Original Article

Maternal Plasma Lipid Profile and Risk of Spontaneous Preterm Labor Study in a Sample of Iranian Women in 2019

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Abstract

Background: Neonatal problems and adverse outcomes may be minimized by up to 90–75% when preterm delivery is diagnosed early and managed properly. This study aimed to determine the association of maternal plasma lipid indices with the occurrence of spontaneous preterm labor. **Material and Methods:** This matched pair case–control study was performed on 80 pregnant women referred to a teaching hospital in Tehran for childbirth in 2019. The lipid profile was assessed in women with spontaneous preterm labor and term birth. According to age, Body Mass Index (BMI), pregnancy number, employment status, and educational level, the women in each group were paired. Data were analyzed using an independent-samples t-test, Mann–Whitney U-test, Chi-square, linear regression, and conditional logistic regression. **Results:** Mean serum levels of total cholesterol, triglycerides, and low-density lipoprotein were all significantly higher in the case group compared with the control group ($p < 0.05$). The conditional logistic regression test confirmed that this association remained significant even after adjusting the effect of potentially confounding factors such as maternal age and body mass index. In addition, in linear regression the increased levels of triglyceride, total cholesterol, and low-density lipoprotein were found to be associated with 3.33-fold (1.32.–5.32 95% CI, $p < 0.001$), 2.94-fold (1.60–3.14 95% CI, $p = 0.002$), and 2.46-fold (1.31.–2.91 95% CI, $p = 0.006$) increased risk of preterm labor, respectively. **Conclusions:** High triglyceride, total cholesterol, and low-density lipoprotein serum levels may be linked to an increased chance of spontaneous preterm labor, which might be considered a risk factor for this pregnancy problem.

Keywords: *Cholesterol, gestation, lipoproteins, triglycerides, preterm labor*

Introduction

Preterm Labor (PTL) is one of the most common causes of neonatal mortality, which is defined as the delivery of neonate before the completion of 37 weeks of pregnancy, which can be diagnosed by progressive uterine contractions, cervical changes, and intact fetal membranes.[1,2] PTL is responsible for 75–90% of all neonatal deaths, prenatal mortality, and short- and long-term neonatal injuries leading to a preterm birth within 6 days in 75% of cases. The majority of these births occur between 32 and 36 weeks of gestation, so they are classified as late or early preterm births.[3] A systematic review and meta-analysis examined the published literature in this regard from 1995 to 2014 in Iran and estimated the overall prevalence rate of spontaneous preterm birth as 9.2%.[4]

Although most of the causes of PTL are unknown, limited studies have shown that variations of High-Density Lipoprotein Cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), Total Ccholesterol (TC), and Triglyceride (TG) levels are related to the activation of the maternal or fetal Hypothalamic–Pituitary–Adrenal axis (HPA), decidual hemorrhage, inflammation and infection, and pathological uterine distention.[1,5] Cholesterol plays important biochemical and physiological roles in the function of the membranes of the fetus and is one of the important factors in his/her neural development.[6]

This study hypothesized that levels of maternal plasma lipoprotein are significantly different in women with spontaneous preterm and term labor; in other words, abnormal levels of TC, HDL-C, LDL-C, and TG are associated with PTL. Therefore,

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this study aimed to determine the association of maternal plasma lipid indices with the occurrence of spontaneous PTL in pregnant women in Tehran, Iran.

Materials and Methods

This case–control study was performed by recruiting pregnant women who were referred to give birth at Taleghani Hospital, in Tehran, from March 2019 to May 2020. Sampling in both groups (80 participants in the two studied arms) was performed via a convenient method among women who were admitted to the labor ward presented with symptoms of labor. The sample size was calculated according to power analysis with $Z_{1-\alpha/2} = 1.96$, $p = 0.1$, $d^2 = 0.1$, 95% confidence interval, and 80% power. The inclusion criteria for the spontaneous PTL group (case) were as follows: gestational age less than complete 37 weeks based on the last menstrual period or ultrasound in the first trimester of pregnancy, no medical or obstetric disorders including vaginal or cervical infections, severe polyhydramnios, recent physical injury to the abdomen in the current pregnancy, presence of at least one ultrasound of the second or third trimester reporting fetal health in the patient's record, normal results of the first- or second-trimester embryonic screening tests, singleton pregnancy, no history of infertility and recurrent miscarriage, no history of smoking, alcohol consumption, and drug abuse before and during pregnancy, and taking no medication for a long time except for necessary supplements during the participant's current pregnancy.

