Evaluation of TNF-Α, Nitric Oxide, Lipid Profile, Urea and Creatinine Serum Levels for Prediction of Preeclampsia

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ABSTRACT

Background & Aims: TNF-α directly damages the vascular endothelial cells, reduces regional blood flow, causes occlusion of vessels and increases endothelial permeability. Endothelial cell injury after TNF α mediated activation of immune system may result in secretion of vaso-active substances and increase in vascular permeability and intravascular coagulation.

Methods: The current study included 50 pregnant women complicated by pre eclampsia and 50 healthy normal pregnant women as a control group for: Quantitative detection of TNF α by Enzyme-linked Immuno sorbent Assay, Measurement of Nitric oxide by Colorimetric assay of Nitrate Level, determination of urea and creatinine, total cholesterol, triglycerides LDL and HDL by enzymatic colorimetric method.

Results & Conclusions: TNF-α may be involved in the pathogenesis of preeclampsia and may identify the patients who are at high risk of PE and can be a potential marker of the severity of the pre-eclamptic syndrome. Pre-eclamptic women had deranged lipid profile due to abnormal lipid metabolism; this alteration of lipid metabolism may play a key role in the development of symptoms of Pre-eclampsia. Furthermore, changes to lipid metabolism may contribute towards the endothelial lesions observed in pre-eclampsia.

Keywords: preeclampsia, TNF– α, Lipid per-oxidation and nitric oxide.

INTRODUCTION

Hypertensive disorders of pregnancy are the most common medical disorders of pregnancy [1]. They are responsible for high maternal and peri-natal mortality, especially in developing countries [2].

The initiating event in pregnancy induced hypertension (PIH) has been implicated to be reduced utero-placental perfusion as a result of abnormal extra-villous cytotrophoblast invasion, focal ischemia, hypoxia, deportation of hypoxemic trophoblast cells and abnormal expression of various placental biological molecules particularly the cytokines are thought to lead to widespread activation/dysfunction of the maternal vascular endothelium [3].

Lipid per-oxidation in the placental and maternal tissues is hypothesized to cause endothelial dysfunction [4]. Oxidative stress and uncontrolled lipid peroxidation are considered to be key events in pre-eclampsia [5].

Reis et al., [6] indicated that the excessive or deficient release of some placental hormones in association with gestational diseases may reflect an abnormal differentiation of the placenta, an impaired fetal metabolism or an adaptive response of the feto-placental-unit to adverse conditions such as hypertension, hypoxia, and infection.

Since trophoblastic abnormalities play a central role in the development of preeclampsia and precede the appearance of clinical signs and symptoms, thus some placental hormones change in the maternal circulation, indicating the derangement of placental function. Virtually all aspects of the pathophysiology of pre-eclampsia can be directly or indirectly correlated with the effects of a combination of a relative nitric oxide (NO) deficiency and peroxy-nitrite anion (ONOO⁻) excess [7].

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The monocyte/macrophage generally serves as the principal reservoir of pro-inflammatory cytokines and are the first cells activated in the non specific immune responses, thus they might represent good candidates for the inappropriate synthesis of pro-inflammatory cytokines during pre-eclampsia [8]. TNF-α promote both structural and functional changes in endothelial cells including oxidative stress and secretion of vasoconstrictors [9].

Abnormalities in the maternal immune system and insufficiency of gestational immune tolerance seem to play major roles in pre-eclampsia. One of the main differences found in pre-eclampsia is a shift toward the responses and the production of IFN-γ. The origin of IFN-γ is not clearly identified and could be the natural killer cells of the uterus, the placental dendritic cells modulating responses of T helper cells, alterations in synthesis or response to regulatory molecules or changes in the function of regulatory T cells in pregnancy [10].

Aberrant immune responses promoting pre-eclampsia may also be due to an altered fetal allo-recognition or to inflammatory triggers. It has been documented that fetal cells such as fetal erythroblasts as well as cell-free fetal DNA are increased in the maternal circulation in women who develop pre-eclampsia. These findings have given rise to the hypothesis that pre-eclampsia is a disease process by which a placental lesion such as hypoxia allows increased fetal material into maternal circulation that leads to an immune response and endothelial damage ultimately resulting in pre-eclampsia and eclampsia [11].

