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Original Research Paper

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OCCURENCE OF ADVERSE PREGNANCY OUTCOMES AND ITS RELATION TO LIPID PROFILE IN EARLY PREGNANCY IN WOMEN ATTENDING IN TERTIARY CARE CENTRE.

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ABSTRACT **Background:** Maternal dyslipidemia has been linked to adverse perinatal outcomes. Hypercholesterolemia and elevated triglycerides in early pregnancy have been associated with an increased risk for gestational hypertension and adverse perinatal outcomes. The present study aimed to know the occurrence of adverse pregnancy outcomes among dyslipidemic pregnant females in first trimester and the relationship between maternal lipid profile in early pregnancy and birth outcomes. **Material and methods:** Serum lipid levels of total 124 pregnant females were taken in first trimester in a large tertiary care teaching hospital in New Delhi and they were followed up for their pregnancy and perinatal outcomes. The outcomes were stratified by normal and elevated lipid levels. **Results:** 41.9% pregnant females were found to be dyslipidemic. The common morbidities were gestational Hypertension (10.5)% and gestational diabetes (16.1%). The overweight females (BMI, 25-30 kg/m2) in hyperlipidemia group (61.5%) were more than normal lipid group (36.1%). ($p<0.01$). Babies with birth weight between 3.5- 4 kg were all born to mothers having hyperlipidemia during first trimester (N=8). ($p<0.01$). Babies with birth weight falling under large for gestation (LGA) category were significantly more in hyperlipidemia group (15.4%) compared to normal lipid group (2.8 %) ($p<0.05$). Mean serum total cholesterol and triglyceride was significantly higher in women >30 years compared to women less than 30 years. **Conclusion:** Risk of gestational hypertension, preeclampsia and gestational diabetes was higher in females with hyperlipidemia in first trimester. Hyperlipidemia and gestational diabetes were responsible for large for gestation birth weights.

KEYWORDS : Female, hyperlipidemia, pre-eclampsia, cholesterol, triglyceride, gesational diabetes, complications, pregnancy

INTRODUCTION

Pregnancy is a condition where enormous physical, biochemical and physiological changes occur that contribute to the alteration in lipid profiles of healthy gestating women. Lipoprotein lipid physiology in pregnancy has important implications for the developing fetus and newborn as well as the mother [1]. Cholesterol plays an important role in formation of cell membranes, membrane integrity, preserving membrane associated signaling cascades and acting as precursor to hormones, such as steroids, vitamin D and bile acids [1-3]. As the pregnancy advances, lipid physiology transitions to catabolic phase with breakdown of fat deposits and levels of lipoprotein lipids maximize near term [4,5].

Maternal dyslipidemia is lined to adverse perinatal outcomes such as risk of spontaneous preterm delivery [6-7], pre-eclampsia and gestational diabetes [8,9]. In observational and large cohort studies, increasing maternal triglycerides in early pregnancy have been associated with higher rates of pre-eclampsia and gestational diabetes [10,11].

It is also postulated that however, dyslipidemia may be silent with no symptoms, this might be an early sign of an impending metabolic syndrome [12].

The present study was conceived to add to the current literature to advance into the understanding of maternal lipids relationship to fetal development. The objective of the study was to know the proportion of adverse pregnancy outcomes among hyperlipidemic pregnant females in first trimester and to know the relationship between maternal lipid profile in early pregnancy and birth outcomes

MATERIAL AND METHODS

Study design

The present study was a prospective in nature with follow up where pregnant mothers attending their first prenatal visit were enrolled and were followed up till the time of delivery.

Study duration

The study commenced from August 2019 and was completed in July 2020 with duration of one year.

Study subjects

The study subjects were pregnant mothers attending the Obstetrics outpatient department of a multispecialty hospital in New Delhi, India.

Inclusion and exclusion criteria

The study included those subjects with singleton pregnancy, attending their first prenatal visit, in the age group of 20 to 45 years and able to provide written informed consent. Subjects with multiple gestation, chronic disorders such as heart diseases, diabetes, hypertension, renal diseases and on therapy of lipid altering medication such as antiepileptic drugs, steroids, insulin, antidepressants, thyroid hormones and sleep medication were excluded.

Sample size

Assuming a proportion of adverse maternal and neonatal outcomes as 8%, precision of 5% and 95% confidence level, the sample size was calculated as 113 subjects.

Study procedure

All the eligible subjects presenting to outpatient obstetrics department were asked for their written informed consent. After obtaining the consent, detailed history was taken. A thorough general physical examination was conducted. Under aseptic conditions, a sample of blood was drawn by venipuncture in tubes containing EDTA which were subjects to biochemical analysis using automated methods. The subjects were followed up at regular intervals to monitor their

pregnancy as well as to collect data on pregnancy complications and outcomes.

