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THE LIPID METABOLISM IN NORMAL AND DIABETIC PREGNANCY

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Synopsis In order to study the lipid metabolism in normal and diabetic pregnancy, the serum obtained in the third trimester and postpartum was fractionated into VLDL, LDL, and HDL by ultracentrifugation. The lipid concentrations in each lipoprotein fraction were determined. The hyperlipidemia induced by pregnancy was mainly due to the increase in the amount of VLDL-triglyceride, which was enhanced in diabetic pregnancy. Each lipid in the VLDL fraction was increased, but compositionally unchanged from that observed in non-pregnant women. On the contrary, the percentage of triglyceride in the LDL and HDL increased with reciprocal percentage reductions in cholesterol and phospholipid. This tendency was more prominent in diabetic pregnancy than in normal pregnancy. PHLA, which was determined to study the catabolism of triglyceride, was suppressed in the third trimester in normal and diabetic pregnancy, compared to that in non-pregnant women. Moreover, the ratio of apo C II/C III_1+C III_2 in the VLDL was investigated and found to be significantly lower in the third trimester in normal and diabetic pregnancy than that in non-pregnant women. The impaired removal of VLDL-triglyceride was one of the factors which caused hyperlipidemia during pregnancy. In addition, the overproduction of VLDL-triglyceride affected hyperlipidemia in diabetic pregnancy.

Key words: Pregnancy • Lipoproteins • Diabetes mellitus • Lipoprotein lipase • Apoproteins

Introduction

Previous studies have demonstrated that maternal serum lipid value show a marked and successive increase toward the third trimester in human pregnancy[24)27)]. It is generally believed that the hyperlipidemia of pregnancy is mainly due to a huge increase in triglyceride. Triglyceride, cholesterol and phospholipid, except for free fatty acids (FFA), exist in blood in the form of lipoprotein which contains some kinds of apoproteins. The studies are sparse on lipid metabolism with respect to the major lipoproteins; i.e., very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL). Moreover, in order to manage diabetic mothers and their fetuses, it is necessary to understand the difference of lipid metabolism in the major lipoproteins between normal and diabetic pregnancy. Therefore, the author determined the concentrations of triglyceride, cholesterol and phospholipid in the VLDL, LDL and HDL on normal and diabetic pregnancy. The compositional analysis of triglyceride, cholesterol and phospholipid in each lipoprotein was also studied in the present study.

The clearance of circulating triglyceride is thought to be mediated primarily by triglyceride lipase. Postheparin lipolytic activity (PHLA) has been used to assess the activity of triglyceride lipase. In order to study the huge increase in serum triglyceride during pregnancy, PHLA was determined on normal and diabetic pregnancy.

Apoproteins in the C family are considered to be implicated in the activation of extrahepatic triglyceride lipase: Lipoprotein lipase (LPL) based on *in vitro* studies[7)15)]. Changes in apoprotein C ratios were reported in other endogenous hypertriglyceridemias[2)3)9)]. However, there is little information available about the changes of apoprotein C ratios during pregnancy. Therefore, the ratio of apo C II/C III_1+C III_2 in the VLDL were investigated on normal and diabetic pregnancy. The studies were performed during the third trimester and postpartum.

Materials and Methods

1. Subjects

Thirty-six normal pregnant women were studied for lipid analysis in the third trimester (35-41 weeks of gestation) and twenty-one of them were studied at postpartum (6-8 weeks). On the other hand sixteen diabetic pregnant women were studied in

the third trimester (33-38 weeks) and nine of them were studied at postpartum (6-8 weeks). Their mean age was 28.0 (21-33 years) and 27.8 years (24-39 years), respectively. There were no statistical differences on maternal ages and gestational weeks between normal and diabetic pregnant women. Oral glucose tolerance tests (50g) were examined for diabetic pregnant women during pregnancy and 6 weeks or more postpartum. Hourly glucose levels were determined on plasma and interpreted according to the criteria of the Japan Diabetic Society[17]; 1 hr; 160mg/dl, 2hrs; 130mg/dl. They were grouped in relation to the degree of severity of the diabetes according to White classification[5]. Nine women were judged as gestational diabetes (abnormal GTT during pregnancy), one woman as class A (diet alone, any duration or onset age), and six women as class B (onset age 20yr or older and duration less than 10yr). Twenty-six healthy non-pregnant women (age 21-35 years) served as controls. The subjects for PHLA determination included 21 normal pregnant, 9 diabetic pregnant and 15 non-pregnant women. Out of them 13 normal pregnant, 6 diabetic pregnant and 9 non-pregnant women were investigated for apoprotein C.

