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LIPID PROFILE CHANGES IN PREGNANCY INDUCED HYPERTENSION

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Abstract

We tested the hypothesis that the plasma lipid and lipoproteins concentrations are increased markedly in women with pregnancy induced hypertension (PIH) relative to women with uncomplicated pregnancy and that these lipids decrease postpartum and to clarify the relation of lipid profile changes with the severity of pregnancy induced hypertension.

This study is a prospective, case-control study conducted at Basrah Maternity and Child Hospital extended through a period of 12 months from the first of August 2000 till the first of August 2001.

Pre-labor venous blood samples were collected for 90 women with pregnancy-induced hypertension and 110 women with normal uncomplicated pregnancy with an age range (16-40) years and gestational age range (34-42) weeks after 12 hours fasting. Venous blood samples were also collected from only 30 women with PIH and 30 women with normal uncomplicated pregnancy after 24-48 hours postpartum. Serum was analyzed for concentrations of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C).

Pre-labor serum (TG), (TC), (LDL-C) and (VLDL-C) were increased in women with PIH relative to uncomplicated pregnancies respectively P value (<0.001). (HDL-C) concentration does not differ between studied groups (P = 0.1). Concentrations of all lipids decreased significantly (P value <0.001) in both groups within the first 24-48 hours postpartum. However the levels of these lipids remained higher in women with PIH but were statistically not significant. Serum triglyceride and VLDL concentrations but not total cholesterol, HDL-C and LDL-C were significantly higher in severe PIH group in comparison with mild PIH. There was no correlation between the age, parity and the lipid profiles changes in both groups. There was a positive correlation between each of the (TG), (TC), (LDL-C) and (VLDL-C). (HDL-C) does not correlate significantly with other different types of lipid. In conclusion, plasma lipids and lipoproteins but not HDL-C are increased in PIH relative to normal pregnancy and hypertriglyceridemia found in severely PIH may contribute to endothelial dysfunction in PIH.

Introduction

Pregnancy induced hypertension (PIH) is a common obstetrical disorder and remains a major cause of maternal and prenatal morbidity and mortality worldwide and may complicate 5-7% of all pregnancies[1,2]. PIH is associated with endothelial cell dysfunction, such dysfunction could be caused by oxidative stress, the unsaturated lipids in cell membranes are susceptible to free radical attack. There is evidence of increased free radical activity in PIH[3]. The concentrations of lipids in plasma increase appreciably during pregnancy and throughout gestation[1,4]. Activities of adipose tissue lipoprotein lipase and hepatic lipase are substantially decreased during normal pregnancy (due to insulin resistance and

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estrogen, respectively)[4]. Plasma total cholesterol and triglyceride concentrations rise during the second and third trimesters in most pregnant women[4,5]. Plasma concentrations of VLDL and LDL increase progressively with gestational age as reflected by increases in serum triglyceride and cholesterol (~300% and 25-50% by term, respectively)[5].

The supra-physiological hypertriglyceridemia during pregnancy is considered as a risk of permanent hyperlipidemia postpartum[6]. After delivery the concentrations of lipids and lipoproteins decreases at different rates, cholesterol and triglyceride concentrations fell rapidly within the first 24 hours after delivery but remained elevated over the non-pregnant population at 6 weeks postpartum[7].

Disturbed lipid metabolism, including hypertriglyceridemia, was noted to be a feature of hypertensive disorders of pregnancy over 60 years ago[5]. Mean plasma triglyceride and free fatty acid concentrations undergo near doubling in hypertensive pregnant women relative to normal pregnant women[4].

Heightened insulin resistance in PIH probably increase mobilization of fatty acid from visceral adipocytes, fueling over production of VLDL by the liver, and suppresses activity of lipoprotein lipase culminating in elevated serum free fatty acids from maternal circulation[4,5]. Therefore our aims were: evaluation of the concentrations of TG, TC, HDL-C, LDL-C and VLDL-C in Iraqi women from Basrah before their deliveries with history of PIH in relation to those with uncomplicated pregnancy and to observe lipid profile changes in both groups postpartum, and to clarify the relationship between lipid profile changes and severity of PIH.

