Maternal Plasma Lipid Concentration in Third Trimester of Women with Preeclampsia and Normotensive Pregnancy

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**ABSTRACT**

**Background:** Preeclampsia is one of complications of pregnancy. It is responsible for morbidity for mother and fetus. Preeclampsia is a pregnancy multisystem disorder. Abnormal lipid profile has an effect on endothelial dysfunction. The association of serum lipid profile with preeclampsia is suggested to reflect new diagnostic tools. Pregnancy dyslipidemia is associated with an increased risk of preeclampsia. Compared to healthy pregnancy, women with preeclampsia have an abnormal lipid profile.

**Aim of the work:** The aim of this work is comparison between normotensive women and preeclamptic women by serum lipid profile at third trimester.

**Patients and Methods:** The present study conducted on 70 pregnant women in the Department of Obstetrics and Gynecology, at Al-Azhar University hospital [Damietta], which was conducted during 2019 [from April to December]. A study comprised 35 normotensive pregnant women as controls and 35 preeclampsia cases. The blood samples were analyzed for serum triglycerides (TGs), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density Lipoprotein-Cholesterol (LDL-C), very low-density Lipoprotein-Cholesterol (VLDL-C), Apo lipoprotein- A1 [Apo-A1] and Apo lipoprotein- B [Apo-B].

**Results:** There was significant difference between group A and B as regard Apo B/ Apo A1, cholesterol, TGS, LDL and VLDL. They are higher in group B.

**Conclusion:** In the third trimester of pregnancy, preeclamptic women have altered levels of serum lipid profile. The most significant test is Apo B/A1 ratio with accuracy [72.7%].

**Keywords:** Preeclampsia; Lipids; Apolipoprotein; Cholesterol; Triglycerides.

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INTRODUCTION

Preeclampsia is a pregnancy specific multi-system disease. It is featured by new onset of hypertension [blood pressure ≥140/90 mmHg in previously normotensive women after the 20th week of pregnancy] and proteinuria [≥300 mg/24hr urine collection]. The etiology and development of preeclampsia is abnormal placentation related to immune mechanisms and maladaptation of the placenta. It is clear that one mechanism causing the syndrome preeclampsia does not exist. Instead, many mechanisms can act together and even multiply each other. Abnormal lipid profile is one of the causes of atherosclerosis and leads to endothelial abnormality. Hypertension is a mainly significant characteristic in preeclampsia which cause the vasospasm in the kidney, uterus, placenta, and brain. Dyslipidemia leads to reduction of PGI: TxA2 relation which leads to development of preeclampsia. Therefore, dyslipidemia seems significant in the development of preeclampsia. Moreover, the relationship of dyslipidemia with preeclampsia is strongly suggested to reveal recent diagnostic methods. First trimester dyslipidemia is highly related with development of preeclampsia.

Compared to normotensive pregnancy, preeclamptic women have dyslipidemia with high levels of TGs. The possible relation between maternal levels of Apo Band Apo A1 and preeclampsia has also been analyzed. Apo lipoproteins are lipoproteins implicated in the provocation of inflammatory process and elimination of overload cholesterol. However, the relation of these metabolites in preeclampsia etiology remains indistinguishable.

AIM OF THE WORK

In this work we do a comparison between normotensive women and preeclamptic women by serum lipid profile at third trimester. This may help in improvement of fetal and maternal health.

PATIENTS AND METHODS

Our research included 70 pregnant women from obstetrics and gynecology department [Al-Azhar University hospital, Damietta]. It is a cross-sectional comparative study. Our work was done during 2019 [from April to December]. The study comprised 35 normotensive pregnant women as controls and 35 preeclampsia patients as the study group, from those attending antenatal outpatient department or getting admitted in their last trimester of pregnancy. Informed permissions were taken from whole individuals shared in our research.

Sample size calculation:

The calculated sample size of the study was determined to be 30 participants for each group at 5% level of significance and 80% power, using the following formula. Where, Z1-α / 2 = 1.96, Z1-β = 0.842, σ = SD [0.54, 0.29], δ = Expected difference detected among the studied groups regarding LDL/HDL ratio [0.2], α = Level of acceptability of a false positive result [level of significance = 0.05], β = Level of acceptability of a false negative result [0.20], 1-β = power [0.80]. The sample size should be enlarged to 35 pregnant ladies for each group to balance for protocol difficulties with unfinished data and to improve the strength of the research.

The groups of the study were:

Group [A] [controls]: Thirty-five individuals who have the following inclusion criteria: Gravid women, normotensive pregnant woman in the last trimester [gestational age of >32 weeks], single live singleton pregnancy and without any other systemic or endocrine disorder, and prepregnancy body mass index [BMI] ≤ 25 were included in the study.