Occasionally there is impaired trophoblast invasion that results in inadequate alterations to the uterine spiral arteries. It is hypothesized that the developing embryo releases biochemical signals that result in the woman developing hypertension and preeclampsia so that the fetus can benefit from a greater amount of maternal circulation of nutrients due to increased blood flow to the impaired placenta [12].

Trophoblast cells of first trimester human placenta express high levels of NOS activity, and the predominant isofrom is the constitutive, Ca²⁺ dependant endothelial or type III NOS. Placental NOS III activity appears to be regulated by a dual pathway involving concentration changes of Ca²⁺ and tetrahydrobiopterin. In placent homogenate the activating action of Ca+2 occurs within narrow concentration limits; the presence of Ca²⁺ is indispensable for enzyme activity [13].

The placenta lacks autonomic innervations, suggesting that placental vascular tone must be regulated by humoral or autocrine-paracrine mechanisms. The synthesis of nitric oxide a potent vasodilator, in the human placental vasculature has been demonstrated. Nitric oxide is thought to contribute to the maintenance of low placental vascular tone in part by attenuating the action of several vasoconstrictors in human placental villous vasculature [14].

Cytokines and growth factors have been identified as functional proteins in the placenta, but their roles in normal placent development and in pathological placental disease have not been determined. Pathologically secreted TNF-α damage the vascular endothelial cells, causes occlusion of vessels, reduces regional blood flow and increases permeability of endothelium. TNF-α mediated activation of immune system may result in secretion of vaso-active substances due to endothelial injury and lead to vascular permeability and intravascular coagulation [15].

TNF-α is a pro-inflammatory cytokine and its biological activity is inflammation and endothelial cell activation. The sources of TNF-α production in pre-eclampsia are neutrophils and monocytes and possibly Placenta. One possible mechanism in preeclampsia is factors derived from placenta which stimulate monocytes and neutrophils to produce TNF-α that lead to endothelial disturbances [16].

The increased serum TNF-α may be a part of pre-eclamptic pathology.

TNF-α can modify the growth and invasion of trophoblasts in maternal spiral arteries. Moreover, it may contribute to abnormal placentation, oxidative stress and endothelial disturbances [17].

The women who developed pre-eclampsia had disturbed lipid profile due to abnormal lipid metabolism, increased triglycerides levels, delayed triglycerides clearance and high blood pressure are the reasons for the development of pre-eclampsia, this association may be significant in understanding the pathological process of pre-eclampsia and may help in developing strategies for prevention and early diagnosis of pre-eclampsia [18].
The renal system undergoes marked changes in function during pregnancy due to hormonal effects, increased metabolic load of the fetus and outflow obstruction of the ureters by the enlarging uterus. The glomerular filtration rate increases up to 50% in pregnancy, which is an indication of increased renal function. The increase in renal blood flow and glomerular filtration rate is attributable to increased cardiac output, increase in progesterone and aldosterone. As a result of increase in glomerular filtration rate, the clearance of urea, uric acid and creatinine increases and their plasma levels are lowered in pregnancy [19].

During normal pregnancy reduced systemic vascular resistance leads to activation of renin-angiotensin system with elevation of circulating angiotensin2 levels, however due to the physiological decrease in response to angiotensin-2 seen in normal pregnancy, blood pressure remain low [20]. In pre-eclampsia the decreased response to Ang-2 is abolished, the systemic vascular structures and the kidney are exposed to high levels of circulating Ang-2 without the protective effect of a reduced response to Ang-2, the net result is elevated blood pressure and a decreased in GFR [21]. Hypertension, proteinuria and increase in uric acid level in blood and decrease in clearance tests may be present for days or weeks before she has any subjective complaints. Hence, the importances of peri-natal care a primary objective of which is the early detection of the signs and laboratory parameters in pre-eclampsia [22].

The aim of this study was to identify predictive markers for early diagnosis of women who are at risk of gestational hypertension.

