

Association of hypertriglyceridaemia with pre-eclampsia, preterm birth, gestational diabetes and uterine artery pulsatility index

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ABSTRACT

Background. We aimed to determine whether high plasma triglyceride levels in the second trimester of pregnancy are associated with adverse pregnancy outcomes including preterm birth, gestational diabetes mellitus, pre-eclampsia and high uterine artery pulsatility index.

Methods. This prospective cohort study was done between 2008 and 2010. Plasma levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride were measured after 8 hours of overnight fasting. We compared the outcomes of 45 pregnant women who had high triglyceride levels (≥ 195 mg/dl) with 135 pregnant women with triglyceride levels < 195 mg/dl. The main outcome measures were the incidence of preterm birth, gestational diabetes, pre-eclampsia and uterine artery pulsatility index.

Results. Eight women with high triglyceride levels had pre-eclampsia (17.8% v. 3.7% in the control group, $p < 0.004$), preterm birth occurred in 24.4% and 5.9% in the high triglyceride group and the control group, respectively (OR 5.1, 95% CI 1.9–13.8, $p < 0.0001$). The incidence of gestational diabetes in the high triglyceride group was significantly higher than that in the control group. There was no difference in uterine artery Doppler ultrasound between the two groups.

Conclusion. There is a positive relation between hypertriglyceridaemia and pre-eclampsia, preterm birth and gestational diabetes.

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INTRODUCTION

Preterm birth (PTB), that is a delivery at < 37 weeks of gestation, is one of the major causes of perinatal mortality and morbidity.¹

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Also pre-eclampsia is an important cause of maternal, and perinatal mortality and morbidity.

Pre-eclampsia is a pregnancy-specific condition with a multifactorial aetiology associated with proteinuria and hypertension.^{2,3} Previous studies have shown a relationship between serum lipid levels (dyslipidaemia) and gestational glucose intolerance,⁴⁻⁷ pre-eclampsia^{4,6,8-11} and PTB.¹²

Plasma lipids and lipoproteins increase during pregnancy. The mechanism for pregnancy-induced changes in lipids is not completely understood, but appears to be partly caused by elevated oestrogen, progesterone and human placental lactogen.^{4,6,13,14} Lipid levels in women with PTB¹² or pre-eclampsia^{4,6,8-11} are reported to be higher than those in healthy pregnant women.^{4-9,11,13}

The pulsatility index (PI) of the uterine artery is an indirect measure of vascular resistance in the uteroplacental circulation.⁵ There is a positive relationship between vascular dysfunction and adverse pregnancy outcomes such as pre-eclampsia. Hence, changes in the uterine artery PI have been used to predict pre-eclampsia.⁵ On the other hand, dyslipidaemia causes vascular dysfunction.⁶ We investigated if hypertriglyceridaemia is an independent risk factor for changes in the uterine artery PI.^{13,15} An association between pre-eclampsia and PTB may help to intervene so as to prevent maternal and neonatal mortality and morbidity.

METHODS

This prospective study was conducted between 2008 and 2010 at Tehran Women General Hospital.

Study participants

All normal pregnant women 20–35 years of age referred for routine prenatal care with gestational age 16–20 weeks, gravid ≥ 2 , and body mass index (BMI) of 20–25 kg/m² were included in the study. We excluded women with a history of PTB, pre-eclampsia, diabetes or gestational diabetes (GD). Also primigravida, those with a BMI > 25 and high maternal age (> 35 years) were excluded because these are risk factors for pre-eclampsia. High maternal age and high BMI are also risk factors for GD.^{5,16}

We enrolled 440 pregnant women in their second trimester. Their fasting blood sugar, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride (TG) levels were measured after an overnight fast using Auto Analyzer Hitachi 704 with Eitech kit 902. All the 45 women who had the highest triglyceride (HTG) levels (≥ 195 mg/dl, ≥ 90 th percentile for this group) were included as cases. Of

the remaining 395 women, 135 pregnant women with TG levels <195 mg/dl were included as controls by simple randomization. None of the women received any treatment or lifestyle modification. We were also unaware of the results of the laboratory tests until the end of pregnancy.

Two expert perinatologists measured the uterine artery PI using Acuson SEQUIA 512 between 16 and 20 weeks of pregnancy. The PI was assessed by Doppler velocimetry of the uterine arteries. Each uterine vessel was demonstrated by colour Doppler as it crossed over the hypogastric artery and vein just before it enters the uterus at the uterine-cervical junction.⁸ The average of the right and left uterine arteries was defined by the mean PI and was adjusted for gestational age. Inter-observer reliability was 87%.

