Lipids and lipoproteins in plasma from early pregnancy to postpartum and associations with ethnic background: a population-based cohort study from Norway

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Running title: Ethnic differences in maternal lipid levels.

Abstract

Objective

To describe ethnic differences in plasma lipid levels and their changes during pregnancy to postpartum.

Design

Population-based cohort study

Setting

Primary antenatal care, Eastern Oslo, Norway

Population or Sample

Healthy pregnant women, 59% with ethnic minority background (n=806).

Methods

Fasting lipid levels were measured at gestational week (GW) 15, 28 and 14 weeks postpartum. We performed linear regression models and linear mixed models to explore the total effect of ethnicity on lipids, adjusting for GW or week postpartum, age and education.

Main Outcome Measures

Levels of triglycerides, HDL-, LDL- and total cholesterol.

Results

At GW 15, triglyceride levels were lower in women of African origin (1.03 mmol/mol (95% CI: 0.90, 1.16)) and higher in women of South Asian (1.42 mmol/mol (1.35, 1.49)) and East Asian origin (1.58 mmol/mol (1.43, 1.73)) compared with Western Europeans (1.26 mmol/mol (1.20, 1.32)). Women of Asian and African origin had a smaller increase in triglycerides, LDL and total cholesterol from GW 15 to 28. At GW 28 LDL-cholesterol levels were lowest among East Asians at (3.03 mmol/mol (2.72, 3.34)) compared with Western Europeans (3.62 mmol/mol

(3.50, 3.74)). Triglyceride and HDL-cholesterol levels were lower postpartum than in early pregnancy in all groups, but LDL-cholesterol levels were higher, except in Africans. South and East Asian women had lower HDL-cholesterol and higher triglycerides postpartum, while African women had lower triglyceride levels than Western Europeans.

Conclusion

We found significant differences in lipid levels and changes during pregnancy and the early postpartum period related to ethnic origin.

Key words; ethnicity, lipids, pregnancy, postpartum.

Tweetable abstract

The first study to report ethnic differences in lipid levels from early pregnancy to postpartum in a multi-ethnic population.

Introduction

During normal pregnancy, physiological changes in glucose and lipid metabolism occur to ensure continuous supply of nutrients to the growing foetus.[1,2] After an initial decrease in early pregnancy, there is a progressive increase in plasma triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and total cholesterol as pregnancy progresses.[1-6] These elevations are partly reversed postpartum, although affected by hormone levels and lactation.[7-9]

The increase in maternal lipid levels has physiologic advantages. The early changes in lipid metabolism promote the accumulation of maternal fat stores in early and mid-pregnancy, allows fat mobilization as a maternal energy source in late pregnancy and facilitate transport of lipids across the placenta.[1] Triglycerides are hydrolysed by lipases on the maternal side of the syncytiotrophoblast, and free fatty acids are released and taken up by the placenta. Cholesterol is important for placental and foetal growth and maturation and necessary for steroid hormone synthesis. The foetus uses maternal cholesterol transferred across the placenta, and later in pregnancy also cholesterol from own synthesis. Cholesterol is probably delivered to the placenta by LDL-cholesterol, taken up by endocytosis. Data utilizing four-vessel sampling at caesarean section indicate that HDL-cholesterol is involved in the release of cholesterol from the placenta to the foetal circulation.[10]

High maternal levels of triglycerides, LDL- and total cholesterol and low HDL-cholesterol are found to be associated with several pregnancy complications, such as pregnancy-related hypertension[11], pre-eclampsia[12,13], preterm birth[14-17], gestational diabetes (GDM)[18,19] and foetal overgrowth.[20-23] The most consistent associations seem to be present for triglycerides.[2] The

