Serum Tumor Necrosis Factor Alpha Receptor 2 in Pregnant Females Prior To Pre-Eclampsia

Khaled K. Aly[1], Mohammad AbdelHameed M. Nasr AdDeen[1], Gehane M. Hamed[2] and Nermeen G. Mohamed[1]

[1]Department of Obstetrics and Gynecology, [2] Department of Physiology,
Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT: This study aimed to measure the level of circulating soluble serum TNF-R2 to assess its accuracy as a predictor of pre-eclampsia during early pregnancy. Ninety pregnant women at 22-26 weeks of gestation having criteria making them liable to develop pre-eclampsia attending to the antenatal care and obstetric clinic department, at the faculty of Medicine, Ain Shams University, Maternity Hospital. They included 2 groups of women: Group I (n=45) including women who developed pre-eclampsia; and Group II (n=45) including women who remained normotensive and non-proteinuric till delivery. Both groups were subjected to careful history taking and physical examination, all the cases were subjected to serum collection within 22-26 wks of gestation, the blood was collected for determination of soluble tumor necrosis factor receptor-2 level using ELISA technique. The results of the present study showed that there were no significant differences between women of both groups concerning age and gestational age at recruitment. The mean value of serum level of TNF-R_2 was significantly higher in women who developed pre-eclampsia when compared to women of the control group. In addition, significant increase in mean serum TNF-R_2 was found in women who developed severe preeclampsia. Also, there was a significant positive correlation between serum TNF-R2 and each of systolic, diastolic and mean arterial blood pressure in preeclamptic women.

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Introduction

Preeclampsia (PE) affects 5% -7% of healthy nulliparous women and is a major cause of maternal and fetal morbidity and mortality ***(Sibai et al., 2005).*** It is further subclassified into early onset and late onset PE, mild and severe PE, and into a maternal and fetal syndrome ***(Von Dodelszen et al, 2003).*** The syndrome is characterized by hypertension and proteinuria, and a common fetal feature is intrauterine growth restriction ***(ACOG, 2002).***

The pathophysiologic processes that underlie preeclampsia have been proposed by ***Roberts & Gamil (2005)*** to occur in two stages: stage 1; reduced placental perfusion, and stage 2; the maternal clinical syndrome**.** The authors added that placental ischemia/hypoxia causes release of a variety of placental factors that have profound effects on blood flow and arterial pressure regulation ***(Roberts & Gamil, 2005).*** Up till now, there is no effective prevention or treatment strategies for women with this disease , except for early delivery of fetus and placenta.

The initiating event in preeclampsia is thought to be inadequate trophoblastic invasion into the uterine spiral arteries early in gestation that leads to a reduction in uteroplacental perfusion with the potential for placental ischemia ***(Roberts & Gamil, 2005***). Placental ischemia is accompanied with a widespread dysfunction of the maternal vascular endothelium and the release of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), Interleukin-1 (IL-1) and Interleukin-6 (IL-6); which have been shown to be elevated approximately two folds in women with preeclampsia as well as in placental explants from preeclamptic pregnancies compared to those from normal pregnant women cultured in hypoxic environment ***(Conrad & Benyo, 1997).***

TNF-α exerts its effect by interacting with two receptors, which have distinct biological effects, the 55 KDa TNF- receptor (TNF-R_1) that induces apoptosis and the 75- KDa (TNF-R_2) that induces proliferation through activation of the transcription factor ***(Bazzoni & Beutler, 1996).*** Shedding of the soluble receptors of TNF-α from the cell membranes plays a role in the regulation of TNF-α biological functions by decreasing its availability as a ligand ***(Aderka et al., 1998).***

TNF-R_1 is constitutively expressed in most tissues and seems to be the key mediator of TNF signalling. In contrast, TNF-R_2 is strongly regulated and predominantly found in immune cells indicating that this receptor plays a major role in the lymphoid system . The extracellular domains of both receptors can also be cleaved from the membrane resulting in

the production of soluble TNF (sTNF) receptors ***(Grell et al., 1995).***

Most, but not all studies reported elevated circulating maternal TNF-α ***(Page et al., 2000; Tosun et al., 2010),*** TNF-R_1, and TNF-R_2 concentrations during overt preeclampsia ***(Schipper et al., 2005).*** We could locate only 2 studies reporting elevations in sTNF-R_1 concentrations ***(Williams et al., 1999; Schipper et al., 2005)***, and one evaluating sTNF-R_2, prior to clinical manifestations of the disease ***(Sibai et al., 2009).*** Thus, this study aimed to measure the level of circulating serum sTNF-R_2 to assess its accuracy as a predictor to pre-eclampsia during early pregnancy in those at risk for development of preeclampsia.

