ATHEROGENIC INDICES IN CASES OF IDIOPATHIC PRETERM PREMATURE RUPTURE OF MEMBRANES AND HEALTHY PREGNANT CONTROLS: A COMPARATIVE STUDY

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ABSTRACT

Objective: To evaluate and compare atherogenic indices in women with idiopathic Preterm Premature Rupture of Membranes (pPROM) and gestational age matched healthy pregnant controls. Material and methods: In the Departments of Biochemistry and Obstetrics & Gynecology at UCMS & GTBH-Delhi, a cross-sectional comparative pilot study was carried out from August 2023 to July 2024. The study comprised 60 participants: 30 women with idiopathic pPROM (26-34 weeks gestation) and 30 controls with uncomplicated pregnancies who were matched for gestational age. We computed the following atherogenic indices: non-HDL-C, Lipoprotein Combined Index (LCI), LDL-C/HDL-C, TC/HDL-C, Atherogenic Coefficient (AC) and Atherogenic Index of Plasma (AIP) and analysed the data. Results: HDL-C levels were lower in idiopathic pPROM group. TC, TG, and LDL-C levels were higher in cases of idiopathic pPROM group. CRP levels were also higher in cases of idiopathic pPROM group. indicating increased systemic inflammation. All atherogenic indices except non-HDL-C were significantly elevated in the idiopathic pPROM group. Conclusion: Compared to healthy pregnant age-matched controls, women with idiopathic pPROM had a significantly pro-atherogenic lipid profile, elevated atherogenic indices and a higher inflammatory milieu. These findings also suggest a potential mechanism that links dyslipidaemia with proinflammatory state with membrane weakening and ultimately resulting in premature rupture of membranes. Thus, these women require closer monitoring for timely interventions to alleviate adverse outcomes.

Key words: Pregnancy, pPROM, Dyslipidaemia, Atherogenicity, Atherogenic Indices (*Source: MeSH, NLM*)

INTRODUCTION

Pregnancy is a dynamic state wherein physiological changes occur in almost all the organ system to sustain the developing embryo. Metabolic pathways are no exception and undergo changes to sustain the energy demands of the growing embryo. These changes include increased levels of energy substrates such as circulating glucose and lipids. Literature has documented increase in circulating levels of total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), highdensity lipoprotein cholesterol (HDL-C), and phospholipid from the beginning of the 12th week of and they continue to increase throughout pregnancy.[1] These changes are linked to insulin that developed along resistance is dyslipidaemia in pregnant women.

Dyslipidemia denotes a derangement in a patients fasting lipid profile characterized by low level of HDL-C with higher levels of LDL-C and TG. It is linked to an increased risk of atherogenicity and its associated sequelae. There are various studies that have explored the possible connection between maternal lipid levels and risk for adverse pregnancy outcomes. Vrijkotte TG et., 2012 reported that triglycerides concentration during early stages of pregnancy was linearly linked with the occurrence of pregnancy-induced HTN, pre-eclampsia, preterm birth (PTB).[2] Another study by Jelliffe-Pawlowski LL et al. (2014)[3] analysed 842 pregnant patients and reported a strong link between mid-trimester maternal dyslipidaemia and risk of PTB.[4] Increased levels of oxidized LDL-C in maternal plasma has also been linked to a greater risk of preeclampsia.[5]

Further highlighting the link between dyslipidemia and adverse pregnancy outcomes, CatovJ. M. et al. [6] reported higher serum levels of TC and TG in pregnant women at 8 weeks of GA who subsequently developed spontaneous preterm birth (sPTB) or pPROM; suggesting the role of dyslipidemia in adverse pregnancy outcomes even before maternal adaptations are fully established. Consequently, CatovJ.M. et al. [7] further reported that the risk of sPTB at <34 weeks was elevated when both inflammation and dyslipidemia were present before 21 weeks of gestation.

Dyslipidemia is intricately linked to endothelial dysfunction which is a precursor to atheroma formation.[8] In addition, inflammation and its resultant oxidative stress (OS) are also implicated in the development of an atheroma. sPTB and pPROM are known to be pro-inflammatory states by themselves with studies [9] documenting increased levels of inflammatory markers in these patients compared to healthy pregnant controls. Therefore, these women may be predisposed to increased atherogenicity and cardiovascular risk; however, there are no studies documenting the same. Atherogenic dyslipidemia is postulated to have a role in the cases of pPROM via promoting an environment rich in oxidizable lipids leading to excess generation of free radical which culminates in OS. It also promotes a state of low-grade inflammation which not only induces the expression of cytokines but also matrix metalloproteinases. Lastly it is linked with endothelial dysfunction which may adversely affect placental vascular health.

