A STUDY OF MALONDIALDEHYDE AND LIPID PROFILE IN PREGNANCY INDUCED HYPERTENSION

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ABSTRACT

Pregnancy Induced Hypertensive disorders are one of the commonest complication of the Pregnancy which accounts for most of the Maternal and Perinatal Mortality and Morbidity. The diseased placenta, Lipid peroxides produced due to oxidative stress and Maternal Dyslipidemia promote a vicious cycle of events that makes a cause and effect likely to contribute to Pre-eclampsia. The subjects were of age 18-30 years, stratified in 3 groups, Non Pregnant Normal women (NN), Normal Pregnancy (NP) and Pregnancy Induced Hypertension (PIH). Pregnant cases were in their third trimester. The present study is to evaluate Serum Lipid Profile and Lipid peroxidation product Malondialdehyde (MDA). The results are evaluated for Mean, Standard deviation and Probability was assessed by subjecting the results to T-test, 95% (P<0.05). MDA a lipid peroxidation product was significantly increased in Normal pregnant (NP) in comparison with the Non-pregnant normal controls (NN) (P<0.05), also there is significant rise between normal pregnancy and PIH (Preeclampsia) (P<0.005). Lipid profile parameters TG, TC showed significant rise in NP in relation to NN. A comparison of these values in PIH with NP, showed a significant rise in TG, but the TC mean values did not show statistically significant rise. The HDL-C levels in the study, showed significant decrease in PIH compared to NP. The present study shows that an abnormal lipid metabolism and high lipid peroxide concentrations may contribute to promotion of Hypertension and vascular dysfunction seen in PIH. An inclusion lipid profile in the routine antenatal investigations may warn us of cases at risk for PIH.

KEY WORDS: Malondialdehyde, PIH, Oxidative stress. Lipid peroxidation.

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B - 167
INTRODUCTION

Pregnancy induced hypertensive disorder is a pregnancy specific syndrome complex occurring after 20th week of gestation, which subsides post partum. All over the world about 4 million cases occur each year. Incidence in India is 8-10%. Pre-eclampsia is the second leading cause of maternal mortality, accounting for 12-18% of pregnancy-related maternal deaths. Pregnancies occurring in patients with Essential hypertension, Renal hypertension and other causes of hypertension does not come under PIH. A PIH case presents itself with only Hypertension or along with Proteinuria and/or edema which is termed as Pre-eclampsia. When these cases present themselves with complication of seizures it is termed as Eclampsia. PIH is a multi organ disorder due to the vascular dysfunction, which results in increase permeability, hypercoagulability, and diffuse vasospasm responsible for various symptoms and fatal complications. Reduced uteroplacental blood flow is responsible for fetal outcome. Complications: Maternal - Abruptio, Eclampsia, Renal failure, Visual disturbances, Pregnancy loss, Coagulation disorders such as disseminated Intra vascular coagulation and HELLP Syndrome, PPH. Fetal outcomes include Stillbirth, Intrauterine growth retardation, low birth weight, and Prematurity.

