

Study of serum lipid profile in pregnancy and its correlation with preeclampsia

Abstract

Objective: To study serum lipid profile between 13-20 week of pregnancy & to look for correlation, if any, of serum lipid levels in pregnancy with preeclampsia and to find out correlation, if any, between serum lipids profile and fetomaternal outcome.

Material and methods: We carried out a Longitudinal, Descriptive type of observational study in the department of Obstetrics and Gynecology at SDMH, Jaipur from June 2016 to April 2017. Total 125 patients were enrolled in study fulfilling inclusion and exclusion criteria between 13-20 weeks of gestation at SDMH, Jaipur, 14 patients were lost during follow up finally 111 patients remained for analysis. Serum lipid profile was done in all patients and these were followed till delivery for presence and absence of preeclampsia.

Results: The mean level of TC in participants developed preeclampsia was 224.36 ± 43.68 mg/dl. This was significantly higher as compared to normotensive group 180.77 ± 36.58 mg/dl.

Conclusion: Early prediction of preeclampsia can be used as a tool for primary prevention before the development of the disease. There is no single specific test available to predict the preeclampsia till date. So there is need of further research to discover the specific test to predict preeclampsia

Keywords: preeclampsia, lipid profile, pregnant woman

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Dr Nidhi,¹ Dr Brinderjeet Kaur,² Dr S Fayyaz,³

¹Senior Resident, Obstetrics & Gynecology, Santokhba Durlabhji Memorial Hospital, India

²Asst Consultant, Obstetrics and Gynecology, Santokhba Durlabhji Memorial Hospital, India

³HOD, Senior Consultant, Obstetrics & Gynecology, Santokhba Durlabhji Memorial Hospital, India

Correspondence: Dr Brinderjeet Kaur, Asst Consultant, Obstetrics and Gynecology, Santokhba Durlabhji Memorial Hospital and Research Center, Bhawani Singh Road Jaipur, India, Tel 9829229289, Email dr.bjkaur@gmail.com

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Introduction

There has been improvement in antenatal care all round the globe during past few decades. Pre-eclampsia is a serious complication of second half of Pregnancy that occurs with a frequency of 5-10%. The disease is a leading cause of maternal morbidity which can lead to maternal death, fetal growth retardation, infant morbidity and mortality.¹ Preeclampsia is defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on 2 occasions at least 4 hrs apart after 20 weeks gestation in women with a previously normal blood pressure or ≥ 160 mmHg systolic or ≥ 110 mmHg diastolic, and proteinuria ≥ 300 mg/ 24hrs or a Protein/creatinine ratio ≥ 0.3 mg/dl or a dipstick reading of $\geq 1+$.²

The pathogenesis of preeclampsia is unclear,³ however two important components have been identified, trophoblast cells and an accelerated maternal systemic response to trophoblastic tissue.⁴ A two-step model has been described for pathophysiology of preeclampsia.⁵ The first one pertaining to abnormal placentation leading to placental ischemia causing secretion of soluble factors that induce endothelial dysfunctioning and maternal preeclampsia⁶ in pregnant women. The second one is related to increase in free radicals and Reactive oxygen species causing cell damage⁷ and increased vascular tonicity causing preeclampsia.⁸ It implies that an abnormal lipid profile has a direct effect on endothelial dysfunction leading to decrease in PGI-TxA2 ratio and subsequent fibrinoid necrosis at uteroplacental implantation site.⁹ The possible correlation between the altered lipid profile and the severity of renal lesions, as reflected by proteinuria, may contribute towards clarify the complex patho physiology of preeclampsia.

Our study was designed to find any correlation, if any between serum lipids levels in pregnancy (13-20 weeks) by lipid profile estimation with preeclampsia and maternal outcome at term. The study is useful as maternal lipid levels can be easily measured in all clinical laboratories with routine, well-established lipid panels; thus, inexpensive lipid panels could serve as a cost-effective method for identifying pregnant women at risk for developing preeclampsia. These can be used as "powerful predictive tool" for obstetrician for early identification and expert management.