Patients and methods

A prospective case-control study was conducted in Basrah Maternity and Child Hospital extended through a period of one year, from the first of August 2000 till the first of August 2001**.**

Patients were divided into two groups, the case group which included a total number of 90 women with clinical features suggestive of PIH whom attend our hospital during the period of the study. The control group which includes 110 apparently healthy pregnant women as indicated by clinical and physical examination. All of them have matched criteria of the case group.

Those patients who delivered vaginally usually left the hospital within the next 6-12 hours after delivery and since our aim was to take blood samples for lipid profile 24-48 hours after delivery, only 30 patients, most of them delivered by caesarian section inadvertently, were included.

All the cases included in the presenting study were collected from labor and obstetrical ward of Basrah Maternity and Child hospital. Hypertension was either diagnosed antenatal before admission to hospital or diagnosed before labor. Mild degree of PIH was defined as a blood pressure of $\geq$ 140 /90 mm/Hg on two separate readings at least six hours a part. Sever degree of PIH was defined as a blood pressure of $\geq$ 160/110mmHg[1]. Mid stream clean catch urine specimen was taken for detection of proteinuria which is defined as the persistent presence of protein in the urine of $\geq$ (+) on urine heating, from those who show signs of hypertension[8]. Measurement of the B.M.I and examination for edema was performed for each woman.

Five milliliters of venous blood sample was collected from each woman in this study after 12 hours of fasting both pre-labor and 24-48 hours post-labor. Serum concentrations of TC, TG, HDL-(after precipitation with sodium phos-

phortungstate-MgCl2) were determined enzymatically using kits from BioMerieux, France. All procedures were followed according to the instructions of the manufacturer. LDL-C and VLDL-C serum concentrations were calculated using the Friedewald formula[9] LDL-C = TC- (HDL-C+TG/5) and VLDL-C = TG/5.
(The above formula is applicable when serum TG level is less than 400 mg/dl). Quality control sera from BioMerieux were included in each assay batch for all the above analytes. The inter-assay coefficient of variation was 4% for TC and TG, 6% for HDL-C.

Chi-Square and student t- tests were used for the analysis of our results. $P<0.05$ was considered to be statistically significant.

Results

Table I shows the demographic characteristics of the studied groups. In this table most of patients were nilliparous women (55.6%, 45.5% in case and control groups respectively).

Table II showed significantly higher systolic and diastolic blood pressure relative to normal pregnant women ($P < 0.001$). The majority of women with PIH in this study had pathological edema 72 (80%), while proteinuria was reported in 55 (61%) of all women with PIH, which was highly significant.

Table III shows women with PIH (pre-delivery) had significantly higher levels of TG, TC, LDL-C and VLDL-C ($P < 0.001$) relative to normal pregnant women. While, statistically insignificant differences of HDL-C level in both groups ($P > 0.1$) was observed.

Table IV showed that pregnant women with severe hypertension had a significantly higher level of TG ($P= 0.004$) and VLDL-C ($P= 0.005$) in comparison with mild hypertensive pregnant women. While, there was statistically insignificant difference in TC, HDL-C and LDL-C levels in both previous groups of hypertensive pregnant women.

It is obvious from table V that the mean levels of TG, TC, LDL-C and VLDL-C concentrations decreased by 24 to 48 hours postpartum in both groups and this is statistically highly significant ($P < 0.001$). Although the mean levels of serum TG, TC, LDL concentrations decreased by ap-proximately 24%, 21%, and 24% respectively in the PIH group versus 22%, 17% and 18.5% respectively in the control group. This was not statistically significant between the groups.

The mean levels of TG, TC, HDL, LDL and VLDL 24-48 hours postpartum remained higher in PIH group relative to control group, but were statistically not significant.