Diverse causes in Placenta and Maternal constitution interact with one another and converge to form the oxidative stress. Dyslipedemia a maternal factor favour oxidative stress. The oxidative stress leads to endothelial dysfunction. Lipid peroxidation and oxidative damage is increased in the placenta of women with PIH. Placentas of women with preeclampsia produce significantly more lipid peroxides than placentas of women with normal pregnancy, and the lipid peroxides are secreted primarily toward the maternal circulation. Oxidative stress, the excess of Reactive oxygen species beyond the buffering capacity of endogenous antioxidants, is considered a prime candidate for linkage of the placental and maternal stages. Placental tissue from women with pre-eclampsia show an increased capacity to generate Superoxide anion. Lipid peroxides and ROS, particularly the superoxide anion radical, are known to cause endothelial oxidative stress and dysfunction which may inhibit the synthesis of prostacyclin (PGI₂) and increase the production of thromboxane (TxA₂), which is a potent vasoconstrictor and stimulator of platelet aggregation. The alterations in lipid profile in PE may be a maternal response to placental insufficiency and an increased requirement to deliver fuel to the placenta. However the marked dyslipidaemia may contribute to endothelial activation and dysfunction and to promotion of oxidative stress. Lipid peroxides have been reported to be increased in blood and tissues of women with preeclampsia for many years. MDA, a major break down product of lipid peroxide was one of the first biomarker found to be raised. Gestational hyperlipidaemia fulfils the physiological role of supplying both cholesterol and triglyceride to the rapidly developing fetus. There is approximately 40% rise in TC, TG FFA, and Phospholipids in the normal pregnancy with the peak values around 32-36 weeks. In Pre-eclampsia TG levels in the third trimester are near double those seen in normal pregnancy.
Reversal of the Physiologic hyperlipidemia of pregnancy begins within hours of delivery and is essentially complete by 6-10 weeks post partum. Activities of adipose tissue lipoprotein lipase and hepatic lipase are substantially decrease during normal pregnancy due to insulin resistance and oestrogen, respectively. Oestrogen increases hepatic output of VLDL, and decreases hepatic lipase activity promoting accumulation of triglycerides in lipoproteins. Heightened gestational insulin resistance may accentuate the suppression of lipoprotein lipase activity. In PIH there is Elevated serum free fatty acid, overproduction of VLDL hypertriglyceridemia, and decreased HDL. Mean plasma TG and FFA levels undergo near doubling in women with PIH relative to normal pregnancy, roughly one third of the women with preeclampsia develop plasma TG values above 400mg/dl. Elevations in serum triglyceride and FFA levels are already present before 20 weeks’ gestation in women with future preeclampsia. The increase in intracellular triglyceride is associated with decreased release of prostacyclin. In the systemic circulation, oxidative stress may be explained by free radical generation by activated neutrophils or by formation of products of lipid peroxidation (e.g. malondialdehyde.)

MATERIALS AND METHODS

The study was performed in the department of Biochemistry Gandhi medical college & hospital, Hyderabad, in collaboration with its Obstetrics department. The subjects were ranging in age group of 18-30 years. Pregnant cases were in their third trimester. The subjects selected were stratified into 3 groups. Group-NN: Non pregnant Normal women. (n=25) Group-NP: Normal uncomplicated Pregnancy. (n=25) Group-PIH: Women with Preeclampsia. (n=25). Pregnant controls were selected from out patients who are healthy and with out complications of pregnancy and other medical disorders. PIH cases were from ante natal ward and labour room admitted for moderate to severe hypertension. The cases are with out history of essential hypertension and other medical complications. Pregnancies with history of Eclampsia, essential hypertension and with other diseases are excluded from the study. Fasting venous samples were estimated on the same day for the following parameters: Malondialdehyde, Total cholesterol, triglycerides, HDL, VLDL, and LDL.

Malondialdehyde Estimation
Thiobarbituric acid method. (R. P. Bird et al) (Nadiger et al)

Malondialdehyde
CH₂ (CHO)₂ Lipid peroxides, derived from polyunsaturated fatty acids, are unstable and decompose to form a complex series of compounds. These include reactive carbonyl compounds, of which the most abundant is Malondialdehyde therefore, measurement of malondialdehyde is widely used as an indicator of lipid peroxidation.

Principle
The malonaldehyde in the serum reacts with thiobarbituric acid in acidic medium and give rise to pink colored complex, which is measured at 532 nm against distilled water in
a spectrophotometer. Malondialdehyde is calculated from its Molar extinction coefficient (Molar absorptivity) (Mahfouz et al, 1986). Molar extinction coefficient of MDA in a 1 cm path length is 1.5 x 10^5 M^-1.

**Lipid profile**

Triglycerides, Total cholesterol, HDL cholesterol: enzymatic colorimetric method (Chylomicrons, VLDL and LDL fractions precipitated by polyethylglycol) VLDL Cholesterol calculated by using the formula VLDL = Triglycerides/5. LDL cholesterol is calculated based on Friedewald’s equation.

