

Lipoprotein lipase and apoE polymorphisms: relationship to hypertriglyceridemia during pregnancy

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Abstract Pregnancy is associated with increases in plasma total cholesterol (TC) and triglycerides (TG). Individuals with decreased LPL activity have a mild form of hypertriglyceridemia. Variations in the apolipoprotein E (apoE) gene have been associated with increases in plasma TG in addition to differences in plasma TC, LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C). Because of the overproduction of TG-rich VLDL, normal pregnancy challenges the lipolytic capacity of LPL and the clearance of remnants particles. During pregnancy, LPL and apoE polymorphisms may contribute to hypertriglyceridemia. This study investigated the impact of three LPL polymorphisms and the apoE genotypes on lipid levels during pregnancy. Fasting plasma lipids were measured and analyses of the LPL and apoE polymorphisms were performed in 250 women in the third trimester of pregnancy. S447X carriers had lower TG ($P = 0.003$), and N291S carriers had lower HDL-C ($P < 0.02$) and higher fractional esterification rate of HDL (FER_{HDL}) ($P = 0.007$), a measure of HDL particle size, than the noncarriers. The E2 allele was associated with lower TC, LDL-C, and FER_{HDL} ($P < 0.05$) compared to the E3/E3 genotype. These findings support that LPL and apoE polymorphisms play an important role in lipid metabolism in pregnancy. The relationship of these polymorphisms to risk of coronary heart disease in women requires further study.—McGladdery, S. H., and J. J. Frohlich. Lipoprotein lipase and apoE polymorphisms: relationship to hypertriglyceridemia during pregnancy. *J. Lipid Res.* 2001. 42: 1905–1912.

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The role of plasma lipids and lipoproteins in the development of coronary heart disease (CHD) has been extensively studied. There is now a large body of data based on epidemiological studies (1–5), experimental research (6–8), genetics (9, 10), and clinical trials (11, 12) that relates elevated total serum cholesterol and particularly LDL cholesterol (LDL-C) as well as low serum HDL cholesterol (HDL-C) to increased risk of CHD. Although the role of TG in the development of CHD has been controversial (13), it has been shown that high TG in combination with low HDL-C accounts for twice as many cases of CHD as low HDL-C alone (14). In addition, TG-rich particles of

the apolipoprotein B (apoB) family are significant predictors of CHD progression (15).

LPL and apoE genes are likely to be involved in modulating the risk for dyslipidemia and atherosclerosis. In addition, environmental factors (including pregnancy) may also lead to increased risk of CHD.

The primary role of lipoprotein lipase is the hydrolysis of triglycerides from the core of triglyceride-rich lipoproteins in plasma. LPL is also critical in maintaining optimal plasma lipid levels (16). There has been a great deal of research on the effects of decreased LPL activity on the risk of atherosclerosis, yet the results have been inconclusive (17, 18). ApoE plays a major role in regulating the metabolism of chylomicrons, VLDL, and HDL via the apoE receptor and by the LDL (apoB, E) receptors (19). It is responsible, in part, for uptake of dietary cholesterol in the form of chylomicron remnants, clearance of VLDL remnants, and removal of excess cholesterol from peripheral tissues through hepatic clearance of HDL containing apoE.

Severe hypertriglyceridemia can develop in the late gestation of pregnancy as a consequence of either genetic mutations in genes such as LPL or apoE or other causes such as diabetes, alcohol consumption, or weight gain. In some cases, extremely high TG levels (chylomicronemia) may result in acute pancreatitis (20–24). Some hypertriglyceridemic women have normal TG levels postpartum, which suggests that these individuals may be “prelipemic” (analogous to gestational diabetes) (25).

As a result of the increase in TG-rich VLDL, normal pregnancy presents a challenge to the lipolytic capacity of LPL and the ability to clear remnants via the apoE receptor. Thus, pregnant women carrying these common LPL and apoE polymorphisms have an associated increased TG level during the course of pregnancy. We have investi-

Abbreviations: apo, apolipoprotein; CHD, coronary heart disease; FER_{HDL} , fractional esterification rate of HDL; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; TC, total cholesterol.