prevalence of GDM, preterm birth and low birth weight differs by ethnicity, and we and others have reported ethnic differences in foetal growth.[24] Adverse lipid profiles are strongly related to cardiometabolic diseases, but of note, women with pregnancy complications like preeclampsia and GDM are also at higher risk of later cardiovascular disease (CVD) and type 2 diabetes,[21,25-27] Ethnic differences in lipid levels outside pregnancy are well documented, with women of South Asian origin displaying higher triglycerides, lower HDL-cholesterol and more small, dense LDL-cholesterol particles related to insulin resistance, compared with women of Western European origin.[28,29] Findings also suggest that women of African origin have lower triglycerides.[30] Nevertheless, few studies have explored ethnic differences in plasma lipid profiles in pregnancy.[31-34] Furthermore, consensus about normal reference values for lipids during pregnancy and postpartum is lacking. Our aims were to describe ethnic differences in plasma lipid levels and their changes during pregnancy to postpartum.

Methods

Study population and data collection

The Stork Groruddalen study is a longitudinal, population-based cohort study of 823 healthy pregnant women (59% from non-Western ethnic minority groups) representative for the largest ethnic groups in Norway, set up in 2008 at three Child Health Clinics in Groruddalen, Oslo, Norway. The study methods have been described in detail elsewhere.[35,36] In short, fasting blood samples were drawn, and data from questionnaires and physical examinations including anthropometric measurements were collected according to a detailed protocol at three time points: mean (SD) gestational week (GW) 15 (3.4), GW 28 (1.3) and 14 (2.8) weeks postpartum.[37] Women were included in the study if they 1) lived in one of the three study

districts, 2) planned to give birth at one of the two study hospitals, 3) were < 20 weeks pregnant, 4) could communicate in Norwegian, Arabic, English, Sorani, Somali, Tamil, Turkish, Urdu or Vietnamese and 5) could give informed written consent.[37] Women with known pre-pregnancy diabetes or other diseases necessitating hospital follow-up during pregnancy were excluded.[37] The interviews were performed by midwifes, and assisted by professional translators when needed. This work was funded by the authors' institutions. Data collection for the STORK Groruddalen was funded by The Research Council of Norway, The South-Eastern Norway Regional Health Authority and participating city districts. Although the STORK Groruddalen study is based on extensive collaboration with user organizations, no formal patient or public panel was set up in relation to this study.

Primary outcomes

Fasting triglycerides, HDL-, LDL-cholesterol and total cholesterol, all measured in mmol/L at inclusion, in GW 28 and 14 weeks postpartum, were primary outcomes. Fasting triglycerides, HDL- and total cholesterol were analysed in serum with a colorimetric method (Vitros 5.1 FS, Ortho clinical diagnostic). LDL-cholesterol was calculated using Friedewald`s formula[38] as follows: LDL-cholesterol = total cholesterol – HDL-cholesterol – (0.45 x triglycerides) mmol/L, which correlate well with directly measured LDL both early and late in pregnancy (r=0.97).[39] No women used lipid-lowering agents at any visit.

Exposure variable – ethnicity

Ethnicity may be defined as the social group a person belongs to, implying a shared culture, history, geographical origin, language, lifestyle factors, physical, genetic and other factors.[40] In

this study, ethnic origin was based on the participant's country of birth or that of the participant's mother if the mother was born outside Europe or North-America, and further categorized as Western Europe (primarily Norway, Sweden and Denmark), South Asia (primarily Pakistan and Sri Lanka), the Middle East (primarily Iraq, Turkey, Morocco and Afghanistan), Africa (primarily Somalia, Eritrea and Ethiopia), East Asia (primarily Vietnam, Philippines and Thailand), and Eastern Europe (primarily Poland, Russia and Kosovo). Nearly all women with non-Norwegian background were born in their country of origin, except for women of Pakistani origin (32 % born in Norway).

