr>
</tbody>
</table>
MI in pregnancy

- **Myocardial Infarction in Diabetic Pregnancy**
  Coronary heart disease and myocardial infarction are uncommon complications during pregnancy. Preexisting diabetes, metabolic syndrome, obesity, pre-eclampsia further increase the risk of acute coronary events complicating pregnancy. Symptomatic coronary artery disease in women with pregestational diabetes mellitus is most commonly seen in those with long standing disease, nephropathy and hypertension.

- Women with type 1 diabetes have a much greater risk of serious coronary heart disease, but few cases of myocardial infarctions occurring during pregnancy have been reported. Women with type 1 diabetes have an increased risk of coronary artery disease and seem to lose the protective effect of estrogen that limits the incidence of coronary artery disease in women without diabetes. The experience at the Joslin Clinic has suggested that, in patients with type 1 diabetes, arterial age equals chronologic age plus the number of years of diabetes. Thus, the risk of a 30 year old women with type 1 diabetes for 20 years might approximate that of a 50 year old individual.\(^{22}\)

- The reported maternal mortality in diabetic women with myocardial infarctions during pregnancy seems to be higher than in the nondiabetic patient, but comparisons are difficult given the small number of patients. Of the 10 patients reported, maternal mortality was 50 percent and foetal loss 60 percent. The amount of cardiac function remaining after infarction appears to be a major determinant of pregnancy outcome.\(^ {23}\)
The hyperlipidemia of pregnancy in normal and complicated pregnancies

- Alterations in the concentrations of the cholesterol and triglyceride moieties of lipoproteins separated by ultracentrifugation and precipitation methods were studied at frequent intervals throughout pregnancy and the puerperium in a group of 43 women. The plasma cholesterol concentration rose on the average by about 50 per cent, the major increase occurring in the second trimester. The plasma triglyceride concentration rose threefold, reaching its peak during the third trimester. All major lipoproteins participated in these changes: in very-low-density lipoproteins, both lipids rose in proportion to the ratio in nonpregnant women, but in low-density and high-density lipoproteins, the ratio of triglyceride to cholesterol rose. The triglyceride enrichment in low-density lipoproteins reflected the inclusion of intermediate-density lipoproteins (d 1.006 to 1.019). The occurrence of hypertension or pre-eclampsia led to a further increase in lipids in very-low-density lipoproteins. Hypercholesterolemia was greatest in women with pre-existing hypercholesterolemia, and women in the third pregnancy showed higher plasma cholesterol concentrations than women in the first pregnancy. Both cholesterol and triglyceride concentrations decreased significantly within 24 hours of delivery and this was reflected in all lipoproteins. However, while triglyceride levels continued to decrease rapidly returning to nonpregnant levels during the puerperium, cholesterol in low-density lipoprotein remained elevated for at least six to seven weeks post partum.

PUBLISHED | 1979 in American Journal of Obstetrics and Gynecology [IF: 5.23]
DOI | 10.1016/0002-9378(79)90469-1
Possible discussion on mi and preg
- Placental transfer of statins
- Atorva and Rosuva found in breast milk
Statins and other lipid-lowering therapy and pregnancy outcomes in homozygous familial hypercholesterolaemia: A retrospective review of 39 pregnancies
Theunis C. Bothaa, *, Gillian J. Pilcherb, Karen Wolmaransc, Dirk J. Blomc, Frederick J. Raal

LDLR dysfunction. The prevalence of HoFH is 1 in 160,000 to 1,000,000 worldwide but in founder populations, such as the Afrikaners in South Africa, the prevalence can be as high as 1 in 30,000 [1–3].
atogenicity when ezetimibe was used in high dosages [19]. Lomitapide was found to be teratogenic at therapeutic dosages. Animal studies did not show any teratogenicity with the use of mipomersen however [20]. Studies that evaluated the safety of the PCSK9 inhibitor evolocumab showed no negative effect during pregnancy but did confirm placental transfer to the infant [21].
Women with FH & Pregnancy

- Cholesterol increases significantly during pregnancy by about 25-50%. Women with FH experience the same increase, but since they are starting out at a much higher baseline, they can get extremely high cholesterol during pregnancy.
Maternal dyslipidemia during pregnancy may increase the risk of preterm birth: A meta-analysis

- The present meta-analysis found that maternal dyslipidemia during pregnancy, either the elevated total cholesterol or triglycerides, was associated with an increased risk of PTB.
- These findings indicate that a normal level of maternal lipid during pregnancy may reduce the risk of PTB.
Preterm delivery and low maternal serum cholesterol level: Any correlation?

