Role of non-HDL-cholesterol in evaluation of dyslipidemia in preeclampsia

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ARTICLE INFO

Article history:
Received 09-02-2019
Accepted 31-07-2019
Available online 21-09-2019

Keywords:
Atherogenesis
Dyslipidemia
Lipid profile
Non-HDL-C
Preeclampsia

ABSTRACT

Introduction: Physiological changes in lipid metabolism observed during pregnancy is exaggerated in preeclampsia (PE). The latest recommendations of European and American Cardiological Associations and National Cholesterol Education Program Adult treatment panel III (NCEP ATP III), emphasize the role of non-High-Density Lipoprotein cholesterol (non-HDL-C) in evaluating the risk of atherogenesis, as a marker of dyslipidemia, especially in presence of hypertriglyceridemia. The aim of this study was to measure non-HDL-C to assess dyslipidemia in PE, a state of hypertriglyceridemia.

Materials and Methods: Study was conducted on fifty preeclamptic women and fifty age matched apparently healthy pregnant women attending the Antenatal clinic in Department of Obstetrics and Gynecology, Rajarajeswari Medical College and Hospital. Lipid profile was estimated in Erba auto analyzer EM 360 by enzymatic method and Non-HDL-C was calculated by subtracting HDL-C from Total cholesterol (TC).

Results: Hypertriglyceridemia was observed in both the groups. Serum non-HDL-C level was 161.76 ± 44.74 mg/dl and 143.75 ± 21.80 mg/dl in cases and controls respectively. Non-HDL-C was increased moderately (p<0.05) whereas LDL cholesterol (LDL-C) was mildly increased (p<0.1) in cases compared to controls. Despite of normal LDL-C, High non-HDL-C was observed in five preeclamptic women (12%).

Conclusion: Dyslipidemia is observed in PE which results in atherogenesis and endothelial dysfunction. Non-HDL-C predicts dyslipidemia better than LDL-C in PE. The health of the mother and her fetus are intertwined, hence the non-HDL-C should be recommended to be a part of routine investigation during pregnancy, to institute prompt management strategies to prevent deleterious effects of dyslipidemia associated with PE.

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1. Introduction

Hyperlipidemia seen in normal pregnancy due to hormonal influences: Hyperoestrogenemia, hyperinsulinemia, elevated Human Placental Lactogen (HPL) and decreased LPL activity is not atherogenic. In few pregnancies with genetic predisposition or yet undefined reason, there is defect in the mechanism of adjusting this physiologic hyperlipidemia resulting in clinical consequences. One such consequence is Preeclampsia, a pregnancy specific syndrome that occurs after 20 weeks of gestation, clinically characterized by new onset of hypertension, proteinuria with or without edema, with high morbidity and mortality for both mother and the fetus.2

Preeclampsia has multifactorial etiology; Oxidative stress has been proposed to play a key role in the etiopathogenesis. Dyslipidemia (hypercholesterolemia, hypertriglyceridemia, high LDL-C and a low HDL-C concentration) promote oxidative stress and vascular dysfunction and thus increases the risk of preeclampsia. Hypercholesterolemia promotes the formation of free radicals.3 Low levels of HDL-C may compromise the non-atherogenic function. LDL -C (specially oxidized LDL -C) increases artery sensitivity to presser agents and inhibits endothelial-dependent vasodilatation2 and
accounts for the hypertension, the most important feature of PE. But hypertriglyceridemia may compromise vascular function in several ways. Metabolic changes producing hypertriglyceridemia generally shift the spectrum of LDL subfractions toward a proportional increase of smaller, denser LDL-C which have high susceptibility to oxidative modification. Thus hypertriglyceridemia affects the quality (composition) of LDL-C rather than the quantity of LDL-C. In fact, once triglyceride levels exceed 100 mg/dl, the atherogenic small, dense LDL particles predominate. Triglyceride rich lipoprotein may induce platelet activation, decrease in PGI$_2$ : TXA$_2$ ratio and endothelial dysfunction.