PATIENTS AND METHODS

The study was carried out on 50 pregnant women complicated by pre eclampsia and 50 healthy normal pregnant women as a control group who were matched in age and gestational age to the patients(mean gestational age for both group is 33weeks ±3). The patients were recruited before treatment administration among the attendants of gynecology and obstetric department, AL-azhar assiut university hospital. The diagnosis of pre-eclampsia was established according to the criteria developed by the national high blood pressure education programmed working group: systolic blood pressure was more than140 mmHg, diastolic blood pressure was higher than 90 mmHg on two different occasion after the 20th week of pregnancy and proteinuria defined as urine secretion of 0.3gm of protein or higher in a 24-hours urine specimen. All women had similar socioeconomic status, nonsmokers and none permanent drug users. Patients with renal diseases, chronic hypertension, renal and urinary infection, fetal disorders, multiple pregnancy and immunologic diseases were excluded from the study. An informed consent was obtained from all women participating in the study.

For each of patients and control group the following items were done:

History was taken, clinical examination was done and samples were collected and prepared as follow:

6 ml venous blood samples were collected without using an anticoagulant by vacutainer system under complete aseptic conditions, samples were allowed to clot for 30 min. at 25°C, centrifuged at 3000 rpm for 15 min, serum layer was pipetted without disturbing the white Buffy layer, stored serum at-80°C for estimation of the:

Quantitative detection of TNF-alpha by Enzyme-linked Immuno sorbent assay (RayBio® Catalog #: ELR-TNFα ). Measurement of Nitric oxide by Colorimetric assay [23].

Determination of urea (Catalog #: 1051), creatinine (Cat. No.: 46161, 46161S), LDL (CATALOG NO. 280 001), HDL (CATALOG NO. 280 001), triglycerides (CATALOG NO. 314001), total cholesterol (CATALOG NO. 314002) by enzymatic colorimetric method.

Statistical Analysis

Data were expressed as Mean ± SD, comparisons were performed for normal distributed data using t.test for independent groups, comparisons were performed for skewed or small size groups using Mann-Whitney Rank Sum test (non parametric test). Correlations were performed using person correlation. P.value considered insignificant if it > 0.05, significant if it ≤ 0.05, highly significant if it ≤0.01 and very highly significant if it ≤0.001. The statistical analysis were done using SPSS V.11.0 program.

RESULTS

Table 1. Serum TNF-alpha levels in preeclampsia patients and control group

<table>
<thead>
<tr>
<th>Factor</th>
<th>PE patients (N=50)</th>
<th>Control (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF in pg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean± SD</td>
<td>29.9±0.19539</td>
<td>0.000±0.00</td>
</tr>
<tr>
<td>- Minimum</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>- Maximum</td>
<td>853.30</td>
<td>0.00</td>
</tr>
<tr>
<td>- median</td>
<td>426.65</td>
<td>0.00</td>
</tr>
<tr>
<td>- P. value</td>
<td>&lt;.0001</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Fig 1. Serum TNF-alpha levels in preeclampsia patients and control group

Table 2. Serum NO levels in PE patients and control group

<table>
<thead>
<tr>
<th>Factor</th>
<th>PE patients (N=50)</th>
<th>Control (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO in ng/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean± SD</td>
<td>3.5078±1.40873</td>
<td>23.1770±7.57250</td>
</tr>
<tr>
<td>- Minimum</td>
<td>1.60</td>
<td>8.98</td>
</tr>
<tr>
<td>- Maximum</td>
<td>6.10</td>
<td>34.50</td>
</tr>
<tr>
<td>- median</td>
<td>4.50</td>
<td>25.52</td>
</tr>
<tr>
<td>- P. value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
</tbody>
</table>

Fig 2. Serum (NO) levels (ng/ml) in PE patients and control group

Table 3. Serum TG levels in PE patients and control group

<table>
<thead>
<tr>
<th>Factor</th>
<th>PE patients (N=50)</th>
<th>Control (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TG) in mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Mean± SD</td>
<td>181.3800±52.85478</td>
<td>137.4600±30.8242</td>
</tr>
<tr>
<td>- Minimum</td>
<td>55.00</td>
<td>85.00</td>
</tr>
<tr>
<td>- Maximum</td>
<td>320.00</td>
<td>190.00</td>
</tr>
<tr>
<td>- median</td>
<td>265.00</td>
<td>105.00</td>
</tr>
<tr>
<td>- P. value</td>
<td>&lt;.0001</td>
<td></td>
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</tbody>
</table>