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gated whether selected polymorphisms in the LPL and apoE gene are associated with exaggerated hypertriglyceridemia in pregnancy, an effect which may be associated with increased risk of CAD.

MATERIALS AND METHODS

Study participants

The cohort consisted of 250 unrelated pregnant women recruited from the Lower Mainland and Greater Vancouver area of British Columbia, Canada between March 1996 and October 1998. The subjects were recruited from prenatal classes or by responding to an advertisement. Informed consent, approved by University of British Columbia and St. Paul's Hospital ethics committees, was obtained from all study participants.

All individuals completed a questionnaire covering their personal and family medical history as well as other parameters such as age, height, weight change, week gestation, current medication(s), diet, alcohol consumption, number of previous pregnancies, and any past or present medical health information. There was no age restriction, but all individuals had to be in their third trimester and either pregnant for the first time or to have had previous uncomplicated pregnancies. Individuals with disorders affecting lipoprotein metabolism including diabetes mellitus, thyroid, hepatic, or renal disease were excluded from the study. In addition, subjects taking medications known to affect lipid metabolism (such as diuretics, beta-blockers, and lipid lowering drugs) and those with heavy alcohol intake were also excluded.

Materials

The QIAamp Blood Midi kits for DNA extraction and the HotstarTaq were obtained from QIAgen Co. (Mississauga, Ontario, Canada). The agarose-1000 and primers were produced by Canadian Life Technologies (Mississauga, Ontario, Canada). The dNTPs were purchased from Promega Co. (Madison WI), and the restriction enzymes (*HhaI*, *TaqI*, *RsaI*, and *MspI*) were obtained from New England Biolabs Ltd. (Mississauga, Ontario, Canada). The DNA ladder was purchased from Invitrogen (Carlsbad, CA), and the radiolabeled cholesterol was from Amersham. All other reagent grade chemicals were purchased from Sigma Inc. (Mississauga, Ontario, Canada).

Plasma lipid analysis

Fasting plasma samples were collected in 10-l EDTA-coated vacutainer tubes. Plasma was separated by centrifugation at 2,000 rpm for 10 min. Plasma TG was determined as previously described (26), and plasma TC was determined by an enzymatic method (27). HDL-C was determined after heparin manganese precipitation of apoB containing lipoproteins (28), and LDL-C was calculated using the Friedewald formula (29, 30). The remainder of the plasma was stored at -70°C until needed. The red cells and buffy coat were stored at -20°C until DNA was extracted.

Fractional esterification rate of HDL (FER_{HDL})

FER_{HDL} was determined by an isotopic assay method that has been previously described (31, 32). Briefly, apoB containing lipoproteins VLDL and LDL was precipitated from the plasma by the addition of phosphotungstic acid and MgCl_2 . A trace amount of tritiated cholesterol was applied to a paper disk, added to the plasma, and incubated on ice for 18 h to allow spontaneous transfer to occur. The labeled samples were incubated in a shaking water bath at 37°C for 30 min. The reaction

was stopped with the addition of 1 ml of ethanol, and the lipid extract was subjected to TLC. The radioactivity of the free and esterified cholesterol fractions was determined by liquid scintillation. The FER_{HDL} was then calculated as the percentage of radiolabel found in the esterified cholesterol fraction after incubation over the total radioactivity in the sample. The normal value for healthy women is $10.6 \pm 3.6\%/h$ (33).

DNA analysis

DNA was extracted from leukocytes using the standard protocol of the QIAamp Blood Midi Kit. All the samples were then screened for the D9N (34, 35), N291S (36), and S447X (37) mutations in the LPL gene and the apoE variants (38) by PCR and restriction endonuclease digestion of amplified product, as previously described.

