DYSLIPIDEMIA IN EARLY SECOND TRIMESTER IS MAINLY A FEATURE OF WOMEN WITH EARLY ONSET PRE-ECLAMPSIA

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ABSTRACT

To investigate whether hypertriglyceridemic dyslipidemia is a risk factor for risk factor for either early or late onset pre-eclampsia. **Design:** Prospective cohort study. It was carried out in AL.ZAHRAA maternity and pediatric teaching hospital in AL-Najaf during period between 15th of March to 10th of October 2011. **Participants:** 200 pregnant women. Blood samples were obtained from non-fasting subjecting at 18 weeks of gestation. All samples were analyzed for triglycerides, total cholesterol, low density lipoprotein and high density lipoprotein. Thirty six women developed early onset pre-eclampsia and thirteen women developed late onset pre-eclampsia. In the cohort model, women with triglycerides above 2.4 mmol/l had increased risk of early onset pre-eclampsia compared with those with triglycerides level ≤ 1.5 mmol/l.

**Keywords:** Hypertriglyceridemic, dyslipidemia, risk factor, pre-eclampsia

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INTRODUCTION

Pre-eclampsia is a hypertensive complication of pregnancy associated with well documented risks for the mother & the fetus. Among all cases of the preeclampsia. And the global incidence of preeclampsia has been estimated at 5-14% of all pregnancies. In developed nations, the incidence of the disease is reported to be 4-18% and with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths in these countries. Pre-eclampsia is multisystem disorder characterized by hypertension and proteinuria and is thought to arise from the placenta and the medical consensus is lacking regarding the values that define preeclampsia, but...
reasonable criteria in a woman who was normotensive before 20 weeks gestation include a systolic blood pressure greater than 140 mmhg and a diastolic blood pressure greater than 90 mmhg on successive measurements, 4-6 hours apart. Pre-eclampsia in a patient with preexisting essential hypertension is diagnosed if systolic blood pressure has increased by 30 mmhg or if diastolic blood pressure has increased by 15 mmhg. Pre-eclampsia is mild in 75% of cases and severe in 25%. In its extreme, the disease may lead to liver and renal failure, disseminated intravascular coagulopathy, and central nervous system abnormalities. If pre-eclampsia-associated seizures develop, the condition is called eclampsia. Mild pre-eclampsia is defined as the presence of hypertension (BP > 140/90 mmHg) on 2 occasions, at least 6 hours apart, but without evidence of end-organ damage. In the patient, severe pre-eclampsia is defined as the presence of 1 of the following symptoms or higher or diastolic BP of 110 mmhg or higher on 2 occasions at least 6 hours apart:

* Proteinuria of more than 5g in a 24-hour collection or more than 3+ on 2. Random urine samples collected at least 4 hours apart.
* Pulmonary edema or cyanosis
* Oliguria (<400ml in 24h)
* Persistent headaches
* Epigastric pain and/or impaired liver function
* Thrombocytopenia
* Oligohydramnios, decreased fetal growth, or placental abruption.