Besides, all of the aforementioned criteria were used to select the samples in the control group, with the exception of term gestational age based on the first day of the last menstrual period or the first ultrasound of the first trimester of pregnancy, 37 full weeks to 41 weeks. After stating the objectives and research methods and obtaining informed written consent from the eligible women to enter the study, sampling was performed for the case group consisting of participants with less than 37 weeks of gestational age who were diagnosed by an obstetrician in the hospital as having symptoms of labor, with early onset of uterine contractions (with or without pain) with no rupture of fetal membranes. Moreover, they were referred to the hospital and then hospitalized with a diagnosis of PTL. The research comprised 40 women who met all of the study's inclusion requirements. The control group was made up of pregnant women with a full gestational age of 37 weeks or more who were admitted to the labor ward for spontaneous labor and with the approval of hospital obstetrician, according to the inclusion criteria. For this purpose, the participants in the control group were pair-matched with the participants in the case group based on the maternal Body Mass Index (BMI) (BMI), age range, pregnancy number, employment status, and educational level.

A demographic information questionnaire, researcher-made maternal and neonatal information checklist, Hitachi 912 Auto-Analyzer (Hitachi, Tokyo, Japan), and Bionik Lipid Kit (Bionik, Tehran, Iran) were used to measure plasma lipoproteins. To collect the required data, information was first recorded using the questioning method and in terms of some information included in the pregnancy file. Thereafter, a non-fasting blood sample in the morning (approximately from 8 to 9 AM) was taken by the first researcher from the antecubital vein with a 5-ml syringe, kept in the test tube as a clot sample at a standard temperature of 22 to 24°C, and then, it was taken to the Taleghani Hospital laboratory of the sampling place within one hour to measure TC, LDL-C, HDL-C, and TG on the same day of sampling. Each blood sample was tested independently for the abovementioned indicators on the day of blood sampling; however, the researcher collected test results from the laboratory at the end of each week for statistical analysis. All the study participants were followed up by the constant presence of the first researcher in the hospital until the birth of the newborn, and then, information such as the Apgar score, weight, and height of the baby was recorded in the obstetrics information checklist. Regarding the uncertainty of the exact time of childbirth among the participants of two arms of the study, especially in the case group, the interval between plasma sample collection and labor time was different in the two groups. For this reason, it was initially decided that if a sample was taken from a patient who did not enter the active phase of labor within 6 days or a patient who was discharged due to the cessation of uterine contractions and with an obstetrician's order, the sample would be excluded from the study. However, the interval between sampling from the participants to childbirth was on average 43 hours. Therefore, because the interval from sampling until delivery in all the participants was less than one week, no participant was excluded for this reason.

The obtained data were analyzed by SPSS version 21 (SPSS Inc., Chicago, IL., USA). Besides, the Kolmogorov–Smirnov test was used to test the normality of distribution of data. Moreover, the Chi-square test was used for qualitative variables, and the two independent-samples t-test and Mann–Whitney U-test were used for quantitative variables to examine the first step of the study hypothesis stated previously. Then, simple linear regression and conditional logistic regression tests were applied to check the second step of the hypothesis. A p value less than 0.05 was considered statistically significant.

Ethical considerations

The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNM.1396.760(. Written informed consent was obtained from all participants to enter the study.

Results

Most of the participants in both groups were homemakers (85%), nulliparous (95%), and had a university degree (53.70%). The mean (SD) score of gestational age in the case and control groups was 32.40 (1.9) and 38.80 (1) weeks. In these two study arms, there were no statistically significant differences between demographic factors [Table 1]. Only the rate of Normal Vaginal Delivery (NVD) in the control group was significantly greater than in the case group ($p < 0.001$). The mean TC and TG levels, as well as LDL-C levels, were significantly higher in the case group than in the control group. However, HDL-C levels were not significantly different between these two groups. In other words, adverse values of lipid patterns were significantly higher in the case group than in the control group [Table 2].

After adjusting the effects of age and BMI, findings indicated that the increasing levels of TG, TC, and LDL-C were associated with an increased risk of PTL [Table 3]. In other words, if TG levels increased more than normal levels, the odds of PTL increased by 3.32 times (1.32–5.32 95% CI, $p < 0.001$). Similarly, along with increasing levels of TC and LDL-C compared with normal levels of these indices, the odds of PTL increased by 2.92 (1.60–3.14 95% CI, p: 0.002) and 2.60 (1.31–2.91 95% CI, p: 0.006), respectively [Table 4].

Discussion

The results show that serum levels of TC, TG, and LDL-C were higher in the women with PTL than in the women with term labor; however, no significant difference between the two groups was found in terms of HDL-C levels. Similarly, hypercholesterolemia, hypertriglyceridemia, and a high level of low-density lipoprotein all raised the risk of spontaneous PTL.