Within each pregnancy subgroup, the mean levels of TG and TC did not correlate significantly with age and parity ($P>0.1$) as shown in table VI.

Table VII showed that there was a direct correlation between the mean levels of TG, TC, LDL, and VLDL concentrations in both case and control group "$P< 0.01$". While the mean level of HDL -C concentrations did not correlate significantly with each of other lipid parameters mention above.

Discussion

PIH remains a major cause of maternal and perinatal morbidity and mortality worldwide. Although numerous basic, clinical and epidemiological studies have been conducted over the last century, its cause and pathogenesis are still illusive[10]. There is evidence of increased free radical activity in PIH[3]. Accordingly, a considerable interest in the role of alerted lipids in the promotion of oxidative stress and vascular dysfunction in this disorder was observed[11]. Progressive in-creases of LDL and VLDL in the maternal

circulation as reflected by increase in TC and TG[11] and reversed postpartum[12] characterize normal human pregnancy. On the other hand, disturbed lipid metabolism, including hypertriglyceridemia, which is primarily due to enhanced entry of TG rich lipoproteins (especially VLDL) into the circulation rather than to diminish removal, was noted to be a feature of PIH over 60 years ago[5,13].

Our data demonstrate that there was a significance increment in the pre-labor levels of TG and VLDL in women with PIH in comparison with those who had normal uncomplicated pregnancy (Table III). This finding goes with different other previous studies[4,5,12]. These studies showed that such increment is due to the over production of hepatic synthesis of VLDL and TG, because of an increase in the level of maternal estrogen throughout gestation. The mechanisms underlying abnormal evaluation of TG and VLDL in PIH are poorly understood. One possibility; Heightened insulin resistance in preeclampsia probably increases the mobilization of fatty acids from visceral adipocytes, fueling overproduction of VLDL by the liver, and suppresses activity of lipoprotein lipase, culminating in elevated serum free fatty acids and TG[5,12].

In regard to the severity of PIH, we found that only serum TG and VLDL concentrations were significantly higher ($P = 0.004$ and $P = 0.003$) respectively, in severe PIH group in comparison with mild PIH (table 5). However, there was insignificance difference in other lipid parameters (TC, HDL-C and LDL-C) in both mild and severe PIH groups. In this aspect, our finding was in agreement with that of Cong et al[14], who found that lipid profile in severe PIH was characterized by type IV hyperlipidemia and suggested that this high lipid level during normal late pregnancy might be physiological phenomenon which represents a risk factor for PIH Consequently, marked increase of TG and VLDL in severe PIH may result in lipid peroxide (LPO) which is very toxic compound causing damage to the cell membrane and contributes to endothelial cell dysfunction and oxidative stress in PIH.

Normal pregnancy is characterized by gestational increase in TC and LDL-C concentrations followed by progressive decrease during the puerperium[12,15]. These studies were incompatible with results of our study, where the levels of TC and LDL-C concentrations were significantly higher in PIH group relative to normal pregnancy (table III), However, our findings were in agreement with other different studies[11,16]. Placental changes might contribute to dyslipidemia in PIH. LDL receptor increase in the placenta late in normal pregnancy and to a lesser extent in PIH. This may decrease receptor uptake of maternal LDL by the placenta and thus reduce its clearance[5]. Hubel et al[11] found that the hypertriglyceridemia of PIH, relative to normal pregnancy is accompanied by increased qualitative shift toward smaller, denser LDL particles that are highly atherogenic.

With regards to the age of pregnant women under study and the lipid profiles, no correlation was observed between the TG and TC concentrations with age of these women (Table VII), and was in agreement to the previous studies[11,17]. This could be attributed to habitual and dietary factors.

The effect of parity on each of lipid parameters in both groups also studied, and we found that there was no significance correlation of parity on each lipid parameters. In this aspect, our finding was in agreement with that of Kabbachi[18]. No reason was given for lipid elevation after subsequent pregnancies and more studies are needed to conclude that multiparity influences the risk for dyslipidemia.

