

Hyperlipidaemia during Normal Pregnancy, Parturition and Lactation

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Abstract

Excessive accumulation of one or more of the major lipids in plasma can produce a marked increase in the risk of coronary heart diseases and other vascular complications. During and after pregnancy, changes in the levels of total cholesterol, triglyceride, low density lipoprotein-cholesterol, and high density lipoprotein-cholesterol have been described, but the amount of change varies from study to study. Therefore, the present study investigated changes in lipids and lipoproteins throughout the pregnancy and puerperium. We also investigated for the factors which may affect the plasma lipids during pregnancy. Concentrations of cholesterol and triglyceride of total plasma and lipoproteins were determined in 42 pregnant women throughout their pregnancy and puerperium together with a control group of 42 non-pregnant women. Compared to the control group, concentrations of cholesterol and triglyceride of total plasma and lipoproteins increased significantly during the second trimester and reached maximum in the third trimester. Concentrations of both, cholesterol and triglyceride, decreased significantly during post-partum. There was, however, a strikingly more rapid fall of plasma triglyceride and cholesterol in those mothers who breast-fed their infants compared with that in those in whom lactation was never established. In the majority of subjects, cholesterol and triglycerides remained significantly high until the fourth week of post-partum. The magnitude of the plasma cholesterol increment appeared in part to be related to that of plasma triglycerides, but these increments appeared to be independent of age, weight gain, numbers of previous pregnancies and sex of the foetus. This study concludes that hyperlipidaemia is a common finding during pregnancy and during post-partum. The concentrations of both cholesterol and triglycerides remain significantly higher in bottle-feeding than in breast-feeding mothers.

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Introduction

Increase in the plasma lipid fractions in normal pregnancy have been described but irregularity of sampling, difference in materials studied (whole blood, serum, and plasma) and the variations in the method of reporting precluded any comparison of results.^{1,2} In Western populations normal pregnancy leads to an increase in cholesterol concentration by approximately 25% while the triglyceride concentration increases two-fold to three-fold.^{3,4} Changes in lipoprotein composition have also been reported with both lipid and protein moieties being affected. However, in Pakistani women, these changes have never been reported. Moreover previous Western studies have concentrated on the last trimester of pregnancy. This study describes the longitudinal changes in the concentrations of cholesterol and triglyceride in total plasma and their distribution among the lipoprotein

fractions of plasma during the whole course of the pregnancy and puerperium. We also analysed our data to see any possible effect of lactation, age, weight gain, diet, parity and sex of the foetus on the plasma lipids concentrations.

Materials and Methods

All experimental procedures adhered to the Declaration of Helsinki of the World Medical Association. The work was approved by the Ethics Committee of the Institution and subjects gave informed consent. Forty-two volunteer subjects in the first trimester of pregnancy were chosen from those attending routine antenatal outpatient department, while the same numbers of controls were taken among the nurses. In the control subjects no one was taking contraceptives. For all pregnant women the date of the last menstrual period (LMP) was accu-

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rately known. All participants were of the same age group, ranging between 21 and 25 years. Differences in all other demographic characteristics of control versus pregnant subjects were statistically insignificant. All the subjects met the following health conditions: 1) those who were not under medical treatment, 2) those who did not have a history of cardiac or hepatobiliary disease, and who had no abnormal subjective symptoms, and 3) those who did not exhibit abnormalities during routine physical examinations.

