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Original article

Some biochemical markers that can predict pre-eclampsia

Mohammad Sayyed Bakheet^{a,*}, Mohamed Ismail Seddik^b, Abdelzاهر^c, Mohammad Mohammad Abolfotoh^d, Abdelaziz Eldarwesh^e, Alomairi Mostafa^f, Maher Abdelshakor^g

^{a,c,d,f}Department of Biochemistry, Faculty of Medicine, Al-Azhar University, Assuit, Egypt.

^bDepartment of clinical pathology, Faculty of Medicine, Assuit University, Egypt.

^eDepartment of obstetrics and gynecology, Faculty of Medicine, Al-Azhar University, Assuit, Egypt.

^gDepartment of physiology, Faculty of Medicine, Al-Azhar University, Assuit, Egypt.

*Corresponding author; Department of Biochemistry, Faculty of Medicine, Al-Azhar University, Assuit, Egypt.

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ABSTRACT

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 vasoactive substances and increase in vascular permeability and intravascular coagulation. 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 preeclamptic syndrome. Preeclamptic 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.

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1. Introduction

Hypertensive disorders of pregnancy are the most common medical disorders of pregnancy (Podymow, 2007). They are responsible for high maternal and peri-natal mortality, especially in developing countries (Chhabra and Kakani, 2007). The initiating event in pregnancy induced hypertension (PIH) has been implicated to be reduced utero-placental perfusion as a result of abnormal extravillous 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 (Heimrath et al., 2007). Lipid per-oxidation in the placental and maternal tissues is hypothesized to cause endothelial dysfunction (Redman and Sargent, 2005). Oxidative stress and uncontrolled lipid peroxidation are considered to be key events in pre-eclampsia (Biri et al., 2007). Reis et al., (2002) 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 pre-eclampsia 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 patho-physiology 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 (Lowe, 2000). 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 (Luppi and DeLoia, 2006). TNF- α promote both structural and functional changes in endothelial cells including oxidative stress and secretion of vasoconstrictors (Anim-Nyame et al., 2003).

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 of or response to regulatory molecules, or changes in the function of regulatory T cells in pregnancy (Drife, 2004). Aberrant immune responses promoting pre-eclampsia may also be due to an altered fetal allorecognition 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 (Laresgoiti-Servitje et al., 2010).

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 (Arulkumaran and Lightstone, 2013). Trophoblast cells of first trimester human placenta express high levels of NOS activity, and the predominant isoform is the constitutive, Ca⁺² dependant endothelial or type III NOS. Placental NOS III activity appears to be regulated by a dual pathway, involving concentration changes of Ca⁺² and tetrahydrobiopterin. In placental homogenate the activating action of Ca⁺² occurs within narrow concentration limits; the presence of Ca⁺² is indispensable for enzyme activity (Chotigeat et al., 2007).

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 (Myatt et al., 1991). Cytokines and growth factors have been identified as functional proteins in the placenta, but their roles in normal placental 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 (Hayashi et al., 2005).

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 (Jonsson et al., 2006). 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 (Noyan et al., 2006). 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 (Ray et al., 2006).

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 by 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 (Kallner et al., 2012). 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 (Jeyabalan and Conrad, 2007), 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 (Mathew et al., 2007). 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 (Bories and Bories, 1995).

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

2. Materials and methods

The current study included 50 pregnant women complicated by pre eclampsia .The study also included 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 33 weeks \pm 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 of more than 140 mmHg, diastolic blood pressure 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
- Measurement of Nitric oxide by Colorimetric assay of Nitrate Level (Bories and Bories, 1995)
- Determination of urea by enzymatic, colorimetric method
- Determination of creatinine by enzymatic, colorimetric method

- Determination of LDL&HDL by enzymatic, colorimetric method
- Determination of triglycerides by enzymatic, colorimetric method
- Determination of total cholesterol by enzymatic, colorimetric method

3. Results and discussion

Data were expressed as Mean \pm 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 \leq 0.05, highly significant if it \leq 0.01 and very highly significant if it \leq 0.001. The statistical analysis were done using SPSS V.11.0 program.