Although hypertension and proteinuria are the simple clinical criteria for diagnosis of pre-eclampsia, the pathophysiological mechanism that lead to the disorder are by all evidence very diverse. Pre-eclampsia develops in a particular woman following an unfortunate combination of maternal (trophoblast-independent) risk factors and an excessive maternal response to the trophoblast/trophoblast-derived factors. The maternal risk factors include disorders associated with endothelial dysfunction such as chronic hypertension, diabetes, kidney disease and dyslipidemia, as well as more specific defects such as protein C or protein S deficiencies, activated protein C resistance, anticardiolipin antibodies and
hyperhomocysteinemia\textsuperscript{1,5}. Early onset pre-eclampsia exhibits features that are unusual in late onset disease\textsuperscript{6}. For example, the recurrence risk of pre-eclampsia is relatively high in women with early onset disease, the proportion of women with chronic hypertension is higher, fetal growth restriction is much more common and multiorgan involvement, as reflected in HELLP syndrome, is more frequent\textsuperscript{6-8}. Thus early and late onset preeclampsia seems, at least partly, to be pathophysiologically different. A further clarification of these difference is of clinical interest because early onset disease is associated with a higher prevalence of iatrogenic prematurely, intrauterine growth restriction and sever maternal disease\textsuperscript{6,9}. In normal pregnancy the circulating concentrations of triglycerides and cholesterol increases progressively\textsuperscript{10-13}. Human pregnancy is associated with pronounced physiological hyperlipidemia. In normal pregnancy this feature is not atherogenic and is believed to be due to hormonal alteration\textsuperscript{14,15}. Pregnancy induced hypertension is a multisystem disorder of unknown etiology induced by pregnancy after the twentieth week and is a leading cause of maternal morbidity and mortality. Endothelial dysfunction may play a pivotal role in the genesis of the multisystem disorder developed in preeclampsia. The mechanism involved in the induction of endothelial cell dysfunction are poorly understood disorders of the lipoprotein metabolism are a major cause of endothelial dysfunction that may result in hypertension and proteinuria, clinical hallmarks of preeclampsia. In women with preeclampsia the serum lipid show a shift towards a dyslipidemic profile: the serum triglycerides are further elevated, there is a higher proportion of low density lipoproteins of small sizes, high density lipoprotein decreased and serum free fatty acids are increased\textsuperscript{10,16-18}. The pre-eclamptic dyslipidemia is not a consequence of the disease because it is present long before the disorder becomes clinically overt and tends to be present after pregnancy\textsuperscript{17,19-21}. Because the pathogenesis of early and late onset preeclampsia seems to differ slightly we want to investigate if hypertriglyceridemic dyslipidemic patterns are risk factors for both these two variants of the disorder. The aim of the study to investigate whether Hypertriglyceridemia dyslipidemia is a risk factor for either early or late onset preeclampsia.

**MATERIALS AND METHODS**

The setting of present study was done in ALZahraa teaching hospital in Najaf city, which until the end of September 2011 covered defined geographical areas of AL Najaf city, representing all socioeconomic classes. Approximately 80\% of pregnant women in the
these area gave birth at this hospital. Blood samples from 200 women were obtained and all of them delivered at AL Zahraa teaching hospital after excluding women with twin pregnancies. Diagnosis of preeclampsia required the presence of proteinuria and pregnancy-induced hypertension. Proteinuria was defined as ≥ + 1 on dipsticks (300mg/24h) found twice at least six hours apart. Pregnancy-induced hypertension was defined either as blood pressure ≥ 140/90 mmHg or as an increase in diastolic pressure of ≥ 15mmHg, compared with the average before 20 weeks of gestation. In both cases two measurements at least six hours apart were required. The pre-eclamptic women were divided into groups of early and late onset preeclampsia (i.e. delivered before and after 37 weeks of gestation, respectively). Blood samples were drawn in non-fasting state and allowed to coagulate before centrifugation. The serum sample left for 5 minutes at 37°C. In the cohort (n=200) we measured serum concentration of triglycerides, total cholesterol and high density lipoprotein cholesterol and low density lipoprotein. The control matched for age and parity. The rationale for choosing the parameters above was based on previous observations: fasting triglycerides but not cholesterol at 18 weeks of gestation. In both cases two measurements at least six hours apart were required. The pre-eclamptic women were divided into groups of early and late onset preeclampsia (i.e. delivered before and after 37 weeks of gestation, respectively). Blood samples were drawn in non-fasting state and allowed to coagulate before centrifugation. The serum samples left for 5 minutes at 37°C. In the cohort (n=200) we measured serum concentration of triglycerides, total cholesterol and high density lipoprotein cholesterol and low density lipoprotein. The control matched for age and parity. The rationale for choosing the parameters above was based on previous observations: fasting triglycerides but not cholesterol at 18 weeks of gestation are increased in women with subsequent pre-eclampsia indicating enhanced production and/or impaired degradation of triglyceride-rich lipoprotein.