- Based on this study, low maternal serum cholesterol (hypocholesterolaemia) is associated with preterm delivery. It is therefore recommended that pregnant women should be encouraged to follow a healthy balanced diet intake in order to maintain an optimal range of maternal serum cholesterol during pregnancy to avoid preterm delivery.
Our analysis showed an increased rate of preeclampsia and/or gestational diabetes in women with low HDLc and high triglycerides values prior to conception. In view of the severity of these pregnancy complications, we believe this finding warrants a routine screening for the abnormal lipid profile among women of a child-bearing age.

Outcome rates in patients with triglyceride level above and below 150 mg/dL.
General estimating equation (GEE) for the prediction of the composite outcome (preeclampsia/GDM).

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>1.08</td>
<td>1.06–1.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>1.02</td>
<td>1.01–1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>1.04</td>
<td>1.03–1.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fertility treatments</td>
<td>1.60</td>
<td>1.12–2.28</td>
<td>0.01</td>
</tr>
<tr>
<td>History of repeated abortions</td>
<td>1.80</td>
<td>1.32–2.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Party</td>
<td>0.91</td>
<td>0.88–0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose by 10 mg/dL</td>
<td>1.05</td>
<td>1.02–1.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Compared to triglycerides &lt;150 mg/dL and HDLc &gt; 50 mg/dL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides ≥150 mg/dL</td>
<td>1.51</td>
<td>1.29–2.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDLc, mg/dL ≤50</td>
<td>1.33</td>
<td>1.09–1.63</td>
<td>0.01</td>
</tr>
<tr>
<td>TGL ≥150 and HDLc ≤50 mg/dL</td>
<td>2.32</td>
<td>1.80–2.99</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
EFFECTS OF HYPERCHOLESTEROLAEMIA ON THE FETUS

- Foetal effects on adult disease
  - fetal atherosclerosis
Dyslipidemia in pregnancy may contribute to increased risk of congenital heart defects

- Increases in the LDL-c and apolipoprotein B levels may be involved in the pathogenesis of CHD

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Case group (n=18)</th>
<th>Control group (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>6.48±0.97</td>
<td>6.38±0.99</td>
</tr>
<tr>
<td>Triglycerides, mmol/l</td>
<td>2.49±0.64</td>
<td>2.51±0.74</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/l</td>
<td>1.9±0.43</td>
<td>1.95±0.74</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/l</td>
<td>4.15±0.88*</td>
<td>3.45±0.76</td>
</tr>
<tr>
<td>Total cholesterol/HDL-cholesterol</td>
<td>3.47±0.45</td>
<td>3.46±0.78</td>
</tr>
<tr>
<td>Apolipoprotein A-1, g/l</td>
<td>2.35±0.48</td>
<td>2.32±0.47</td>
</tr>
<tr>
<td>Apolipoprotein B, g/l</td>
<td>2.23±0.2*</td>
<td>1.78±0.19</td>
</tr>
<tr>
<td>Apolipoprotein B/A-1</td>
<td>0.54±0.13</td>
<td>0.46±0.09</td>
</tr>
<tr>
<td>Homocysteine nmol/ml</td>
<td>0.44±0.38*</td>
<td>0.17±0.1</td>
</tr>
</tbody>
</table>

Dyslipidemia in pregnancy may contribute to increased risk of congenital heart defects

- In conclusion, the results of this study showed that the LDL-c and apolipoprotein B levels were significantly higher in the case group than in the control group. After adjusting for potential confounders, a lipid profile with apolipoprotein B > 1.81 mg/dl was associated with a higher incidence rate of CHD. Taken together, our results suggest that dyslipidemia in pregnancy may contribute to an increased risk of CHDs.
Fatty Streak Formation Occurs in Human Fetal Aortas and is Greatly Enhanced by Maternal Hypercholesterolemia

Familial Hypercholesterolemia and Pregnancy: Risk and Management
Oxidatively modified LDL particles in the human placenta in early and late onset intrauterine growth restriction

- IUGR shares common patho-mechanisms with atherosclerotic diseases in which increased lipid peroxidation and oxidation of mainly low-density lipoproteins (LDL) to oxidized LDL in the vascular wall.
- Oxidatively modified LDLs become unrecognizable by the LDL receptor and thus accumulate within tissues where they provoke an inflammatory reaction.
- Conclude that the reduced maternal LDL cholesterol concentration in IUGR pregnancies is attributed to increased accumulation of oxidized LDL particles within the placenta at least in early onset IUGR.

http://dx.doi.org/10.1016/j.placenta.2013.10.006

/ Placenta 34 (2013) 1142e1149
**IUGR**

**Intrauterine growth restriction (IUGR)**

Small for gestational age newborn

**MOTHER**
- insufficient trophoblast development
- atherosclerotic placental lesions
- low maternal LDLc-C and TC

**FETUS**
- HDL-C and LDL-C decrease in the cord blood
- oxLDL/LDL ratio increase
- TG significantly increased

**OUTCOME**
pathogenic links between low birth weight for gestational age and adulthood cardiovascular events is suggested.
Although the relative increase in TC and TG levels is about the same in those with FH compared with unaffected individuals, the absolute serum concentrations are usually much greater in those with FH.