Covariates

Age of study participants and timing of lipid measurements (GW and weeks postpartum) were used as continuous variables.[36] Week was mean centred at each visit. Educational levels were categorised as "primary school or less", "high school/secondary school" or "college/university" (completed education equivalent to at least a bachelor's degree). From the cohort, we have information about a large variety of factors that may be on the causal pathway between ethnicity and lipid levels (i.e. mediators). However, we considered maternal body fat (measured by a Tanita-weight BC 418 MA (Tanita, Tokyo, Japan), to be the most important possible mediating variable to be included in supplementary analyses, and hence fat mass index (kg/m^2) was calculated (total fat mass (kg)/height $(meter)^2$). Information about breastfeeding was recorded at the postpartum visit using the response categories "exclusive", "partial" and "never" during the last 14 days.[41]

Study sample

In total, 823 women were included at mean GW 15. We excluded women with South- or Central American origin (n=12) due to low numbers, and women with missing values for fasting lipids (n=5) at enrolment, leaving an eligible sample of 806 women with valid data from GW 15 on triglycerides, HDL-cholesterol, LDL-cholesterol and total cholesterol. Of these, 759 (94%) women attended at GW 28 and 653 (81%) women attended 14 weeks postpartum (Figure S1). At the postpartum visit, due to resource limitations, women with ethnic minority background were prioritized for fasting blood samples, so we lack data on lipids for about seventy women, mostly ethnic Norwegians.[42]

Statistical analyses

Characteristics of the cohort by ethnic groups are presented by mean values, standard deviation (SD) and numbers/proportions (%). Shapiro-Wilk and the Kolmogorov Smirnov tests indicated that all outcome variables, except triglycerides, were normally distributed. However, we ran models without transforming the triglyceride data, as we assumed that the linear regression was robust to this diversion from normality.

As our aim was to explore the total effect of ethnicity on lipids, a direct acyclic graph (DAG) was drawn prior to analyses to depict causal structures of possible pathways and associations between ethnicity and plasma lipids (Figure S2). Per definition there are no real confounders to these relationships, as no other factors could affect the participant's ethnicity. However, study inclusion varied by ethnic groups, this could happen as a result of selection. GW (visit 1 and 2), and weeks postpartum (visit 3), age and educational level may be related to selection and lipid levels, thus we illustrated the selection mechanism in the DAG by including a

binary variable S (1=included, 0=not included). Several arrows collide in the selection variable S. Study participants by definition have S=1, this condition induces "collider stratification bias", which is one type of selection bias.[43] To control for selection bias in the primary analyses exploring the total effect of ethnicity, we adjusted for these covariates associated with selection, but we did not adjust for variables that are part of the causal chain. To examine ethnic group differences at each of the three time points, we ran linear regression models adjusting for GW or weeks postpartum (Model 1), additionally adjusted for age (Model 2), and additionally adjusted for educational level (Model 3). Linear mixed effect regression models were fitted with an interaction term between time and ethnic group to explore ethnic differences in changes in plasma lipids from early pregnancy to GW 28 and from early pregnancy to 14 weeks postpartum, using similar model building as the cross-sectional analyses.

In Model 4, we also assessed the effect of ethnicity after having closed the mediating path through fat mass by including fat mass index (total kg fat mass/m^2). In cross-sectional analyses, we used the simultaneously measured fat mass index in the models, and in analyses of changes in lipids we included fat mass index at inclusion. Lastly, we also included maternal breastfeeding, considered as an important mediator, in the analyses of postpartum outcomes (Model 5).

Results from the regression analyses are presented as adjusted means and regression coefficients (β) with 95% confidence intervals (CIs). For consistency when reporting ethnic differences, we used women with Western European origin as reference group. Stata/SE 16.1 was used for all analyses. RStudio version 3.3.2 (2016-10-31) was used to create the figures.

Results

Among the 806 women, mean age at inclusion was 29.8 (SD: 4.8) years (Table 1). About 17% had primary school education or less, and 44% had completed education at college/university level. Mean GW was 15.0 (3.4) at inclusion, 28.3 (1.3) at the second visit and the third visit was 14.2 (2.8) weeks postpartum. Pre-pregnant BMI was 24.5 (4.8) kg/m^2 and mean fat mass index (kg/m^2) at inclusion was 8.8 (3.6) kg/m^2, and displayed some variation between ethnic groups.