Material and methods

The descriptive observational study was carried out in department of obstetrics and gynecology at SDMH, Jaipur from June 2016 to April 2017. The study was approved by institutional ethics committee. Patients were explained about nature and purpose of study including cost of investigations. After obtaining their written informed consent they were enrolled in the present study. The participants were all pregnant women between 13-20 weeks of gestation, Singleton uncomplicated pregnancy, blood pressure reading: systolic less than 140 mm Hg & diastolic less than 90 mm Hg and those who were willing to follow up & deliver at SDM Hospital. The exclusion criteria were the presence of any of the following: Multiple pregnancy, Molar pregnancy, Chronic diseases (chronic hypertension, diabetes mellitus, severe anaemia, Grade III & Grade IV heart disease, renal disease), Patients with bad obstetrics history, Smoking and H/o hypertensive disorder in previous pregnancy. A total of 125 patients were included in study after sample size calculation at 95% confidence level & 80% study power, considering 11 independent variables for the prediction of preeclampsia.⁷⁴

Venous blood from antecubital vein was withdrawn under strict aseptic condition after 12 hours fasting period. Patients were classified depending upon Serum lipid levels according to The National Cholesterol Education Program (NCEP) guidelines¹⁰ (Table 1) and on presence or absence of Preeclampsia these groups were studied further and statistical analysis was done using Medcalc 16.4.0 version software. Continuous variables were summarized as mean & standard deviation, whereas Nominal/Categorical variables as proportions. Unpaired T test was used for analysis of continuous variable while Chi sq test/fisher exact test was used for Nominal/Categorical variables. Odds ratio was calculated for all suspected predictors, Univariate analysis was done to identify independent predictors of preeclampsia. P<0.05 was taken as significant.

Table 1 Lipid profile interpretation as per The National Cholesterol Education Program (NCEP) guidelines: (units in mg/dl)

Total Cholesterol	Desirable : <200
	Borderline high- 200-239
	High: > or=240
Triglycerides	Normal: <150
	Borderline high: 150-199
	High: 200-499
HDL Cholesterol	Very high: > or =500
	Low(removed HDL): <40
	Normal: 40-60
LDL Cholesterol	High: >60
	Optimal: <100
	Near Optimal: 100-129
	Borderline high: 130-159
	High: 160-189
	Very high: > or = 190

Discussion

Preeclampsia is a systemic syndrome of pregnancy originating in the placenta. The present study was conducted to evaluate serum lipid profile between 13–20 weeks of gestation and to look for its correlation with preeclampsia. Total of 125 subjects were recruited in present study, 14 (11.2%) subjects lost during follow-up. Finally 111 subjects remained in the study for analysis. The maximum number of participants from preeclampsia group and control group was between 26-30 years. The difference between the groups was not statistically significant. (p>0.05) (Table 2). 65(58.56%) of participants were primigravidas in which 15(23.08%) developed pre-eclampsia & 50(76.92%) remained unaffected. 46(41.44%) of participants were multigravidas in which preeclamptic and normotensives were 3 (6.52%) & 43(93.48%) respectively, the difference was statistically significant (Table 3).

Table 2 Distribution of Study Participants According to Age

Age (Years)	Normotensive		Pre-eclampsia		Total	
	No.	%	No.	%	No.	%
21-25	41	89.13	5	10.87	46	41.44
26-30	42	77.78	12	22.22	54	48.65
>30	10	90.91	1	9.09	11	9.91
Total	93	83.78	18	16.22	111	100

Chi-square =2.813 with 2 degrees of freedom; P=0.245

Table 3 Distribution of Study Participants w.r.t. Gravidity

Gravida	Normotensive		Pre-eclampsia		Total	
	No.	%	No.	%	No.	%
Primi	50	76.92	15	23.08	65	58.56
Multi	43	93.48	3	6.52	46	41.44
Total	93	83.78	18	16.22	111	100

Odds ratio=4.300 (95% confidence interval: 1.166 to 15.856)

Chi-square=4.284 with 1 degree of freedom; P=0.038

11(61.11%) participants developed pre eclampsia & 6(6.45%) unaffected participants delivered at <37 weeks of gestation while 87 (93.55%) of participants remained unaffected & 7 (38.89%) of participants developed pre eclampsia delivered at >37 weeks of gestational age. The difference is statistically highly significant (P<0.05) (Table 4). Out of total pre eclamptic patients 8(44.44%) were delivered by LSCS as compared to 13(13.98%) unaffected participants. This difference was statistically significant. (p <0.05) (Table 5).