2. Materials and Methods

This study was carried out on 600 pregnant women at 22-26 weeks of gestation attending to the antenatal care and obstetric clinic department, at the faculty of Medicine, Ain Shams University, Maternity Hospital during the period between January 2010 to October 2010.

Study size:

An assumption that incidence of preeclampsia is up to 10% in high risk group and to demonstrate a 30% difference in TNF-R2 between normal and preeclamptic pregnant women at a power of 80 and α-error of 0.05 in addition to an estimated drop at rate of 20% , it had mandated us to include 600 cases to be recruited originally to obtain a final number of 90 cases divided in to 2 equal .

Criteria of selected group:

Primigravida, subjected to detailed history with special reference to present, past, family and obstetric histories. Present history: Age, duration of marriage , occupation, residence, special habits; Past history: history of chronic illness especially hypertention, history of previous operations, blood transfusion, drug allergy; Family history: Consangunity, history of twin, history of congenital anomalies, history of preeclampsia, or hypertention with pregnancy; Obstetric history: Primigravid ; Menstrual history: Rhythm, rate, last menstrual period; Contraceptive history: Type of contraception , its duration, its side effects if found.

Complete physical examination:

- Blood pressure measured in a semi-recumbent position with a standard mercury sphygmomanometer with an appropriate sized cuff that will be placed at the level of the heart then two blood pressure recordings 6 hours apart will be obtained.
- Blood pressure is measured regularly every one month till 26 weeks of gestation then every two weeks till 36 weeks of gestation then every one week till delivery.

Methods of study

Serum was collected within 22-26 wks gestation, the blood was collected into plain tubes, centrifuged, and the serum fraction was aliquotted and was stored at -70° C for the future studies. After follow-up, cases developed pre-eclampsia were recorded, after exclusion of drop out cases, 45 cases were selected randomly to be enrolled in the analysis. On the other hand, 45 cases from the normotensive cases were selected randomly to be compared with the analysis.

Laboratory investigations:

Serum level of soluble tumor necrosis factor receptor-2 was measured using ELISA technique, as described by ***Tartaglia & Goeddel (1992).***

Statistical analysis:

The collected data were organized, tabulated and statistically analyzed by computer software using SPSS version 16 ***(Armitage & Berry, 1987)*** for quantitative data, the mean, standard deviation were calculated. Parametric data was compared using student T test, non parametric data was compared using chi square test. Correlation was analysed using Pearson correlation test. The diagnostic value of TNF-R2 was analyzed using sensitivity specifity positive & negative predictive values & accuracy. Area under the curve suggested the value that could be considered to be a cut of value for TNF-R_2. Significance was adopted at $P< 0.05$ for interpretation of the results of tests of significance.

3. Results

After exclusion of drop out cases, 52 cases had developed pre-eclampsia, from which 45 cases (Group I) were selected randomly to be enrolled in the analysis, and 45 women (Group II) including women who remained normotensive and non-proteinuric till delivery.

Both groups were matched concerning age and gestational age at recruitment ($P> 0.05$) (table-1). The mean gestational age at delivery was significantly lower in women who developed pre-eclampsia when compared to women of the normotensive group ($P< 0.001$) (table-1, figure-1).

The distribution of TNF-R_2 values in included cases and controls showed a non-normal (positively-skewed) distribution. Extreme values (3 in group I and 3 in group II) were, therefore, excluded from

analysis, in order to apply parametric tests on TNF-R_2 (Kolmogorov Smirnov test).

The mean serum level of TNF-R_2 was significantly higher in women who developed pre-eclampsia when compared to women of the control group (P< 0.001) (table-2, figure-2).

Receiver operator characteristics (ROC) curve was constructed for serum level of TNF-R_2 as predictor of development pre-eclampsia (figure-3). Area under the curve was 1.0 [95% CI (1.0 to 1.0), p<0.001] (table-3). The best cutoff point of serum TNF-R2 as predictor of developing preeclampsia was ≥ 2866 pg/ml [sensitivity 100%, specificity 100%, PPV 100%, NPV 100%, overall accuracy 100%, LR+ ∞, LR- 0] (table-4).