2. Lipid analysis

Venous blood was obtained following an overnight fast. The serum was taken off after centrifugation and kept at 4℃. Ultracentrifugal fractionation of lipoprotein was immediately performed according to the method by Hatch and Lees[6]. Ultracentrifugation runs were performed using a Beckman L5-50B ultracentrifuge and rotor type 50. Each lipoprotein fraction was collected by aspiration with a 18 gauge needle and syringe. Chylomicron was not detected in the present study. The LDL and HDL were dialyzed for 24 hours at room temperature against 10 liters of 0.15M NaCl containing 0.001M EDTA at pH8. Duplicate determinations of triglyceride, cholesterol and phospholipid were performed in each fraction. Triglyceride was determined by acetyl-acetone method (Triglyceride-Test kit, WAKO PURE CHEMICAL INDUSTRIES, LTD.). Cholesterol and phospholipid were determined by the enzymatic methods (CHOL-E kit, IATRON LABORATORIES INC., Phospholipid Enzyme kit, WAKO PURE CHEMICAL INDUSTRIES, LTD.). The recoveries during the procedure were determined by adding triglyceride, cholesterol and phospholipid of all fractions from each subject and comparing these with the results obtained from the unfractionated serum. The recoveries of triglyceride, cholesterol and phospholipid were 85.0±16.3%, 88.6±9.1% and 83.4±11.2% (mean ±S.D.), respectively. The composition of triglyceride, cholesterol and phospholipid in each fraction was calculated as follows. Triglyceride, cholesterol and phospholipid in each fraction were added to yield the total lipid of that fraction, and each component was expressed as a percent of total lipids.

3. Postheparin lipolytic activity

Ten min. after intravenous injection of heparin (0.1mg/kg) following an over night fast, 4.5ml of blood was collected in a centrifuge tube containing 0.5ml of 0.1M trisodium citrate. The plasma was taken off after centrifugation and stored at −20℃. PHLA was measured by Itaya-Ui method[16]. Fig. 1 shows the outline of the procedure. Palmitic acid (64.1mg) was dissolved in 100ml of chloroform to prepare the standard solution. This concentration was equivalent to 0.5μmole FFA/ml/min. triglyceride lipase activity. Each solution, whose concentration was equivalent to 0.1, 0.2, 0.3, 0.4μmole FFA/ml/min triglyceride lipase activity, was prepared by dilution with chloroform. Optical density (O.D.) was determined by using SHIMADZU UV-210 spectrophotometer (SHIMADZU CORP.). The difference of O.D. between Specimen II and Specimen I was the PHLA of each sample. PHLA was read directly on the standard curve. Reproducibility of measurement was examined to perform 8 repeated measurements on an unknown sample. The mean value was 0.125±0.012 (mean ±S.D.) μmole FFA/ml/min. The coefficient of variation was 9.6%.

4. Apoproteins C in the VLDL

Analysis of apoproteins C was performed using the disc gel electrophoresis according to the method by Kane[10]. The outline of the procedure is shown in Table 1. Apparatus for the disc gel electrophoresis were as follows; electrode tank SJ-1060 D (ATTO. CORP.), Electrophoresis constant power supply ECPS 3000/150 (Pharmacia Fine Chemicals), SHIMADZU CS-910 Photoscanner (SHIMADZU CORP.), Photometric scanning of apoproteins C in the VLDL was shown in Fig 2. Each area of apo C II, C III_1 and C III_2 peak was calculated. The