Table 4 Comparison between Groups According to Gestational Age at Delivery

Groups	GA at delivery				Total	
	Preterm		Term		No.	%
	No.	%	No.	%		
Pre-eclampsia	11	61.11	7	38.89	18	100
Normotensive	6	6.45	87	93.55	93	100
Total	17	15.32	94	84.68	111	100

Odds ratio=22.786 (95% confidence interval: 6.476 to 80.165)

Chi-square=30.654 with 1 degree of freedom; P<0.001

Table 5 Distribution of Study Participants According to Mode of Delivery

Groups	Mode of delivery				Total	
	LSCS		Vaginal delivery		No.	%
	No.	%	No.	%		
Pre-eclampsia	8	44.44	10	55.56	18	100
Normotensive	13	13.98	80	86.02	93	100
Total	21	18.92	90	81.08	111	100

Odds ratio=4.923 (95% confidence interval: 1.640 to 14.776)

Chi-square=7.247 with 1 degree of freedom; P=0.007

Total cholesterol was deranged in 26(23.42%) participants, in which 10(38.46%) developed preeclampsia and 16(61.54%) remained normotensive, difference was statistically significant (p=0.001) (Table 6). The mean level of TC in participants developed preeclampsia 224.36±43.68mg/dl was significantly higher as compared to normotensive group 180.77±36.58mg/dl (p<0.001). Difference between the groups was statistically significant in this study and above mentioned studies. Similar results were also found in studies of Archana S et al.¹¹ and Leela KP et al.¹² The association of TC concentration with preeclampsia might explained by the fact that Hypercholesterolemia promoted the formation of free radicals.

Table 6 Association of Total Cholesterol with Preeclampsia

TC	Normotensive		Pre-eclampsia		Total	
	No.	%	No.	%	No.	%
Normal	77	90.59	8	9.41	85	76.58
Deranged	16	61.54	10	38.46	26	23.42
Total	93	83.78	18	16.22	111	100

Odds ratio=6.016 (95% confidence interval: 2.054 to 17.615)

Chi-square=10.321 with 1 degree of freedom; P=0.001

HDL was deranged in 29(26.13%) participants, in which 9(31.03%) w developed preeclampsia and 20(68.97%) were remained normotensive. This difference was statistically significant. (p<0.05) (Table 7). The mean level of HDL in participants developed preeclampsia 39.68±7.50mg/dl was significantly lower as compared to normotensive group 43.72±7.35mg/dl (p=0.036) Difference between the groups was statistically significant in this study and above mentioned study. Similar results were also found in studies of Soundararajan P et al.¹³; El Khouly N¹⁴ and Leela KP et al.¹² The association of HDL with pathogenesis of preeclampsia could explain as HDL cholesterol facilitates reverse cholesterol transport by caring excess, potentially harmful cholesterol from peripheral tissue to liver. The Low level of HDL in preeclampsia because of hypo-oestrogenaemia & insulin resistance causes excess harmful cholesterol involve in pathogenesis of preeclampsia.

LDL was deranged in 32(28.83%) participants, in which 11(34.38%) developed preeclampsia and 21(65.63%) remained normotensive, the difference was statistically significant (p=0.003) (Table 8). The Mean level of LDL in participants developed preeclampsia 132.87±23.74mg/dl was significantly higher as compared to normotensive group 112.14±25.15mg/dl(p=0.002). Difference between the groups was statistically significant in this study and above mentioned studies. Similar results were also found in studies of Archana S et al.¹¹; Soundararajan P et al.¹³; El Khouly N¹⁴ and Leela KP et al.¹² The association of LDL concentration with preeclampsia is biologically plausible. It has been seen that oxidized LDL increased sensitivity to the presser agents and inhibit epithelial dependent vasodilatation .It is found that the lipid fractions increased in pre-eclamptic patients and plasma lipid peroxidase and free radicals were activated. Also platelet and erythrocyte membrane antioxidant systems were inactivated.

VLDL was deranged in 39(35.14%) participants, in which 11(28.21%) developed preeclampsia and 28(71.79%) remained normotensive. This difference was statistically significant. (p<0.05) (Table 9) The mean level of VLDL in participants developed

preeclampsia 36.51±8.10mg/dl was significantly higher as compared to normotensive group 31.10±6.64mg/dl (p=0.003). Difference between the groups was statistically significant in this study and above mentioned study. Similar results were also found in studies of Archana S et al.¹¹; Soundararajan Pet al.¹³ and Leela et al.¹² In pathogenesis of preeclampsia, VLDL lipoproteins accumulate over the maternal vascular endothelium, particularly those of uterine and renal vessels & may cause injury to the endothelium.