Lipid levels and changes during pregnancy and from early pregnancy to postpartum

Lipid levels by ethnic groups, only adjusted for GW at each visit, are presented in Table 2. Estimates obtained from the cross-sectional analyses (Model 1) changed marginally after additional adjustments for age (Model 2) and education (Model 3) (Table S1a-c). Results for Model 3 are visualized in Figures 1a-d. Compared with women of Western European origin, triglycerides were lower in women with African origin in early pregnancy, and higher in women of South- and East Asian origin. LDL-cholesterol was lower in women of East Asian origin, while for HDL- and total cholesterol no ethnic differences were observed (Figures 1a-d).

Changes in plasma lipids (during pregnancy and from early pregnancy to postpartum) are presented in Tables S2a-b and Figures 2a-d. From GW 15 to 28 all lipids increased in all ethnic groups. In women of Western European origin, triglycerides increased by 60%, LDL-cholesterol by 32%, total cholesterol by 26% and HDL-cholesterol by 9% (Figures 2a-d). The increase in triglycerides was smaller in women of African and South Asian origin, and the increase in LDL-

and total cholesterol was generally smaller in women of non-European origin compared with Western and Eastern Europeans. Therefore, in GW 28, compared with women of Western European origin, triglycerides were lower in women with African origin, LDL-cholesterol levels lower in women of South Asian, Middle Eastern and East Asian origin, and total cholesterol levels lower in women with South Asian and Middle Eastern origin. HDL-cholesterol levels were higher in women with East Asian origin (Figures 1a-d).

At 14 weeks postpartum, triglyceride and HDL-cholesterol levels were reduced compared with GW 15 in all ethnic groups, while LDL-cholesterol levels were higher in all groups, and no changes were observed for total cholesterol (except for women of African origin) (Figures 2a-d). The reduction in HDL-cholesterol was more pronounced in women of South- and East Asian origin and Eastern Europeans compared with Western Europeans. At the postpartum visit, triglycerides were lower in women of African origin compared with Western Europeans, while higher in women of South Asian origin, who also had lower HDL-cholesterol, while no ethnic differences were observed for LDL-and total cholesterol (Figures 1a-d).

We also explored the direct effect of ethnicity after additionally adjusting for fat mass index (kg/m^2) (Model 4 in Tables S1a-c, S2a-b), and found that all estimates for lipid levels at each time-point and for changes in lipids during pregnancy and from early pregnancy to postpartum changed only marginally. Further, adding breastfeeding to the model at the postpartum visit had no impact on the effect estimates for the ethnic differences (Model 5 in Tables S1c).

Discussion

Main findings

To the best of our knowledge, this is the first study to report ethnic differences in lipid levels from early pregnancy to postpartum in a multi-ethnic population. Ethnic differences varied by GW and type of lipids. Compared with Western Europeans, women of African origin had lower triglycerides at all time-points, while women with origin from South Asia had higher triglycerides in early pregnancy and postpartum, and lower HDL-cholesterol levels postpartum. As the increase in triglycerides, LDL- and total cholesterol levels during pregnancy was generally smaller in most non-European ethnic minority groups, Europeans had the highest LDL- and total cholesterol levels at GW 28, while East Asians had the lowest LDL- and the highest HDL-cholesterol level. At the postpartum visit, triglycerides and HDL-cholesterol levels were lower than in early pregnancy, but LDL-cholesterol levels were still higher than in early pregnancy in all groups except for Africans.

Strengths and limitations

The strengths of this study include the population-based design, the large proportion of ethnic minority women, minor loss to follow-up during pregnancy[37] and measurements of fasting lipids measured by standard methods from three time-points. However, heterogeneity within relatively broad ethnic groups probably exists, the number in some ethnic groups was low, and some loss to follow-up at the postpartum visit was observed. Further, we lack information about lipid values before pregnancy.