Elevations in apo B-containing particles (VLDL, intermediate-density lipoprotein (IDL), LDL-C (including small, dense LDL) and lipoprotein (a), which have the potential to deliver cholesterol into the arterial wall are considered a “root cause” of atherosclerosis and of primary importance for prevention. Hence there is a need for a lipid parameter that better reflects the amount of cholesterol within all atherogenic particles. The calculated lipid parameter non-HDL may predict risk of dyslipidemia better than LDL-C because it not only measures the atherogenic risk captured by LDL-C measurement but also all the apolipoprotein-B containing lipoproteins. In this regard non-HDL-C has been measured to assess dyslipidemia in preeclampsia and compared with controls.

2. Materials and Methods

Fifty pregnant women, both primigravida and multigravida who have been clinically diagnosed with preeclampsia and fifty apparently healthy pregnant women of more than 20 weeks of gestation, with no bad obstetric history attending the Antenatal clinic in Department of Obstetrics and Gynecology, Rajarajeswari Medical college hospital, Bengaluru, were the cases and controls of our study respectively. Pregnant women with h/o smoking, alcoholism, gestational diabetes, diabetes mellitus, hypertension, cardiovascular disease, chronic liver and kidney diseases, anemia, multiple pregnancies and other chronic diseases that interfere with the study were excluded from the study.

Ethical clearance was obtained from Institutional ethical clearance committee. After obtaining informed consent and under full aseptic precautions, from both the study groups, 5 ml of fasting venous blood sample was collected in vacutainers containing clot activators. Lipid profile was estimated in Erba autoanalyzer EM 360 by enzymatic method using kits supplied by Transasia and Non-HDL-C was calculated by subtracting HDL-C from TC.

Total cholesterol (TC) was estimated by cholesterol oxidase-peroxidase method (CHOD-POD). Reference range: Desirable Total Cholesterol < 200 mg/dl, Borderline TC : 200 – 239 mg/dl. High TC ≥ 240 mg/dl. HDL-C was estimated by modified polyvinyl sulfonic acid (PVS) and polyethylene- glycol methyl ether (PEGME) coupled classic precipitation method. Reference range: Females: 35-75 mg/dl. LDL -C was estimated by direct enzymatic colorimetric method. Desirable range: <100mg/dl. Triglycerides (TG) is also estimated enzymatically by GPO method: TG are also estimated enzymatically. According to NCEP ATP III classification TG<150m/dl-Desirable level, 150-199 mg/dl–borderline high, 200-499mg/dl-high, >500mg/dl-very high. VLDL was calculated by the formula TG/5. Non-HDL-C was estimated by calculation. Non-HDL-C = Total Cholesterol – HDL cholesterol.

2.1. Statistics

Descriptive statistical analysis was carried out using Social Science statistics one - way Anova calculator. $P$ value $<0.1$ indicates Mild significance, $P \leq 0.05$-Moderate Significance, $P$ value $\leq 0.01$strongly significant. The Pearson correlation coefficient is used to measure the strength of a linear association between lipid profile parameters and Non- HDL-C, where the value $r = 1$ means a perfect positive correlation and the value $r = -1$ means perfect negative correlation. Nearer the value is to zero, the weaker the relationship.

3. Results

It was a cross sectional study with fifty clinically diagnosed preeclamptic women (cases) and fifty apparently healthy pregnant women (controls). Majority of the cases (78%) and controls (64%) were primigravida (Table 1). Mean age of the cases and controls was 25±4 years and 23±3 years respectively (Figure 2). Mean gestational age of both cases and controls was 34 weeks (Figure 3). There was significant difference in the systolic (P $<0.001$) and diastolic (P $<0.001$) blood pressure among cases and controls (Table 2).

| Gravida          | Cases | % | Controls | % |
|------------------|-------|---|----------|---|
| Primigravida     | 39    | 78| 32       | 64|
| Multigravida     | 11    | 22| 18       | 36|
| Total            | 50    | 100| 50       | 100|

In our study lipid profile values in cases and controls was as follows (Table 3). Mean non-HDL-C level was above the desirable range (<130mg/dl) in both cases 161.76±44.74 mg/dl and controls 143.75±21.80 mg/dl with moderate significant difference (P<0.05).