Statistical analyses

Between-group comparison was performed using an ANOVA followed by the parametric *t*-test. Due to skewed distribution of TG, all TG analyses were performed on logarithmically transformed values. Statistical analyses were performed using Microsoft Excel Data Analysis Package (Microsoft, Inc.).

RESULTS

Cohort characteristics

The cohort consisted of 250 healthy pregnant women in their third trimester. The ethnic backgrounds are displayed in **Fig. 1**. The majority (78.4%) of the women in this group reported being of European descent, and nearly two-thirds of those stated that they were of British, Irish, or Scottish ancestry. Roughly 9.6% of the cohort was Asian, predominantly Chinese, and 4.4% reported being of Indo-Canadian, Punjabi, or Sri Lankan origin. The remainder of the group (7.6%) was of either other or unknown ethnic backgrounds.

The average age of the group was 31.8 ± 0.4 years with a range of 20–41 years. The average week of gestation was 35.4 ± 0.1 with a range of 31–42 weeks. The number of previous pregnancies ranged from 0 to 5 with an average of 0.8 ± 1.1 . The majority of the women (53%) reported this being their first pregnancy, 25% had one previous

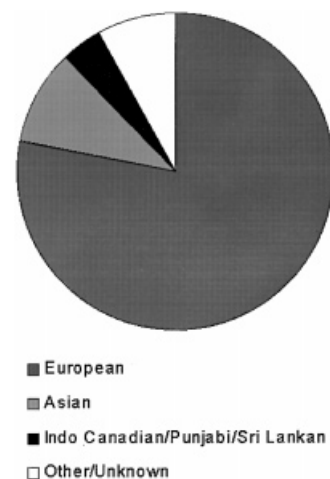


Fig. 1. Breakdown of the various ethnic groups within the cohort.

TABLE 1. Cohort lipid levels

	Mean (n)	Range	Normal Pregnant Range (Nonpregnant Range)
			mmol/L
TG	2.7 ± 1.0 (250)	1.0–6.5	1.0–5.3 (<2.3)
HDL	1.7 ± 0.4 (249)	0.9–3.1	1.2–2.4 (>1.1)
LDL	3.4 ± 1.1 (249)	1.2–7.1	2.3–5.6 (<3.4)
Cholesterol	6.4 ± 1.2 (250)	4.1–10.1	4.7–8.6 (<5.2)
FER _{HDL}	19.5 ± 5.4 (224)	8.5–38.4	— (10.7 ± 3.7)

pregnancy, 15% had two previous pregnancies, and the remaining 7% reported three, four, or five previous pregnancies. There was no significant difference in lipid levels between the women with numerous previous pregnancies and primagavidas. The average height of the subjects was 163.1 ± 7.3 cm (132–197 cm), and their average weight gain during the current pregnancy was 12.8 ± 4.0 kg (1.4–28.6 kg).

Based on the questionnaires, the majority of women reported consuming a regular diet, with the exception of 23 (9%) who reported following various vegetarian diets. None of the women reported frequent (>5 drinks per week) alcohol consumption, and only 58 (23%) reported drinking occasionally (1–5 drinks per week); the remainder stated they never drank alcohol.

The lipid data, including FER_{HDL}, for the cohort are presented in **Table 1**. The mean values for TG, HDL-C, LDL-C, and total cholesterol (TC) all fell within the normal range for the third trimester of pregnancy.

Frequency of LPL variants and their effects on plasma lipids

All 250 subjects were screened for the D9N, N291S, and S447X polymorphisms in the LPL gene. The frequencies of homozygous and heterozygous carriers and noncarriers are presented in **Table 2**. The D9N and N291S mutations displayed low allele and carrier frequencies, whereas the allele and carrier frequencies of the S447X were high, all of which were similar to previously published data (39).