Serum TG and TC concentrations decreased sharply by 24-48 hours postpartum in PIH group and control group, although the serum TG and TC concentrations at postpartum remained higher in PIH group, but was statistically not significant in comparison with control group. This was in agreement with different studies[5,7,12,15]. These events may be due to the fact that as term approaches, placental and mammary gland lipoprotein lipase activity normally increases, whereas adipose and liver lipoprotein lipase activity decreases, thus these physiological adaptations may serve to enhance transfer of maternal essential fatty acids to the growing fetus as well as lactation[12]. However, no explanation was given to the sustained rise in TG and TC in PIH group that required further study.

Similarly, the serum levels of VLDL and LDL decreased markedly within the first 24-48 hours after delivery in both groups (table VI). However, there were no statistical significance differences in PIH group and control group in the decrease of these lipids postpartum. Our finding was in agreement with the different previous studies[7,12]. On the other hand, in both groups under study, the levels of HDL-C concentrations returned to non-pregnant value within the first 24-48 hours postpartum. In this aspect, our finding was in agreement with previous studies[12,15]. These above changes may reflect the return of many physiologic parameters back to normal after the removal of placenta and the fetus.

Previous reports have also indicated that the fall in TC in the puerperium is slower than that of TG. Since the rebound increase occurred only in LDL, it probably resulted from rapid catabolism of VLDL and conversion to LDL. The rapid fall in VLDL and TG concentrations may partly reflect the decrease in free fatty acid concentration, which occurs after delivery of the placenta, although increased clearance is also likely to be a factor[19].

The correlation between each of lipid parameters was also studied. A positive correlation between each of TG, TC, LDL-C and VLDL was noticed. However, there was no significant correlation between HDL-C and each of other lipid parameters. This result was in agreement with that of other studies[7,19].

The mechanisms underlying for such correlation was explained by Potter and Nestle[19] who suggested that if the distribution of TC and TG in each fraction is expressed in terms of percentages of the total present in the plasma and found that the proportion of cholesterol carried in VLDL increase 4.5% in non pregnant women to 11% at term. LDL and HDL levels decrease from 64% and 31% to 60% and 26% respectively. The percentage of total plasma TG carried in VLDL was unchanged, but increase in LDL and decrease in HDL, thus indicating a correlation in lipids metabolism during pregnancy that is mainly under hormonal control[7,19].

In conclusion**,** we can say that human gestation is associated with an atherogenic lipid profile that is further enhanced in PIH. This profile: firstly, could be associated with enhancement of pathological lipid deposition in predisposed vessels such as the uterine spiral arteries. Secondly, may be a potential contributor to endothelial cell dysfunction and oxidative stress in PIH. Further investigation of the oxidative damage, and its correlation with lipid profile in normal pregnancy and PIH is suggested.

Table I:The characteristics of women enrolled in this study.

Variables	Case group (N=90)	Control group (N=110)	Significance P-value
Age (years) Mean ± SD Range	 28.3 ± 6.6 18 – 40	 28.6 ± 6.4 16 - 40	 NS*
Parity / No. (%) - Nilliparous - Parity (1-5) - Parity >5	 50(55.6) 19(21.1) 21(23.3)	 50(45.5) 38(34.5) 22(20.0)	NS
Gestational age (week) Mean ±SD Range	 38.5 ± 1.9 34 – 41	 39 ± 1.5 34 - 42	NS
Type of Delivery No.(%) - Vaginal delivery - Caesarian section	 49(54.4) 41(45.6)	 73(66.4) 37(33.6)	NS
Family History of H.T No. (%)	5(5.6)	7(6.4)	NS
Past History. of PIH No. (%)	17(18.9)	2(1.8)	NS
B.M.I Mean ± SD Range	 28.3 ± 4.2 19-38	 27.4 ± 3.3 19-36	NS

Values were expressed as mean ± SD or No. (%) as appropriate. * NS= Non Significant

Table II: The clinical signs of PIH group in comparison with control group.