Group [B] cases: Thirty-five individuals who have the following inclusion criteria: gravid women, preeclamptic pregnant patient in the third trimester [gestational age of >32 weeks], single, live singleton pregnancy and pregnant women without any other disease, and prepregnancy body mass index [BMI] ≤ 25 were integrated in the work.

Exclusion criteria were: diabetics mellitus, obesity, severe anemia [hemoglobin <6g/dl], or individuals who have any disease and multiple pregnancy.

Laboratory investigations: we measured the serum levels of the following: [Apo-A1, Apo-B, Apo B/Apo A1 ratio, CHOL, TGS, HDL, LDL and VLDL]

Ethical consideration:

Study protocol was submitted for approval by Institution Research Board [IRB] of the Damietta faculty of Medicine, Al-Azhar University [Egypt]. Informed consent was obtained and confidentiality and personal privacy was respected in all steps of
the work.

Collection of samples: Seven milliliters of fresh blood were withdrawn from each subject under complete aseptic precautions. 2ml placed in a tube containing ethylene diamine tetra acetic acid [EDTA] for complete blood count [CBC]. The rest of blood was placed in sterile vacationers and was left to clot for 30 minutes. Serum was then separated by centrifugation at 3000 rpm for 15 minutes and divided into two aliquots; one aliquot for immediate assay of routine lab.

The determination of cholesterol level was carried out as described by Ellefon and Caraway[8]. Determination of Triglycerides level done as described by Roeschlan[9]. Determination of HDL, LDL and VLDL levels done as originally described by Friedwald et al.[10]. Determination of Apo B level was performed as made by Contois et al.[11]. Determinations of Apo A1 level was completed as described by Colantonio et al.[12].

Statistical analysis information was analyzed by the Statistical Package of Social Science [SPSS] program for Windows [Standard version 21]. The normality of information was first analyzed with one-sample Kolmogorov-Smirnov test. Qualitative data were presented by using number and percent. Relation among categorical variables was experienced using chi-square test. Permanent variables were described as mean±SD [standard deviation] for parametric data. Group A and group B were tested with student t-test. Pearson correlation was made to correlate continuous parametric statistics. Sensitivity and specificity at multiple cut off levels were analyzed by ROC curve. [13]

RESULTS

Table [1] shows no significant difference as regard age among two groups [A and B]. The mean age for group A and B was [27.83±5.01] and [29.63±6.81] respectively. There was significant difference as regard GA between group A and B with mean [36.08±2.27] and [34.48±2.06] so there is increase of prematurity among preeclamptics [PET]. Table [2] showed significant difference between groups A and B as regard parity and gravidity. PET is significant increase of primigravida [28.6%] and nullipara [31.4%] in group B when compared to compared to group A [primigravida [8.6%] and nullipara [11.4%]]. On the other side, there was insignificant difference between both groups regarding mode of labor as well as abortion.

Table [3] showed significant difference between groups regarding levels of Apo A1 [the mean values were 94.68±20.34 and 77.09±12.87 in groups A and B respectively]. However, there was significant decrease of Apo B/A1 ratio in group A when compared to group B [0.786±0.22 vs 1.01±0.18 respectively.

Table [4] shows significant difference among two groups in all lipid profile parameters. The level of cholesterol, TGS, LDL and VLDL were higher in group B. However, the level of HDL was low in group B versus group A.

Table [5] shows that AUC for Apo A1 was equal to [0.776] with CI range from [0.667 to 0.897] at cutoff point (<89.75) and sensitivity [90.9%] and Specificity [54.3%]. PPV for Apo A1 was [65.2] and NPV was [86.4] with total accuracy [72.1%]. In this table, we observed that, AUC for Apo B equal to [0.660] with CI range from [0.530 to 0.791] at cutoff point [>70.5] and sensitivity [67.7%] and Specificity [51.4%]. The PPV for Apo B was [57.5] and NPV was [64.3] with total accuracy [60.3%]. In addition, AUC for Apo B/Apo A1 ratio was [0.793] with CI range from [0.685 to 0.901] at cutoff point [>76.8] and sensitivity [93.5%] and specificity [54.3%], PPV was [64.4] and NPV was [90.5] with total accuracy of [72.7%]. The best predictor for PET is Apo B/Apo A1 ratio with accuracy [72.7%].