Fig. 1 The procedure of PHLA measurement

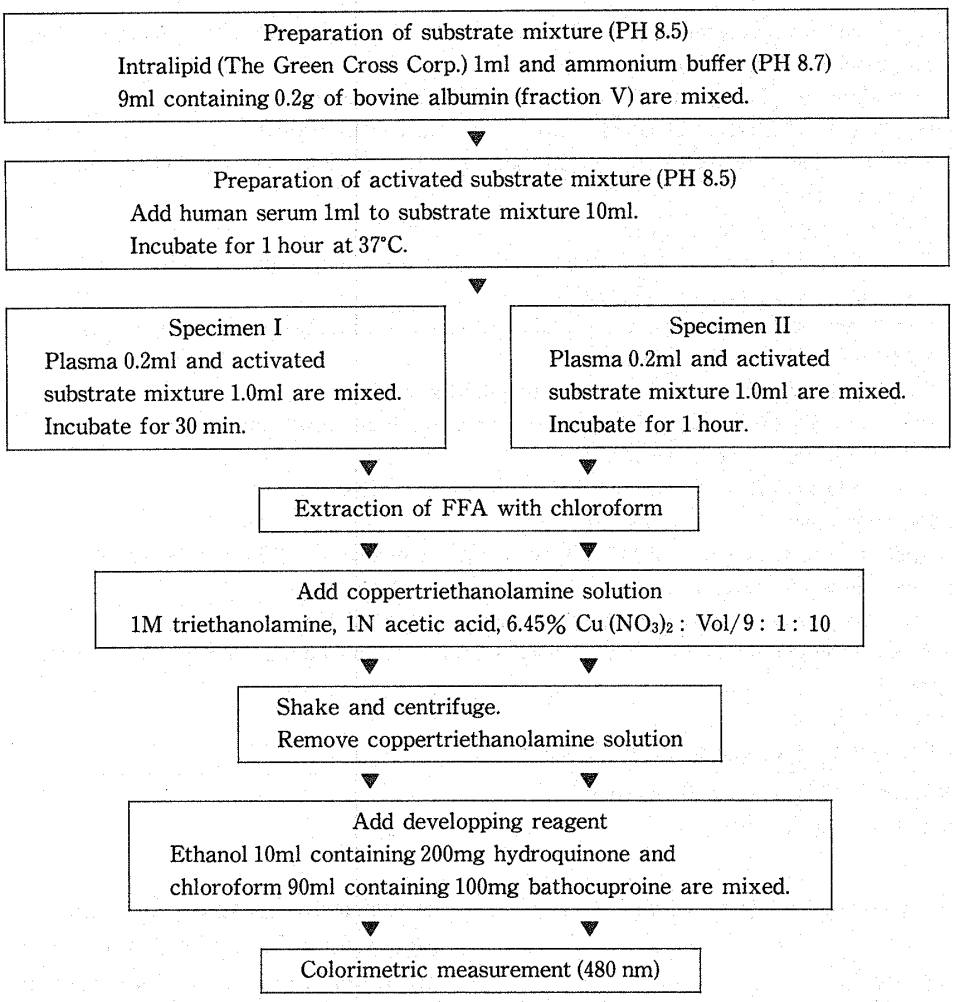


Fig. 2. The diagrams obtained from the photometric scanning of the disc gels.
left ; VLDL from a non-pregnant woman.
right ; VLDL from a normal pregnant woman.
IF=interface between upper and lower gel, R=marker (riboflavin),
→ indicates direction of migration

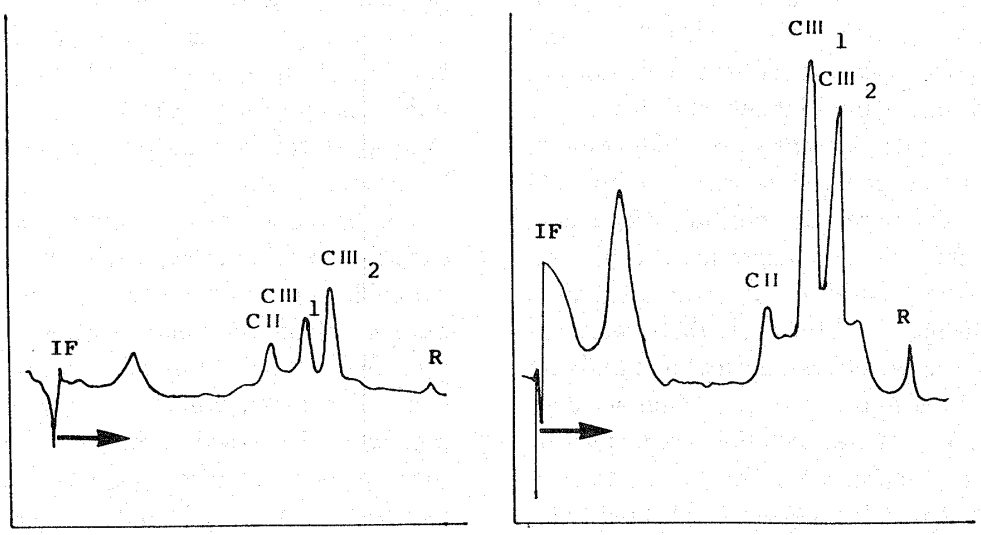


Table 1 The procedure of electrophoresis of apoproteins C in the VLDL

1. Equal parts of monomer and Tris-TMED* solution are mixed and crystalline urea (0.64g/ml) are dissolved. (Mixture I)
2. Crystalline urea (0.64g/ml) are dissolved in persulfate solution. (Mixture II)
3. Equal parts of Mixture I and Mixture II are mixed. (Mixture III)
4. Pour immediately Mixture III into the glass tube (6 mm inside diameter, 130 mm long) to a depth of 80 mm.
5. Polymerization of the lower gel.
6. Equal parts of monomer and Trisphosphate solution are mixed and crystalline urea (0.64g/ml) are dissolved.(Mixture IV)
7. Equal parts of the riboflavin and persulfate solution are mixed and crystalline urea (0.64g/ml) are dissolved.(Mixture V)
8. Equal parts of Mixture IV and V are mixed.(Mixture VI)
9. Pour immediately Mixture VI on the lower gel to a depth of 15 mm.
10. Polymerization of the upper gel.
11. Equal volumes of the VLDL and TMU** are mixed.(Mixture VII)
12. Layer Mixture VII on the upper gel.
13. Apply a constant current of 1.25 mA per gel and increase it to 2.5 mA after the dye band enters the lower gel.
14. Open the circuit when the dye band reaches near the bottom.
15. Remove the gel and stain it in 7% aqueous acetic acid containing Amidschwarze (lg/1) for 1 hr.
16. Destain the gel.
17. Photometric scanning of the gel at 550 nm.