### RESULTS

Table 1: Comparison in certain parameters between patients with early onset pre-eclampsia and control.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Early PE(&lt;37wk)</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The baseline characteristics of the cohort are seen in table 1 in which seen significant changes in serum concentration of triglyceride in patient with early preeclampsia in comparism with serum concentration of triglyceride in control patient.

Table 2: Comparison in certain parameters between patients with late onset preeclampsia and control

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Late PET(≥37wk)</th>
<th>control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>23 ± 3.8</td>
<td>24 ± 5.3</td>
<td>0.524</td>
</tr>
<tr>
<td>Systolic BP(mmHg)</td>
<td>146 ± 7.9</td>
<td>122 ± 4.6</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic BP(mmHg)</td>
<td>95 ± 4.9</td>
<td>80 ± 5.2</td>
<td>0.000</td>
</tr>
<tr>
<td>LDL(mg/dl)</td>
<td>114.26 ±14.87</td>
<td>112.55±15.79</td>
<td>0.795</td>
</tr>
<tr>
<td>HDL(mg/dl)</td>
<td>49.78±8.96</td>
<td>53.42±9.58</td>
<td>0.384</td>
</tr>
<tr>
<td>CH(mg/dl)</td>
<td>254.83±27.63</td>
<td>223±43.72</td>
<td>0.125</td>
</tr>
<tr>
<td>TG(mg/dl)</td>
<td>190.83±44.91</td>
<td>137.73±38.71</td>
<td>0.061</td>
</tr>
</tbody>
</table>
The baseline characteristics of the cohort are seen in table(2) in which seen no significant changes in serum concentration of triglyceride in both groups.

Table3: The relation between parity and preeclampsia

<table>
<thead>
<tr>
<th>group</th>
<th>control</th>
<th>Early PET</th>
<th>Late PET</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>primigravida</td>
<td>36</td>
<td>10</td>
<td>3</td>
<td>49</td>
</tr>
<tr>
<td>multiparus</td>
<td>115</td>
<td>26</td>
<td>10</td>
<td>151</td>
</tr>
<tr>
<td>total</td>
<td>151</td>
<td>36</td>
<td>13</td>
<td>200</td>
</tr>
</tbody>
</table>

X2 = 6.870 p=0.032

Table4: The relation between the age of patient and the developing early preeclampsia

<table>
<thead>
<tr>
<th>Total</th>
<th>control</th>
<th>Early PET</th>
<th>Late PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&lt;18years</td>
<td>54</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Group 18-35years</td>
<td>69</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>&gt;35years</td>
<td>28</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>total</td>
<td>151</td>
<td>30</td>
<td>12</td>
</tr>
</tbody>
</table>

