The Effect of Cigarette Smoking during Pregnancy on Cord Blood Lipid, Lipoprotein and Apolipoprotein Levels

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SUMMARY

We examined the relationship between maternal smoking during pregnancy and serum lipid, lipoprotein and apolipoprotein levels in newborns. Serum concentrations of total cholesterol, triglyceride, high density lipoprotein cholesterol, low density lipoprotein cholesterol, apolipoprotein A-1, apolipoprotein B and lipoprotein (a) were assessed in blood samples from 38 mothers who were smokers and their newborns obtained at delivery and compared to blood sample from 42 nonsmokers and their newborns. As compared with newborns of nonsmoker mothers, newborns of smoker mothers showed a lower mean level of high density lipoprotein cholesterol (21 versus 26 mg/dl, $p < 0.01$), a higher total cholesterol to high density lipoprotein cholesterol (4.7 versus 3.7, $p < 0.01$), a higher low density lipoprotein cholesterol to high density lipoprotein cholesterol ratios (3.2 versus 2.3, $p < 0.05$), a lower mean level of apolipoprotein A-1 (105 versus 129 mg/dl, $p < 0.01$) and a higher apolipoprotein B to apolipoprotein A-1 ratio (0.44 versus 0.3, $p < 0.01$). These parameters were also different between smoker and nonsmoker mothers. There were no significant differences in TC, TG, LDL-C, Apo B and Lp (a) values between the two newborn groups. These data suggest that maternal smoking during pregnancy markedly affects lipid metabolism in the fetus. (*Jpn Heart J* 1997; 38: 497-502)

Key words: Newborns, Smoking, Lipoproteins, Apolipoproteins

ATHEROSCLEROSIS begins in childhood as arterial intimal lipid deposits and progresses to occlusive arterial lesions in middle age or later.¹⁾ Dyslipidemia is one of the major risk factors for atherosclerosis. The relationship between cigarette smoking and serum lipid, lipoprotein and apolipoprotein levels has been shown in many investigations.²⁻⁷⁾ The identification of newborns with high risk for developing atherosclerosis is important to prevent coronary heart

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Received for publication January 6, 1997.

Accepted January 27, 1997.

disease later in life, because dyslipidemia may continue for many years beyond the newborn period. Thus, high risk groups should be screened and followed up by the pediatrician.

Assmussen reported in several publications⁸⁻¹⁰⁾ on the morphological alterations in the vessels of the umbilical cord and the placentae of neonates whose mothers had smoked cigarettes during pregnancy. Adam et al.¹¹⁾ reported that maternal smoking during pregnancy may cause an atherosclerotic lipid profile in newborns. The aim of the present study was to investigate whether or not there is any relationship between maternal smoking during pregnancy and cord serum apolipoprotein A-1 (apo A-1), apolipoprotein B (apo B) and lipoprotein (a) (Lp (a)) levels, as well as other lipid parameters.

SUBJECTS AND METHODS

Thirty-eight full-term newborns, born at the Departments of Obstetrics and Gynecology, İzmir and Manisa State Hospitals between February and June 1996 and whose mothers had smoked at least five cigarettes per day for at least three years and also during pregnancy were screened for plasma lipids, lipoproteins and apolipoproteins.

The control group consisted of 42 full-term healthy newborns and whose mothers were nonsmokers. The age, body mass index (BMI), still births, live births and social status of the mothers were comparable between the smoker group and the controls. Mothers taking any drug altering lipid metabolism and having any disease such as hyperlipidemia, diabetes mellitus, nephrosis, thyroid dysfunction or liver disease or a family history of coronary heart disease were excluded from the study. Further exclusion criteria were pre-, intra- or postnatal asphyxia of the child and shortened duration of pregnancy.

Immediately after delivery, a total of 80 cord blood samples from newborns and 80 venous blood samples from mothers were collected for assays of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), apolipoprotein A-1 (apo A-1), apolipoprotein B (apo B) and lipoprotein a (Lp (a)). After centrifugation, the sera were stored at -20°C until analyzed. TC and TG were measured by enzymatic colorimetric methods by using a Mitsubishi Z818 autoanalyzer, Japan. HDL-C was quantified by the same enzymatic method in the supernatant after precipitation with phosphotungstic acid-MgCl₂. LDL-C was calculated according to the Friedewald equation (12): $\text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{TG}/5)$. The serum apo A-1 and apo B and Lp (a) concentrations were measured by turbidimetric immunoassay (TIA) (Diasys Co, Germany for Lp (a) and Isolab Inc. Ohio, USA for apo A-1 and apo B).

