ASSOCIATION BETWEEN MATERNAL SERUM LIPID PROFILE AT LATE GESTATION WITH NEONATAL MACROSOMIA

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ABSTRACT

Background

Macrosomia is a serious health problem that is highly prevalent and can negatively affect neonatal and maternal outcomes. Pregnant women and neonates can be negatively influenced by dyslipidemia (high maternal serum lipids) which also results in the development of fetal macrosomia..

Objectives

The current study aimed to determine how maternal lipid profile during the third trimester of pregnancy correlated with fetal birthweight.

Patients and Methods

A prospective cohort study was conducted in Sulaimani Maternity Teaching Hospital over eight months, starting from the 1st of September 2018 till the 30th of April 2019. The study included 123 pregnant with a viable singleton pregnancy, gestational age > 32 weeks, delivered between 37 and 42 weeks of gestational age, and women suffering from thyroid disorders and hypertension. For all women, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and serum triglycerides (TG) were measured. In addition, the women were followed up until their childbirth, and the correlation between the mothers' lipid profile and their neonates' weight was measured..

Results

The mean age ± SD (standard deviation) of the studied women was 31.10± 3.65 years, ranging from (25 to 38) years. Regarding their parity, 78% of women were multiparous (have 2-4 children), and the remaining (22%) were primipara. Among the 123 participating women, 23 (18.7%) delivered macrosomic babies (weight > 4kg), and 100 (81.3%) delivered babies with normal birth weight. Fifteen women (12.2%) have high cholesterol levels, and all delivered macrosomic newborns, with a statistically significant association (P=0.001) between macrosomia and maternal cholesterol level. Also, the prevalence of macrosomia was significantly higher among women with high serum triglyceride levels (P=0.001).

Conclusion

There is a significant association between increased risk of macrosomia and high serum cholesterol and triglycerides levels during pregnancy.

Keywords: *macrosomia, lipid profile, dyslipidemia, pregnancy.*

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INTRODUCTION

During pregnancy, hormonal changes occur in the body, resulting in subsequent lipid profile changes during different pregnancy trimesters—Moreover, the demand for metabolic fuels for fetal growth and the development of its associated structures increases. [1,2]. Lipoprotein lipids physiology significantly impacts the fetus and mother's development [3].

Early on during pregnancy, fat is deposited. However, by the middle of it, it is also being used as a source of energy and a way to store energy for the high metabolic demands of nursing and late pregnancy [4].

In the first trimester, the maternal metabolic environment gets modified due to a rise in estrogen and progesterone serum levels followed by pancreatic beta-cell hyperplasia leading to a rise in insulin secretion. [5]. Throughout pregnancy, the fetoplacental unit needs lipids, amino acids, and glucose, which can be met if the mother's metabolism adapts. As a result of such adaptation, maternal blood lipid concentrations alter, which causes mothers to fall into a state of physiologically normal hyperlipidemia during pregnancy. [6]. Following the delivery, the lipid concentrations decrease to their levels before pregnancy, which reveals that this increase in blood lipids can have a role in pregnancy physiology and fetus development [7].

Adverse perinatal outcomes are correlated with dyslipidemia which is also remarkably associated with other pathologies in pregnancy, including hypertensive disorders and gestational diabetes [8]. Research has indicated that hyperlipidemia during pregnancy influences the epigenetic programming of a fetus and the subsequent atherogenesis risk for the mothers and their neonates [9]. During the first two trimesters, lipid metabolism is primarily anabolic. Lipid synthesis rises due to a rise in insulin sensitivity and maternal hyperphagia. Additionally, the elevated production of leptin, cortisol, progesterone, and prolactin plays a role in elevated fat storage [10,11] .The switch to the "catabolic phase" in the third trimester involves prominent lipolysis promoted by insulin resistance, enhancing the lipolysis of stored triglycerides in adipocytes [6]. Lipolysis in adipocytes gets stimulated due to elevated human placental lactogen during the third trimester.

During pregnancy, hypertriglyceridemia, which is known as a risk factor for metabolic syndromes, is caused by the elevated production of triglyceride-rich lipoproteins and the reduced clearance of triglyceride-rich lipoproteins.[9]. Indeed, triglyceride levels are significantly elevated in women with hypertensive disorders of pregnancy and gestational diabetes mellitus compared to those without these metabolic syndromes. Such elevations are consistent in pregnancy's first, second, and third trimesters [12]. The composition of lipoproteins and lipids might be responsible for the metabolic changes during pregnancy, which can affect the flux of lipids to the placenta, whereby fetal lipid concentrations will change [7, 13].