Table 7 Association of HDL with Preeclampsia

HDL	Normotensive		Pre-eclampsia		Total	
	No.	%	No.	%	No.	%
Normal	73	89.02	9	10.98	82	73.87
Deranged	20	68.97	9	31.03	29	26.13
Total	93	83.78	18	16.22	111	100

Odds ratio=3.650 (95% confidence interval: 1.280 to 10.410)

Chi-square=4.954 with 1 degree of freedom; P=0.026

Table 8 Association of LDL with Preeclampsia

LDL	Normotensive		Pre-eclampsia		Total	
	No.	%	No.	%	No.	%
Normal	72	91.14	7	8.86	79	71.17
Deranged	21	65.63	11	34.38	32	28.83
Total	93	83.78	18	16.22	111	100

Odds ratio=5.388 (95% confidence interval: 1.857 to 15.630)

Chi-square=9.115 with 1 degree of freedom; P=0.003

Table 9 Association of VLDL with Preeclampsia

VLDL	Normotensive		Pre-eclampsia		Total	
	No.	%	No.	%	No.	%
Normal	65	90.28	7	9.72	72	64.86
Deranged	28	71.79	11	28.21	39	35.14
Total	93	83.78	18	16.22	111	100

Odds ratio=3.648 (95% confidence interval: 1.282 to 10.384)

Chi-square=5.073 with 1 degree of freedom; P=0.024

TGs were deranged in 39(35.14%) participants, in which 11(28.21%) developed preeclampsia and 28(71.79%) remained normotensive. On application of statistical tests the difference was statistically significant (p=0.024). (Table 10) mean level of TG in participants developed preeclampsia 184.48±35.63mg/dl was significantly higher as compared to normotensive group 157.09±28.10 (p<0.001) (Table 11). Difference between the groups was statistically significant in this study and above mentioned studies. Increased TG, found in preeclampsia, is likely to be deposited in predisposed vessels, such as the uterine spiral arteries and contributes to the endothelial dysfunction, both directly and indirectly through generation of small, dense LDL & hypertriglyceridemia may be associated with hypercoagulability.

In this study, 13(27.08 %) participants who had dyslipidemia delivered by LSCS as compared to 8(12.70 %) in unaffected

participants. This difference was not statistically significant ($p > 0.05$) (Table 12).

Table 10 Association of Triglycerides with Preeclampsia

TGs	Normotensive		Pre-eclampsia		Total	
	No.	%	No.	%	No.	%
Normal	65	90.28	7	9.72	72	64.86
Deranged	28	71.79	11	28.21	39	35.14
Total	93	83.78	18	16.22	111	100

Odds ratio=3.648 (95% confidence interval: 1.282 to 10.384)

Chi-square=5.073 with 1 degree of freedom; P=0.024

Table 11 Lipid Profile Levels of Preeclamptic and Normotensive Women

Lipid Profile	Normotensive	Preeclampsia	P value
TC	180.77±36.58	224.36±43.68	<0.001
HDL	43.72±7.35	39.68±7.50	0.036
LDL	112.14±25.15	132.87±23.74	0.002
VLDL	31.10±6.64	36.51±8.10	0.003
TG	157.09±28.10	184.48±35.63	<0.001

Table 12 Association of Dyslipidemia with Mode of Delivery

Dyslipidemia	Mode of delivery				Total	
	LSCS		Vaginal delivery			
	No.	%	No.	%	No.	%
No	8	12.7	55	87.3	63	100
Yes	13	27.08	35	72.92	48	100
Total	21	18.92	90	81.08	111	100

Odds ratio=2.554 (95% confidence interval: 0.961 to 6.786)

Chi-square=2.797 with 1 degree of freedom; P=0.094

The results of our study are similar to those by Deshpande H et al.¹⁵; Vani et al., Khaliq et al., Iftikha et al., Gohil et al., Saha D et al. and Nayan S et al. (Table 13).