The authors of several studies, however, have shown no difference in pregnancy outcomes between those with FH and normal patients.

Guidelines recommend that all women stop taking statins 3 months prior to attempting to conceive.

Women should not resume statin therapy until after they have completed lactation.
HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom

- Pregnancy is hazardous for patients with HoFH.
- Patients should be advised that pregnancy in HoFH is hazardous.
- Pre-conception, women should be referred to a cardiologist. The pressure gradient across the aortic valve and root should be assessed by echocardiography.
- Pre-conception, women with HoFH should be counselled that their children will have HeFH and if their partner has HeFH the risk of HoFH is 1 in 2.
- A clinical trial (NCT02399839) is addressing the effect of flominlapide exposure at conception and during pregnancy on major congenital abnormalities.

Atherosclerosis 255 (2016) 128e139
IN FUTURE

- International pregnancy-specific normal cholesterol reference ranges need to be agreed in order to classify high maternal cholesterol levels and to determine their significance.

- Intervention with a cholesterol-lowering diet may be necessary and prove beneficial (Women who consumed fish > twice/week had lower plasma triglyceride (−11.5 mg/dl) and higher HDL-cholesterol (+2.8 mg/dl) concentrations than women consuming fish < once/week) (1).

- A large-scale statin study is needed to further characterize the teratogenic potential.

Future studies

- 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.
Increased cholesterol synthesis in the liver as the result of increased oestrogen and progesterone

Important part of the **cell membrane**, controlling cell **membrane permeability**

Hyperlipidemia in pregnancy provides a functional reservoir for the foetus – allowing cholesterol, to be used for building foetal cellular membranes, **steroid hormones**, and bile acids

Cholesterol is a **direct precursor of steroid hormones**, including corticosteroids, androgens, oestrogens, progesterone and vitamin D, some of which are produced in the placenta.
Increased cholesterol synthesis in the liver as the result of increased oestrogen and progesterone

Cholesterol is a direct precursor of steroid hormones, including corticosteroids, androgens, oestrogens, progesterone and vitamin D, some of which are produced in the placenta
Normal pregnancy lipid metabolism

- **First trimester**, marked deposition and hypertrophy of maternal adipocytes with increased expression of insulin receptors such that glucose is available to meet the metabolic demand of the growing foetus.

- Increase in maternal insulin in addition to production of progesterone leads to **lipogenesis with diminished lipolysis**, and increased production of lipids, which then are **transported across the placenta** and metabolized; this signifies the essential role of lipids to normal foetal development.

- While both TC and TG rise throughout pregnancy, **disproportionate rise in TG** in comparison to other lipid fractions reaching **two to four times** pre-pregnancy levels by the third trimester.

- These changes are felt to be generally non-atherogenic, and fall precipitously to pre-pregnancy levels following delivery.
While both TC and TG rise throughout pregnancy, disproportionate rise in TG in comparison to other lipid fractions reaching two to four times pre-pregnancy levels by the third trimester.

These changes are felt to be generally non-atherogenic, and fall precipitously to pre-pregnancy levels following delivery.
FH and effect on pregnancy

- Maternal hypercholesterolemia during pregnancy may program lipid metabolism to a certain extent in the foetus

- **THE absolute serum TC/TG concentrations** are usually much greater in mothers with FH
- **No difference in pregnancy outcomes** between those with FH and normal patients
- Guidelines recommend that all women stop taking statins **3 months** prior to attempting to conceive
- Women should not resume statin therapy until **after they have completed lactation**

Arterioscler Thromb Vasc Biol. 2010;30:2673-2677
Lipid drugs

- Ezetimibe, nicotinic acid, and fibrates have all been associated with teratogenic effects in animal studies.

- Only medications currently acceptable to use during pregnancy are the bile acid-binding resins, cholestyramine, because these medications do not pass into the systemic circulation and have not been shown to have any adverse effects.

- Caution should be taken when prescribing BAS to those with triglyceride levels > 300 mg/dL and is contraindicated in those with levels > 400 mg/dL due to increased risk of pancreatitis.

Journal of Clinical Lipidology (2012) 6, 88–91