Hyperlipidemia is common in the second half of pregnancy as a physiologically required mechanism to maintain stable fuel supplementation in the fetus. The rise in the levels of plasma cholesterol is likely because the synthesis of hepatic cholesterol increases [11]. In women without diabetes, fetal birthweight is reported to positively affect the levels of second or third-trimester maternal triglyceride, which can independently predict fetal macrosomia [14,15]. There is less evidence for other lipid parameters.

Birthweight and very-low-density lipoprotein cholesterol (VLDL-C) are negatively associated, while fetal birthweight and low-density lipoprotein cholesterol (LDL-C) are not significantly correlated [16,17]. There has been great interest in studying factors influencing fetal growth in recent years. A combination of genetic and environmental factors determines the development and growth of the fetus. The in-utero environment highly influences fetal growth. Therefore, maternal nutrition plays a major role in the mother's health and has a lasting impact on the normal development and well-being of the baby [18]. After triglyceride and total cholesterol are absorbed by the placenta and metabolized there, they are transported to the fetus. However, high maternal triglycerides and total cholesterol levels are associated with a sizeable gestational age (LGA) fetus, pre-term birth, pre-eclampsia, and pregnancy-induced hypertension [19]. Moreover, total cholesterol and low serum triglyceride levels in the mother are linked to the birth of small for gestational age (SGA) babies and pre-term birth. It is unclear at which point maternal blood lipid concentrations threaten maternal and infant health [18,20].

In pregnancies with large-size infants, the mothers and their neonates are more probably experience the risk of complications like prolonged labor, stillbirth, meconium aspiration syndrome, birth asphyxia, birth injuries, increased use of operative deliveries, and postpartum hemorrhages [21].

In addition, large infants may suffer long-term effects due to increased risk of cardiovascular disease, obesity, diabetes, and cancer [22,23]. A fetal birth weight equal to or over 4 kg, regardless of gestational age, is called macrosomia. It is also defined as a fetus whose birthweight is over the 90th percentile for gestational age [24]. Maternal demographic variables like pre-pregnancy BMI, parity, gestational age at delivery, and weight gain independently predict birth weight [25].

Due to its association with increased morbidity and mortality, extreme fetal weight has attracted remarkable attention. Moreover, although the number of macrosomic infants is growing worldwide, more attention has been given to infants with low birthweights than macrosomic infants [26].

There are two types of macrosomia. The first type is constitutional, or symmetric, macrosomia; this accounts for 70% of cases, results from genetic factors, and does not imply an abnormal supply of nutrients in utero. The fetus is big but average; the only potential problem is avoiding trauma during delivery. [27]. In contrast, the second type, macrosomia, is asymmetric and accounts for 30% of cases.

This form is the typical picture related to maternal diabetes and is characterized by organomegaly and should be considered a pathological entity [28]. It has been proved that macrosomia negatively affects neonatal and maternal health; therefore, it has received remarkable attention. The risk factors associated with elevated risks of fetal macrosomia have been reported as high maternal serum triglycerides and cholesterol [29,30].

PATIENTS AND METHODS

This cohort study was conducted at Sulaimani Maternity Teaching Hospital from the 1st of September 2018 till the 30th of April 2019. The study included 123 pregnant women with viable singleton fetuses without any medical disease complicating their pregnancy and were delivered between (37 – 41) weeks of gestation. The study sample did not include pregnant women with pre-pregnancy or gestational diabetes mellitus, hypertension, thyroid disorder, delivery before 37 weeks of gestational age, and congenital fetal malformation. The last menstrual period was utilized to calculate gestational age, confirmed by an ultrasound scan before 20 weeks. The purpose of the study was explained to the women whose verbal consent was gained before taking a blood sample. After taking a complete history and performing the examination, a 4 ml venous blood sample was drawn under aseptic conditions and at room temperature. Then the samples were centrifuged and sent to measure the lipid profile, including low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and serum triglycerides (TG). The analyses were performed through an automatic biochemical analyzer (Cobas c311).

Afterward, the women were followed up till delivery. Following the delivery, the neonates' gender and birthweight were recorded in the questionnaire, and according to the recorded birthweights, the women were divided into two groups. Group, I: is those who delivered the baby with macrosomia (birthweight ≥4000gm), and group II: is women who had normal-weight babies (< 4000gm). A comparison is made between them regarding their lipid profile.

To measure lipid profile, the studied women needed to be fasting for 12 hours, so the participants were selected from those scheduled for elective cesarean section.