Day to day coefficients of variation (CVs) were 3.8% for assay of TC, 5.4% for HDL-C, 5.2% for TG, 4.7% for apo A-1, 4.4% for apo B and 5.9% for Lp (a). **Statistical analysis:** Unpaired Student's t-test was performed to compare the means of TC, TG, HDL-C, LDL-C, apo A-1 and apo B levels. The distribution of serum Lp (a) levels was skewed to the lower values. Therefore we used the Mann-Whitney U test to compare the Lp (a) levels of subjects and controls.

RESULTS

The characteristics of mothers and newborns are shown in Table I. The mean birthweight of newborns of smoker mothers was significantly lower than that of nonsmokers (Table I). Mean ($\pm$ SD) serum lipid, lipoprotein and apolipoprotein levels in smoker and nonsmoker groups are summarized in Table II.

Table I. Characteristics of the Mothers and Newborns

	Smokers (mean $\pm$ SD)	Nonsmokers (mean $\pm$ SD)
Mothers		
Age (years)	25.8 $\pm$ 4.6	24.8 $\pm$ 5.0
Parity (mean)	1.5 $\pm$ 1.5	1.2 $\pm$ 1.2
Gravidity (mean)	2.8 $\pm$ 1.8	2.2 $\pm$ 1.3
BMI (weight/height ²)	27.0 $\pm$ 2.3	26.9 $\pm$ 2.8
Newborns		
Female/male	16/22	21/21
Birthweight (mean-kg)	3.36 $\pm$ 0.41*	3.45 $\pm$ 0.58
Gestation age (weeks)	39.7 $\pm$ 1.1	40.0 $\pm$ 1.0
Apgar (at 1 minute)	8.9 $\pm$ 0.9	8.8 $\pm$ 0.2

*According to the unpaired Student's t-test, $p < 0.05$.

Table II. Mean ($\pm$ SD) Serum Lipid, Lipoprotein and Apolipoprotein Levels in Smoker and Nonsmoker Groups

	Smoker group		Nonsmoker group		Statistical analysis*	
	Mothers <i>n</i> = 38	Newborns <i>n</i> = 38	Mothers <i>n</i> = 42	Newborns <i>n</i> = 42	<i>P</i> ₁	<i>P</i> ₂
TC (mg/dl)	270 $\pm$ 58	90 $\pm$ 25	259 $\pm$ 50	87 $\pm$ 23	NS	NS
TG (mg/dl)	213 $\pm$ 63	52 $\pm$ 21	219 $\pm$ 75	46 $\pm$ 17	NS	NS
HDL-C (mg/dl)	71 $\pm$ 24	21 $\pm$ 6	85 $\pm$ 23	26 $\pm$ 10	$p < 0.01$	$p < 0.01$
LDL-C (mg/dl)	157 $\pm$ 62	59 $\pm$ 23	130 $\pm$ 51	52 $\pm$ 22	$p < 0.05$	NS
TC/HDL-C	4.3 $\pm$ 1.7	4.7 $\pm$ 1.9	3.3 $\pm$ 1.3	3.7 $\pm$ 1.5	$p < 0.01$	$p < 0.01$
LDL-C/HDL-C	2.6 $\pm$ 1.5	3.2 $\pm$ 1.7	1.7 $\pm$ 1.1	2.3 $\pm$ 1.3	$p < 0.01$	$p < 0.05$
APO A-1 (mg/dl)	325 $\pm$ 57	105 $\pm$ 26	350 $\pm$ 57	129 $\pm$ 36	$p < 0.05$	$p < 0.01$
APO B (mg/dl)	166 $\pm$ 41	42 $\pm$ 19	140 $\pm$ 44	35 $\pm$ 10	$p < 0.01$	NS
APO B/APO A-1	0.53 $\pm$ 0.17	0.44 $\pm$ 0.27	0.42 $\pm$ 0.17	0.3 $\pm$ 0.14	$p < 0.005$	$p < 0.01$
Lp (a) (mg/dl)	14.93 $\pm$ 11.35	5.61 $\pm$ 6.4	14.27 $\pm$ 11.35	3.8 $\pm$ 3.55	NS	NS

*unpaired Student's t-test was used except for Lp (a); Mann-Whitney U test was used for Lp (a); NS = Nonsignificant; *P*₁ = difference between mothers; *P*₂ = difference between newborns.