Records were made of the age, parity, and labour of both pregnant and non-pregnant groups. Blood samples were taken monthly throughout the pregnancy, at the time of delivery, within 12 to 24 hours of delivery (designated d 1) and on the sixth day post-partum. Following discharge from the hospital, further samples were taken until the 20th post-partum weeks after every four weeks. Plasma lipids and lipoprotein's lipid values were also obtained in non-pregnant control women. The subjects were asked to fast overnight, 12 to 16 hours before the test, and they were requested not to do any exercise during the fasting period. Adherence to the requirement of abstinence from exercises, fasting, or both were checked carefully by questioning the participants at the time of their test; any non-fasting individuals were rescheduled. Brachial blood pressure measurements were taken with a calibrated sphygmomanometer in sitting position after a complete rest of 15 minutes in supine posture. All participants were recumbent for no more than a few minutes during blood drawing. Venous blood was drawn into Vacutainer tubes containing 1 mg per ml of ethylenediaminetetraacetic acid (EDTA). Plasma was prepared from the blood within 2 hours and was kept at 4°C. Plasma lipoproteins were separated into very low density (VLDL, having a density less than 1.006 g/l), low density (LDL, having a density between 1.006 and 1.063 g/l), and high density (HDL having a density between 1.063 and 1.21 g/l) lipoproteins. VLDLs were isolated by preparative ultracentrifugation⁵ and LDLs were precipitated with heparin sulfate and manganese chloride.⁶ Lipids were extracted into isopropanol-heptane. The laboratory procedures were standardised according to the criteria for the Lipid Research Clinics.⁷ Concentrations of cholesterol and triglyceride of total plasma, VLDL, LDL and HDL were determined using the procedures by the Lipid Research Clinics.⁷ The analyses were performed on the AutoAnalyzer II (Technicon Instruments, Tarrytown, New York, USA Manual, 1971). Mean recoveries of lipoprotein cholesterol and triglycerides were 93% and 95%, respectively.

All variables descriptive statistics (mean, standard deviation and standard error of mean) were calculated by Statistical Analysis System 76.⁸ Analysis of variance (ANOVA) was used to compare results during various

months of pregnancy and among different post-partum measurements. Differences were regarded as significant when the *P* value was less than 0.05. Actual *P* values were also given.

Results

The duration of pregnancy was 36 to 39 weeks (mean 37.5 ± 0.7 weeks). Out of the 42 pregnant, no one developed any obstetric complications. Blood pressure of all the subjects remained within normal range. There were 23 male and 19 female babies and all were healthy, within a weight range of 2.4 to 3.9 kg. Nine were bottle-fed from birth and the remaining 33 breast-fed till the last measurements were taken. From the replies to the initial diet questionnaire, all the women were eating normal balanced diets. Analysis of the replies to the afterward questionnaires disclosed no consistent trend in the variation of eating habits sufficient to be the primary cause of the large biochemical variations observed.

The plasma cholesterol level showed an overall 52.9% increase during pregnancy, some 34.1 per cent of which occurred within the second trimester. The plasma triglyceride concentration increased 200.1% during pregnancy. Most of this increase took place in the last trimester of pregnancy. There was no significant change in VLDL-cholesterol until midway through gestation, at which time the concentration doubled, rising during the last trimester to a value $4\frac{1}{2}$ times greater than among non-pregnant women. VLDL-triglyceride concentrations were similarly affected. LDL-cholesterol also rose during the second trimester and then increased rapidly, being 40.1% above first-trimester levels close to term. In contrast to the findings in VLDL and LDL the increase in cholesterol that occurred in HDL took place within the second trimester. The triglyceride component of HDL increased by 55.6% in the second trimester and by 100% in the third.

The magnitude of the plasma cholesterol increment appeared in part to be related to that of plasma triglyceride, but no other significant correlating factor for either measurement was found. That is, they appeared to be independent of age, weight gain, diet, numbers of previous pregnancies and sex of the foetus. There were marked variations among individuals in the extent of increase in both cholesterol and triglyceride. Changes in the concentrations of total cholesterol and triglyceride are shown in Figures 1 and 2, respectively. The changes in cholesterol and triglyceride components of lipoproteins are given in Table I. During post-partum, concentrations of both cholesterol and triglyceride decreased significantly and this was reflected in all lipoproteins. There was, however, a strikingly more rapid fall of plasma triglyceride in those mothers who breast-fed their infants compared with that in those in whom lactation was