Table 1
Serum TNF-alpha levels in pre-eclampsia PE patients and control group.

Factor		PE patients (N=50)	Control (N=50)
TNF in pg/ml	-Mean \pm SD	29.9 \pm 0.19539	0.0000 \pm 0.000
	- Minimum	0.00	0.00
	-Maximum	853.30	0.00
	-median	426.65	0.00
	-P. value	<.0001	

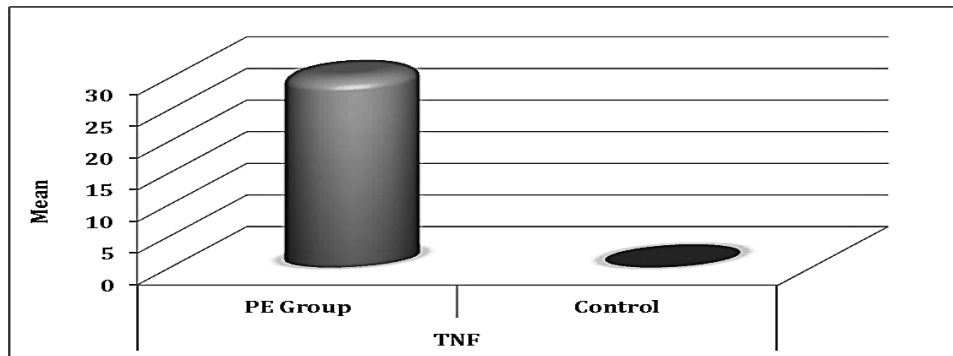


Fig. 1. Scatterogram of serum TNF-alpha (pg/ml) in all patients and control group.

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

Factor		PE patients (N=50)	Control (N=50)
NO in ng/ml	-Mean \pm SD	3.5078 \pm 1.40873	23.1770 \pm 7.57250
	- Minimum	1.60	8.98
	-Maximum	6.10	34.50
	- median	4.50	25.52
	-P. value	<.0001	

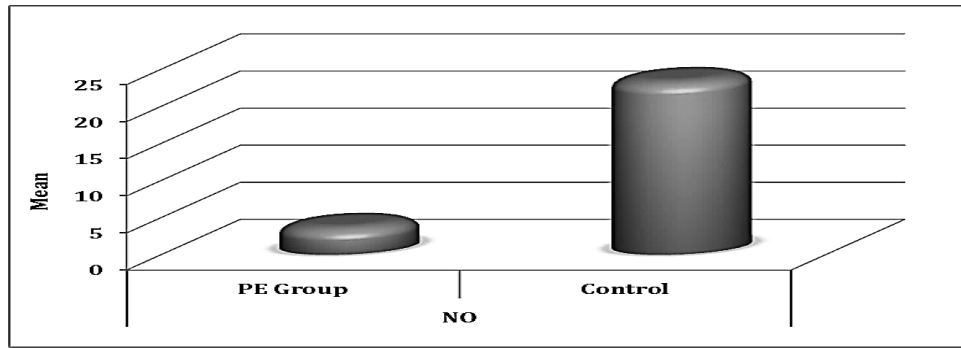


Fig. 2. Scattergram of serum (NO) (pg/ml) in all patients and control group.

Table 3

Serum TG levels in PE patients and control group.