Atherogenic Indices (LDL-C/HDL-C, TC/HDL-C, non-HDL-C, Atherogenic coefficient, lipoprotein combined index and Atherogenic Index of Plasma): representing the pro-atherogenic apolipoproteins to anti-atherogenic lipoproteins levels were developed to optimize the predictive power of the lipid profile without increasing the cost of testing. They have been extensively studied and proven to be potent cardiovascular disease (CVD) risk markers in patients with CVD.

There is no study done till date that has compared the atherogenic indices in cases of idiopathic pPROM and healthy gestational age matched controls. Therefore, this study was designed to compare the atherogenic indices in cases of idiopathic pPROM and healthy gestational age matched controls.

MATERIAL AND METHODS

This research study was done in department of Biochemistry in collaboration with department of Obstetrics and Gynaecology of a tertiary care center in accordance with the declaration of Helsinki from 01.08.2023 to 01.07.2024.

Ethics statement

Ethical approval was promptly obtained from Institutional Ethics Committee-Human Research (IECHR-2023-59-25).

Calculation of sample size

A detailed literature search yielded studies which compared lipid profile and atherogenic indices in spontaneous preterm birth and PROM. There were no studies comparing these parameters in idiopathic pPROM; therefore, this study can be considered as a pilot study. A convenient sampling of 30 participants per group was taken.

Study participants

A total of 60 participants were recruited after obtaining written informed consent. consisted of pregnant women between 26 and 34 weeks of gestation, diagnosed as idiopathic pPROM (n=30). We considered pPROM as the rupture of membranes earlier to 370/7 weeks of gestation. The diagnosis was confirmed by amniotic fluid pooling, ultrasound and positive Amnisure® dipstick test. Women with pPROM due to identifiable causes such as cervical insufficiency, uterine anomalies, polyhydramnios, prior history of interventions (e.g., amniocentesis, chorionic villus sampling) or prior history of pPROM or preterm birth, medical conditions (e.g., diabetes mellitus, hypertension, thyroid disorders, connective tissue or other diagnosed genetic disorder), inflammatory diseases, or infectious diseases or history of smoking during pregnancy were excluded.

Apparently healthy pregnant gestational age matched controls (26-34 weeks) were recruited from the antenatal clinic. Controls were assessed and followed uptill term to document any complications which might develop later in pregnancy. If any of the controls developed any pregnancy related complication, post recruitment, they were excluded and a fresh gestational aged, matched controls were recruited and the same procedure followed. This was done until 30 matched controls were recruited. Hence. participants with antepartum complications. including gestational diabetes mellitus, pregnancyinduced hypertension, antepartum hemorrhage, or pre-existing medical conditions (e.g., thyroid

disorders, heart disease, diabetes mellitus, hypertension), were excluded from the study. In both study groups, blood samples were collected at the time of recruitment (24-36 weeks).

Routine biochemical parameter and fasting lipid profile was performed on DXC 700 Autoanalyzer (Beckman Coulter) using company reagent packs via enzymatic method.

CRP was performed on Randox Imola Autoanalyzer by using company reagent packs via immunoturbidimetry method

Atherogenic Indices were calculated as follows:

- LDL-C to HDL-C Ratio = LDL-C (mg/dL) / HDL-C (mg/dL)
- TC to HDL-C Ratio = LDL-C (mg/dL) / HDL-C (mg/dL)
- Non HDL C = HDL-C (mg/dL) TC (mg/dL)
- Atherogenic Co-efficient = Non-HDL-C (mg/dL) / HDL-C (mg/dL)
- Lipoprotein Combined Index = <u>[TC (mg/dL) × TG (mg/dL)</u> × <u>LDL-C (mg/dL)]</u>
 HDL-C (mg/dL)
- Atherogenic Index of Plasma = Log [TG (mg/dL) / HDL-C (mg/dL)] [10]

Statistical Analysis

Data was analyzed using SPSS software Version 30 (SPSS Inc., USA) and data represented as Mean ± SD. Normality of data was tested using the Kolmogrov-Smirnov test. Student's T test or Mann Whitney U test were used to compare different variables depending on the normality of the data. Correlation analysis was done using the Spearman rho correlation test. ROC (Reciever Operating Curve) and Multiple linear regression analysis were done using the SPSS software. p value less than 0.05 were considered statistically significant.

RESULTS

Data of 60 participants were analysed including 30 cases of idiopathic pPROM and 30 gestational age matched controls, who delivered normally at term. Kuppuswamy's scale was used for socio-economic status. All the participants were of lower or lower middle socio-economic status.