Mean total cholesterol level was higher than the desirable level in cases, whereas mean TG, VLDL, LDL and non-HDL-C levels were high in both cases and controls. Though mean HDL-C was in reference range in both cases and controls, but it was towards the lower limit of the reference range.
Table 2: Comparison of Blood pressure of study groups

| Blood pressure | Cases (n=50) | Controls (n=50) | P value |
|---------------|-------------|----------------|---------|
|               | %           | %              |         |
| Systolic BP (mm Hg) |          |                |         |
| <120          | 0           | 41             | 0.001** |
| 120-139       | 3           | 9              | 0.0     |
| 140-159       | 27          | 0              | 0.0     |
| 160-179       | 15          | 0              | 0.0     |
| ≥180          | 5           | 0              | 0.0     |
| Diastolic BP (mmHg) |          |                |         |
| <80           | 0           | 22             | 0.0     |
| 80-100        | 15          | 27             | 0.0     |
| 100-110       | 23          | 0              | 0.0     |
| >110          | 12          | 1              | 2.0     |
Table 3: Comparison of Lipid profile and Non-HDL-C among study groups

| Lipid parameters with desirable levels | Cases          | Control       | P value |
|---------------------------------------|----------------|---------------|---------|
| Total cholesterol (<200mg/dl)         | 211.7±53.14    | 194.66±26.92  | 0.046*  |
| HDL-C (40-60 mg/dl)                   | 49.94±11.82    | 50.91±8.87    | 0.641   |
| LDL-C (<100mg/dl)                     | 116.5±35.23    | 105.5±20.66   | 0.06    |
| VLDL (<30 mg/dl)                      | 49.95±15.17    | 41.84±11.13   | 0.0039**|
| TGL (<150mg/dl)                       | 249.7±73.51    | 206.6±49.93   | 0.00100**|
| Non-HDL-C (<130mg/dl)                 | 161.76±44.74   | 143.75±21.80  | 0.012*  |

4. Discussion

Increasing clinical and biochemical evidences suggest that disturbance in the normal endothelial cell function induced by dyslipidemia and oxidative stress may be a primary cause in the etiopathogenesis of preeclampsia. In clinical practice LDL-C is popularly used as a marker of atherogenesis but it has disadvantages which can be overcome using non-HDL-C which measures the cholesterol content of all atherogenic apo B containing lipoproteins, including LDL-C. It can be calculated easily from a standard lipid profile (non-HDL-C= TC – HDL-C) and thus economical. It can be measured from a sample in a non-fasting patient, especially important in pregnancy who cannot be kept fasting. Hypertriglyceridemia seen in pregnancy decreases the accuracy of risk prediction for atherogenesis when LDL-C is used for this purpose (TG>400mg/dl is the limitation of Friedewald formula), whereas non-HDL-C retain predictive capability in this patient population. When non-HDL-C and LDL-C are discordant, risk is more closely aligned with non-HDL-C. Measuring apo B concentration is expensive and is not yet standardized. Non-HDL-C testing is universally available, requires no additional cost, and may be measured in the non-fasting state. Non-HDL-C is listed first in the panel of target therapy for dyslipidemia and is considered as better primary target for therapy than LDL-C. Thus, by paying attention to non-HDL-C may obviate the need for expensive tests that measure LDL particle number, total apo B concentration or LDL phenotype (type A or B). Non-HDL-C is extensively studied and used in the field of atherogenic cardiovascular diseases. In south Indian PE population this study is first of its kind. Hence, Non-HDL-C has been measured to assess dyslipidemia in PE.

In this study cases and controls were age and gestationally age matched. Majority of the study subjects were primigravida.