Groups indices	PIH Group N=90	Control Group N=90	Significance P-value
Systolic BP(mm/Hg) Mean ± SD Range	 154 ± 16 140 – 180	 114 ± 14 100 - 120	0.001 HS*
Diastolic BP (mm/Hg) Mean ± SD Range	 104 ± 12 90 –140	 74 ± 5 60 - 80	0.001 HS
Proteinuria No. (%)	55(61)	0(0)	
Pathologic edema No. (%)	72(80)	0(0)	

Table III: The pre-delivery changes in the mean levels of lipid profile among women under study.

Parameters (mg/dl)	Case group N=90	Control group N=110	Significance P- value
TG	257 ± 90	196 ± 65	0.001 HS
TC	246 ± 65	212 ± 47	0.001 HS
HDL-C	64 ± 16	61 ± 16	0.1 NS
LDL-C	131 ± 55	113 ± 43	0.01 HS
VLDL	51 ± 19	39 ± 13	0.001 HS

Values were expressed as mean ± SD.

Table IV: The relationship of mean levels of lipid and lipoprotein concentrations with severity of PIH.

Severity of PIH	No.	TG (mean ± SD)	TC (mean ± SD)	HDL-C (mean ± SD)	LDL-C (mean ± SD)	VLDL (mean ± SD)
Mild-PIH BP ≥ 140/90	56	234 ± 70	238 ± 55	64 ± 17	127 ± 49	46 ± 14
Severe PIH BP ≥ 160/110	34	305 ± 95	260 ± 73	64 ± 15	136 ± 65	60 ± 21
Significance P – value		0.004 HS	NS	NS	NS	0.005 HS

Table V: The mean levels of lipid and lipoprotein concentrations pre- and post-labor among women in studied groups.

Lipid parameters (mg/dl)	Case group N=30				Control group N=30			
	Pre-labor	Post-labor	P-value	% Reduction	Pre-labor	Post-labor	P - value	% Reduction
TG	275 ± 100	208 ± 77	0.001 HS	24	203 ± 98	156 ± 49	0.001 HS	22
TC	263 ± 65	209 ± 55	0.000 HS	21	214 ± 43	176 ± 35	0.001 HS	17
HDL	64 ± 16	57 ± 15	0.01 HS	11	60 ± 13	52 ± 13	0.01 S	12
LDL	143 ± 56	108 ± 42	0.001 HS	24	113 ± 39	92 ± 33	0.001 HS	18
VLDL	54 ± 21	42 ± 17	0.001 HS	22	41 ± 12	31 ± 10	0.001 HS	24

The values were expressed as mean ± SD

Table VI: The correlation between the blood lipids with the age and parity of studied groups.

	Case		Control	
	R	P	R	P
Age vs. TG	- 0.067	0.596 NS	0.174	0.194 NS
Parity vs. TG	0.114	0.295 NS	- 0.1035	0.263 NS
Age vs. TC	0.0712	0.504 NS	0.163	0.211 NS
Age vs. TG	0.0568	0.594 NS	0.0528	0.453 NS

R = Correlation Coefficient.

Table VII: The correlation among lipid parameters in case and control groups.

Lipid	TG		TC		HDL-C		LDL-C		VLDL	
	Case	Cont.	Case group	Control group	Case group	Control group	Case group	Control group	Case group	Control group
TG			0.552 0.001*	0.432 0.001*	0.086 0.211	0.126 0.094	0.290 0.003*	0.433 0.002*	0.988 0.001*	0.997 0.001*
TC					0.205 0.096	0.250 0.094	0.923 0.001*	0.872 0.001*	0.557 0.001*	0.432 0.001*
HDL-C							0.067– 0.264	-0.106 0.134	0.073 0.248	-0.120 0.106
LDL-C									0.298 0.002*	0.322 0.003*

*** Highly Significant.**

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