The lipid data for carriers of the N291S mutation versus noncarriers are summarized in **Table 3**. There was a significant decrease in HDL-C levels in the carrier group versus

TABLE 2. Frequency of LPL polymorphisms

Genotype	D9N	N291S	S447X
+/+	0	0	1/240 (0.4%)
+/-	2/231 (0.9%)	10/236 (4.6%)	43/240 (18.0%)
-/-	229/231 (99.1%)	226/236 (95.8%)	197/240 (82.1%)
Allele frequency	0.4%	2.3%	9.4%
Expected carrier frequency ^a	2–4%	1–7%	17–22%

^a Witttrup, Tybjaerg-Hansen, and Nordestgaard (39).

TABLE 3. Lipid levels in N291S carriers and noncarriers

	Carriers (n)	Noncarriers (n)	P
	mmol/l		
TC	6.3 ± 0.5 (10)	6.3 ± 0.1 (226)	0.9
TG	3.2 ± 0.4 (10)	2.7 ± 0.1 (226)	0.2
HDL-C	1.4 ± 0.1 (10)	1.7 ± 0.03 (225)	<0.02
LDL-C	3.4 ± 0.5 (10)	3.3 ± 0.1 (225)	0.8
FER _{HDL}	24.1 ± 7.0 (10)	19.2 ± 5.5 (197)	0.007

the noncarrier group (1.5 ± 0.1 and 1.7 ± 0.03, *P* < 0.02). There was also a significant increase in FER_{HDL} in carriers compared with noncarriers (23.8 ± 7.0 and 19.3 ± 5.5, *P* < 0.01). Although there was a trend to increased TG in the carriers, this was not statistically significant.

A similar comparison was done for carriers of the S447X mutation versus noncarriers (**Table 4**). A significant decrease in TG in the carrier group was the only difference found between the two groups (2.3 ± 0.1 and 2.8 ± 0.1, *P* < 0.003). Due to a small number of D9N carriers (*n* = 2), statistical analysis could not be performed.

Frequency of apoE variants and their effects on plasma lipids

The 250 subjects were also screened for apoE genotype, and the frequency of the alleles is shown in **Table 5**. As expected, the apoE3 allelic frequency was high (81%), whereas the allelic frequencies for apoE2 and apoE4 were low (7.9% and 10.7%).

The lipid data for the various apoE genotypes are displayed in **Table 6**. Significant differences were found in TC, LDL-C, and FER_{HDL}. Significantly lower levels of TC were found in the E2/E4 individuals and apoE2 carriers (E2/E2 and E2/E3) compared with the E3/E3 individuals (*P* < 0.05). There was also significantly higher plasma LDL-C in the E3/E4, E4/E4, E3/E3 individuals compared with the apoE2 carriers (E2/E2 and E2/E3) (*P* < 0.05). In addition, significantly lower FER_{HDL} values were found in the apoE2/E3 and apoE2 carriers (E2/E2 and E2/E3) compared with the E3/E3 carriers (*P* < 0.05). There were no differences in TG or HDL-C levels between any of the groups.

DISCUSSION

Cohort characteristics

Among many effects of pregnancy are alterations in the level of sex hormones, which profoundly affects lipid me-

TABLE 4. Lipid levels in S447X carriers and noncarriers

	Carriers (n)	Noncarriers (n)	P
	mmol/l		
TC	6.5 ± 0.2 (43)	6.3 ± 0.1 (197)	0.4
TG	2.2 ± 0.1 (43)	2.8 ± 0.1F (197)	0.003
HDL-C	1.8 ± 0.1 (43)	1.7 ± 0.03 (198)	0.5
LDL-C	3.6 ± 0.2 (43)	3.3 ± 0.1 (198)	0.06
FER _{HDL}	19.2 ± 5.4 (40)	19.6 ± 5.8 (173)	0.66

TABLE 5. ApoE allele frequencies

ApoE Allele	Number	Allelic Frequency %
E2/E2	1/223	0.4
E2/E3	28/223	12.6
E2/E4	4/223	1.8
E3/E4	37/223	16.6
E4/E4	4/223	1.8
E3/E3	149/223	66.8
ApoE2	34/446	7.6
ApoE3	363/446	81.4
ApoE4	49/446	11.0

tabolism. In addition, there are numerous genetic and environmental factors that may play a role in altering lipid metabolism in pregnancy and could result in changes in lipid levels. We hypothesized that differences in plasma lipid levels during pregnancy are due, in part, to the presence of genetic polymorphisms in LPL and apoE, and pregnancy is a "stress" that enhances the effect of these genetic factors.