The average value of serum TG is < 150 mg/dl, the desirable level of TC is < 200 mg/dl, LDL < 100 mg/dL and HDL is good > 60 mg/dl. We used "IBM SPSS statistics version 25" "(Statistical Package for the Social Science) for the analysis of the data. A P-value of (<0.05) was considered statistically significant, and a P-value of (<0.001) was statistically highly significant.

RESULTS

The mean± SD (standard deviation) of the age of the studied women was 31.10± 3.65 years, with 67 (54.5%) above 30 years old. Regarding parity, 96 (78%) were multiparous, and 27 (22%) were primipara. The studied women's lipid profiles (Table 2) were as follows; normal levels of serum cholesterol and TG were recorded among 87.8% and 50.4%, respectively. More than three-quarters of the study women had normal HDL (78%) and LDL (78.9%). Finally, 52.7% have a high VLDL level. The neonatal birthweight ranged from 3 to 4.6 Kg with a mean of 3.50 Kg and SD of ± 0.36 Kg. Among the 123 women, 23 (18.7%) of them delivered a macrosomic baby (weight >4kg), and 100 (81.3%) delivered normal birthweight newborns, (Figure 1).

All of the pregnant women with hypercholesterolemia (15 women) delivered macrosomic newborns, with a statistically significant association (P=0.001) between macrosomia and maternal cholesterol

level, and also the proportion of macrosomia was significantly higher among women with high serum triglyceride levels (P= 0.001).as shown in Table3. As revealed by logistic regression analysis, the TG level was found to be significant, independent and

un-confounded risk factor for macrosomia as indicated in Table (4). Receiver operating characteristic (ROC) curve analysis was constructed for cholesterol level as an indicator of macrosomia. As shown in Table (5) and Figure (2), the cut point of cholesterol level was 190 mg/dl, so serum cholesterol > 190 mg/dl is predictive for macrosomia as a large significant area under the curve (AUC=87.1%) indicating a significant association between a high level of cholesterol and macrosomia. Cholesterol level was 69.5% sensitive, 100% specific, and 94.3% accurate as a marker for the prediction of macrosomia. ROC curve analysis was constructed for the TG level as an indicator of macrosomia. The cut point of TG level was 240 mg/dl, so serum TG > 240 mg/dl is predictive for macrosomia as a large significant area under the curve (AUC= 90.8%), indicating a significant association between high TG level and macrosomia. The level of TG was 69.5% sensitive, 100% specific, and 94.3% accurate as a marker for the prediction of macrosomia, Table (6) and Figure (4).

Table. Distribution of pregnant women by general characteristics.

Variable	No. (n=123)	Percentage (%)
Age (years):	56	
≤ 30	67	45.5
>30		54.5
Mean± SD	31.10± 3.65	
Gestational age (weeks)		
37-39	29	23.6
39- 41	94	76.4
Parity:		
Primipara	27	22
Multipara	96	78

Table2. Lipid profile of the studied women.

Variable	No. (n=123)	Percentage (%)
Cholesterol		
Normal	108	87.8
High	15	12.2
Triglycerides		
Normal	62	50.4
High	61	49.6
HDL		
Normal	96	78
Low	27	22
LDL		
Normal	97	78.9
High	26	21.1
VLDL		
Normal	58	47.2
High	65	52.7

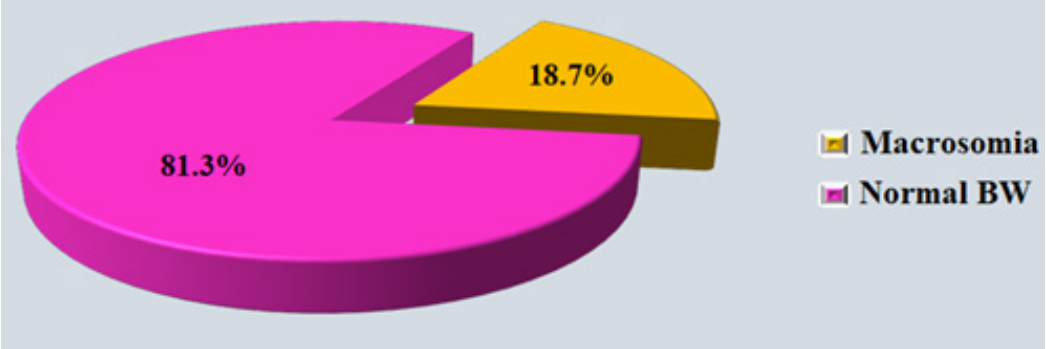

Figure 1. Distribution of cases according to birth weight.