Hypertriglyceridemia was observed in both the pregnant groups. Following table (Table 4) shows the importance of measuring non-HDL-C in presence of hypertriglyceridemia. Five preeclamptic women with desirable LDL-C had high non-HDL-C levels.
Table 4: High levels of non-HDL-C in preeclamptic women with desirable LDL-C levels

| No. of PE patients | TGL (Desirable value < 150mg/dl) | LDL-C (Desirable value < 100mg/dl) | Non-HDL-C (Desirable value < 130mg/dl) |
|-------------------|----------------------------------|------------------------------------|--------------------------------------|
| 1                 | 503                              | 79.4                               | 180                                  |
| 2                 | 226                              | 93.6                               | 138.8                                |
| 3                 | 240                              | 94                                 | 164                                  |
| 4                 | 251                              | 90.1                               | 140.3                                |
| 5                 | 151                              | 80.1                               | 141                                  |

Table 5: Correlation of Non-HDL-C with other lipid profile parameters in both the study group

| Lipid parameters | Non-HDL-C | Cases ‘r’ value | Controls ‘r’ value |
|------------------|-----------|-----------------|-------------------|
| TC               |           | 0.9854          | 0.0059            |
| HDL-C            |           | 0.6447          | 0.0141            |
| LDL-C            |           | 0.8613          | -0.0637           |
| VLDL             |           | 0.3751          | 0.1152            |
| TG               |           | 0.4992          | 0.1262            |

Positive correlation was observed between non-HDL-C and TC and between non-HDL-C and LDL-C.

Like fine pregnant women. Though there was no significant difference in HDL-C level among the study groups, the levels were towards the lower limit of the reference range. Thus, dyslipidemia was observed in this study. This study findings correlate with previous studies who observed high levels of LDL-C levels in preeclampsia women than those who remained normotensive throughout pregnancy.11 Like this study findings, in previous studies10,18–23 significantly high levels of TG, VLDL and non-HDL-C were observed in preeclamptic women than among controls.

In our study if LDL-C alone is considered to assess dyslipidemia, five pregnant women which accounts for 12% of the cases, would have missed the diagnosis of dyslipidemia. In contrast we observed high levels of non-HDL-C in these five preeclamptic women with optimum LDL-C (Table 5). In addition, Non-HDL-C was significantly high in preeclamptic women compared to apparently healthy pregnant women. Though LDL-C and HDL-C levels are deranged since it is distinct LDL-C or HDL-C subpopulations which exert differential effects on atherosclerosis, non-HDL-C can be considered as a better marker of dyslipidemia than LDL-C, especially in context of hypertriglyceridemia.

Literature search24,25 shows that lipid levels increase parallel to the severity of the disease, being normal in normotensive group compared with the gestational hypertensive, chronic hypertensive, preeclamptic, superimposed preeclamptic and worst in the eclamptic group. This is also parallel with the prognosis of the disease. It also stated that early pregnancy dyslipidemia is associated with increased risk of preeclampsia. Recently, non-HDL-C was shown to be a better predictor of cardiovascular diseases than LDL-C, even in patients with triglyceride levels below 200 mg/dl.26 Like type 2 diabetes a state of hypertriglyceridemia, in PE also, failure to consider the importance of non-HDL-C may result in under diagnosis of dyslipidemia.27 Thus, lipids have an important role in the etiopathogenesis of preeclampsia and must not be underestimated during the hypertensive diseases of pregnancy.28 This study supports the role of atherogenic lipid profile in PE and simple measurement of non-HDL-C may be of good predictive value of dyslipidemia in preeclampsia.

5. Conclusion

There is dyslipidemia leading to atherogenesis and endothelial dysfunction in PE. Non-HDL-C predicts dyslipidemia better than LDL-C. The health of the mother and her fetus are intertwined, hence the lipid panel especially non-HDL-C should be recommended to be a part of routine investigation during pregnancy, to institute prompt management strategies to prevent deleterious effect of dyslipidemia associated with PE.

6. Limitation of the study

It is a cross sectional study with small sample size.

7. Recommendations

Study of non-HDL-C in patients has to be performed in large population of early pregnancy itself and if elevated non-HDL-C subjects are found to develop PE, then estimation of non-HDL-C can be recommended as a simple screening test to recognize dyslipidemia.

8. Acknowledgements

Our sincere thanks to the all the pregnant women involved in the study, Department of Biochemistry, Department of
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Cite this article: Reena R, Usha SMR, Rupakala BM, Shetty HV. Role of non-HDL-cholesterol in evaluation of dyslipidemia in preeclampsia. *Int J Clin Biochem Res* 2019;6(3):369–374.