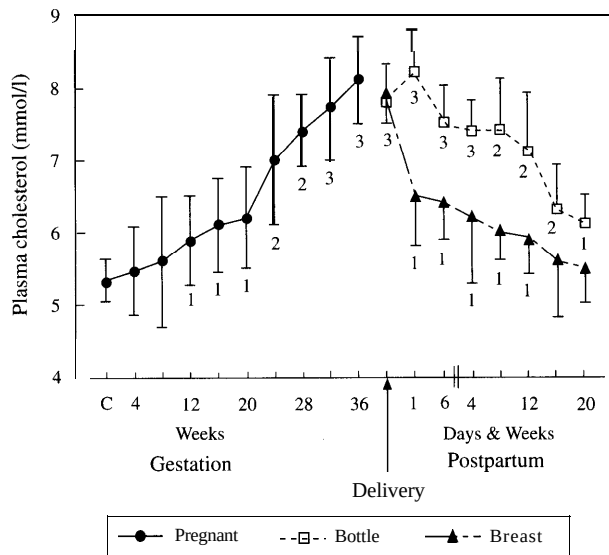


Fig. 1. Changes in plasma cholesterol concentrations during pregnancy, at delivery, and in the puerperium up to the 20th week. The symbol represents the mean and the vertical lines represent one standard deviation. Numbers are indicating that differences are significant (¹ $P < 0.05$; ² $P < 0.02$; ³ $P < 0.001$) as compared to control (C) group. The differences between breast-feeding and bottle-feeding mothers were significant up to 16th post-partum weeks (up to 12th week $P < 0.001$; 16th week $P < 0.05$).

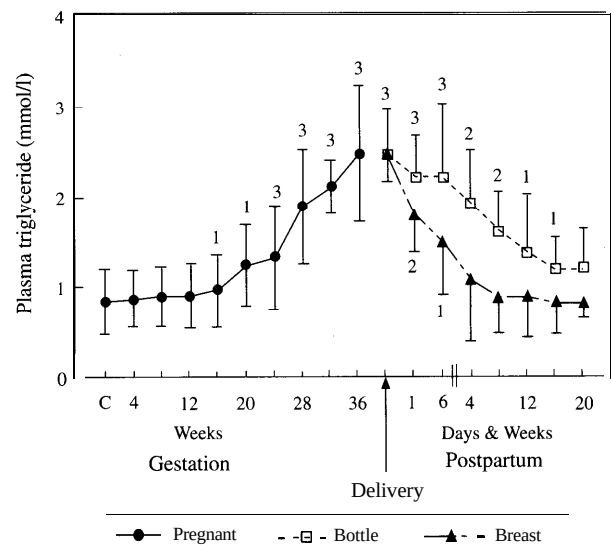


Fig. 2. Changes in plasma triglyceride concentrations during pregnancy at delivery, and in the puerperium up to the 20th week. The symbol represents the mean and the vertical lines represent one standard deviation. Numbers are indicating that differences are significant (¹ $P < 0.05$; ² $P < 0.01$; ³ $P < 0.001$) as compared to control (C) group. The differences between breast-feeding and bottle-feeding mothers were significant up to 12th post-partum weeks (up to 8th week $P < 0.01$; 12th week $P < 0.05$).