In consistent with the results of the present study, the findings of a large nested case–control study performed between 2013 and 2015 included 600 age-matched pregnant women in two groups, indicating that increasing maternal serum levels of TG, TC, and LDL-C was all significantly higher in the PTL group than in the term group, except for HDL-C.[7] In the same vein, the results of a cohort study that examined more than 3,000 pregnant women from five US communities indicated that high levels of TC, TG, and

Table 1: Comparison of maternal and neonatal variables in the two groups of women with preterm and term labor

Group Variable	Preterm labor *n* (%)	Term labor *n* (%)	*p*
Weeks of pregnancy			
<30	9 (22.50)	-	<0.001*
31-33	16 (40)	-	
34-36	15 (37.50)	-	
37	-	5 (12.50)	
38-39	-	21 (52.50)	
40	-	14 (35)	
	Mean (SD)	**Mean (SD)**	***p***
Gestational age	32.40 (1.90)	38.80 (1)	<0.001**
Maternal age (years old)	26.80 (5.20)	26.60 (4.90)	0.861**
Body Mass Index (BMI)	23.80 (1.40)	24.0 (1.5)	0.426**
Perinatal variable			
Birth weight (g)	2113 (342)	3523 (450)	<0.001**
Birth height (cm)	47.80 (1.50)	48.9 (0.8)	<0.001**
Baby head circumference (cm)	31.87 (0.71)	32.75 (0.70)	<0.001**
Duration of NVD (h)	3.71 (1.92)	3.43 (1.66)	0.496 **
	Frequency (%)	**Frequency (%)**	***p***
Newborn gender			
Boy	20 (50)	19 (47.50)	0.824*
Girl	20 (50)	21 (52.50)	
Mode of childbirth			
NVD****	22 (55)	29 (72.50)	>0.001*
Cesarean section	18 (45)	11 (27.50)	
APGAR score			
1st min	28 (70)	8 (20)	>0.001*
≥7			
<7	12 (30)	32 (80)	
5th min	29 (72.50)	0 (0)	>0.001 ***
≥8			
<8	11 (27.50)	40 (100)	

*Chi-square test, **Two independent-samples *t*-test, ***Mann-Whitney *U*-test, ****Normal vaginal delivery

Table 2: Comparison of adverse plasma lipid profile ratios in the women included in the two groups of preterm and term labor

Group	Term labor *n* (%)	Preterm labor *n* (%)	*p**
Plasma lipid profile levels			
High levels of total cholesterol	7 (17.50)	25 (62.50)	>0.001
High levels of triglyceride	5 (12.50)	32 (80)	>0.00
Low levels of high-density cholesterol lipoprotein	6 (15)	8 (20)	0.559
High levels of low-density cholesterol lipoprotein	3 (7.50)	13 (32.50)	0.005

*Chi-square

Table 3: Linear relationship between plasma lipid profile values and gestational age in the women participating in the study

Plasma lipid profile components	*B**	95% CI**	*p****
Total cholesterol (mg/dL)	-0.039	0.026 to -0.052	<0.001
Triglyceride (mg/dL)	-0.036	-0.027 to 0.045-	<0.001
High-density cholesterol lipoprotein (mg/dL)	-0.071	0.006 to -0.148	0.071
Low-density cholesterol lipoprotein (mg/dL)	-0.036	-0.008 to -0.063	0.008

*Unstandardized beta, **Confidence interval, ***Linear regression

Table 4: Odds ratio and confidence interval of preterm labor according to plasma lipid indices of the women participating in this study

	Odds ratio	95% CI**	*p****
Triglyceride			
Raw model	3.33	1.33-5.32	<0.001
Adjusted* for maternal age and Body Mass Index (BMI)	3.32	1.32-5.32	>0.001
Total cholesterol			
Raw model	2.94	1.73-3.15	0.002
Adjusted* for maternal age and BMI	2.92	1.60-3.14	0.002
High-density lipoprotein cholesterol			
Raw model	0.51	-0.1-92.94	0.484
Adjusted* for maternal age and BMI	0.67	-0.2-87.20	0.395
Low-density lipoprotein cholesterol			
Raw model	2.46	1.21-2.72	0.022
Adjusted* for maternal age and BMI	2.60	1.31-2.91	0.006

*Adjusted for maternal age and BMI, **Confidence interval, ***Conditional logistic regression

LDL-C increased the risk of spontaneous preterm birth.[8] Despite growing body fat deposition during early normal pregnancy, data suggest that fat depots decrease in late pregnancy due to fetal development.[9] As a result, the differences in research designs may not have a significant impact on lipid indicators.