Operational definitions

Standard definitions for pre-eclampsia, preterm delivery, small for gestation age (SGA), Low birth weight, large for gestational age (LGA), chronic and gestational hypertension, preterm and term birth and gestational diabetes have been described elsewhere and were followed [10]. Lipid markers assessed were total cholesterol, total triglyceride, LDL cholesterol and HDL cholesterol where the values above 95th percentile were considered as hyperlipidemic state. The 95% confidence interval value of total cholesterol, total triglyceride, LDL cholesterol and HDL cholesterol were 3.66-4.60, 1.77-2.73, 2.08-2.45 and 1.45-1.77 mg/dl respectively.

Ethical considerations

The study was performed as per Helsinki declaration, 2000. Informed written consent was taken before inclusion in the study. The subjects were free to leave the study anytime without any effect on the clinical care and management. The study was approved by Institutional scientific and ethical committee.

Statistical analysis

The data was analysed using SYSTAT software for Windows version 13.2. Qualitative data was presented as frequency and proportions whereas quantitative data was presented as mean and standard deviation. Chi-square test was used for comparison of qualitative variables whereas independent sample t-test was used for comparison of continuous data. Calculation of correlation coefficient was done to know the linear relationship between variables. Point of statistical significance was considered when $p<0.05$.

RESULTS

A total of 124 females were recruited for the study. Normal lipid levels were found in 72 (58.1%) subjects whereas 52 (41.9%) subjects had raised lipid levels. Pregnancy related complication found were gestational hypertension (10.5%), pre-eclampsia (8.9%), gestational diabetes (16.1%) and intrahepatic cholestasis of pregnancy (4.0%). Among the subjects with raised lipid markers, the corresponding figures were 17.3%, 15.4%, 23.1% and 5.8% respectively.

There was significantly higher proportion of multigravida subjects among hyperlipidemic pregnant females. There was no statistical difference in the mode of delivery with proportion of lower segment caesarean section similar in both normal (44.4%) and hyperlipidemic group (46.2%). (Table 1)

Table 1: Distribution of maternal characteristics among normal and raised lipid levels

Variables	Categories	Normal lipids	Hyperlipidemia
Maternal age (years)	20 or less	2 (2.8%)	0
	21-25	22 (30.6%)	14 (26.9%)
	26-30	30 (41.7%)	16 (30.8%)
	31-35	16 (22.2%)	18 (34.6%)
	>35	2 (2.8%)	4 (7.7%)
Gravida	Primigravida	32 (44.4%)	8 (15.4%)
	Multigravida	40 (55.6%)	44 (84.6%)
BMI (Kg/m2)	18.5-24.99	42 (58.3%)	16 (30.8%)
	25.0-29.99	26 (36.1%)	32 (61.5%)
	30 and above	0	4 (7.7%)
Type of delivery	Vaginal	40 (55.6%)	28 (53.8%)
	LSCS	32 (44.4%)	24 (46.2%)

Regarding newborn characteristics, birth weight and gestation age with relation to weight was tabulated (Table 2). Small for gestational age (SGA), Appropriate for gestational age (AGA) and large for gestational age (LGA) were the categories for classification.

Table 2: Distribution of fetal characteristics among normal and raised lipid levels

Variables	Categories	Normal lipids	Hyperlipidemia
Birth weight (kg)	2 and more	4 (5.6%)	0
	2.0-2.5	28 (38.9%)	22 (42.3%)
	2.51-3.0	24 (33.3%)	16 (30.8%)
	3.1-3.5	16 (22.2%)	6 (11.5%)
	3.51-4.0	0	8 (15.4%)
Gestational age in relation to weight	SGA	20 (27.8%)	10 (19.2%)
	AGA	50 (69.4%)	34 (65.4%)
	LGA	2 (2.8%)	8 (15.4%)

Lipid levels were compared among subjects with different age groups to see the effect of age. Except for LDL levels, there was significant difference between the two age categories (Table 3).

Table 3: Difference between lipid parameters among mothers of different age group

Variables	Mothers aged 30 years or less	Mothers aged 30 years and above	P-value
S. Total cholesterol	170.1±25.4	182.8±30.8	0.033
S. Triglycerides	109.0±33.0	135.5±68.3	0.004
S. LDL	104.2±21.9	111.9±28.5	0.09
S.HDL	52.3±10.8	48.3±9.1	0.034

Independent t-test

There was no significant difference in the lipid marker levels among term and pre-term delivered newborns. The hospital stay in days was similar in both groups with mean duration of stay 3.1±1.2 days and 3.14±1.3 days among subjects with normal and raised lipid levels respectively.