Deshpande H et al.¹⁵ conducted comparative observational study on 60 pregnant women with objective to analyze the lipid profile in normotensive & preeclamptic patients and to assess abnormal lipid profile in relation to severity of hypertension, maternal outcome & perinatal outcome. It was seen that mean Cholesterol level in PIH cases was 208.8±12.64mg/dl and in normal cases was 163.8±8.83mg/dl, mean HDL level in PIH cases was 38.06±3.01mg/dl and in normal cases was 49.56±4.08mg/dl, mean LDL level in PIH cases was 140.36±10.8 mg/dl and in normal cases was 120.2±7.98mg/dl, mean VLDL level in PIH cases was 52.76±4.96mg/dl and in normal cases was 35.4±3.62mg/dl and mean Triglyceride level in PIH cases was

201.06±10.67mg/dl and in normal cases was 158.8±9.96mg/dl. The association of Mean cholesterol, HDL, LDL, VLDL and Triglyceride level among normal and PHT cases are statistically significant. ($p < 0.05$). They concluded that the association between dyslipidemia and risk of preeclampsia is biologically plausible and is compatible with what is known about pathophysiology of preeclampsia.

Vani I et al.¹⁶ conducted an open labeled clinical study to compare the lipid profile in normotensive and hypertensive pregnant women. The study included two groups-50 normotensive and 50 preeclamptic pregnant women in whom fasting blood samples were sent for estimation of serum lipid profile during their third trimester. There was a significant increase ($p < 0.5$) in total cholesterol, LDL cholesterol, VLDL cholesterol and triglycerides in preeclamptic group compared to normotensive group. There was a significant decrease in HDL cholesterol in preeclamptic group compared to normotensive group. This study in correlation with various other studies concluded that dyslipidemia plays an important role in the pathogenesis of preeclampsia.

Khaliq F et al.¹⁷ performed a cross sectional study to determine serum lipid and lipoprotein cholesterol in pre-eclamptic women in their third trimester, taking normal pregnant women in third trimester as controls. The values were compared in patients of different parity. It was observed that serum triglycerides (TG), cholesterol (CholD, LDL-c, VLDL-c, phospholipids (PL) and total lipids (TL) were significantly raised, while HDL-c, was significantly lower in pre-eclampsia compared to normal pregnancy. TG and VLDL-c were found to be increased significantly with parity.

Iftikhar U et al.¹⁸ conducted a comparative cross-sectional study to assess the relation between serum leptin levels and lipid profile in women with pre-eclampsia and to evaluate their atherogenic role in the pathophysiology of pre-eclampsia. They found that all the variables of the lipid profile of pre-eclamptic patients, were found to be significantly elevated as compared to controls. The total lipid profile was also compared to the severity of pre-eclampsia and total cholesterol was found to be significantly raised ($p < 0.01$) in severe pre-eclampsia when compared to mild. On correlating serum leptin with lipid profile, again total cholesterol was found to be significantly high ($p < 0.05$) in pre-eclamptic group compared to controls. This study concluded that serum leptin levels during pre-eclampsia are strongly associated with total cholesterol whereas association with other variables is insignificant. With severity of pre-eclampsia when leptin level rises, total cholesterol also rises. These changes may be the result of oxidative stress and may contribute to atherogenesis and pathogenesis of pre-eclampsia.

Gohil et al.¹⁹ conducted study to evaluate lipid profiles in subjects with preeclampsia and to determine if there is any change in lipid profiles in subject of preeclampsia as compared to normal antenatal females, non-pregnant females and postpartum females. Each serum sample from different groups was evaluated for Total cholesterol (mg/dl), Triglyceride (mg/dl), HDL-cholesterol (mg/dl), LDL-cholesterol (mg/dl) and VLDL-cholesterol (mg/dl). They found that Dyslipidemia in the form of significantly decreased HDL concentration and significantly increased total cholesterol, LDL, VLDL & Triglycerides concentration is conspicuously evident in subjects of preeclampsia as compared to non pregnant, normotensive pregnant and postpartum subjects & concluded that Dyslipidemia is significantly evident in preeclampsia and plays an important pathological role.

