Pregnancy-Related Hyperlipidemia and Endothelial Function in Healthy Women

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Background The purpose of the present study was to investigate pregnancy-related changes in the maternal serum lipid profile and endothelial function.

Methods and Results As part of the population-based, prospective cohort Cardiovascular Risk in Young Finns study conducted in Finland, 57 pregnant Finnish women and 62 control women matched for age and smoking were examined throughout gestation. Serum triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were determined and concomitantly endothelium-dependent brachial artery flow mediated dilation (FMD) was measured by ultrasound. During pregnancy serum TC, LDL-C, HDL-C, TG and very-low-density lipoprotein cholesterol increased significantly when compared with the non-pregnant state (p<0.001 for each) and towards the end of pregnancy (p<0.001, p<0.001, p=0.007, p<0.001, p<0.001). FMD increased towards the end of pregnancy and there was a statistically significant direct correlation between gestational age and FMD% (r=0.345, p=0.010). Brachial artery diameter at rest and FMD% were negatively correlated in pregnant (r=–0.280, p=0.035) and non-pregnant women (r=–0.360, p<0.004). The univariate correlation analysis showed a direct correlation between maternal serum TC (r=0.333, p=0.012) and TG (r=0.366, p=0.006) and FMD%, whereas a negative non-significant correlation was found in non-pregnant women. In a multivariate model, vessel size (l=–0.436, p=0.001) and TG (l=0.502, p<0.001) were the most powerful predictors for FMD% in pregnancy, the influence of other lipids was non-significant.

Conclusions In healthy pregnant women increased gestational age is associated with improved endothelium-dependent vasodilation responses regardless of concurrently appearing lipid changes. (Circ J 2006; 70: 768–772)

Key Words: Endothelial function; Flow-mediated vasodilation; Hypercholesterolemia; Pregnancy

In pregnancy all women experience a significant progressive elevation of serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and apolipoprotein B.1 The physiological significance of hypercholesterolemia and elevated TG may be related to the increased production of sex steroids and maintenance of adequate supply of nutrients to the pregnant mother and fetus. It is not known whether the observed hyperlipidemia of pregnancy is atherogenic because clinical studies pertaining to parity present conflicting results: no association with, protection against as well as increase in the risk of cardiovascular disease.2 However, the Framingham Heart Study reported that women with a history of more than 6 pregnancies had a significantly elevated risk of developing cardiovascular disease3 because of increased NO bioactivity. Endothelial dysfunction, including failure to increase NO production or increased NO wastage, precedes clinically apparent atherosclerosis4 and is also believed to be a key event in pre-eclampsia.5 Attenuated FMD is associated with other cardiovascular risk factors, including advancing age, elevated systolic blood pressure (SBP), smoking6 obesity7 and hyperlipidemia8 and low HDL-C concentrations.9 Cholesterol reduction by lipid-lowering therapy improves endothelial function within days10 and within hours by plasmapheresis.11

The aim of this study was to examine whether the changes in endothelium-dependent vasodilation during pregnancy correlate to changes in serum lipids.

Methods

Participants

The local ethics committee approved the study and all patients gave written informed consent before participating in the study.

The Cardiovascular Risk in Young Finns Study is an ongoing population-based 5-center follow-up study of atherosclerosis risk factors in Finnish children and adolescents.
The first cross-sectional survey was conducted in 1980. The original sample size was 4,320 children and adolescents aged 5, 6, 9, 12, 15 and 18 years. The individuals were randomly chosen from the national register. There were 3,596 participants who participated in 1980. We re-examined 2,283 of these individuals in 2001 when they were aged 24–39 years. The loss of participants was 34%. Out of this sample 62 of the participants were pregnant and 57 had complete data of endothelial function. There were 13 women (23%) in first trimester (≤14 weeks), 20 women (35%) in the second trimester (15–27 weeks) and 22 women (39%) in the third trimester (≥28 weeks); the gestational age data were not available for 2 patients (3%). The mean gestational age was 23±9 weeks. For the present analysis we chose these 57 pregnant women and 62 non-pregnant women matched for age and smoking status.