Dietary intake of the subjects was correlated with the levels of lipid markers which were not correlated and non-significant. However, birth weight of the newborn was moderately correlated with gestational diabetic subjects with statistical significance ($p=0.004$).

DISCUSSION

The present study conducted in a North Indian tertiary care centre reiterated the findings of the previous studies that maternal lipid levels play important role in pregnancy and fetal outcomes. The lipid markers range were pre-defined and only the values more than 95 percentile were marked as hyperlipidemic.

The incidence of gestational hypertension found in our study was comparable to Indian studies. Preeclampsia occurs in 3-6% of all pregnancies and the incidence is 1.5 to 2 times higher in first time pregnancies [13]. The findings of present study were comparable to the incidence reported by Indian study by Yadav et al [14] who reported incidence of hypertensive disorders in pregnancy as 17.5%.

In an Indian study, Vidyabati et al [15] observed that concentration of total cholesterol and VLDL in women who developed PIH were significantly higher than that of normotensive women. Mean triglyceride value was higher in PIH groups. There was increased LDL in PIH group which was statistically significant. Based on these findings, the authors opined that maternal dyslipidemia at second trimester are very good non- invasive predictors of PIH. However, present study had single assessment of lipid levels in only first trimester and could conclude that maternal dyslipidemia in first trimester are very good non-invasive predictors of Gestational Hypertension.

Clausen et al [16] reported that hypertriglyceridemic dyslipidemia before 20 weeks of gestation is associated with

the risk of developing early but not late onset pre- eclampsia. They observed that Women with dyslipidemic picture developed early onset pre-eclampsia. Women with triglycerides above 2.4mmol/L had increased risk (OR 5. 1; 95% CI 1.1-23.1) of early onset pre-eclampsia compared with triglycerides levels < or = 1.5mmol/L

Increasing evidence suggests that elevated plasma lipids, including TG or its related remnants, may induce endothelial dysfunction [17,18]. Increased peroxidation of these elevated plasma lipids causes enhanced oxidative stress by progressively producing free radicals and lipid peroxides [19].

Although in our study, all the first trimester lipid parameters were raised in GDM (hyperlipidemia group) they were non significantly higher than proportion in GDM (normal lipid group). Unlike Ryckman's study, we could not measure triglycerides throughout the pregnancy and establishing relationship of GDM with triglycerides [20].

We found that the mean values of all the lipid parameters were comparable and non- significantly different suggesting that lipid levels in first trimester were not correlated to pregnancy term.

In contrast, Catov JM et al [21] in a nested case control study of women with spontaneous preterm birth reported that high cholesterol or triglyceride less than equal to 15 weeks were associated with a 2.8-fold and 2.0-fold increased risk for preterm birth <34 weeks and ≥34-37 weeks, respectively. This difference may be influenced by population consisting black race and significant smoking history which was not present in our study. The levels of cholesterol, triglyceride and LDL were significantly higher in age group more than 30 years which was consistent with the findings of ABCD study [22].

We did not found significant relation of lipid levels with SGA or AGA which was in similar trend with the ABCD study which reported that TG levels were not associated with preterm birth, SGA, and child loss [22]. The prevalence in the same study for SGA was 9.3%, for LGA 9.3%, and for child loss was 1.4%. We observed 30 cases of SGA and 10 cases of LGA but did not have any perinatal mortality.

In ROLO Study, dietary saturated fat intake in trimester one was positively associated with total cholesterol in early pregnancy (p=0.02). Likewise, dietary intakes of mono unsaturated and polyunsaturated fat were positively associated with total cholesterol at this timepoint (P = 0.005 and P = 0.038, respectively). Dietary fat intake was not associated with triglyceride concentrations in early pregnancy. [23]

There is a scarcity of data on the association between blood lipids during pregnancy and infant outcomes, with the limited knowledge focusing on women with gestational diabetes mellitus (GDM). Triglyceride concentrations in women with hyperglycaemia during pregnancy have been shown to be associated with increased birth weight [24-25]

Thus, estimation of maternal lipid profile in the first first trimester will bring about early recognition and better management of patients at risk of pregnancy-induced hypertension, before the clinical syndrome and complications of gestational hypertension, preeclampsia and GDM appear. Also early treatment of such cases is essential for a better feto-maternal outcome.

The study has some limitations which may reduce its external validity. Firstly, the sample size was small to draw conclusions. Secondly, the study was conducted in hospital which is not a representative of whole population.

CONCLUSION

The present study found females aged above 30 years and multigravida were at significant risk of hyperlipidemia in the first trimester. Early lipid markers assessment in first trimester can lead to early recognition and better management which is essential for better feto-maternal outcome. Further studies are warranted with prospective lipid marker testing to further establish the relation between feto-maternal outcome and lipid levels.

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