Interpretation

Through our systematic search we identified only five studies assessing ethnic differences in lipids/lipoproteins in pregnancy; three from Europe[31-33] and two from the US,[14,44] all based on one

266single measurement, and none reported changes during pregnancy or from pregnancy to
267postpartum. Comparisons are further hampered by methodological issues such as differences in
268design (prospective, case control and cross-sectional studies), timing of measurements, fasting
269status, differential adjustment for confounders and mediators, and different ethnic groups
270included. Some studies included mainly high risk groups[14,32], thus not representative for the
271general population of pregnant women. One study from UK found that women of African origin
272had lower fasting triglycerides, LDL- and total cholesterol and higher HDL-cholesterol in GW
27330 than Caucasians[32], in line with our results from GW 28 (for triglycerides, LDL-and total
274cholesterol), with studies from the US[14,44] and with studies outside pregnancy.[30] Similarly, lower
275non-fasting total cholesterol levels were found in early pregnancy in African-Caribbean,
276Ghanaian and Moroccan women (in contrast to our findings), and lower triglycerides in
277Ghanaians than in Dutch women, while Turkish and South Asian origin (Surinam-Hindustani)
278had slightly higher levels, in line with our findings.[33] Two other studies have also found that
279women of South Asian origin had higher levels of triglycerides than Europeans both in early
280pregnancy[44] and in GW 26.[31]

281 Pregnancy is considered a "natural stress test" for women, as complications like GDM
282and preeclampsia seem to be early markers of metabolic disturbances, endothelial dysfunction
283and/or hypertension that predict future risk of type 2 diabetes,[26] and CVD.[45] The dysmetabolic
284pattern observed in women of South Asian origin during pregnancy and postpartum, is in line
285with their higher risk of insulin resistance during pregnancy and postpartum,[46] higher postpartum
286weight retention[47] and fat mass,[48] with studies outside pregnancy[29] and in childhood.[49] Further,
287the earlier onset of type 2 diabetes and CVD in South Asians than in Europeans,[50,51] seems to be
288partly related to differences in body composition and a particular susceptibility for an obeso-

genetic environment.[29] In contrast, the healthier lipid profile outside pregnancy for African origin populations,[30] which may be reflected in our study, seems to be related to differences in physiology, with relatively more accumulation of fat in the subcutaneous than visceral compartment, greater lipoprotein lipase activity and a higher insulin response than in Europeans.[30] The risk of CVD in subjects of African origin seems to be more driven by blood pressure, while associations with lipids are weaker.[30,52]

The pregnancy induced elevations in lipid concentrations usually drop within 24 hours postpartum[4], while LDL-cholesterol may remain elevated for at least seven weeks postpartum.[3] We found that levels of LDL-cholesterol were still higher than in early pregnancy at the visit 14 weeks postpartum in all ethnic groups, except in women of African origin. If we assume that the ethnic differences in early pregnancy reflect similar differences before conception, pregnancy might promote an adverse development in LDL-cholesterol and risk of CVD, in line with what we previously have found for development of blood pressure[53] and postpartum weight retention,[54] and is worrisome in relation to the next pregnancy.[55]

Cultural factors, socioeconomic status and integration impose a strong influence on lifestyle, not least the diet[56], over generations[29], and may contribute to ethnic differences in lipid levels, mediated by body fat[30] or weight gain during pregnancy.[57] Our secondary analyses indicate that maternal body fat contributes only marginally to the observed ethnic differences in lipids. However, body composition, the proportion of visceral fat, the role of lipoprotein lipase and of insulin resistance differ by ethnicity, probably related to genetics and/or epigenetics,[28-30] and influence lipid and lipoprotein metabolism. Furthermore, hormonal changes (e.g. oestrogen) may drive the increase in triglyceride levels[7], but little is known about ethnic differences in hormone levels during pregnancy and postpartum. Human breast milk has a high content of

triglycerides, and women who breastfeed tend to have lower levels of total cholesterol, triglycerides and very low density lipoprotein (VLDL)-cholesterol than women who do not breastfeed.[8] Pregnancy induces an atherogenic lipid profile, which seems to be partly reversed by lactation.[8,58] Nevertheless, ethnic differences in lipid levels postpartum were not explained by differences in breastfeeding in our study.