ROC curve was constructed for serum level of TNF-R_2 as predictor of development pre-eclampsia at gestational age < 34 weeks (figure-4). Area under the curve was 0.991 [95% CI (0.972 to 1.009), p<0.001] (table-5). The best cutoff point of serum TNF-R_2 as predictor of preeclampsia at gestational age < 34 weeks was ≥ 3586.5 pg/ml [sensitivity 100%, specificity 81.2%, PPV 84.1%, NPV 100%, overall accuracy 90.6%, LR+ 5.3, LR- 0] (table-6).

ROC curve was constructed for serum level of TNF-R_2 as predictor of delivery at gestational age < 34 weeks among pre-eclamptic women (figure-5). Area under the curve was 0.943 [95% CI (0.880 to 1.005), p<0.001] (table-7). The best cutoff point of serum TNF-R_2 as predictor of delivery at gestational age < 34 weeks was ≥ 3815 pg/ml [sensitivity 100%, specificity 89.5%, PPV 90%, NPV 100%, overall accuracy 94.4%, LR+ 9, LR- 0] (table-8).

There was a significant positive correlation between serum TNF-R_2 and each of systolic blood pressure (r_s=0.495, p=0.001), diastolic blood pressure (r_s=0.403, p=0.006) and mean arterial blood pressure (r_s=0.445, p=0.002) [table-9, figures 6-8].

The mean serum TNF-R_2 was significantly higher in women with severe pre-eclampsia when compared to women with mild pre-eclampsia (table-10, figure-9).

ROC curve was constructed for serum TNF-R_2 as predictor of severe pre-eclampsia. There was a significant association [AUC = 0.900, 95% CI (0.802 to 0.999), p<0.001] (figure-10, table-11). The best cutoff value of serum TNF-R_2 as predictor severe pre-eclampsia was ≥ 3801 pg/ml (sensitivity 87.5%, specificity 81.1%, PPV 50%, NPV 96.8%, overall accuracy 82.2%, LR+ 4.6, LR- 0.15) [table-12].

Table-1: Difference between the Study Groups concerning Initial Characteristics

	Group I [Pre-eclamptic Women] (n=45)	Group II [Control Women] (n=45)	*P**
Age (Years)			
Range:	17 – 35	17 – 39	>0.05
Mean ± SD:	23.62 ± 4.22	24.18 ± 5.4	NS
Gestational Age at Recruitment (Weeks)			
Range:	22 – 26	22 – 26	>0.05
Mean ± SD:	23.73 ± 1.42	24.24 ± 1.26	NS
Gestational Age at Delivery (Weeks)			
Range:	31 – 39	36 – 40	<0.001
Mean ± SD:	36.71 ± 1.69	38.78 ± 1.24	HS

* Analysis using Independent Student's t-Test NS: non-significant HS: highly significant

Table-2: Difference between the Study Groups concerning Serum Level of TNF-R_2

	Group I [Pre-eclamptic Women] (n=45)	Group II [Control Women] (n=45)	*P**
Serum TNF-R2 (pg/ml)			
Range:	3170 – 4250	1290 – 2562	<0.001
Mean ± SD	3681.19 ± 223.29	1597.69 ± 349.17	HS

* Analysis using Independent student's t-test HS: highly significant

Table-3: Area under the ROC Curve for Serum TNF-R_2 as Predictor of Pre-eclampsia

	AUC	*P*	95% CI
TNF-R2 as Predictor of Developing Pre-eclampsia	1.0	<0.001 HS	1.0 to 1.0

AUC area under the curve HS: highly significant 95% CI: 95% Confidence Interval

Table-4: Diagnostic Accuracy of Serum TNF-R_2 as Predictor of Pre-eclampsia

	Sensitivity	Specificity	PPV	NPV	Overall Accuracy	LR+	LR-
TNF-R2 as Predictor of Developing Pre-eclampsia ≥ 2866 pg/ml	100%	100%	100%	100%	100%	∞	0

PPV positive predictive value, NPV negative predictive value, LR+ positive likelihood ratio, LR- negative likelihood ratio

Table-5: Area under the ROC Curve for Serum TNF-R2 as Predictor of Developing Pre-eclampsia at Gestational Age < 34 weeks

	AUC	*P*	95% CI
TNF-R2 as Predictor of Developing Pre-eclampsia	0.991	<0.001 HS	0.972 to 1.009