Table3. Association between maternal serum lipid level and fetal macrosomia.

Variable	Study Groups: Macrosomia Total No=23 No (%)	Normal weight Total No=100 No (%)	Total No=123 No (%)	p-value
Cholesterol				
Normal	8 (7.4)	100 (92.6)	108 (87.8)	0.001
High	15 (100.0)	0(0.0)	15(12.2)	
TG				
Normal	1(1.6)	61(98.4)	62 (50.4)	0.001
High	22 (36.1)	39 (63.9)	61(49.6)	
HDL				
Normal	21(21.9)	75(78.1)	96 (78.0)	0.089
Low	2 (7.4)	25 (92.6)	27(22.0)	
LDL				
Normal	17(17.5)	80(82.5)	97(78.9)	0.519
High	6 (23.1)	20 (76.9)	26 (21.1)	
VLDL				
Normal	14 (24.1)	44(79.1)	58(47.2)	0.143
High	9 (13.8)	56 (86.2)	65(52.7)	

Table 4. Determinant of macrosomia by logistic regression analysis.

Factors	Odd ratio	95% C.I.		P – Value
		lower	upper	
TG Level	10.98	1.29	90.9	0.028

Table5. Diagnostic accuracy of cholesterol level for fetal macrosomia.

Cholesterol level (mg/dl)	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
	190	69.5%	100%	100%	93.4%	94.3%

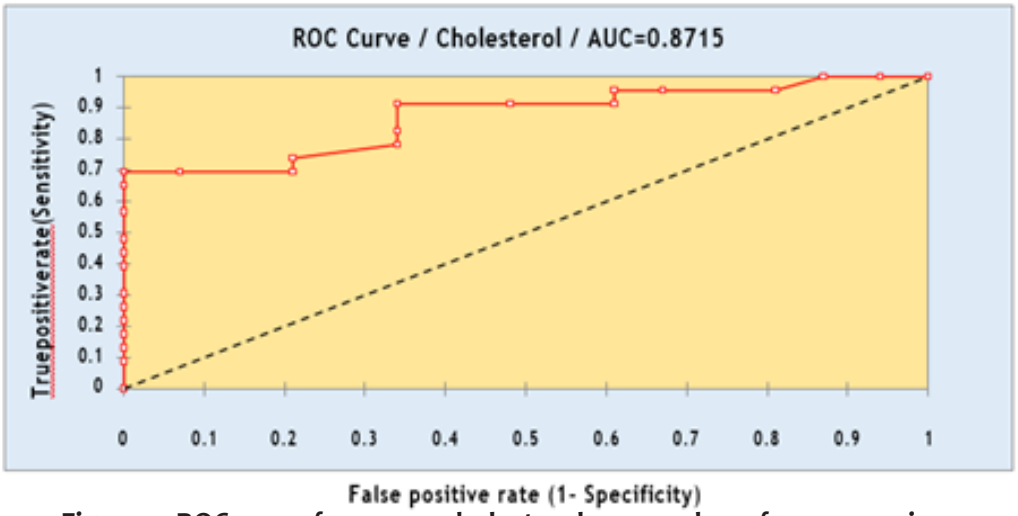

Figure 3. ROC curve for serum cholesterol as a marker of macrosomia.

Table 6. Diagnostic accuracy of triglycerides level as a test of macrosomia.

	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
TG level (mg/dl)	240	69.5%	100%	100%	93.4%	94.4%