Factor		PE patients (N=50)	Control (N=50)
(TG) in mg/dl	-Mean± SD	181.3800±52.85478	137.4600±30.8242
	- Minimum	55.00	85.00
	-Maximum	320.00	190.00
	- median	265.00	105.00
	-P. value	<.0001	

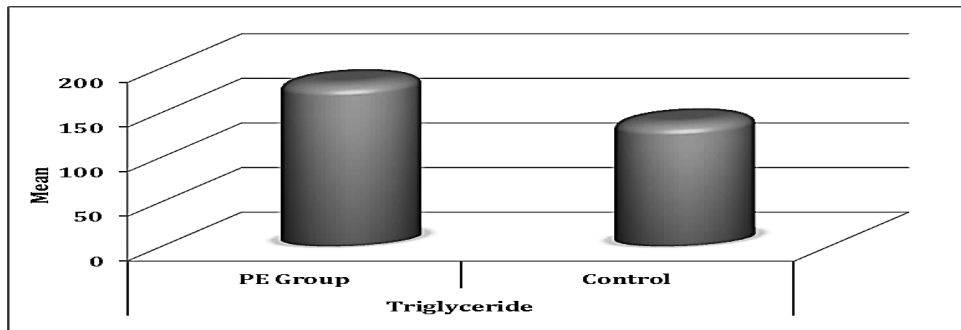


Fig. 3. Scattergram of serum (TG) (mg/dl) in all patients and control group.

Table 4

Serum cholesterol levels in PE patients and control group.

Factor		PE patients (N=50)	Control (N=50)
(TC) in mg/dl	-Mean± SD	185.9800±51.42837	155.06±34.25
	- Minimum	90.00	100.00
	-Maximum	309.00	215.00
	- median	219.00	115.00
	-P. value	<0.001	

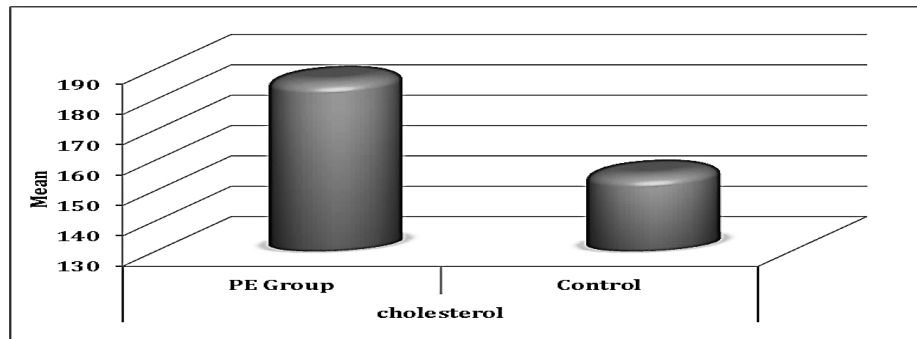


Fig. 4. Scatterogram of serum (TC) (mg/dl) in all patients and control group.

Table 5

Different serum LDL levels in PE patients and control group.

Factor		PE patients (N=50)	Control (N=50)
(LDL) in mg/dl	-Mean± SD	199.5360±47.80324	167.8520±37.67012
	- Minimum	101.00	101.00
	-Maximum	292.00	228.60
	- median	191.00	127.60
	-P. value	<.0001	

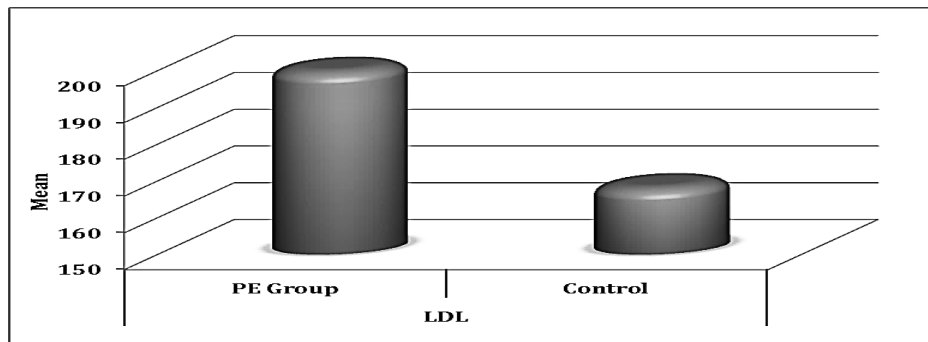


Fig. 5. Scatterogram of serum LDL (mg/dl) in all patients and control group.