As compared with newborns of nonsmoker mothers, newborns of smoker mothers had lower serum levels of HDL-C and apo A-I and higher LDL-C to HDL-C, TC to HDL-C and apo B to apo A-I ratios. These parameters were also different between the two groups of mothers. There were no significant differences in TC, TG, LDL-C, apo B and Lp (a) values between the two newborn groups, whereas smoker mothers had higher serum levels of LDL-C and apo B.

DISCUSSION

There are only a few studies^{11,13)} which have examined the lipid profile in newborns whose mothers smoked during pregnancy. In our study we confirmed the findings of decreased HDL-C and raised TC to HDL-C and raised LDL-C/HDL-C ratios in newborns of smoker mothers. Our study provides further evidence of decreased apo A-I and raised apo B to apo A-I ratio and unchanged apo B and Lp (a).

Our results also confirmed previous studies showing lower birthweights in newborns of smoker mothers compared to nonsmokers. Nicotine, which can easily cross the placenta and accumulate in fetal blood at levels higher than maternal serum levels has been greatly responsible for the effects of cigarette smoking on the fetus.¹⁴⁾ It has been shown that lipoprotein lipase activity (LPL) is markedly increased in smokers. This may be induced by nicotine.^{15,16)} This enzyme catalyzes the degradation of triglyceride rich chylomicrons and VLDL and thus is important in the formation of LDL-C.¹⁷⁾ Increased LPL activity may be responsible for elevated serum LDL-C levels in smokers. Nicotine also increases plasma free fatty acid concentration through enhanced lipolysis resulting from sympathoadrenal stimulation.¹⁸⁾ Another effect of nicotine on lipid metabolism is delay of the plasma clearance of LDL¹⁹⁾ and increase in the circulation time of chylomicrons.²⁰⁾ The latter effect of the alkaloid is related to decreased hepatic sinusoidal endothelium. Diminished removal of LDL is of particular importance because an extended residence time of these particles in the circulation would increase the likelihood of their deposition in the arterial wall. Different mechanisms may also contribute to the lipid alterations observed. Cigarette smoking extract inhibits *in vitro* oxidative modification of LDL-C induced by chemical pro-oxidants, cupric chloride or 2 amidinopropane hydrochloride and fragmentation of apo B-100.²¹⁾ Thus, it can be speculated that increase in serum LDL-C and apo B levels may be related to inhibition of oxidation of LDL-C and inhibition of fragmentation of apo B. Cigarette smoking also inhibits the activity of lecithin: cholesterol acyl transferase, the enzyme that catalyzes the formation of cholesterol ester in HDL and thereby promotes HDL maturation. The inhibition of LCAT activity by cigarette smoke may contribute to the development of athero-

sclerosis by impairing HDL metabolism and the reverse cholesterol.²²⁾

It has been showed that cigarette smoking causes liver injury by increasing lipid peroxidation in rats.²³⁾ Thus, it can be speculated that cigarette smoking-induced liver injury may play a more primary role in eliciting changes in apo A-1.

Cigarette smoking causes many metabolic and biochemical changes other than dyslipidemia, such as elevated vasopressin, changed thrombogenic balance of prostacyclin and thromboxane A₂, increased fibrinogen and platelet aggregation. These effects of smoking have not been studied in the present investigation.

Increased levels of lipids and lipoproteins may continue for many years beyond the newborn period. Tsang,²⁴⁾ Darmady²⁵⁾ and Lauer²⁶⁾ have shown a positive correlation between total cholesterol in cord serum and total cholesterol after the newborn period. Fonnebo²⁷⁾ has also shown a positive correlation between cord serum VLDL and LDL cholesterol levels and VLDL and LDL cholesterol later in life. It may be possible that an atherosclerotic lipid profile observed in newborns of smoker mothers may continue beyond the newborn period. Therefore these children should be followed-up for developing atherosclerosis during later life.

ACKNOWLEDGMENTS

The authors are grateful to Üzeyir Kırca, MD and Haluk Erkur, MD from İzmir Maternity Hospital and Hilmi Yücel, MD from Manisa Maternity Hospital, for providing facilities to collect blood samples from mothers and newborns, and laboratory support.

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