The blood pressure, height and weight, habits, smoking, using narcotics, obstetric and medical history were also checked. The incidence of PTB, GD and large for gestational age (LGA, >90th percentile of weight) and pre-eclampsia in both groups were recorded.

Gestational age was assessed based on an early pregnancy ultrasound. PTB was defined as spontaneous birth before 37th week of pregnancy without any complication dependent or independent of pregnancy such as placental haemorrhage, infection, pre-eclampsia, GD, trauma and accidental events.

Pre-eclampsia was diagnosed when the systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on two occasions at least 6 hours apart (in a patient with previously normal blood pressure) accompanied with significant proteinuria (≥ 300 mg per 24 hours urine specimen or $\geq 1+$ or more protein in dipsticks in two measurements repeated at an interval of 4 hours). The diagnosis of GD was based on a 3-hour, 100 g oral glucose tolerance test done after an abnormal 1-hour glucose challenge test (>130 mg/dl) between 24 and 28 weeks of pregnancy.

The study was approved by the review board of perinatal department, Tehran University of Medical Sciences and all participants gave written informed consent.

Statistical analysis

The statistical software package SPSS for Windows, version 11.5 was used to analyse the data. Means, standard deviations (SD) and ranges were used to summarize quantitative variables, whereas percentages were used for categorical variables. The normality of quantitative variables was checked by One-Sample Kolmogorov-Smirnov test, and statistical comparison was carried out by independent *t*-test or Mann-Whitney test. The categorical outcome variables were compared with chi-square test or Fisher exact test when appropriate.

Inter-observer reliability was estimated by correlation coefficient. Stepwise multiple logistic regression analysis was used to identify predictors for high TG levels. The independent variables entered were GD, PTB, LGA, pre-eclampsia and

gestational age. Odds ratios (OR) and 95% confidence intervals (CI) were used to quantify the extent of association. The significance level was set at 0.05.

RESULTS

The two groups were comparable with regards to maternal age, BMI and gravidity (Table I). The median (range) gestational age at delivery was one week less in the HTG group ($p=0.04$). History of abortion was present more frequently in the HTG group compared with the control group while the control group had a higher parity (Table I). The HTG group also had higher cholesterol and LDL levels. GD ($p=0.005$), PTB ($p<0.0001$), LGA ($p=0.011$) and pre-eclampsia ($p=0.004$) were significantly more frequent in the HTG group than in the control group (Table II).

In logistic regression analysis, the odds of GD, PTB and pre-eclampsia were more in the HTG group compared with the control group. There was no significant difference in the adjusted mean PI for gestational age or the presence of a notch in the two groups ($p=0.6$; Table II).

Four (8.9%) neonates born to mothers in the HTG group and 15 (11.1%) to those in the control group were small for gestational age (<10th percentile of weight).

TABLE I. Maternal and clinical characteristics in hypertriglyceridaemia and control groups

Characteristic	High triglyceride group (n=45)	Control group (n=135)	p value*
Maternal age (year)	28.1 (4.5)	28.2 (4.2)	0.9
Body mass index (kg/m ²)	23.2 (1.3)	23.2 (1.2)	0.9
High-density lipoprotein	48.5 (9.8)	50.8 (10.4)	0.2
Low-density lipoprotein	169.8 (18.9)	110.6 (10.8)	<0.0001
Cholesterol	294.1 (17.3)	194.7 (19.9)	<0.0001
Gestational age (week)	37.5 (2.8)	38.5 (2.1)	0.04
Neonatal weight (g)	3167.3 (898.2)	3113.2 (647.7)	0.7
<i>Gravid (%)</i>			
2	29 (64.4)	86 (63.7)	0.9†
3	11 (24.4)	35 (25.9)	
4	4 (8.9)	9 (6.7)	
5	1 (2.2)	5 (3.7)	
<i>Parity (%)</i>			
0	3 (6.7)	1 (0.7)	0.03†
1	37 (82.2)	98 (72.6)	
2	4 (8.9)	27 (20)	
3	1 (2.2)	9 (6.7)	
<i>Abortion (%)</i>			
0	30 (66.7)	112 (83)	0.02†
1	12 (26.7)	22 (16.3)	
2	2 (4.4)	1 (0.7)	
3	1 (2.2)	0	

Quantitative data are presented as mean (SD) * *t*-test † Fisher exact test

TABLE II. Comparison of pregnancy outcome in hypertriglyceridaemia and control groups