Table 6

Serum HDL levels in PE patients and control group.

Factor		PE patients (N=50)	Control (N=50)
(HDL) in mg/dl	-Mean± SD	41.4800±9.8338	39.6800±64997
	- Minimum	25.00	30.00
	-Maximum	73.00	60.00
	- median	48.00	30.00
	-P. value	<.286	

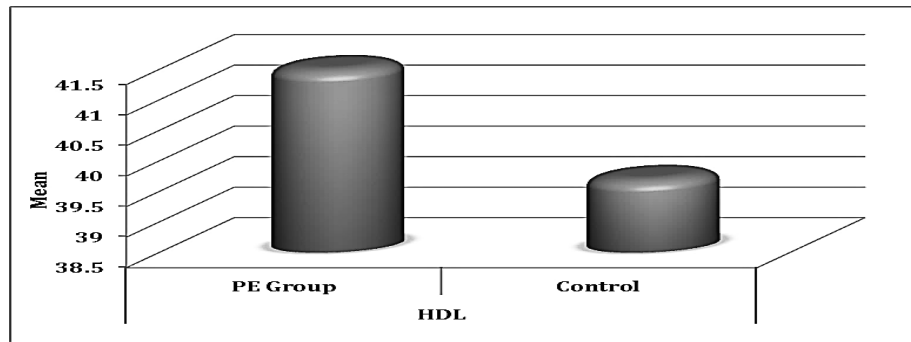


Fig. 6. Scatterogram of serum HDL (mg/dl) in all patients and control group.

Table 7

Serum urea levels in PE patients and control group.

Factor		PE patients (N=50)	Control (N=50)
Urea in mg/dl	-Mean± SD	35.84±13.33	27.12±7.50
	- Minimum	15.00	15.00
	-Maximum	75.00	45.00
	- median	60.00	30.00
	-P. value	<0.001	

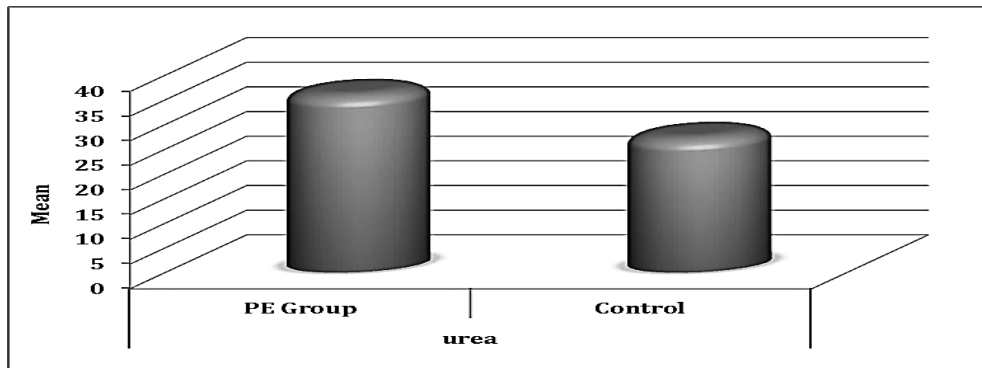


Fig. 7. Scatterogram of serum urea (mg/dl) in all patients and control group.

Table 8

Serum creatinine levels in PE patients and control group.