*N,N,N;N; -Tetramethylethylenediamine
**1, 1, 3, 3, -Tetramethylurea

results were expressed as the ratio of apo C II/C III_1+C III_2.

5. Statistical analysis

Statistical analysis was carried out by Student's t-test

Results

The lipid concentrations in the whole serum, VLDL, LDL and HDL from normal and diabetic pregnancy in the third trimester and the control (non-pregnant) are presented in Table 2. In the whole serum, each lipid concentration of normal pregnancy was significantly higher than that of the control. Triglyceride increased 4 fold, though cholesterol and phospholipid showned about 1.5 fold increase. Compared to normal pregnancy, triglyceride of diabetic pregnancy increased more prominently. Seven cases of diabetic pregnancy showed over 400mg/dl. However, there were no significant differences between normal and diabetic pregnancy in cholesterol and phospholipid concentrations. In the VLDL, each lipid component of normal pregnancy increased 4 fold, compared to that of the control. Moreover, each lipid concentration of diabetic pregnancy was significantly higher than that of normal pregnancy. In the LDL, all lipid components of normal pregnancy increased significantly than those of the control. Diabetic pregnancy also showed a similar increment in triglyceride as in normal pregnancy. Nevertheless, cholesterol and phospholipid indicated slightly lower values than those of normal pregnancy. In the HDL, each lipid concentration of normal pregnancy was significantly higher than that of the control. There was no significant difference between normal and diabetic pregnancy in each lipid concentration. But while, the concentration of cholesterol in diabetic pregnancy indicated a lower mean value.

The lipid concentrations in the whole serum and each lipoprotein in the postpartum are presented in Table 3. In the whole serum, the mean values of cholesterol and phospholipid in normal and diabetic pregnancy remained higher than those in the control. The mean value of triglyceride in normal pregnancy decreased to the level of the control, but four cases in diabetic pregnancy showed higher values. In the VLDL, only cholesterol level was

Table 2 Lipid concentrations in the whole serum, VLDL, LDL, and HDL in the third trimester

	Control (non-pregnant) n§=26	Normal pregnancy n=36	P Normal pregnancy VS. Control	Diabetic pregnancy n=16	P Diabetic pregnancy VS. Normal pregnancy
Whole serum	mg/dl	mg/dl		mg/dl	
Triglyceride	70.2±25.7	289.4±79.4	<0.01	370.2±158.3	N S
Cholesterol	173.9±25.7	256.7±43.9	<0.01	230.8± 49.2	N S
Phospholipid	187.0±23.4	296.9±57.1	<0.05	303.3± 60.1	N S
VLDL					
Triglyceride	28.3±12.7	113.6±50.0	<0.01	163.5± 79.3	<0.01
Cholesterol	6.8± 3.7	30.3±10.8	<0.01	40.4± 22.0	<0.05
Phospholipid	9.9± 4.4	39.2±13.1	<0.01	58.9± 28.7	<0.01
LDL					
Triglyceride	20.1± 7.9	81.0±19.4	<0.01	92.3± 32.0	N S
Cholesterol	94.9±21.2	127.9±31.5	<0.01	100.1± 33.3	N S
Phospholipid	60.8±13.3	97.9±20.6	<0.01	84.0± 23.1	N S
HDL					
Triglyceride	12.1± 4.8	48.9±18.6	<0.01	46.8± 17.0	N S
Cholesterol	59.5±15.6	69.8±17.9	<0.05	56.3± 20.2	N S
Phospholipid	82.0±18.9	118.5±29.3	<0.01	110.2± 35.1	N S

Each estimation represents mean±S.D.