The plasma lipid levels from our cohort agree with those found in a number of other studies (40–43) and are representative of what is expected of a healthy pregnant population. Although a pregnancy range has not been established for FER_{HDL}, Ordovas, Pocius, and Grande (44) showed that the esterification rate of HDL increases during the first half of gestation and remains steady or slightly decreases throughout the second half. The mean FER_{HDL} in this group was higher than the nonpregnancy value for women of this age (33), which supports the previous finding.

Environmental factors such as weight gain and dietary and alcohol habits may influence lipid metabolism during pregnancy. Weight gain during pregnancy has been associated with increased TG levels (45–47). In our cohort, the average weight gain was 12.8 ± 4.0 kg; however, the range (1.4–28.6 kg) was quite large and may have been related to the inaccuracies of self reported data. Diet and alcohol habits have also been associated with changes in lipid levels (47). A diet rich in TG leads to increased plasma TG levels during pregnancy, and chronic alcohol use also alters lipid levels during pregnancy, resulting in lower LDL-C and HDL₂ and increased HDL₃ and VLDL (48). The ma-

majority of women in this cohort reported being on normal diets, with only 9% following a vegetarian diet. Similarly, 77% of the women reported never drinking during their pregnancy, but 23% reported drinking occasionally.

Lipoprotein lipase polymorphisms and plasma lipids

Various ethnic groups have been studied, and it has been found that the frequency of the LPL polymorphism varies among these groups (49–52). The carrier frequencies for the LPL polymorphisms in our cohort were not different from those published in a meta-analysis by Wittrup, Tybjaerg-Hansen, and Nordestgaard (39) and the Framingham Offspring Study (53).

Significantly lower HDL-C level ($P < 0.015$) and higher FER_{HDL} ($P < 0.007$) were found in N291S carriers, but no significant differences were found in serum TG levels (Table 3). Lower HDL-C in carriers of the N291S mutation has been found in some studies of nonpregnant subjects (36, 54–56) but not in others (57–59). Also, several studies did not show significant differences in TG between N291S carriers and noncarriers (58–60) whereas others did (54–57, 61). Two studies did not report an association between the N291S variant and either HDL-C or TG levels (58, 59). The dissociation of TG and HDL-C in the N291S carriers that we found in the third trimester of pregnancy has been reported in nonpregnant heterozygotes for FH (60). Pregnancy and FH are both associated with increased TG levels, which may mask the effects of the N291S variant on TG levels between carriers and noncarriers. In addition, they are both associated with increased CETP activity (62, 63), which may result in a decrease in HDL leading to lower HDL-C levels in spite of similar TG levels.

Significantly lower levels of TG ($P < 0.002$) in S447X carriers were also previously reported in men in the Framingham Offspring Study, who had higher HDL-C levels (53). Conflicting results concerning the variants' effect on its catalytic function have been published (64–67). It has been suggested that the S447X variant may result in increased production of both LPL protein and lipolytic activity (65, 67, 68). The lower TG levels seen in the S447X carriers in our population likely resulted from increased LPL activity associated with the S447X polymorphism. There was a trend to higher LDL-C levels in the S447X carriers ($P < 0.06$), which may reflect increased conver-