Table [1]: Demographic data among the both groups

<table>
<thead>
<tr>
<th>Age/ years [Mean ± SD]</th>
<th>Group [A] [n=35]</th>
<th>Group [B] [n=35]</th>
<th>Test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min-Max</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20 y</td>
<td>27.83±5.01</td>
<td>29.63±6.81</td>
<td>t=1.26</td>
<td>0.212</td>
</tr>
<tr>
<td>20-35 y</td>
<td>19-39</td>
<td>16-40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;35 y</td>
<td>2 [5.7%]</td>
<td>4 [11.4%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32 [91.4%]</td>
<td>25 [71.4%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 [2.9%]</td>
<td>6 [17.1%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GA [Mean ± SD]</td>
<td>36.08±2.27</td>
<td>34.48±2.06</td>
<td>t=3.09</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

*: student t-test, χ²: Chi square test; Group [A]: Normotensive group; Group [B]: Preeclampsia group
Table [2]: Obstetric data among the studied groups

<table>
<thead>
<tr>
<th>Obstetric data</th>
<th>Group [A] [n=35]</th>
<th>Group [B] [n=35]</th>
<th>χ²</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gravidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primigravida</td>
<td>3 [8.6%]</td>
<td>10 [28.6%]</td>
<td>4.63</td>
<td>0.031*</td>
</tr>
<tr>
<td>Multigravida</td>
<td>32 [91.4%]</td>
<td>25 [71.4%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nullipara</td>
<td>4 [11.4%]</td>
<td>11 [31.4%]</td>
<td>4.16</td>
<td>0.041*</td>
</tr>
<tr>
<td>Multipara</td>
<td>31 [88.6%]</td>
<td>24 [68.6%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4 [11.4%]</td>
<td>11 [31.4%]</td>
<td>5.47</td>
<td>0.065</td>
</tr>
<tr>
<td>CS</td>
<td>27 [77.2%]</td>
<td>18 [51.4%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VD</td>
<td>4 [11.4%]</td>
<td>6 [17.1%]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abortion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 [20%]</td>
<td>7 [20%]</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>No</td>
<td>28 [80%]</td>
<td>28 [80%]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table [3]: Apo A1, Apo B and Apo B/ A ratio among both studied groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group [A] [n=35]</th>
<th>Group [B] [n=35]</th>
<th>t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo A1</td>
<td>94.68±20.34</td>
<td>77.09±12.87</td>
<td>4.23</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Apo B</td>
<td>71.77±18.01</td>
<td>79.14±14.18</td>
<td>1.86</td>
<td>0.066</td>
</tr>
<tr>
<td>Apo B/ A ratio</td>
<td>0.786±0.22</td>
<td>1.01±0.18</td>
<td>4.28</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

Table [4]: Lipid profile among the studied groups

<table>
<thead>
<tr>
<th>Lipid profile</th>
<th>Group [A] [n=35]</th>
<th>Group [B] [n=35]</th>
<th>Test of significance</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>135.82±6.45</td>
<td>153.73±13.37</td>
<td>7.138</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>TGS</td>
<td>122.59±20.23</td>
<td>141.42±45.71</td>
<td>2.229</td>
<td>0.029*</td>
</tr>
<tr>
<td>HDL</td>
<td>43.14±3.19</td>
<td>23.23±4.46</td>
<td>21.491</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>LDL</td>
<td>68.35±15.41</td>
<td>102.22±14.21</td>
<td>9.558</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>VLDL</td>
<td>24.52±5.13</td>
<td>28.28±7.36</td>
<td>-2.485</td>
<td>0.015*</td>
</tr>
</tbody>
</table>

Table [5]: Diagnostic accuracy of Apo A1, Apo B and Apo B/ A ratio in prediction of preeclampsia

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>95% CI</th>
<th>Cutoff</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apo A1</td>
<td>0.776</td>
<td>0.667</td>
<td>0.885</td>
<td>&lt;89.75</td>
<td>90.9%</td>
<td>54.3%</td>
<td>65.2</td>
<td>86.4</td>
</tr>
<tr>
<td>Apo B</td>
<td>0.660</td>
<td>0.530</td>
<td>0.791</td>
<td>&gt;70.5</td>
<td>67.7%</td>
<td>51.4%</td>
<td>57.5</td>
<td>64.3</td>
</tr>
<tr>
<td>Apo B/ A ratio</td>
<td>0.793</td>
<td>0.685</td>
<td>0.901</td>
<td>&gt;76.8</td>
<td>93.5%</td>
<td>54.3%</td>
<td>64.4</td>
<td>90.5</td>
</tr>
</tbody>
</table>

Figure [1]: Receiver operating characteristics curve [ROC] for Apo B and Apo B/ A ratio in prediction of preeclampsia

DISCUSSION

Our work was carried out to compare between normotensive women and preeclamptic women by serum lipid profile at third trimester. This may help in improvement of fetal and maternal health.