Tabla 1. Comparison of Lipid Profile between Idiopathic pPROM cases and healthy controls

Parameter (Mean ± SD)	Idiopathic pPROM (n=30)	Controls (n=30)	p value
Total Cholesterol (mg/dl)	243.70 ± 43.13	233.90 ± 65.04	0.494
Triglycerides (mg/dl)	243.17 ± 64.9	211.90 ± 77.19	0.264
High-Density Lipoprotein (mg/dl)	54.37 ± 12.91	63.60 ± 17.28	0.001
Low-Density Lipoprotein (mg/dl)	140.70 ± 41.92	127.92 ± 61.07	0.348

The mean age of patients in idiopathic pPROMgroup was 26.97 ± 4.35 years and that of the control group was 26.13 ± 4.22 years. The mean gestational age of patients in idiopathic pPROM group was 32.30 ± 1.84 weeks and that of the control group was 32.16 ± 1.63 weeks.

In this study, serum C reactive protein levels were higher in cases of idiopathic pPROM compared to gestational age matched controls (4.74 \pm 2.58 vs 1.79 \pm 1.61). Serum TC, TG and LDL-C levels were higher in the pPROM group compared to controls. HDL-C levels were lower in the pPROM group compared to the control group (Table 1).

Atherogenic indices i.e. LDL-C/HDL-C, TC/HDL-C, atherogenic coefficient, lipoprotein combined index and AIP were higher in the idiopathic pPROM group compared to control group. Non-HDL-C level was higher in the idiopathic pPROM group. (Table 2)

DISCUSION

Dyslipidaemia contributes to the generation of reactive oxygen species (ROS), which promote OS and systemic inflammation, thereby impairing endothelial function and contributing to atherogenicity. [11]

In our study, serum TC, serum TG and serum LDL-C levels were noted greater in patients with idiopathic pPROM than in the control group, while HDL-C levels were lower. Many trimester-specific reference intervals for lipid profiles during pregnancy have been proposed, which can help differentiate between physiological changes and potential pathological conditions. However, there is no universally accepted standard, and values can vary based on population, methodology, and regional factors.

Tabla 2. Comparison of Atherogenic Indices between Idiopathic pPROM cases and healthy controls

Parameter (Mean ± SD)	Idiopathic pPROM (n=30)	Gestational Age Matched Controls (n=30)	p Value
LDL-C / HDL-C	2.69 ± 0.96	2.02 ± 0.94	0.00001
TC / HDL-C	4.63 ±1.04	3.78 ± 0.90	0.012
Non-HDL-C	189.33 ± 39.2	170.30 ± 54.97	0.120
Atherogenic Coefficient	3.63 ± 1.04	2.78 ± 0.90	0.0012
Lipoprotein Combined Index	160342.42 ± 76923.68	97237.50 ± 55910.89	0.0005
AIP	0.65 ± 0.16	0.51 ± 0.22	0.0115

LDL-C: Low- Density Lipoprotein-Cholesterol; HDL-C: High-Density Lipoprotein-Cholesterol: TG: Triglycerides; AIP: Atherogenic Index of Plasma

Like our study, A.T. Ottun et al. [12] reported that higher levels of TC and LDL-C in cases of PTB (n=24) were higher to those who delivered at term (n=212) while HDL-C and TG values were comparable in both groups. In their study, among women (68.6%) who pregnant hyperlipidaemia, 20 women (12.4%) experienced sPTB. Of the women who delivered preterm, 4 (16.7%) had normal lipid levels, while 20 (83.3%) had hyperlipidaemia involving one or more lipid subtypes. The difference in findings could be explained by the small sample size in the case group and from the fact they compared lipid profile done in cases at 14-18 weeks to that done in healthy controls at term. However, the association between spontaneous preterm delivery and hyperlipidaemia was not statistically significant in this cohort.

Vrijkotte et al. [2] also reported higher levels of TG and TC at 13 weeks of gestation in those women who later had PTB, compared to healthy controls, however the difference was not statistically significant. They further reported no association of serum TG and TC levels with pre-term delivery. Niyaty S et al. [13] reported 18 cases of PTB among 203 pregnant women. 10 cases among them were pPROM, out of which 8 cases of pPROM had a TG value of more than 150mg/dL while 9 cases had a TC value more than 200 mg/dL. They reported no cases of pPROM with HDL-C levels less than 50 mg/dl. However, the lipid profile was estimated between 24 and 28 weeks of gestation.