TABLE 6. ApoE polymorphisms and plasma lipid levels

apoE (n)	TC (n)	TG (n)	HDL-C (n)	LDL-C (n)	FER _{HDL} (n)
	<i>mmol/l</i>				
E2/E2	5.78	2.29	1.83	2.91	15.02
E2/E3	6.0 ± 1.0 (28)	2.6 ± 1.0 (28)	1.8 ± 0.4 (28)	2.9 ± 0.7 (28)	17.1 ± 4.4 ^a (27)
E2/E4	5.1 ± 0.9 ^a (4)	2.3 ± 0.9 (4)	1.6 ± 0.3 (4)	2.5 ± 0.8 (4)	21.5 ± 8.5 (4)
E3/E4	6.4 ± 1.4 (37)	2.7 ± 0.9 (37)	1.7 ± 0.4 (37)	3.5 ± 1.3 ^b (37)	20.5 ± 5.2 (33)
E4/E4	6.9 ± 1.7 (4)	3.0 ± 0.9 (4)	1.5 ± 0.4 (4)	3.4 ± 1.2 ^b (4)	20.3 ± 3.2 (4)
E3/E3	6.4 ± 1.2 (149)	2.8 ± 1.1 (149)	1.7 ± 0.4 (148)	3.4 ± 1.1 ^b (148)	19.9 ± 5.9 (132)
Apo E2 (2/2 + 2/3)	5.9 ± 0.9 ^a (29)	2.6 ± 0.9 (29)	1.8 ± 0.4 (29)	2.9 ± 0.9 (29)	17.1 ± 4.4 ^a (28)

^a Lower than apoE3, $P < 0.05$.

^b Higher than apoE2, $P < 0.05$.

sion of remnants into LDL. This observation has not been previously reported and may be due to the increased TG (VLDL) levels during pregnancy. In our cohort, there were no differences in plasma HDL-C levels; increases in HDL-C in carriers of the S447X variant have only been previously reported in men (37, 53).

Apolipoprotein E and plasma lipids

There were significant differences in plasma TC, LDL-C, and FER_{HDL} levels between the various apoE genotypes (Table 6). Similar to the nonpregnant state, the TC was significantly lower in the E2/E4 group than the E3/E3 group (69, 70). Contrary to previous findings (71), no significant differences in TC were found between E2/E3, E3/E4, or E4/E4 when compared with the E3/E3 group. LDL-C levels were lower in the E2/E3 group compared with the E3/E4, E4/E4, and E3/E3 groups, which agrees with previous reports on the apoE2 allele and plasma LDL-C (72). We expected to find increased LDL-C in E4 carriers as well (73), but this was not seen in our cohort.

Although TG levels have been previously found to be higher in subjects carrying the apoE2 allele and in subjects with the apoE3/E4 genotype than in individuals with the apoE3/E3 genotype (71), no significant differences in TG levels were observed between any of the groups in our cohort. Large variations in TG levels among and within individuals (13) could mask the effects of the apoE phenotypes on TG levels (71). Similarly, no differences were found in HDL-C between any of the apoE genotypes in our study, whereas a meta-analysis reported HDL-C levels to be lower in the apoE3/E4 nonpregnant subjects (71). The finding of lower FER_{HDL} in the E2/E3 group compared with the E3/E3 group suggests a change in HDL, an increase in the proportion of larger HDL subpopulations with apoE2 allele. The known lower binding capacity of the apoE2 allele may slow down the catabolism of HDL and prevent its removal by the liver, resulting in an increase in the HDL2 pool (resulting in lower FER_{HDL}) in the carriers of the apoE2 allele.

The phenotypic expression of the apoE alleles may change in pregnancy. Because there is an overall decrease in LPL activity (~85%) during pregnancy (74, 75), the conversion of chylomicrons and VLDL to chylomicron and VLDL remnants may be impaired. This, in turn, lowers the apoE substrate pool and may decrease the need for uptake of apoE-containing particles by the liver. Therefore, the differences in lipid levels between the apoE4, E3, and E2 carriers are eliminated. It is also possible that there were no differences in the levels of LDL-C in the apoE4 carriers because of the age of the women studied. It has been shown that the differences in LDL-C levels with different apoE genotypes are smaller in premenopausal than in postmenopausal women (76).