Table 13 Comparison with other studies

	Total cholesterol	HDL	LDL	VLDL	Triglyceride
Deshpande H et al. ¹⁵	N=163.8±8.83	N=49.56±4.08	N=120.2±7.98	N=35.4±3.62	N=158±9.96
	P= 208.8±12.64	P=38.06±3.01	P= 140.36± 10.8	P=52.76±4.96	P=201.06±10.6
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Vani I et al. ¹⁶	N=199±34	N=58±5	N=101±32	N=39±8	N=196±41
	P=227±31	P=51±5	P=132±34	P=43±10	P=219±58
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Khaliq F et al. ¹⁷	N=187.66±31.87	N=53.77±10.45	N=94.61±28.23	N=39.31±7.01	N=196.62±35.06
	P=220.95±45.38	P=77.17±11.89	P=124.61±40.88	P=52.10±15.46	P=260.83±77.35
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Iftikhar U et al. ¹⁸	N=209±13.6	N=35.4±2.7	N=148.4±13.6	N=36.8±4.8	N=186.3±20.9
	P= 238±28.8	P=32.8±3.40	P=162.1±24.8	P=50.1±11.1	P=2.45±53.5
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Gohil JT et al. ¹⁹	N=219.1±3.1	N=60.3±1.2	N= 115.7±3.4	N=43.04±0.40	N=215.2±1.9
	P=232±2.9	P= 41.75±3.40	P=135.8±4.1	P=54.1±0.31	P=270±2.1
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Saha D et al. ²⁰	N=219.23±3.27	N=60.28±3.20	N=114.27±3.188	N=42.45±1.525	N=215.20±1.6
	P= 235.37±4.125	P= 41.75±3.41	P= 135.97±3.659	P= 53.89±1.15	P=273.12±8.1
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Nayan S et al. ²¹	135±8.7	N=61.1±2.8	N=83±4.7	N= 26±5	N=120±20
	348±4.5	P= 34.3±4.3	P=210±17.6	P=107±11	P=368±39
	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001

Saha D et al.²⁰ conducted a case-control study to evaluate the association of lipid profile in pre-eclampsia mother as compared to no pregnant woman and normotensive pregnant mother. They evaluated 180 patients of which 60 were non-pregnant normotensive, 60 were pregnant normotensive and 60 were pre-eclamptic mother. Serum lipid profile of all patients were monitored. They found in preeclampsia there is significant decrease of High density lipoprotein (HDL) and significantly increase of Low density lipoprotein (LDL), Very low density lipoprotein (VLDL) and Triglycerides concentration seen compared to non pregnant normotensive and pregnant normotensive subjects. They concluded that lipid metabolism plays a key role in the pathophysiology of Pre-eclampsia and Eclampsia.

Nayan S et al.²¹ conducted study to compare the serum lipid levels in women with pregnancy induced hypertension and normal pregnancy. Forty women were selected in each group after applying exclusion and inclusion criteria. After a detailed history and clinical examination, routine investigation and lipid profile of all was evaluated and data analyzed. Serum lipid levels in the PIH group were significantly higher compared to normal group. Women with PIH had significantly higher values of total cholesterol (348mg/dl, SD+45), Triglycerides (368mg/dl, SD+39), LDL (201mg/dl, SD+17) and VLDL (107mg/dl, SD+11) as compared to normotensive pregnant

women, total cholesterol (135mg/dl, SD+8.7), Triglycerides (120mg/dl, SD+20), LDL (83mg/dl, SD+4.7) and VLDL (26mg/dl, SD+ 5) with p value of 0.0001. However HDL level is found to be significantly higher (p value<0.05) in normal group (61 mg/dl, SD 2.81) as compared to PIH group (34.3mg/dl, SD 4.3). They concluded, women with PIH have higher total cholesterol, triglycerides, LDL, VLDL and low HDL levels as compared to normotensive pregnant women. Antenatal screening for serum lipids levels can be useful in early detection of PIH.

From our perspective, these conflicting results might be explained, by differences in research design, small sample sizes, incomplete adjustment for confounders, and differences in study populations. Another point of concern is with the sampling time. Future parallel studies are required to explore the underlying mechanisms of this discrepancy. Our hospital is a private hospital, here maximum patients are booked patients who are otherwise on regular antenatal checkup and treatment, so viewing major complications is less.

Recommendations

Early prediction of preeclampsia can be used as a tool for primary prevention before the development of the disease. So, if there is any test to predict the preeclampsia which can be easily measured

& available will be helpful to classify the patient. There is no single specific test available to predict the preeclampsia till date. So there is need of further research to discover the specific test to predict preeclampsia.

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Conflicts of interest

Author has no conflict of interest to declare.

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