Table 4. Serum total cholesterol levels in PE patients and control group

<table>
<thead>
<tr>
<th>Factor</th>
<th>PE patients(N=50)</th>
<th>Control group (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(TC) in mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>285.98±51.428</td>
<td>185.06±34.25</td>
</tr>
<tr>
<td>Minimum</td>
<td>190.00</td>
<td>150.00</td>
</tr>
<tr>
<td>Maximum</td>
<td>309.00</td>
<td>235.00</td>
</tr>
<tr>
<td>Median</td>
<td>219.00</td>
<td>182.00</td>
</tr>
<tr>
<td>P. value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. Serum LDL levels in PE patients and control group

<table>
<thead>
<tr>
<th>Factor</th>
<th>PE patients (N=50)</th>
<th>Control (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(LDL) in mg/dl</td>
<td>Mean± SD: 199.53±47.80, Minimum: 111.00, Maximum: 292.00, median: 191.00, P. value: &lt;.0001</td>
<td>Mean± SD: 167.85±37.67, Minimum: 101.00, Maximum: 228.60, median: 127.60</td>
</tr>
</tbody>
</table>

Table 6. Serum HDL levels in PE patients and control group

<table>
<thead>
<tr>
<th>Factor</th>
<th>PE patients (N=50)</th>
<th>Control (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(HDL) in mg/dl</td>
<td>Mean± SD: 41.48±9.83, Minimum: 25.00, Maximum: 73.00, median: 48.00, P. value: &lt;.286</td>
<td>Mean± SD: 39.68±6.49, Minimum: 30.00, Maximum: 60.00, median: 30.00</td>
</tr>
</tbody>
</table>

Table 7. Serum urea levels in PE patients and control group

<table>
<thead>
<tr>
<th>Factor</th>
<th>PE patients (N=50)</th>
<th>Control (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea in mg/dl</td>
<td>Mean± SD: 35.84±13.33, Minimum: 15.00, Maximum: 75.00, median: 60.00, P. value: &lt;.0001</td>
<td>Mean± SD: 27.12±7.50, Minimum: 15.00, Maximum: 45.00, median: 30.00</td>
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</tbody>
</table>

Table 8. Serum creatinine levels in PE patients and control group

<table>
<thead>
<tr>
<th>Factor</th>
<th>PE patients(N=50)</th>
<th>Control (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine in mg/dl</td>
<td>Mean± SD: 0.80±0.25, Minimum: 0.40, Maximum: 1.50, median: 1.10, P. value: &lt;.432</td>
<td>Mean± SD: 0.76±0.23, Minimum: 0.40, Maximum: 1.30, median: 0.90</td>
</tr>
</tbody>
</table>
DISCUSSION

The maternal complications due to pregnancy induced hypertension (PIH) include placental abruption, intracranial hemorrhage, liver lesions, acute renal disorders, disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS). Newborn infants of mothers with PIH suffer from intrauterine growth restriction (IUGR), prematurity, dysmaturity and necrotizing enterocolitis [24].

The initiating event in PIH has been implicated to reduce utero-placental perfusion as a result of abnormal extravillous, cytotrophoblast invasion, focal ischemia, hypoxia and deportation of hypoxic trophoblast cells and abnormal expression of various placental biological molecules particularly the cytokines that thought to lead to widespread activation / dysfunction of the maternal vascular endothelium [3].

In addition to the previous mediators, lipid peroxidation in the placental and maternal tissues is hypothesized to cause endothelial dysfunction [4].

In the present study, we evaluated levels of TNF-alpha, nitric oxide, HDL, LDL, total cholesterol, triglycerides, urea and creatinine.

We observed that the pre-eclamptic group has significant higher serum levels of TNF-alpha, lipid profile parameters and urea, also, we observed that nitric oxide levels were significantly decreased in pre-eclamptic group as compared to control group, but we observed that there is no significant difference in serum creatinine levels in both groups (tables 1,2,3 and figures 1,2,3,4).

TNF- α is produced by activated macrophages, B lymphocytes, T lymphocytes NK cells, lymphokine-activated killer cells, granulocytes, mast cells, fibroblasts and epidermal cells. TNF-α limits the extent of trophoblast invasion via the recruitment of excess macrophages [25].