**STATISTICAL ANALYSIS**

- The results are evaluated for Mean, Standard deviation and Probability was assessed by subjecting the results to T-test, 95% confidence limits were taken as level of significance. (P <0.05).
- NN are taken as controls for NP, and NP as controls for PIH.

**Table 1**

*Comparison of MDA in the three groups*

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ±S.D</th>
<th>Significance P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NN</td>
<td>186.31 ± 38.88</td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>226.28 ± 48.86</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PIH</td>
<td>291.7 ± 65.79</td>
<td>&lt;0.005</td>
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</tbody>
</table>

**Table 2**

*Comparison of Triglyceride values in the three groups*

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ±S.D</th>
<th>Significance P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NN</td>
<td>122.56 ± 16.00</td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>147.78 ± 24.58</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PIH</td>
<td>175.70 ± 19.84</td>
<td>&lt;0.005</td>
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</table>
Table 3
Comparison of Total cholesterol in the three groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>±S.D</th>
<th>Significance P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NN</td>
<td>142.37</td>
<td>20.06</td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>203.57</td>
<td>54.12</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PIH</td>
<td>218.94</td>
<td>47.37</td>
<td>NS</td>
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Table 4
Comparison of HDL values in the three groups

<table>
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<th>Group</th>
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<th>±S.D</th>
<th>Significance P value</th>
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<tr>
<td>NN</td>
<td>56.75</td>
<td>9.64</td>
<td></td>
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<tr>
<td>NP</td>
<td>62.14</td>
<td>7.40</td>
<td>NS</td>
</tr>
<tr>
<td>PIH</td>
<td>55.29</td>
<td>9.62</td>
<td>&lt;0.05</td>
</tr>
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Table 5
Comparison of VLDL values in the three groups

<table>
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<th>Group</th>
<th>Mean</th>
<th>±S.D</th>
<th>Significance P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NN</td>
<td>24.51</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>NP</td>
<td>29.55</td>
<td>4.91</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PIH</td>
<td>35.14</td>
<td>3.99</td>
<td>&lt;0.005</td>
</tr>
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Table 6
Comparison of LDL values in the three groups

<table>
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<th>Group</th>
<th>Mean</th>
<th>±S.D</th>
<th>Significance P value</th>
</tr>
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<tbody>
<tr>
<td>NN</td>
<td>61.11</td>
<td>21.18</td>
<td></td>
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<tr>
<td>NP</td>
<td>111.87</td>
<td>51.68</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>PIH</td>
<td>128.50</td>
<td>49.01</td>
<td>NS</td>
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</tbody>
</table>
DISCUSSION

Oxidative stress has been implicated in many diseases. Lipid peroxidation i.e., oxidation of the PUFA along with the augmented hyperlipidemic conditions in pregnancy is being much supported by studies in etiopathogenesis of PIH. In the present study Malondialdehyde a lipid peroxidation product was significantly increased in Normal pregnant ( NP) in comparison with the Non-pregnant normal controls (NN ) (P<0.05)., also there is significant rise between normal pregnancy and PIH. (Preeclampsia),(P<0.005). A Study by (Hubel, Carl A, 1996) showed ante partum concentrations of malondialdehyde were 50% higher in women with preeclampsia (p < 0.01). A higher statistically significant levels of MDA with P<0.001 was shown in the studies of Usha Adigar, sadanand Patil. Serum MDA levels has showed no significant difference between NP and NN(P>0.05), in the study by Nguyen Thị Thu Uyên, Nguyen Nghiem Luật /2007, but the study has shown a significant increase of MDA level in the PIH compared in NP subjects.(P<0.005). (P.M. Gangadhara. Swamy, 2014) Hubel, et al, and Kharb, et al, have also shown that serum lipid peroxides are known to increase in pregnancy and this increase was exaggerated in pre-eclampsia. Lipid peroxides damage endothelial cells, inhibit the synthesis of prostacyclin (PGI2) and increase the production of thromboxane (TxA2), which is a potent vasoconstrictor and stimulator of platelet aggregation. Normal pregnancy is characterized by progressive increase in body fat and in serum lipid levels. During the third trimester a 40% and 50%, change over average total serum cholesterol and triglyceride are seen the respectively. This atherogenic profile is well tolerated during normal pregnancy and is disrupted in PIH... In present study lipid profile parameters are estimated to elucidate the role of dyslipidemia in pre-eclampsia. An elevated triglyceride in the major lipoprotein fractions in pregnancy is confirmed. In the present study statistically significant rises are seen in serum Triglyceride in NP compared NN controls (p<0.005), and in PIH in relation to pregnant normal, showed significance of (P< 0.005), which is consistent with the findings of previous researches (Wakatsuki et al., 2000). Antepartum serum triglyceride concentrations were increased approximately twofold in women with pre-eclampsia relative to uncomplicated pregnancies (p < 0.02). The Total Cholesterol levels in the present study revealed significant rise in normal pregnant compared to non pregnant controls ( P < 0.05), though the Mean values have risen in