X2 = 14.585 p=0.006
DISCUSSION

It well documented that in all pregnancies plasma lipid level change towards a hyperlipidemic lipid profile. Although total cholesterol and high density lipoproteins cholesterol are increased, hypertriglyceridemia is the most prominent characteristic. All lipoprotein fractions show increased content of triglycerides\textsuperscript{10,11}. Increased synthesis of triglyceride-rich lipoprotein as well as decreased degradation (lipolysis) seems to contribute to the gestational hyperlipidemia\textsuperscript{10,22,23}. In women with overt preeclampsia the hypertriglyceridemia is even more pronounced\textsuperscript{10,17,27}. The preeclamptic dyslipidemia-like pattern of plasma lipids is apparently not a simple exaggeration of the physiological changes because there is usually on further increase in total cholesterol and high density lipoproteins compared with normal pregnancies\textsuperscript{10}. In women with overt preeclampsia, plasma high density lipoproteins cholesterol and apoprotien A-I are usually decreased\textsuperscript{10,16}. In our study we found that dyslipidemia-like changes in plasma lipids at 18 weeks of gestation are associated with early but not late onset preeclampsia. Because the prospective design of study we can conclude that the observed plasma lipid pattern was not a late consequence of the pathophysiological changes in preeclamptic women. Using non-fasting blood samples as in the our study lead to greater variation especially in the triglycerides simply because of intestinally derived triglyceride-rich lipoproteins (chylomicrons). Despite this, early and late onset preeclampsia could clearly be predicted already at 18 weeks of pregnancy. In previous studies of plasma lipids of pre-eclamptic women, distinction between early and late onset disease has not been made. As demonstrated. In our study such distinction had major impact on the results and provides support to the notion that early and late onset preeclampsia may differ pathophysiologicaly, there is no general agreement with respect to the definition of early and late onset preeclampsia. We defined a women as having early onset disease if she was delivered because of preeclampsia before 37 weeks of gestation. The lipid changes that were associated with increased risk of early onset preeclampsia were characterized by high plasma triglycerides in absolute terms and relative to non-high density lipoprotein-cholesterol. We cannot exclude the fact that the special lipid patterns found in many of those with early onset pre-eclampsia developed during the first 18 weeks of pregnancy. However, the increasing evidence that pre-eclampsia is associated with atherosclerotic cardiovascular disease later in life indicates that these women have changes in their lipid,
glucose or energy metabolism that are independent of pregnancy, insulin resistance may be involved because increased prevalence is found in pre-eclamptic women and because the lipid patterns presently found in women with early onset pre-eclampsia bear some similarities to those described in non-pregnancy women with non-insulin dependent diabetes. The differences in the plasma triglycerides between the women with and without subsequent pre-eclampsia could either be due to higher endogenous (liver-produced) triglyceride-rich lipoproteins (apoB-100 containing lipoproteins), to the intestinal B-48 dominated lipoproteins or to both. We have reported previously that fasting triglycerides are increased at 18 weeks of gestation in women with eventual pre-eclampsia. Thus at least parts of elevated plasma triglycerides are likely to be of endogenous origin. Traditionally, fasting plasma lipids have been used in studies of cardiovascular disease. It is however, evident that post-prandial lipid changes are also associated with an increased risk of atherosclerotic and prothrombotic disease. The post-prandial increase in triglyceride-rich lipoproteins are not only due to intestinal chylomicrons but also to accumulation of endogenous very low density lipoproteins. This seems mainly to be caused by competition between very low density lipoproteins and chylomicrons for the lipoprotein lipase sites resulting in reduced degradation rate of very low density lipoprotein. As already suggested, the elevated triglycerides found among many women with early onset pre-eclampsia may be due to a combination of higher endogenous very low density lipoproteins and increased chylomicron bound triglycerides resulting from a competition for the binding sites at lipoprotein lipase alternatively, or in addition, the activity of lipoprotein lipase may be lower in women with early onset pre-eclampsia. There are several mechanisms by which hypertriglyceridemic dyslipidemia may contribute to preeclampsia. It is well established that dyslipidemic changes in plasma lipid in general may induce endothelial disturbances. In pregnancy a dyslipidemic lipoprotein profile may add to other factors that contribute to the endothelial dysfunction found in women with preeclampsia. Hypertiglyceridemic dyslipidemia could also augment development of atherotic changes in the spiral arteries as well as promote prothrombotic mechanisms. Finally, lipid or lipidderviates may interfere with trophoblast invasion. Our study shows that hypertriglyceridemic dyslipidemic pattern of non-fasting plasma lipid at 18 weeks of gestation is associated with the increased risk of developing early but not late onset preeclampsia. In agreement these observations give further support to previous reports that abnormalities in plasma lipids or lipoproteins contribute to the development of
preeclampsia. These studies like a brief overview of maternal triglycerides as a risk factor of preeclampsia at 16 of January 2006 and dyslipidemia in pregnancy induced hypertension done in India at 2009. The finding that hypertriglyceridemic dyslipidemia as associated only with early onset preeclampsia underscores the notion that early and late onset disease may not share all risk factors as well as being pathophysiologically different 6-8,14.

CONCLUSION

Hypertiglyceridemic dyslipidemia before 20 Weeks of gestation is associated with the risk of developing early but not late onset preeclampsia, giving support to the contention that these two variants of the disease are at least partly pathogenically different

ETHICAL CLEARANCE

The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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