§ Number of subjects in each group

Table 3 Lipid concentrations in the whole serum, VLDL, LDL, and HDL in the postpartum period

	Control (non-pregnant) n§=26	Normal pregnancy n=21	P Normal pregnancy VS.Control	Diabetic pregnancy n=9	P Diabetic pregnancy VS. Normal pregnancy
Whole serum	mg/dl	mg/dl		mg/dl	
Triglyceride	70.2±25.7	81.8±27.9	N S	141.9±94.0	N S
Cholesterol	173.9±25.7	222.0±47.7	<0.01	214.3±43.2	N S
Phospholipid	187.0±23.4	232.3±30.4	<0.01	240.9±61.3	N S
VLDL					
Triglyceride	28.3±12.7	28.4±17.0	N S	65.3±53.0	<0.05
Cholesterol	6.8± 3.7	12.1±10.4	<0.05	25.1±18.2	<0.05
Phospholipid	9.9± 4.4	13.2± 9.4	N S	28.9±18.1	N S
LDL					
Triglyceride	20.1± 7.9	24.0± 5.6	N S	36.0±17.9	<0.05
Cholesterol	94.9±21.2	115.8±33.0	<0.05	102.0±30.3	N S
Phospholipid	60.8±13.3	78.4±19.4	<0.01	77.8±27.1	N S
HDL					
Triglyceride	12.1± 4.8	13.9± 4.9	N S	18.9± 8.9	N S
Cholesterol	59.5±15.6	63.0±13.3	N S	56.1±13.2	N S
Phospholipid	82.0±18.9	91.0±18.4	N S	82.4±15.0	N S

Each estimation represents mean±S.D.

§ Number of subjects in each group

significantly elevated in normal pregnancy, but in diabetic pregnancy both triglyceride and cholesterol concentrations were significantly elevated as compared to the control. In the LDL, no significant difference was found between normal pregnancy and the control in triglyceride, though diabetic pregnancy showed a significant higher value in triglyceride than normal pregnancy. The

Table 4 The ratio of each lipid composition in the whole serum, VLDL, LDL, and HDL in the third trimester and postpartum.

	Control (non-pregnant) n§=26	Normal pregnancy		Diabetic pregnancy	
		3rd trimester n=36	postpartum n=21	3rd trimester n=16	postpartum n=9
Whole serum	%	%	%	%	%
Triglyceride	*16.2±5.9	34.1±6.9$^{\gamma}$	15.2± 4.7	39.7±8.2$^{\epsilon}$	22.5± 8.6$^{\zeta}$
Cholesterol	40.3±3.8	30.6±3.7$^{\gamma}$	41.2± 3.5	25.9±4.0$^{\zeta}$	36.8± 6.2$^{\epsilon}$
Phospholipid	43.4±3.0	35.2±4.9$^{\gamma}$	43.5± 3.2	34.3±6.1	40.7± 4.1
VLDL					
Triglyceride	62.9±5.1	61.7±4.2	55.4±14.9$^{\alpha}$	62.4±5.1	55.0±13.0
Cholesterol	14.9±3.6	16.5±2.9	21.3± 9.5$^{\beta}$	15.1±3.2	20.1±10.8
Phospholipid	22.3±3.3	21.9±2.9	23.4± 5.6	22.4±2.3	24.9± 4.6
LDL					
Triglyceride	12.0±5.3	26.8±5.3$^{\gamma}$	11.6± 2.5	33.4±7.5$^{\zeta}$	16.3± 5.2$^{\zeta}$
Cholesterol	53.6±3.4	41.4±4.3$^{\gamma}$	52.9± 2.2	36.2±5.5$^{\zeta}$	47.9± 6.9$^{\zeta}$
Phospholipid	34.4±2.1	31.8±1.5$^{\gamma}$	35.4± 1.1	30.5±2.5$^{\epsilon}$	35.9± 5.1
HDL					
Triglyceride	8.3±3.6	21.6±5.4$^{\gamma}$	8.5± 3.3	21.6±4.1	12.1± 5.5$^{\delta}$
Cholesterol	38.4±3.3	29.5±3.3$^{\gamma}$	37.4± 2.5	26.7±5.1$^{\delta}$	35.4± 4.5
Phospholipid	53.3±3.2	48.9±8.0$^{\beta}$	54.1± 2.1	51.7±4.6	52.5± 1.9

§ Number of subjects in each group

* mean±S.D.

α,β,γ Significance of the difference between mean and corresponding mean in the control.
α,P<0.05 β,P<0.01 γ,P<0.001

δ,ϵ,ζ Significance of the difference between mean and corresponding mean in normal pregnancy.
δ,P<0.05 ϵ,P<0.02 ζ,P<0.01

concentrations of cholesterol and phospholipid in normal pregnancy were significantly higher than those of the control. In diabetic pregnancy, however, the mean value of cholesterol tended to be lower than that in normal pregnancy. No difference was found between normal and diabetic pregnancy in phospholipid. In the HDL, each lipid concentration in normal and diabetic pregnancy remained same to that in the control. Concerning cholesterol in diabetic pregnancy, the mean value was 56.3mg/dl in the third trimester and 56.1mg/dl in the postpartum. As a result, no elevation was found in the third trimester.