Height and weight were measured. Blood pressure was measured with a random zero sphygmomanometer (Hawksley & Sons Ltd, Lancin, UK) while seated after 5 min rest. Korotkoff’s fifth phase was used as the sign of diastolic blood pressure and first phase as the sign of SBP. Readings to the nearest even number of millimeters of mercury were performed at least 3 times for each subject and the average of these measurements was used in the analysis. For determination of serum lipoprotein levels venous blood samples were drawn from the right antecubital vein of recumbent subjects after an overnight fast. All lipid determinations were done using standard methods as previously described.

Ultrasound Imaging

Ultrasound studies were performed using Sequoia 512 ultrasound mainframes (Acuson). To assess brachial FMD, the left brachial artery diameter was measured both at rest and after reactive hyperemia. Increased flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mmHg for 4.5 min, followed by release. Three measurements of arterial diameter were performed at end-diastole at a fixed distance from an anatomic marker at rest and at 40, 60, and 80s after cuff release. The vessel diameter in scans after reactive hyperemia was expressed both as the change in absolute diameter (FMD) and as the percentage relative to the resting scan (FMD%).

Statistical Analysis

Descriptive data are expressed as means±SD. The Kolmogorov-Smirnov test was used to evaluate data normality. The significance of difference was assessed by 2 independent samples t-test for observations that were normally distributed and when appropriate by nonparametric tests (Mann-Whitney U-test). When more than 2 groups were compared we used the nonparametric Kruskal-Wallis test. Univariate correlations were performed using the Pearson correlation. Multivariate analysis with linear regression was used to determine independent predictors of FMD. A p-value <0.05 was considered statistically significant. We used SPSS version 11.5.1 (Chicago, IL, USA) for the statistical analyses.

Results

Clinical characteristics, lipid profiles, blood pressure values and ultrasound measurements of the control group and the pregnant women according to the gestational age are shown in Table 1. In both groups there were 6 smokers (9.7% of non-pregnant women and 10.7% of pregnant women, p=0.84). In the first trimester mean weight, TC, LDL-C, TG, very-low-density lipoprotein cholesterol (VLDL-C) were diminished compared with the control group and with the second and third trimesters of pregnancy. Lipid profiles showed that in the third trimester of pregnancy the mean concentrations of TC, LDL-C, HDL-C, TG and VLDL-C had increased up to 36, 35, 26, 116 and 115% respectively, when compared with the values of non-pregnant women. Marked hypercholesterolemia associated with increased HDL-C concentrations is common during pregnancy, Because 38% (21/56) of the pregnant women had a
serum TC concentration exceeding 7.0 mmol/L.

There was a trend towards increased mean brachial artery diameter at rest in the pregnant women compared with the controls (3.17±0.31 vs 3.06±0.32 mm) (p=0.062). The mean brachial artery diameter in the non-pregnant state and in the pregnant women is given by trimester in Table 1. Vessel size tended to increase during pregnancy but the correlation was not statistically significant (p=0.089).

Endothelium-dependent FMD during reactive hyperemia increased towards the end of pregnancy (Table 1). The increase in absolute FMD was statistically significant (p=0.008). FMD in the first trimester was diminished compared with the non-pregnant controls and the increase in FMD% was statistically significant among the 3 trimesters (p=0.04).

In pregnancy, FMD% correlated directly with gestational age (Fig 1A), vessel size (Fig 1B), TC (Fig 1C) and TG (Fig 1D), but not with LDL-C or HDL-C. In the non-pregnant women, FMD% did not correlate with any of the serum lipid values. Overall, the univariate correlation analysis between FMD% and the other parameters during pregnancy showed a significant correlation for maternal serum TC, TG and vessel size, whereas in non-pregnant women, the vessel size was the only significant correlate of FMD%. A multiple regression analysis (Table 2) was used to identify independent variables best predicting FMD% during pregnancy and these were TG and vessel size.

**Table 2 Multivariate Correlates of FMD% in Pregnant Women**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Regression coefficient B±SE</th>
<th>Standardized coefficient □</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel size at rest</td>
<td>-5.763±2.094</td>
<td>-0.346</td>
<td>0.008</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.226±0.68</td>
<td>0.417</td>
<td>0.02</td>
</tr>
<tr>
<td>Vessel size</td>
<td>-6.817±1.888</td>
<td>-0.436</td>
<td>0.001</td>
</tr>
<tr>
<td>TG</td>
<td>2.742±0.659</td>
<td>0.502</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Statistically significant variables from univariable models including vessel size at rest, gestational age (TC, HDL-C, and TG) were entered simultaneously. TG and gestational age were found to be strongly correlated with each other (multicolinearity), therefore 2 models are presented, one with gestational age and one with TG as the independent variable. Abbreviations see in Table 1.