TABLE I: CHANGES IN PLASMA LIPIDS AND LIPOPROTEINS DURING AND AFTER PREGNANCY

Duration	VLDL		LDL		HDL	
	Cholesterol	Triglyceride	Cholesterol	Triglyceride	Cholesterol	Triglyceride
Control	0.22 ± 0.01	0.49 ± 0.08	3.21 ± 0.09	0.32 ± 0.04	1.51 ± 0.11	0.27 ± 0.05
4 to 12#	0.27 ± 0.04	-0.46 ± 0.11	3.48 ± 0.14	0.46 ± 0.10	1.74 ± 0.14	0.33 ± 0.07
16 to 24#	0.56 ± 0.09*	0.94 ± 0.11**	4.20 ± 0.32†	0.84 ± 0.07**	2.16 ± 0.13*	0.42 ± 0.05†
28 to 36#	1.00 ± 0.12†	1.51 ± 0.11†	4.89 ± 0.26†	1.29 ± 0.11†	2.01 ± 0.14*	0.54 ± 0.04†
Delivery						
Breast	1.07 ± 0.13†	1.81 ± 0.14†	5.53 ± 0.41†	1.49 ± 0.21†	2.00 ± 0.10*	0.54 ± 0.08†
Bottle	1.08 ± 0.09	1.79 ± 0.22	5.48 ± 0.43	1.51 ± 0.26	1.99 ± 0.13	0.54 ± 0.11
Day 1						
Breast	0.76 ± 0.09†	1.71 ± 0.13-†	5.07 ± 0.31†	0.80 ± 0.13**	1.91 ± 0.11"	0.51 ± 0.09†
Bottle	1.04 ± 0.19-j.	1.71 ± 0.32†	5.48 ± 0.41-j.	1.41 ± 0.19**	1.97 ± 0.21*	0.51 ± 0.08†
Day 6						
Breast	0.70 ± 0.11†	1.42 ± 0.17**	4.54 ± 0.27†	0.67 ± 0.10	1.74 ± 0.09*	0.41 ± 0.07*
Bottle	0.98 ± 0.17†	1.68 ± 0.23**	4.99 ± 0.45†	1.12 ± 0.25	1.90 ± 0.29*	0.49 ± 0.13*
Wk4						
Breast	0.51 ± 0.13†	1.11 ± 0.13**	3.94 ± 0.31	0.58 ± 0.21	1.71 ± 0.19	0.32 ± 0.06
Bottle	0.89 ± 0.11†	1.53 ± 0.24**	4.49 ± 0.36†	1.01 ± 0.24**	1.84 ± 0.30*	0.43 ± 0.09*
Wk8						
Breast	0.38 ± 0.15	0.61 ± 0.21	3.39 ± 0.33	0.43 ± 0.11	1.69 ± 0.11	0.29 ± 0.04
Bottle	0.71 ± 0.22*	1.10 ± 0.26**	3.84 ± 0.24	0.84 ± 0.19†	1.84 ± 0.19*	0.37 ± 0.07
Wk 12 to 20#						
Breast	0.26 ± 0.08	0.49 ± 0.11	3.39 ± 0.30	0.39 ± 0.08	1.62 ± 0.08	0.29 ± 0.05
Bottle	0.51 ± 0.11	0.73 ± 0.24	3.54 ± 0.39	0.59 ± 0.12	1.76 ± 0.16*	0.33 ± 0.06

All values are in mmol/litre and are expressed as mean ± sem.

Although the measurements were made after every 4 weeks, but values were grouped together because increases were insignificant among these intervals. Differences between breast and bottle feeding mothers are explained in results. Differences are significant (* $P < 0.05$; ** $P < 0.02$; † $P < 0.001$) as compared to control group of respective value.

never established (Fig. 2). All subjects in the lactating group were still breast-feeding when their triglyceride value fell to within 1.5 SD of the individual's mean pre-pregnancy value. A similar pattern was observed for plasma cholesterol concentration (Fig. 1). The plasma cholesterol differences between breast-feeding and bottle-feeding mothers were significant up to 16th post-partum weeks (up to 12th week $P < 0.001$; 16th week $P < 0.05$). In bottle-feeding mother cholesterol remained significantly higher between day 1 and 4th week in VLDL, 4th and 8th weeks in LDL, and at 6th day in HDL. The plasma triglyceride differences between breast-feeding and bottle-feeding mothers were significant up to 12th post-partum weeks (up to 8th week $P < 0.01$; 12th week $P < 0.05$). In bottle-feeding mother triglyceride concentrations remained significantly higher between weeks 4th and 8th in VLDL, and between day 1 and 4th week in LDL. In HDL, triglyceride concentration remained the same in breast and bottle feeding mothers.