Factor		PE patients (N=50)	Control (N=50)
Creatinine in mg/dl	-Mean± SD	0.8040±25149	0.7660±0.2300
	- Minimum	0.40	0.40
	-Maximum	1.50	1.30
	- median	1.10	0.90
	-P. value	<.432	

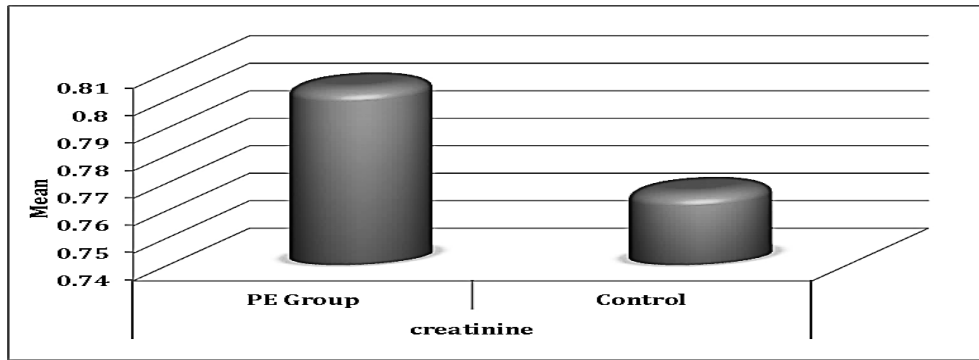


Fig. 8. Scatterogram of serum creatinine (mg/dl) in all patients and control group.

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 (Grujic and Milasinovic, 2006). 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 hypoxemic 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 (Heimrath et al., 2007).

In addition to the previous mediators, lipid peroxidation in the placental and maternal tissues is hypothesized to cause endothelial dysfunction (Redman and Sargent, 2005). In the present study, we evaluated levels of TNF-alpha, nitric oxide, HDL, LDL, 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 1,2,3,4,5,6,7 and 8). 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 (Bauer et al., 2004). Dan Mihu et al., 2008 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., 2010 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 ante-partum 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 preeclamptic 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 preeclamptic 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 (Nunez-Gonzalez et al., 2001; Madazli et al., 2003). La Marca et al., 2007 evaluated the role of inflammatory cytokines in the pathophysiology of hypertension during preeclampsia and found that the initiating event in preeclampsia is postulated to be reduced uteroplacental 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. Supporting a potential role of cytokines are findings that plasma levels of TNF-alpha and IL-6 are elevated in women with preeclampsia. Chronic reductions in placental perfusion in pregnant animals are associated with enhanced production of TNF-alpha and IL-6. Anim-Nyame et al., 2004 concluded that raised TNF alpha correlated positively with blood sugar and uric acid levels in preeclamptic 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 (Schiessl et al., 2005). Preeclamptic 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 (Pridjian and Puschet, 2002). 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., 2012 compare the mean lipid levels in preeclamptic and normal pregnancy. Mean triglycerides levels were (254 mg/dl \pm 0.45 versus 116.59 \pm 4.9) statistically significantly higher in preeclamptic as compared to normal controls ($p < 0.05$). Mean HDL-C levels were (36.92 mg/dl \pm 7.70 versus 51 \pm 5.46) statistically significantly higher in preeclamptic as compared to normal controls ($p < 0.05$). Mean LDL-C levels were (132.95 mg/dl \pm 32.26 versus 99.36 \pm 17.75) statistically significantly higher in preeclamptic as compared to normal controls ($p < 0.05$). Kalar et al., 2012 concluded that Preeclamptic 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., 2011 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 (Ogbe et al., 2013).

Ogbe John Raphael et al., 2013 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, 2013 evaluated the levels of serum uric acid, creatinine and urea in pre-eclamptic and normotensive groups, and reported that the levels of uric acid and creatinine, expressed in mg/ dl were significantly elevated in preeclamptics respectively (5.29 \pm 0.84 and 0.72 \pm 0.387) when compared to normotensives (3.86 \pm 0.92 and 0.58 \pm 0.283). There was a statistically insignificant and small increase in urea level in pre-eclamptics (28.07 \pm 4.97) compared to normotensives (26.46 \pm 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, 2013 concluded that creatinine clearance fall gradually in cases from mild to severe Preeclamptic 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., 2012 [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.

4. Conclusion

In preeclamptic 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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