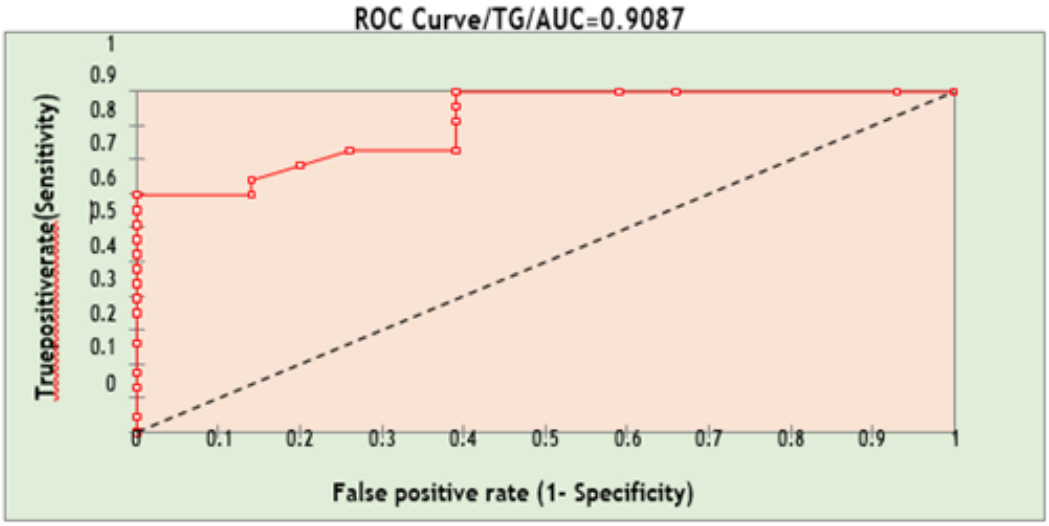

Figure 4. ROC curve for TG level as a marker of macrosomia.

DISCUSSION

There is increasing evidence that maternal metabolism and intrauterine conditions affect the growth and development of children, with their consequences for later health later in life, called the fetal origins hypothesis [19]. Maternal lipid profile, including levels of total cholesterol (TC) and triglycerides (TG), is one of these prenatal metabolic factors. Both TC and TG are crucial factors for optimum fetal development. The placenta takes up, metabolizes, and transports these two lipids in various forms to the fetus [31].

In the current study, the mean and SD of neonatal birthweight was 3.50±0.36 Kg, ranging from 3 to 4.6 Kg. Of the 123 pregnant women, 18.7% delivered macrosomic newborns, and 81.3% had newborns with average birth weight. Different results were observed in a study conducted by Wang and colleagues (2018) [30]. in which they reported the overall macrosomia prevalence as 10.0%. Another lower result was observed in the Mossayebi et al. study (2014) [15], in which they found that the women who delivered macrosomic newborns represented only (5.2%) of the study sample.

In the current study, the association between macrosomia and lipid parameters of recruited women in the third trimester of pregnancy showed a statistically significant association between macrosomia and maternal cholesterol level (P= 0.001), as all pregnant women with hypercholesterolemia delivered macrosomic newborns. So, the risk of giving birth to a baby with macrosomia increases with elevated maternal serum cholesterol.

Similarly, Hou and colleagues in their study (2014) [14]. found that total maternal serum cholesterol was significantly lower in the smaller gestational age group compared to the remaining participants. Moreover, Kulkarni et al. (2013) [29]. reported a significant association between an effective 54 g higher birthweights and one SD higher maternal cholesterol concentrations at 28 weeks ($P < 0.05$).

On the contrary, Wang et al. (2018) [30] observed that pregnant women who delivered macrosomia neonates and those who had normal infants were not significantly different in terms of maternal cholesterol level (P=0.222), which was in line with Jin et al. study in 2016, in which it was noticed that macrosomia and maternal serum cholesterol concentrations were not significantly correlated. In the current study, women with high serum triglyceride levels were found to have a substantially higher proportion of macrosomia (P=0.001). Moreover, there is an association between the risk of giving birth to macrosomic infants and increased levels of maternal serum TG. An agreement was observed in Wang et al. study in 2018 [30], in which they revealed that compared to the control group, the macrosomia group had a remarkably higher median level of serum TG (3.09 mmol/L versus 3.52 mmol/L, $p < 0.001$). They concluded that maternal serum TG levels could independently predict macrosomia at late gestation. Differently, Hou and colleagues in their study (2014) [19] found that levels of maternal TG are significantly higher in the low gestational age group than in other groups included in their research ($P<0.05$). In the current study, a statistically insignificant association was seen between macrosomia and maternal levels of HDL, LDL, and VLDL ($P>0.05$).

On the contrary, Wang, and colleagues, in their study in 2018 [29], found that macrosomia was accompanied by the levels of maternal serum high-density lipoprotein cholesterol (HDL-C). In this regard, they observed that the macrosomia group had a significantly lower level of serum HDL-C than the other group (1.85±0.45 vs.1.96±0.48, $p < .001$).

This study's logistic regression analysis revealed that macrosomia could have resulted from TG level as its significant, independent, and unconfounded risk factor (OR 10.98, CI 95%, P=0.028). In line with a study conducted in 2018 by Wang and colleagues [29], who employed univariate logistic regression analysis and concluded that macrosomia risk rose approximately 1.245-fold with each mmol/L rise in TG, while each one mmol/L rise in HDL-C or LDL-C decreased the risk by 41% or 17%, respectively.

In conclusion, in late pregnancy, there is a significant association between increasing the risk of macrosomia and high serum triglycerides and cholesterol levels.

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