**Discussion**

We found that a markedly elevated serum lipid profile is a common finding during pregnancy, but does not have
adverse effects on endothelial function. Thus, our study results suggest that the short-term hyperlipidemia during pregnancy is not injurious to the endothelium.

In this study, the maternal concentrations of TC, LDL-C and HDL-C showed an overall increase of 30% whereas TG showed a more than 2-fold increase in the third trimester, which is in agreement with a previous study. It has been demonstrated that in the non-pregnant state the hypercholesterolemia associated with low HDL-C concentration is related to impaired endothelial function in human coronary and systemic arteries with or without atherosclerotic disease. However, hyperlipidemia in pregnancy is associated with increased HDL-C concentration, which can protect the endothelium. Increased concentrations of other lipids did not attenuate endothelial function in pregnancy as judged by FMD. On the contrary, univariate correlation analysis showed that FMD was weakly positively, but still significantly, correlated with serum TC and TG concentrations in pregnant women but it is likely that the increasing gestational age that accompanies the lipid changes is by itself more important. Because elevated serum TC and TG were not associated with attenuated endothelial function in pregnancy, it is almost certain that factors other than the maternal lipid profile are important in determining endothelial function during pregnancy.

In pregnancy, the concentration of 17ß-estradiol (E2), progesterone and human placental lactogen are increased markedly already in the first trimester and rise continuously towards term, and changes in plasma lipids, lipoproteins and apolipoproteins positively correlate with these hormonal changes. E2 protects the endothelium by upregulating endothelial nitric oxide synthase and can reverse endothelial dysfunction in an in vitro vascular model. In the present study we did not measure estrogen or other hormonal levels so we could not examine the correlation between E2 and FMD. In pregnancy the naturally occurring increase in E2 seems to protect the endothelium against the adverse lipid changes.

We found that there was a trend for greater brachial artery diameter at rest in the middle and last trimesters than in the first trimester of pregnancy or in the non-pregnant group, which is in accordance with previous studies. In pregnancy, peripheral vascular resistance falls, blood volume expands and cardiac output increases, thus increasing the flow in the systemic and pulmonary circulations. The increase in brachial artery diameter at rest may be caused by increased blood flow and thus increased shear stress, which is stimulus for endothelial NO release. Brachial artery size is known to be an important determinant of the FMD response: smaller vessels dilate relatively more than larger ones. We found that increasing vessel size was associated with decreased FMD responses in both groups, which was somewhat unexpected because FMD and the size of the brachial artery vessel both showed a growing trend with the duration of pregnancy. The pregnant state itself appeared to be a powerful determinant of FMD and its net effect overcame the opposite effect caused by the increasing size of the brachial artery.

Increased FMD in the second and third trimesters of pregnancy supports the hypothesis that basal and stimulated NO activity is enhanced during these stages of a normal pregnancy, but not in the first trimester of pregnancy even though peripheral vascular resistance decreases and blood pressure has already fallen in the first trimester which fits our present data. We found attenuated FMD in the first trimester of pregnancy compared with the non-pregnant group. In addition to FMD TC and TG were also decreased in the first trimester compared with the non-pregnant group. The explanation for these findings remains unclear or they may have occurred by chance; however, this maybe the reason for the more potent correlation between FMD% and TG than between FMD and gestational age.

Clinical Implication

The clinical significance of examining endothelial vasodilator function is the association between endothelial dysfunction and subsequent cardiovascular events. Our results show that increased serum concentrations of TC, TG, LDL-C, and VLDL-C did not lead to endothelial dysfunction during pregnancy. On the contrary, endothelial function improved in the second and third trimesters of the pregnancy, partly because of the increased concentration of HDL-C, which may inhibit the oxidation of low-density lipoprotein and thus protect the endothelium. These findings raise the question whether the increased risk of cardiovascular disease in multiparous women is attributable rather to the burden of motherhood or other socioeconomic factors than to maternal hypercholesterolemia during pregnancy. The physiological short-term increase in serum lipids and improvement of endothelium-dependent vasodilation responses are associated with gestation rather than with each other.

Acknowledgments

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References