Feature	Hyper-triglyceridaemia group (%) (n=45)	Control group (%) (n=135)	p value (95% CI)	Logistic regression*	
				p value	OR (95% CI)
Increased pulsatility index†	5 (11.1)	12 (8.9)	0.6 (0.42–3.81)	–	–
Gestational diabetes	9 (20)	8 (5.9)	0.005 (1.4–11.0)	0.03	3.5 (1.10–11.3)
Preterm birth (<37 weeks)	11 (24.4)	8 (5.9)	<0.0001 (1.9–13.8)	0.01	10.9 (1.6–74.4)
Large for gestational age	10 (22.2)	11 (8.1)	0.011 (1.3–8.2)	0.08	2.6 (0.9–7.9)
Pre-eclampsia	8 (17.8)	5 (3.7)	0.004 (1.7–18.2)	0.05	3.9 (0.9–16.2)

* adjusted for gestational age † presence of notch >95%

TABLE III. Comparison of neonatal birth weight in the hypertriglyceridaemia and control groups stratified by time of delivery

Birth weight (g)	Hypertriglyceridaemia group (n=45)	Control group (n=135)	p value
Term	3700 (2050–4520)	3210 (1790–4650)	<0.001
Preterm	1980 (1030–2670)	1630 (900–2330)	0.091
Total	3470 (1030–4520)	3190 (900–4650)	0.227

Data are presented as median (range)

Subgroup analysis in term and preterm deliveries showed that in both subgroups neonates in the HTG group had a higher birth weight than the control group but it was not significant in relation to PTB ($p<0.001$, $p=0.091$, respectively; Table III). In contrast, the HTG group had higher neonatal birth weight compared with the control group ($p=0.22$; Table III).

DISCUSSION

Our study showed that in the HTG group, the incidence of pre-eclampsia was higher than that in the control group (17.8% *v.* 3.7%, $p=0.004$). This finding is similar to the findings of Wiznitzer *et al.* who reported that elevated serum levels of triglyceride are associated with pregnancy-induced hypertension, GD and pre-eclampsia, compared to women with low TG levels.⁶ Lurba *et al.* showed that 16 of 34 women with pre-eclampsia, had TG levels >250 mg/dl ($p<0.001$).⁸ There are three possible mechanisms for the relationship between dyslipidaemia and pre-eclampsia: (i) the pathological processes of pre-eclampsia are due to lipoprotein lipase dysfunction in dyslipidaemia;⁶ (ii) the metabolic syndrome (glucose intolerance, hyperinsulinaemia and dyslipidaemia) has a relation with pre-eclampsia;¹⁵ and (iii) an increase in plasma lipids may stimulate endothelial dysfunction due to oxidative stress.^{6,10} Oxidative stress markers play an important role in the pathophysiology of pre-eclampsia. We did not estimate oxidative stress in this study.

PTB in the HTG group was higher than that in the control group after adjusting for pre-eclampsia, which is in agreement with previous studies. Catov *et al.* in a prospective study found that high cholesterol or TG levels were associated with a 2.8-fold (1.0–7.9) and 2.0-fold (1.0–3.9) increased risk for PTB at <34 weeks and 34–37 weeks, respectively.¹²

There is a vascular pathological change in dyslipidaemia and vascular changes in some adverse pregnancy outcomes such as pre-eclampsia and intrauterine growth retardation; therefore, we investigated the relationship between PI in the HTG group and the control group. There was no difference in PI between the two groups. This result is in agreement with that of Khoury¹³ that there is no significant difference in mean of both uterine artery Doppler in the familial hypercholesterolaemia group and the control group in the 24th week of pregnancy.

Chekir *et al.* found no relation between serum lipid levels and PI in women with polycystic ovary syndrome.¹⁶ Uterine artery Doppler depends on many factors and it may be the reason why we did not find any association in PI and TG levels between the control group and the HTG group. Another reason is the small sample size and short gestational age of pregnancy measurement of PI. If we measured it later, there might have been a relation between PI and hypertriglyceridaemia.

This study showed that term neonates in the HTG group had an average weight more than those in the control group ($p<0.001$).

There was 3.2-fold higher frequency of LGA in the HTG group than in the control group ($p=0.01$) in term neonates. The observation of Wiznitzer *et al.*⁶ about HTG and its association with pre-eclampsia and GD was confirmed in our study. They showed that LGA was 7.5% in the low TG group and 11.7% in the HTG group ($p=0.008$).

Limitations

This study had a small sample size and we were unable to evaluate serum lipid profile in detail before, during and after pregnancy and neonatal outcomes because of study subjects being admitted in different hospitals.

Conclusion

While there is a positive relation between hypertriglyceridaemia with pre-eclampsia, LGA, PTB and GD, studies are needed to ascertain the cut-off lipid levels before and during pregnancy and their relation to poor pregnancy outcomes.

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Conflict of Interest. None declared.

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