Dan MIHU et al., [26] concluded that:

1. Serum immuno-reactive TNF-α concentrations were significantly increased in the last trimester of gestation in pre-eclamptic women compared to normo-tensive pregnant women and the control group.

2. The positive and significant correlation of TNF-α with diastolic BP and uric acid levels makes this cytokine a potential marker of the severity of the pre-eclamptic syndrome.

3. TNF-α is not an indicator of fetal status at birth in pre-eclampsia.

4. Pre-eclampsia is an exacerbation of a generalized inflammatory response, physiologically present in the last trimester of pregnancy.

Vitoratos et al., [27] evaluated maternal TNF-alpha and IL-6 plasma levels in normo-tensive pregnant women and women with pre-eclampsia. To examine the temporal changes in their levels from the antepartum to the postpartum period correlated with the regression of pre-eclampsia:

No statistically significant differences were found in IL-6 levels, whereas a difference was found in TNF-alpha levels between pre-eclamptic and controls in antepartum period (0.80 pg/ml versus 0.60 pg/ml, P: .04).

Long after delivery, TNF-alpha levels were significantly higher in

Pre-eclamptic compared to normotensive controls (0.86 pg/ml versus 0.60 pg/ml, P : .004), no difference was observed in TNF-alpha before and after delivery in both groups. No difference was noticed in IL-6 levels in women of normotensive group long after delivery compared to that before delivery.

Many authors have investigated s TNF- α levels during the last trimester of pregnancy in pregnant women with preeclampsia compared to normal pregnant women and reported high concentrations of the two receptors in preeclampsia [28] [29].

LaMarca et al., [30] evaluated the role of inflammatory cytokines in the patho-physiology of hypertension during pre-eclampsia and found that the initiating event in preeclampsia is postulated to be reduced utero-placental perfusion, leading to widespread dysfunction of the maternal vascular

endothelium. Inflammatory cytokines such as IL-6 and TNF-alpha are thought to be important links between placental ischemia, cardiovascular and renal dysfunction.

Anim-Nyame et al., [31] concluded that raised TNF alpha correlated positively with blood sugar and uric acid levels in pre-eclamptic patients. TNF-alpha is produced by monocytes, induces apoptosis and inhibits proliferation of trophoblast cells in preeclampsia, the fact that higher circulating levels of TNF-alpha were observed in preeclampsia than in gestational hypertension suggest an association with disease severity.

Endothelial dysfunction may be a pathophysiological link between preeclampsia, recurrent pregnancy loss and future cardiovascular events.

The molecular causes for endothelial dysfunction in preeclampsia, however, may be multifactorial, as decreased nitric oxide synthase (NOS) expression [32].

Pre-eclamptic women have been shown to have reduced endothelial nitric oxide production when compared to normal pregnant women, there was a strong association and linkage between preeclampsia and endothelial nitric oxide synthase gene (NOS III), the common polymorphism of the NOS III gene, renders the enzyme (eNOS) to enhanced proteolytic cleavage and potentially lower concentration, the presence of this polymorphism has been correlated to a vascular abnormality attributed to preeclampsia [33].

In conclusion, NO biosynthesis increases with advancing gestation during normal pregnancy and decreases in preeclampsia. Another factor that had been studied in the present study is lipid profile. Kalar et al., compare the mean lipid levels in preeclamptic and normal pregnancy. Mean triglycerides levels were (254 mg/dl ±0.45 versus 116.59 ± 4.9) statistically significantly higher in preeclamptic as compared to normal controls (p<0.05). Mean HDL-C levels were (36.92 mg/dl ± 7.70 versus 51 ±5.46) statistically significantly higher in preeclamptic as compared to normal controls (p<0.05). Mean LDL-C levels were (132.95 mg/dl± 32.26 versus 99.36± 17.75) statistically significantly higher in pre-eclamptic as compared to normal controls (p<0.05). Kalar et al., [34] concluded that Pre-eclamptic women had deranged lipid profile due to abnormal lipid metabolism. Increased triglyceride levels and delayed triglycerides clearance and high blood pressure are the grounds for the development of preeclampsia. This relationship may be significant in understanding the pathological process of pre-eclampsia and may help in developing strategies for prevention and early diagnosis of pre-eclampsia.

Gohil et al., [35] concluded that dyslipidemia is significantly evident in preeclampsia and plays an important pathological role. The various causative factors for dyslipidemia and its prevention need to be further studied and evaluated.