Discussion

The main finding of the present study showed an increase in cholesterol and triglyceride of total plasma, VLDL, LDL and HDL during pregnancy in Pakistani women. This result is consistent with many other studies conducted in Western countries.^{3,4,9,10} This physiologic hyperlipidaemia is potentially significant from several standpoints: firstly, the increase in plasma triglycerides may enhance the availability of essential and non-essential triglycerides fatty acids for placental transfer to the foetus;¹¹ secondly, the cholesterol rise may increase the supply of cholesterol needed for placental progesterone synthesis¹² and transplacental cholesterol transfer to the foetus;¹³ and thirdly, hyperlipidaemia in pregnancy could itself function as an arteriosclerosis risk factor.¹⁴

The physiological significance of these changes could be related to the initiation and maintenance of lactation. This study reports that during post-partum, the plasma concentrations of both cholesterol and triglycerides remained significantly higher in bottle-feeding mothers than in breast-feeding mothers. During post-partum, the elevated plasma triglyceride concentration decreased rapidly in breast-feeding mothers than in bottle-feeding mother. The significantly greater utilisation of plasma triglyceride in lactating women could be caused by the tissue-specific direction of VLDL towards the mammary gland for milk synthesis. Evidence to support this hypothesis is provided by studies of post-partum rats. Lipoprotein lipase activity is depressed in adipose tissue but greatly elevated in mammary gland. In breast-feeding mothers, triglyceride and cholesterol concentrations of lipoproteins start to decrease but remained significantly higher until the 4th week after delivery, while in bottle-feeding mothers, triglyceride and cholesterol concentrations of lipoproteins remained significant until

the 16th week. The persistent elevation of both cholesterol and triglyceride levels six to seven weeks post-partum has been previously demonstrated.^{3,15,16}

The exact reason that why plasma lipids and lipoproteins' levels remained higher and over the long period of time in bottle-feeding mothers than in breast-feeding mothers is not known. As stated above, it has been shown in rats that after delivery, lipoprotein lipase activity is depressed in adipose tissue but greatly elevated in mammary gland. In breast-feeding mothers, the activation of lipoprotein lipase in mammary gland may cause the rapid decrease in plasma lipids, while in bottle-feeding mother, due to non-utilisation of lipids, their level can remain high. What may be the cause of this difference, this finding indicates one advantage to breast-feeding mothers, because it has been shown by several studies that higher plasma lipid level is a risk factor for cardiac problems. At this time, no data about the incidence of cardiac diseases in breast-feeding and bottle-feeding mothers is present.

The physiological mechanisms responsible for the increase in cholesterol and triglyceride during pregnancy are not clearly known.^{9,10} A number of possible mechanisms can be postulated. This hyperlipidaemia may be hormonally mediated. For instance, altered triglyceride kinetics may be detected up to six weeks after ceasing the use of oral contraceptives.¹⁷ While many physiologic parameters apparently return to normal very quickly after removal of the foetus and placenta (for instance, there is an immediate improvement in the hypertension associated with pre-eclampsia), restoration of other metabolic functions accompanying the return of hormonal equilibrium may take much longer. Corredor et al¹⁸ reported that plasma cholesterol and triglyceride concentrations were positively correlated with 17-estradiol, progesterone, human placental and lactogen levels throughout the whole period of gestation. The hypercholesterolaemia during pregnancy may be related to the increased production of sex steroids.^{19,20} In experimental animals, the activity of enzyme lipoprotein lipase had been shown to decrease during pregnancy.²¹ These changes are specific for the adipose tissue enzyme as lipoprotein lipase activity in the heart, lung, diaphragm and mammary gland is unaffected.²² The decrease of lipoprotein lipase activity in adipose tissue could explain the increase in plasma lipids and lipoproteins during pregnancy. The idea that hyperlipidaemia in pregnancy is itself an arteriosclerosis-promoting event has been debated in previous studies^{3,4,14,19} but is without conclusive proof, which is perhaps not surprising with the present observation that after the 20th week, values mostly became normal. Obviously, more work is required to determine to what extent changes in lipoprotein physiology during pregnancy increase the risk of arteriosclerosis.

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