AUC area under the curve HS: highly significant 95% CI: 95% Confidence Interval

Table-6: Diagnostic Accuracy of Serum TNF-R2 as Predictor of Developing Pre-eclampsia at Gestational Age < 34 weeks

	Sensitivity	Specificity	PPV	NPV	Overall Accuracy	LR+	LR-
TNF-R2 as Predictor of Developing Pre-eclampsia ≥ 3586.5 pg/ml	100%	81.2%	84.1%	100%	90.6%	5.3	0

PPV positive predictive value, NPV negative predictive value, LR+ positive likelihood ratio, LR- negative likelihood ratio

Table-7: Area under the ROC Curve for Serum TNF-R2 as Predictor of Delivery at Gestational Age < 34 weeks among Preeclamptic Group

	AUC	*P*	95% CI
TNF-R2 as Predictor of Delivery < 34 weeks among Pre-eclamptic Women	0.943	<0.001 HS	0.880 to 1.005

AUC area under the curve, HS: highly significant, 95% CI: 95% Confidence Interval

Table-8: Diagnostic Accuracy of Serum TNF-R2 as Predictor of Delivery at Gestational Age < 34 weeks among Preeclamptic Group

	Sensitivity	Specificity	PPV	NPV	Overall Accuracy	LR+	LR-
TNF-R2 as Predictor of Delivery < 34 weeks among Pre-eclamptic Women ≥ 3815 pg/ml	100%	89.5%	90%	100%	94.4%	9	0

PPV positive predictive value, NPV negative predictive value, LR+ positive likelihood ratio, LR- negative likelihood ratio

Table-9 Correlation between Serum TNF-R2 Level and Systolic Blood Pressure among Pre-eclamptic Group

		Systolic Blood Pressure	Diastolic Blood Pressure	Mean Arterial Blood Pressure
Serum TNF-R2	r_s	0.495	0.403	0.445
	P	0.001 S	0.006 S	0.002 S

r_s Spearman's rank correlation coefficient, S: significant

Table-10: Difference between the Mild and Severe Pre-eclamptic Women concerning Serum Level of TNF-R2

Pre-eclamptic Group	Mild Pre-eclampsia (n=37)	Severe Pre-eclampsia (n=8)	*P**
Serum TNF-R2 (pg/ml)			
Range:	3170 – 4250	3710 – 3980	0.043
Mean ± SD	3655.7 ± 223.32	3869.8 ± 108.5	S

* Analysis using Independent student's t-test, S: significant

Table-11: Area under the ROC Curve for Serum TNF-R2 as Predictor of Severity of Pre-eclampsia

	AUC	*P*	95% CI
TNF-R2 as Predictor of Severe Pre-eclampsia	0.900	<0.001 HS	0.802 to 0.999

AUC area under the curve, HS: highly significant, 95% CI: 95% Confidence Interval

Table-12: Diagnostic Accuracy of Serum TNF-R2 as Predictor of Severity of Pre-eclampsia

	Sensitivity	specificity	PPV	NPV	Overall Accuracy	LR+	LR-
TNF-R2 as Predictor of Severe Pre-eclampsia ≥ 3801 pg/ml	87.5%	81.1%	50%	96.8%	82.2%	4.6	0.15

PPV positive predictive value, NPV negative predictive value, LR+ positive likelihood ratio, LR- negative likelihood ratio

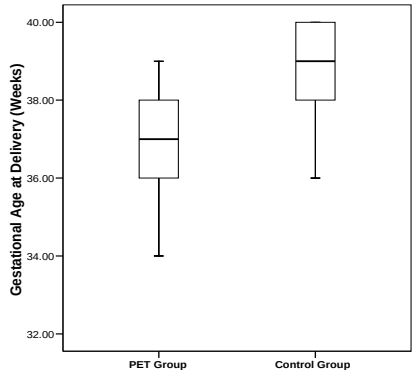


Figure-1: Box-Plot Chart showing Difference between the Study Groups concerning Gestational Age at Delivery.

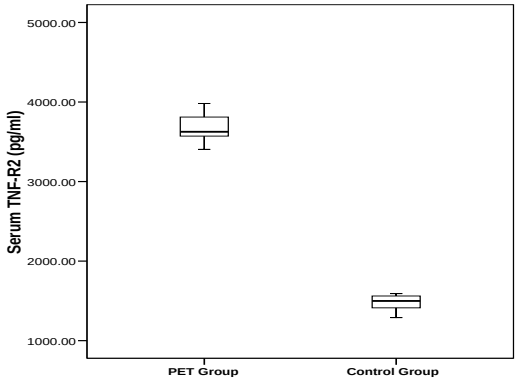


Figure-2: Box-Plot Chart showing Difference between the Study Groups concerning Serum Level of TNF-R2.