Conversely, a case–control study in Spain with 90 pregnant women shows that after adjusting for BMI and smoking, HDL-C, LDL-C, and TC were significantly lower in women with PTL than the women with term labor.[10] Furthermore, in a prospective cohort research of 200 pregnant women in India, by assessing the lipid profile obtained from blood samples of the participants in the 16th and 32nd weeks of pregnancy, it was suggested that although an increased level of maternal TG in the second trimester was associated with a higher risk of PTL, other lipid indices, including TC, LDL-C, and HDL-C, were not the predictors of preterm delivery, which was not consistent with our study's findings.[11] Besides, another similar study performed on 559 pregnant women in the United States found no significant association between elevated serum TG levels and PTL.[12] The final models were adjusted for relevant indices such as age and BMI of pregnant women in those studies that detected a significant correlation in this sector.[9] As a consequence, if the influence of maternal BMI is not controlled in conflicting research, BMI as a mediating variable might change the results. Another point that can be made to justify the conflicting findings among the aforementioned studies is that TG in some studies in the form of fasting is not measured. Regarding serum, TG can be affected by the duration of maternal fasting and different hours of the day, and it seems that this difference can distort the results of the study, which is one of the limitations of the present study.

In diverse populations, such as women in the United States and Spain, a significant association has also been shown between TC and the occurrence of spontaneous PTL.[7,10] Although high levels of TC are highly associated with other risk factors such as high-risk lifestyles and poor eating habits, which explain this unfavorable relationship,[13] total circulating cholesterol indicates that the amounts of cholesterol in HDL-C, LDL-C, and VLDL-C, and LDL-C and HDL-C levels, by having interaction effects on health, undermine the importance of TC levels and its role on PTL occurrence.[14] Nevertheless, in the present study, a high serum level of TC, as an important determinant with nearly threefold odds (1.60–3.14 95% CI, p: 0.002) of PTL, should be considered among the indicators associated with this adverse pregnancy outcome.

However, no significant difference was observed among low levels of HDL-C in the participants of case and control groups; therefore, low levels of this index in labor cannot be associated with the possibility of spontaneous PTL. A retrospective cohort study performed on a population of pregnant women in Mumbai, India, showed no statistically significant relationship between HDL-C serum levels and PTL.[11] However, a case–control study of 559 pregnant women from different races, including African Americans, Hispanics, and Caucasians in the United States, measured fasting blood samples (>8 h) at 20–28 weeks of gestation, and as a result, the study showed that a low HDL-C level in pregnant women was associated with an increased risk of PTL.[12] Moreover, despite differences in serum lipid levels between nonpregnant people of different races and ethnicities, low HDL-C levels during pregnancy might increase the risk of PTL. Since an increasing trend in HDL-C serum levels occurred in pregnant women during the second trimester, and especially in the third trimester,[15] those studies examining plasma samples of pregnant women for this purpose were performed before the end of the second half of pregnancy. Similar to the present study, the possibility of different and inconsistent results from those studies examining HDL-C in the third trimester or during labor is not far-fetched.

An abnormal increase in LDL-C levels by 2.6 times among other factors has increased the odds of PTL. The results of a prospective cohort study performed aimed at identifying etiological factors for PTL in 715 pregnant women[16] in the United States, and a retrospective cohort study performed on 200 women in the third trimester of pregnancy in India[11] showed that elevated serum levels of LDL-C were associated with an increased risk of PTL. Moreover, the results of a prospective cohort study conducted on 2,699 pregnant women in the first trimester of pregnancy in the United States reported incremental changes in TC levels during the first and third trimesters and found elevated LDL-C levels as the most important predictors of spontaneous PTL.[17]

The case–control design of this research, which confirmed the temporal precedence of the causes and variables studied in this study over the occurrence of PTL, might be accompanied by recall bias, for example, citing statements from pregnant women's remarks and relying on their medical records to rule out any systemic disorder before or during pregnancy that might also contribute to PTL. To our knowledge, the present study was conducted for the first time in a small sample of the Iranian pregnant women population to assess the abnormal maternal plasma lipid profile and the risk of PTL; however, the existing limitations are not condoned.

Conclusion

According to the results of this study, the increase in serum levels of TC, TG, and LDL-C was found to be significantly associated with an increase in the risk of PTL, which remained significant even after adjusting for maternal and neonatal characteristics. However, it is recommended that further research be carried out with a larger number of samples and in the form of longitudinal studies beginning in the first trimester of pregnancy.

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Conflicts of interest

Nothing to declare.

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