From our results, we could say that pregnant women with abnormal lipid profile [dyslipidemia] are more prone for preeclampsia. Lipids significantly differ between groups. Comparable results were
discovered by Nagtilak. High lipid profile levels lead to injury of the endothelium. In the endothelium, oxidative stress is motivated by linoleic acid. Maternal lipoprotein levels rise considerably and are twice higher in PET. In addition, physiological changes that occur during pregnancy consist of insulin resistance, hyperlipidemia, and up regulation of inflammatory markers. Both mechanisms could share in elevated blood pressure. [13]

In a research by Gratacos et al. [14], cholesterol levels were not significantly elevated in preeclamptic patients, but triglyceride levels were significantly elevated from two months. This difference could be attributed to different inclusion criteria and variable sample size, and timing of determination of lipid profile.

Adiga et al. [15] observed that serum TGs was statistically significant in preeclamptic women in comparison with normal pregnancy. The main modulator of this high TGs is high estrogen level in pregnancy. Elevatated TGs levels may be associated with hypercoagulability.

In many works, significantly elevated levels of TGs in PET were detected in comparison with healthy pregnant women were concluded which is in high harmony with larger studies. [13, 15-18]

Enquobahrie et al. [5] measured serum lipid level in 57 patients with preeclampsia and 510 pregnant women in the control group and they discovered significantly raised levels of TGs in preeclampsia. [5] In another research, preeclamptic women had important high levels of TGs than in healthy group. Mikhail et al. concluded that elevated TGs in serum causes its major deposition in the endothelium. This may lead to unhealthy endothelium in pregnant women. [19]

In another study done in Spain, at the second trimester, triglyceride levels were significantly elevated in severe PET than in controls. This is also in harmony with the present study. [13]

Increased TGs in PET are liable to be deposited in uterine spiral arteries and cause injury of the endothelium, by direct mechanism and indirect mechanism throughout production of small, dense LDL. [14]

In a study of Wakatsuki et al. [20], HDL-C levels had no significant difference among women with PET and healthy pregnant women. This could be attributed to different sample size and time of sampling for lipid profile measurement.

LDL-C was higher among cases when compared to controls [102.22 ± 14.21 vs 68.35 ± 15.41 respectively], the results were previously reported by Mishra et al. [21] Kandimalla et al. [22] concluded that LDL-C measurements were established to be significantly elevated in the women with PET.

In the current study, VLDL measurements were significantly [P < 0.088] high in the preeclamptic group which may be as a result of high TGs levels causing high entrance of VLDL that carries the endogenous TGs into the circulation. Similar results were seen in the research done via Vani et al. [23]

In contradiction to results of the present work, Ghodke et al. [24] are not capable to expect the incidence of PET, diabetes, and PRL by measuring VLDL-C levels of the mid trimester as the level are within normal concentration.

The Apo E isoforms and gene variants have been postulated and used as probable predictors of PET development. However, the detailed effect of these metabolites in preeclampsia etiology residue uncertain [25]. Furthermore, preeclampsia has a positive correlation with Apo B/ApoA1 ratio, and negative correlation with ApoA1. [26]

Current work revealed elevated Apo B/A1 ratio and Apo B levels among women with PET in comparison with normotensive women but Apo A1 levels were lower in preeclamptic group. Charlton et al. [27] work explored the possibility of Apo A1, a main lipoprotein component of HDL, to improve or reverse the hypertension and placental changes discovered in an animal model of inflammatory cytokine-induced hypertension in pregnancy. They further examined whether Apo A1 has a protective effect in an in vitro model of human being trophoblast invasion and whether this is owing to alterations in adhesion molecules and markers of invasion. The protective effect conferred by Apo A1 on the cytokine-induced hypertension in pregnancy is suggested to be owing to tissue uptake rather than its level in the blood. [27]

Apo A1 mimetic peptides show anti-inflammatory and antioxidant criteria and function by stimulating cholesterol efflux and reverse cholesterol transport via ABCA1. [28, 29] Inflammation and oxidative stress are key potential mechanisms that could make good
changes in the stiffness of arteries. Therefore, anti-inflammatory drugs are recommended to recover arterial stiffness as a potential therapy, while favorable outcome have been revealed in several studies.

Conclusion:

In the third trimester of pregnancy, preeclamptic women have altered levels of serum lipid profile when compared to females with normal blood pressure. The highest significant test is Apo B/A1 ratio with accuracy 72.7%.

Financial and Non-Financial Relationships and Activities of Interest

None

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