PIH in relation to NP they are not statistically significant (218mg% and 203mg% respectively) (Jayanta De 2006) 13, (Md zakir, 2007)25. But total cholesterol were shown to be significantly raised in study by P.M. Gangadhara. Swamy 201421 between NP and PIH. The HDL mean values have increased in NP over NN, though it is not statistically significant, this rise shows a maintenance of the HDL cholesterol level in the pregnancy, distinguishes the pregnancy from other endogenous hypertriglyceridemias where HDL cholesterol is reduced. In the present study HDL cholesterol has significantly decreased in PIH cases in relation to Normal Pregnant (P < 0.05). A study by Jayant De, Rubina A.13,26 showed a decrease HDL-C significantly (P <0.05). In pre-eclampsia the reduced levels HDL-C reveal the failure of HDL to rise during gestation. The low level of HDL - C is also due to the increased insulin resistance in preeclampsia. The results of VLDL in the present study showed significant change in mean values in NP in relation to NN (P<0.005). PIH has also shown similar significantly raised values in relation to NP (<0.005). A 2-4 fold rise in triglycerides in pregnancy and preeclampsia, and the increased insulin resistance in PIH are responsible for Hypertriglyceridemia. LDL values significantly increased in NP in relation to NN(P <0.005), PIH showed increase in mean value which were not significant in relation to NP(128.50 mg%,111.87mg% resp). Studies showed elevated levels of LDL-C (Lorentzen & Henrikson, 1998)27 in PIH compared to NP. Wakat suki et al., 2000 24 reported that there was no difference in the levels of LDL-C between PIH and NP women, which is consistent with our study. Triglycerides and free fatty acids, but not cholesterol, are increased in Pre-eclampsia and correlate with the lipid peroxidation metabolite Malondialdehyde. These interactions may contribute to endothelial cell dysfunction in preeclampsia.

CONCLUSION

PIH is one of the commonest pregnancy specific complication. The etiopathogenesis is still elusive. Delivery is the only cure, with patient recovering with in 48 hrs. The placental factors and various maternal factors, which may be a combination of environmental, genetic and metabolic parameters, interact to cause endothelial cell dysfunction, responsible for clinical features of PIH. The present study shows an increase in oxidative stress in PIH. The estimation of Malondialdehyde, a marker for oxidative stress, showed significant increase in NP (Normal pregnant) in comparison with NN (Normal non pregnant), and in PIH in relation to NP. Lipid profile parameters TG, TC showed significant rise in NP in relation to NN. A comparison of these values in PIH with NP, showed a significant increase in TG, but the TC mean values did not show statistically significant rise. The HDL-C levels in the study, showed significant decrease in PIH compared to NP. These findings suggest that high Triglyceride and low HDL cholesterol concentrations are important risk factors for pre-eclampsia. LDL-C showed significant increase in NP in comparison with NN. There is an increase in mean values LDL-C in PIH. The present study shows that an abnormal lipid metabolism and high lipid peroxide concentrations may contribute to promotion of oxidative stress and vascular dysfunction seen in PIH.

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