Table 4 shows the ratio of each lipid composition in the whole serum and each lipoprotein in the third trimester and postpartum. In the third trimester, the ratio of triglyceride in normal pregnancy increased significantly in the whole serum, LDL and HDL, except for the VLDL. However, the ratios of cholesterol and phospholipid reciprocally decreased as compared to those in the control. This tendency was also remarked in diabetic pregnancy. In the VLDL, there were no statistical changes among them.

In the postpartum, the ratio of triglyceride in normal pregnancy decreased significantly in the VLDL, whereas that of cholesterol increased reciprocally compared to those in the control. But, there were no significant changes in the whole serum, LDL and HDL. In diabetic pregnancy, the similar change was observed in the VLDL as normal pregnancy. However, in the whole serum, LDL and HDL, the ratio of triglyceride increased more remarkably with a reciprocal decrease in cholesterol than in normal pregnancy.

The mean values of PHLA in normal and diabetic pregnancy were 0.050±0.034 and 0.082±0.035μmole FFA/ml/min. respectively in the third trimester. These values were significantly lower than that in the control (0.128±0.041μmole FFA/ml/min.) (Fig. 3). But PHLA in diabetic pregnancy was significantly higher than that in normal

Fig. 3. Postheparin lipolytic activity in the third trimester and postpartum
⊕ represents mean ±S.D.
△: non-pregnant women, ○: normal pregnant women. ●: gestational diabetes, ▲: class B

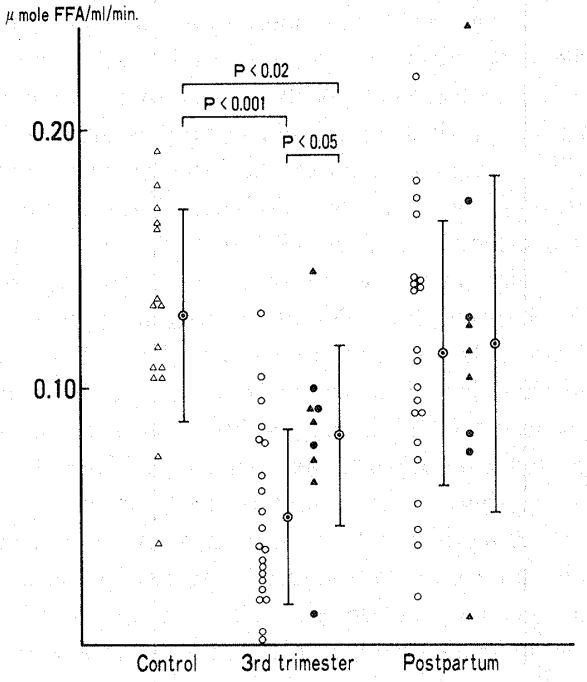
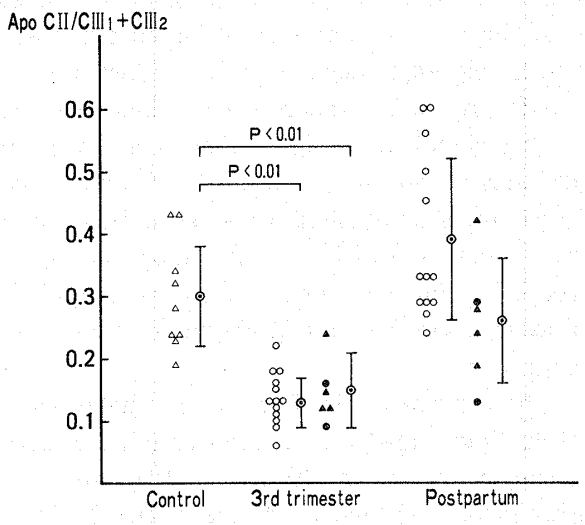


Fig. 4. The ratio of apo CII/CIII$_1$+CIII$_2$ in the VLDL in the third trimester and postpartum
⊕ represents mean ±S.D.
△: non-pregnant women, ○: normal pregnant women, ●: gestational diabetes, ▲: class B



pregnancy in the third trimester. In the postpartum, they returned to the control level.

The ratio of apo C II/C III$_1$+C III$_2$ in normal and diabetic pregnancy were 0.13±0.04 and 0.15±0.06 respectively in the third trimester. These values were significantly lower than that in the control (0.30±0.08) (Fig. 4). They reached the control level in the postpartum, as PHLA did. There were no statistical differences between normal and diabetic pregnancy in the third trimester and postpartum.