The most consistent associations between lipid levels and foetal growth and other pregnancy outcomes seem to be present for triglycerides.[2] We only identified two studies exploring relations between lipids and pregnancy outcomes like preterm delivery[14], pregnancy-induced hypertension, preeclampsia and foetal growth in multi-ethnic samples, with similar results before and after adjustments for ethnicity.[34] However, one study assessing the relation between maternal lipid genetic risk scores and foetal growth, found that associations for triglyceride scores varied by ethnicity, obesity status and offspring sex.[44] From our cohort, we have previously reported that birth weight was lowest in offspring of mothers of Asian origin,[59,60] the ethnic group with the highest triglyceride levels during pregnancy in this study. Further, HDL-cholesterol in GW 28 was inversely associated with birth weight, but not with neonatal sum of skinfolds, and no strong associations with triglycerides were observed.[22] However, LDL-cholesterol is also an important source of cholesterol for the foetus, and the syncytiotrophoblast, the functional unit of the placenta, can take up maternal LDL-cholesterol particles by endocytosis[61]. At this stage we can only speculate if the lower LDL-cholesterol in early pregnancy and the smaller increase in South- and East Asians during pregnancy may be related to slower foetal growth and smaller offspring size.[24,62] If so, ethnic differences in placental transfer and metabolism of lipids may be present, probably involving complex mechanisms.[10]

Conclusions

Increased awareness among clinicians about the striking ethnic differences in lipid levels observed during pregnancy to postpartum seems indicated. A better understanding of causes for these observed ethnic differences in lipids and whether they can be linked to ethnic differences in pregnancy outcomes and long term effects for women and their children are needed. Further, larger studies are recommended to study whether these effects are similar across ethnic groups.

Disclosure of interests

All authors declare that they have no conflict of interest.

Contribution to authorship

CWW, HS, AKJ, KIB and LS have all contributed to the planning and design of the manuscript. CWW, IM and KRR analysed the data. CWW prepared the tables and IM and HS prepared the figures. CWW wrote the first draft of the manuscript with major contribution from AKJ and LS. CWW, IM, HS, AKJ, KIB, NS, TMM, KRR and LS contributed to the interpretation of the data, critically revised the manuscript and approved the final version.

Details of ethic approval

The Regional Ethics Committee (2007/894) and the Norwegian Data Inspectorate (25 October 2007; 07/01355-2/MOF) approved the study protocol.

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the STORK Groruddalen study is based on extensive collaboration with user organizations, no formal patient or public panel was set up in relation to this study. This particular research work was funded by the authors' institutions.

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Supporting information

Additional supporting information may be found online the Supporting Information section at the end of the article.

Table S1a. Plasma lipid levels (mmol/L) at gestational week (GW) 15 by ethnic groups. Values in mean and 95% confidence interval (CI)

Table S1b. Plasma lipid levels (mmol/L) at gestational week (GW) 28 by ethnic groups. Values in mean and 95% confidence interval (CI)

Table S1c. Plasma lipid levels (mmol/L) at 14 weeks postpartum by ethnic groups. Values in mean and 95% confidence interval (CI)

Table S2a. Changes in plasma lipid levels (mmol/L) from gestational week (GW) 15 to 28 by ethnic groups. Values in β and 95% confidence interval (CI)

Table S2b. Changes in plasma lipid levels (mmol/L) from gestational week (GW) 15 to 14 weeks postpartum by ethnic groups. Values in β and 95% confidence interval (CI)

Figure S1. Flow chart of study sample selection.

Figure S2. Causal diagram for the association between ethnicity and plasma lipid. S is defined as a binary selection variable. Our study participants have S=1. U = women included at different time points from early pregnancy to 14 weeks postpartum. The total effect of ethnicity on plasma lipids is found by adjusting for gestational week, education and age.

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