Another factor that had been studied in the present study is urea and creatinine levels. The measurement of serum urea concentration is widely regarded as a test of renal function but not a good guide to renal function as it varies with protein intake, liver metabolic capacity and renal perfusion so measurement of serum creatinine is a more reliable guide as it is produced from muscle at a constant rate and almost completely filtered at the glomerulus.

As a result of increase in glomerular filtration rate, the clearance of urea, uric acid and creatinine increases and their plasma levels are lowered in pregnancy. The lowering of the normal range of values of urea and creatinine during pregnancy has clinical significance, because a normal urea or creatinine level in a pregnant female may actually indicate an underlying renal disease [36].

Ogbe John Raphael et al., [36] concluded that the renal system undergoes marked changes in function during pregnancy due to hormonal effects, the increased metabolic load of the fetus and the outflow obstruction of the ureters by the enlarging uterus. Thus, the decrease in levels of creatinine, urea and uric acid may be due to increase in renal blood flow and glomerular filtration rate caused by increase in cardiac output and increase in the activities of progesterone, aldosterone, deoxycorticosterone and placental lactogen. The decrease in uric acid levels in the 1st and 2nd trimesters of pregnancy, progressive decrease in the levels of creatinine and urea in all trimesters might be attributed to increase in glomerular filtration rate, which occurs in normal pregnancy.

Magna and Sitikantha., [37] evaluated the levels of serum uric acid, creatinine and ura in preeclamptic and normotensive groups, and reported that the levels of uric acid and creatinine,

expressed in mg/ dl were significantly elevated in pre-eclamptics respectively (5.29 ± 0.84 and 0.72 ± 0.387) when compared to normotensives (3.86 ± 0.92 and 0.58 ± 0.283). There was a statistically insignificant and small increase in urea level in pre-eclamptics (28.07 ± 4.97) compared to normotensives (26.46 ± 3.55). There was a lack of any correlation between the positive differences in the values of each parameter with the extent of corresponding raised blood pressure.

Prakash and Sharma, [38] concluded that creatinine clearance fall gradually in cases from mild to severe Pre-eclamptic cases, but the difference in fall of the clearance values were not highly significant in mild and moderate cases when compared to normal 3rd and 2nd trimester values. However, it is a good index to gauge the renal status in these patients. Hidajet Paçarizi et al., [39] concluded that blood urea nitrogen/ creatinine index was significantly increased in pregnant women with preeclampsia in comparison to the group of pregnant women with normal blood pressure, it indicates the prerenal source of urea, this index can be important to estimate the severity of preeclampsia.

**CONCLUSION**

In pre-eclamptic group compared with control group

Serum TNF-alpha levels were significantly higher (p<0.001).

Serum NO levels were significantly lower (p<0.001).

Serum levels of triglycerides were significantly higher (p<0.001).

Serum levels of cholesterol were significantly higher (p<0.001).

Serum levels of LDL were significantly higher (p<0.001).

Serum levels of urea were significantly higher (p<0.001).

We observed insignificant difference in serum levels of creatinine (p<0.432) and HDL (p<0.286) in both groups.

TNF-α may be involved in the pathogenesis of PE and may identify the patients who are at high risk of PE and can be a potential marker of the severity of the preeclamptic syndrome.

The alteration of lipid metabolism may play a key role in the development of symptoms of Pre-eclampsia; changes to lipid metabolism may contribute towards the endothelial lesions observed in preeclampsia.

Endothelial dysfunction may be a patho-physiological link between preeclampsia, recurrent pregnancy loss, and future cardiovascular events.

The molecular causes for endothelial dysfunction in preeclampsia may be multi-factorial, as decreased nitric oxide synthase (NOS) expression. (NO) biosynthesis increases with advancing gestation during normal pregnancy and decreases in preeclampsia. Gestational differences in the response of the uterus to (NO), suggesting that the relaxing effect of NO is enhanced during most of gestation as compared to term or preterm labor. The elevated values of uncorrelated serum creatinine or urea preclude them to be useful for consideration as consistent predictive indicator(s) for preeclampsia or pregnancy related hypertension and blood urea nitrogen/creatinine index can be important to estimate the severity of preeclampsia.

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