Discussion

In normal pregnancy, the mean value of triglyceride in the whole serum showed 4 fold increase in the third trimester as compared to non-pregnant women. The mean values of cholesterol and phospholipid in the whole serum showed 50% and 60% increase respectively. This pattern is similar to those reported by Mizutani[18] and Skryten et al.[24] Lipid increased mainly in the VLDL and LDL. VLDL-triglyceride, in particular, indicated the greatest increase. However, the difference was found between the VLDL and other lipoproteins concerning the lipid composition. Each lipid in the VLDL increased 4 fold, compositionally unchanged from that seen in non-pregnant women. On the other hand, the lipid compositions in the LDL and HDL were altered. The percentage of triglyceride in the LDL and HDL increased remarkably with reciprocal percentage reductions of cholesterol and phospholipid. Other studies have recently demonstrated similar changes in the third trimester[22)27)].

In diabetic pregnancy, triglyceride in the whole serum tended to increase than that in normal pregnancy, which was mainly due to a significant increase triglyceride in the VLDL. In agreement with the present study, Knopp et al.[13] and Skryten et al.[25] reported that serum triglyceride concentrations in diabetic pregnancy were significantly higher than in normal pregnancy. The mean values of cholesterol in the LDL and HDL tended to be lower than those in normal pregnancy. Therefore the percentages of cholesterol in the LDL and HDL were significantly lower than those in normal pregnancy.

Knopp et al.[13] also reported similar result in adult onset diabetic pregnancy.

The lipid changes induced by pregnancy are similar to observations in oral contraceptive subjects[23]. Hazzard et al.[8] also demonstrated that estrogen alone as well as the oral contraceptive caused triglyceride elevation. These quantitative

similarities between the oral contraceptive treatment and pregnancy strongly suggest the hormonal effect on lipid metabolism in pregnancy.

The hypertriglyceridemia of pregnancy is due to an increased formation (anabolism), or a decreased removal (catabolism) of triglyceride. However, the mechanism of hypertriglyceridemia in human pregnancy has not been elucidated. The author determined PHLA to study catabolism of triglyceride. PHLA was significantly lower in normal pregnancy than in non-pregnant women. Fabian et al.[4] also reported a decreased PHLA before delivery in human pregnancy. But while, PHLA has recently been shown to consist of two activities; hepatic triglyceride lipase (H-TGL) and extrahepatic triglyceride lipase (LPL). Kinnunen et al.[11] showed that both H-TGL and LPL were suppressed in the second and third trimester, compared to that seen in non-pregnant women. Hazzard et al.[8] showed, as the hormonal effect for PHLA, a significant decrease of PHLA during oral contraceptive treatment. Applebaum et al.[1] indicated the decrease of PHLA associated with estrogen administration. It is strongly suggested that the decrease of PHLA in the third trimester is due to the effect of estrogen.

The removal of VLDL-triglyceride from plasma is mediated by LPL. According to the in vitro studies[7][15], LPL activity is believed to be activated by apo C II and inhibited by apo C III. The changes of apo C ratios have been reported in estrogen therapy (C II decreased, C III increased)[9], and in type IV and type V hyperlipidemia (C II decreased, C III increased or unchanged)[2][3]. The changes in apo C ratios may regulate VLDL-triglyceride removal in human pregnancy. So, the ratio of apo C II/C III_1+C III_2 in the VLDL was determined in the third trimester. In normal pregnancy, a significant reduction was found in the amount of apo C II relative to C III_1+C III_2 in the third trimester. The similar reduction was observed at 36 weeks gestation[19]. From these observations, the author speculates that the reduction in the amount of apo C II relative to C III_1+C III_2 in the VLDL is one of the factors which impair VLDL-triglyceride removal in the third trimester.

In diabetic pregnancy, PHLA and the ratio of apo C II/C III_1+C III_2 were decreased in the third trimester. But, the mean value of PHLA in diabetic pregnancy was significantly higher than that in normal pregnancy in the third trimester. This suggests that catabolism of VLDL-triglyceride is not impaired as compared with normal pregnancy. On the basis of these results, the higher level of VLDL-triglyceride in diabetic pregnancy cannot be solely ascribed to the impaired catabolism of VLDL-triglyceride. With respect to the anabolic effect of triglyceride, Knopp et al.[12] claimed on the basis of animal studies that the hypertriglyceridemia of pregnancy should be due largely to overproduction, with decreased removal contributing only near term. Kinnunen et al.[11] also suggested that hypertriglyceridemia of pregnancy was not caused solely by impaired removal of VLDL-triglyceride, but was mainly due to the increased synthesis of VLDL-triglyceride caused by the increased level of plasma estrogen. VLDL-triglyceride synthesis occurs preferentially in the liver. Certain metabolic factors, such as blood glucose, plasma insulin and free fatty acids (FFA) appear to influence triglyceride synthesis. An excess of FFA would enhance triglyceride synthesis in the liver[26]. Insulin antagonists, such as human placental lactogen, estrogen, progesterone and cortisol, etc. increase progressively during pregnancy. This is thought to be related to a decrease in insulin "effectiveness". Consequently, lipolysis would be accelerated in the adipose tissue and plasma FFA increase progressively during pregnancy. In earlier studies[18][21], the progressive increase in plasma FFA during pregnancy has been demonstrated. In diabetic pregnancy, the concentrations of plasma FFA are significantly higher than those in normal pregnancy at various gestations[18]. If an excess of FFA becomes available to the liver, it may account for an excess of VLDL-triglyceride production. In diabetic pregnancy, more FFA may promote to synthesize more VLDL-triglyceride than in normal pregnancy.