Smith CJ et al [4] reported that dyslipidaemia was significantly associated with increased odds of preterm birth. Further they established an associated risk for the development of other subcategories of preterm birth, including pPROM. There is still a limited literature available on the association between dyslipidaemia and sPTB, and none studying the relation of atherogenic indices with pPROM.

Atherogenic indices have been proven to have better predictive power than traditional lipid profile.[14] In our study, the atherogenic indices (LDL-C/HDL-C and TC/HDL-C ratios) were higher among cases of pPROM compared to healthy controls. It is like a study done by Bartha JL,[15]in Spain which studied their levels in PTB, and gestational age matched healthy controls. In that

study, the mean gestational age at sample collection was 31.27±2.14 for cases of PTB and 31.56±3.14 for controls. In our study Atherogenic Coefficient, Lipoprotien Combined Index and AIP were higher among cases of idiopathic pPROM than in the gestational age matched controls. There are no studies which have compared the levels of Atherogenic Coefficient, Lipoprotien Combined Index and AIP in cases of idiopathic pPROM. These parameters have been shown to be associated with increased cardiovascular risk in other diseases. In addition, AIP, being a log-transformed value of ratio of TG to HDL-C, is considered a composite index exhibiting greater sensitivity than individual lipid indices.[16]

present study, regression analysis demonstrated that in the subgroup labeled V2 = CT, the model showed moderate correlation (R = 0.532, $R^2 = 0.283$). Among the predictors, serum triglycerides (TG) exhibited a modest statistically significant positive association with the period of gestation (B = 0.035, p = 0.040), whereas atherogenic index of plasma demonstrated a strong negative association with gestational duration (B = -22.455, p = 0.048). In contrast, the model for V2 = C was not statistically significant (adjusted $R^2 < 0$; ANOVA: p = > 0.7), suggested that overall regression model does not significantly predict POG. Receiver operating characteristic (ROC) analysis revealed that Atherogenic indices (TC/HDL, AC, LCI, AIP) shows better discriminatory ability (AUC ~0.70-0.74) compared to conventional lipids (TCH, LDL, HDL). However, our study also observed that triglycerides had a positive association with gestational age in the CT subgroup, contrary to several previous reports that linked hypertriglyceridemia with preterm birth. This discrepancy might be explained by differences in gestational timing of sample collection, subgroup characteristics, or collinearity among predictors. Notably, the SPSS output indicated multicollinearity ("tolerance = 0.000"), reflecting the mathematical interdependence of lipid ratios. Multicollinearity may inflate standard errors. thereby affect regression coefficients and reduce model stability. Thus, while our results support an association between composite atherogenic indices and gestational duration, these findings should be interpreted with caution.

Inflammation and OS are linked to both PTB and increased risk of atherogenicity. Inflammation is both a trigger and perpetuator of cardiovascular disease by contributing to plaque instability, endothelial dysfunction and thrombogenesis. In this study we also recorded higher levels of CRP in cases of idiopathic pPROM compared to gestational age matched controls signifying a greater inflammatory insult. However, maternal serum CRP levels were measured only at the time admission, and no analysis of its longitudinal progression until delivery was done. Bartha JL. [15] suggested that greater inflammatory insult increases the risk of cardio-vascular disease in future, as inflammation is also a predicting factor for CVD.

Despite preterm delivery not being considered as a major risk factor of cardiovascular disease, the American Heart Association, in its 2011 guidelines, has recommended to consider history of adverse pregnancy outcomes including PTB during risk assessment for any cardiovascular risk in women.[17] The guidelines given by European Society of Cardiology, recommends periodic screening of women with history of PTB for hypertension and diabetes.[18] The need for such guidelines was further validated when a meta-analysis done by Wu P et al.[19] on 3,38,007 women showed an increased risk of future adverse cardiovascular outcomes in women with history of PTB.

Another interesting aspect which needs to be explored is the role of dyslipidemia in the pathogenesis of PTB or pPROM. Studies done till date have reported placental oxidation of maternal lipids. Oxidized lipids and inflammatory mediators stimulate placental trophoblast cells to produce additional pro-oxidant and pro-inflammatory signals, creating a self-perpetuating, feed-forward cycle of OS. [20,21] This persistent oxidative environment might lead to degradation of the extracellular matrix, weakening of fetal membranes, and ultimately increase the risk of sPTB or pPROM.

CONCLUSION

Dyslipidaemia contributes to the generation of reactive oxygen species (ROS), which promotes OS and systemic

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The manuscript has been read and approved by all the authors, the requirements for authorship as stated earlier in this document have been met, each author believes that the manuscript represents honest work.