Several research groups have studied the effects and interaction of apoE and LPL on lipid metabolism (77–83). Salah et al. (83) assessed the effects of the LPL S447X polymorphism and apoE genotype on lipids in a nonpregnant population. Their findings are similar to ours. There are no cross-sectional population studies of the effects of

any of the LPL polymorphisms and apoE alleles during pregnancy. However, a small number of case studies have reported dramatically altered lipid levels in individuals with variations in both genes during pregnancy (21). In the majority of these cases, the LPL mutation results in decreased LPL activity, and the apoE genotype is that of E2 heterozygote or homozygote, resulting in increased TG. In our cohort there were no individuals fitting these criteria. We did, however, have one apoE3/E4, N291S heterozygote and one apoE3/E4, D9N heterozygote. The lipid levels for the apoE3/E4, D9N heterozygote were not remarkable, yet the apoE3/E4, N291S heterozygote had higher TG (6.12 mmol/l) and TC (5.83 mmol/l) but low to normal HDL-C (1.47 mmol/l) for this stage of pregnancy. Although no firm conclusions can be drawn from one case, the effect of simultaneous variations in these two proteins during pregnancy merits further study.

Mutations in both LPL and apoE may influence the risk of developing CHD. In addition, we have to take into account the possible risk associated with the altered lipid phenotype temporarily brought on by these variants during pregnancy.


Despite the association of the N291S polymorphism with lipid abnormalities, only one study has shown an increased prevalence of CHD in carriers compared with noncarriers (55). Female carriers of the N291S polymorphism were found more frequently among patients with ischemic heart disease than among the controls. This association was not seen in men despite association with an atherogenic lipid profile (84). A meta-analysis by Hokanson (85) and a more recent study by Minnich et al. (86) suggest that despite its influences on lipid levels, the presence of the N291S polymorphism alone may not be a sufficient factor in the development of CHD. However, in combination with environmental factors, such as obesity (57, 61) and pregnancy (20), the N291S polymorphism may represent a predisposing genetic factor for CHD.

Heterozygosity for the S447X polymorphism is associated with elevated HDL-C and has therefore been considered a potential benefit to carriers (37). The S447X polymorphism has been found at lower frequencies in patients with CHD (87), and recent studies have demonstrated that the S447X polymorphism is associated with significant protection against CHD in men (53). It has been estimated that 9% of CHD in the Framingham Offspring Study was prevented as a result of the S447X polymorphism (53). How these findings relate to lipid changes during pregnancy is unclear. Although we did not find a significant increase in HDL-C levels in the pregnant carriers of the S447X polymorphism, they had significantly lower TG. Whether the changes in plasma TG alone play a role in protection against CHD with respect to the S447X polymorphism has not been determined. However, there is now growing consensus that increased TG level is an independent risk factor of CHD (88, 89).

We found no significant differences in TG, HDL-C, LDL-C, or TC in the apoE4 carriers when compared with the apoE3/E3 group. On the other hand, the apoE2 carriers had significantly lower TC and LDL-C but no significant

differences in TG or HDL-C. This is consistent with the previous findings and suggests a lower risk of CHD compared with the apoE4 and the apoE3/E3 carriers.

It was expected that in our cohort, the effects of the apoE alleles would be more pronounced because of pregnancy-associated hypertriglyceridemia. However, the increased TG levels may mask the effect of the apoE alleles. Yet, on the other hand, these findings may reflect the true lipid profile during pregnancy. If so, the difference in plasma lipids and the risk of CHD between apoE4 and apoE3/E3 carriers may be less evident during pregnancy, whereas apoE2 may still have a protective effect.

More studies need to be done on the effect of genetic variations that alter lipid metabolism during pregnancy. Our study showed, for the first time, that genetic factors affect lipid profile during pregnancy. Currently, we do not fully understand how the lipoprotein changes in pregnancy affect the future risk of CAD in childbearing women. Nevertheless, based on the reviewed literature and our own data, it is reasonable to suggest that lipid abnormalities in pregnancy contribute to risk of CAD. 

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