In the meanwhile, Nichols et al.[20] have demonstrated lipid transfer in human serum incubation experiment, as the mechanism of LDL and HDL-triglyceride enrichment. Namely, the VLDL in high concentration took up some of the cholesterol esters initially bound to the LDL and HDL. In exchange, transfer of triglyceride from the VLDL to the LDL and HDL was observed during incubation. The very high proportions of triglyceride in

the LDL and HDL with high VLDL-triglyceride support this idea. Particularly in diabetic pregnancy compared with normal pregnancy, the LDL on the compositional analysis indicated increment in triglyceride and a decrement in cholesterol. This result may be attributed to the more increase in VLDL-triglyceride. While, Skryten et al.[24] have suggested, as an explanation for triglyceride-rich HDL, the appearance of specific triglyceride-rich lipoprotein originating from the catabolism of VLDL, which is associated or non-associated with lipoprotein families in the HDL.

In the postpartum of normal pregnancy, the concentrations of cholesterol and phospholipid in the whole serum still remained high, though serum triglyceride concentration decreased to that of non-pregnant women. Each lipid concentration in the VLDL and HDL, except for VLDL-cholesterol, fell to that of non-pregnant women. Cholesterol and phospholipid in the LDL, however, showed significantly higher values than those of non-pregnant women. Since PHLA and the ratio of apo C II/C III_1+C III_2 returned to those of non-pregnant women, the restoration of other metabolic functions accompanying the return of hormonal equilibrium may take much longer period.

In diabetic pregnancy, as contrasted with normal pregnancy, the higher levels of triglyceride and cholesterol in the VLDL were characteristic features. The oversynthesis of the VLDL may occur in the postpartum, because PHLA and the ratio of apo C II/C III_1+C III_2 were equal to those in normal pregnancy.

Physiological hyperlipidemia of pregnancy has important implications for fetal growth and development. More triglyceride fatty acid burned by the mother may spare carbohydrate and protein for fetal use[14]. But while, Skryten et al.[25] have already reported a positive association between plasma triglyceride and infant weight in diabetic pregnancy. Therefore, the degree of hypertriglyceridemia in diabetic pregnancy may reflect the condition of diabetic control.

In conclusion, the hyperlipidemia of pregnancy is mainly due to the increase in VLDL-triglyceride, which is enhanced in diabetic pregnancy. Underutilization of VLDL-triglyceride is one of the factors which cause the hyperlipidemia during pregnancy. In diabetic pregnancy, however, overproduction of VLDL-triglyceride affects the hypertriglyceridemia more strongly than in normal pregnancy. Therefore, the lipid analysis in each lipoprotein fraction is important to control diabetic pregnancy. In future, further studies are required to understand more in details the metabolic influence of hyperlipidemia in normal and diabetic pregnancy.

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概要 正常妊娠，糖尿病合併妊娠における脂質代謝を検索する為に，妊娠後期及び産褥期に得られた血清リポタンパクを，VLDL，LDL，HDLに分画し，各分画中のトリグセライド，コレステロール，リン脂質を測定した．またトリグリセライドの分解酵素であるリポタンパクリパーゼを，postheparin lipolytic activity（PHLA）として測定し，同時に同酵素の活性因子であるアポC IIを，抑制因子であるC III_1，C III_2の和との相対比として表わし検討した．

妊娠に伴う高脂血症は，トリグリセライドの増加が主因であり，特にVLDL分画において著増することを知り得た．糖尿病合併妊娠ではこの傾向が，更に強く示された．各分画における脂質の構成比についてみると，妊娠後期ではLDL，HDL分画において，両群共にトリグリセライドの占める割合が増加していた．PHLAは両群共に妊娠後期に低下していたが，正常妊娠群の方がより低下していた．産褥期には両群共に非妊婦レベルにまで回復した．アポC IIは妊娠後期に相対的に減少し，産褥期には非妊婦のレベルにまで回復しており，両群間に有意差は認められなかつた．以上の結果より，トリグリセライドの異化障害が高脂血症をひきおこす一因であり，糖尿病合併妊娠では，トリグリセライドの合成亢進も高脂血症の成因に強く関与していると考える．