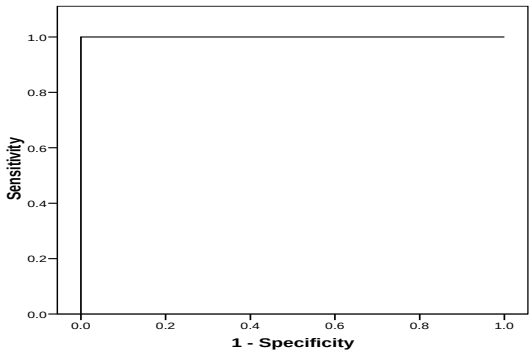


Figure-3: ROC Curve for Serum TNF-R2 as Predictor of Pre-eclampsia.

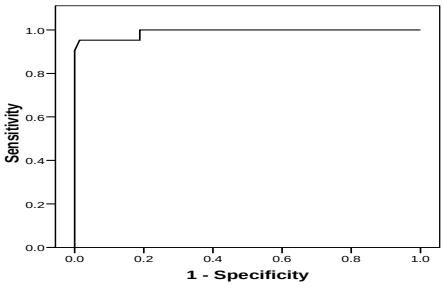


Figure-4: ROC Curve for Serum TNF-R2 as Predictor of Developing Pre-eclampsia at Gestational Age < 34 Weeks

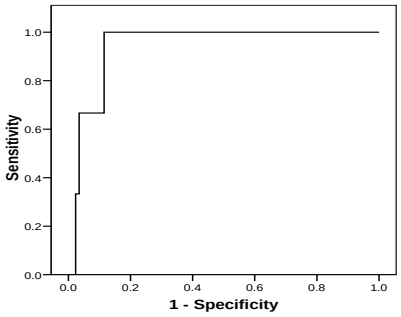
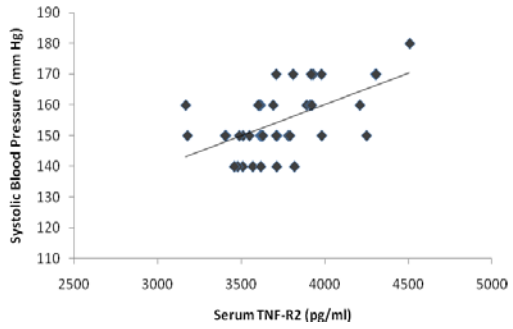
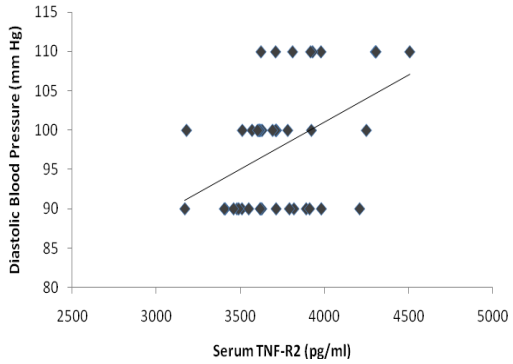


Figure-5: ROC Curve for Serum TNF-R2 as Predictor of Delivery at Gestational Age < 34 Weeks among Pre-eclamptic Women.



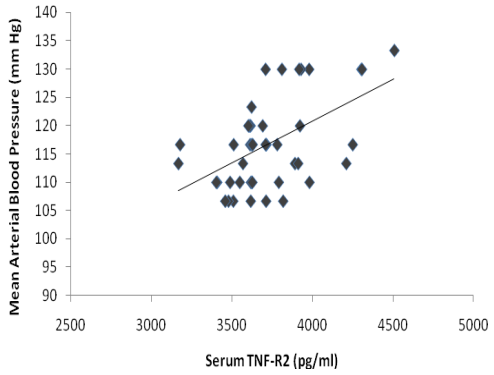
r_s=0.495, p=0.001

Figure-6 Scatter-Plot showing Correlation between Serum TNF-R2 Level and Systolic Blood Pressure among Pre-eclamptic women.



r_s=0.403, p=0.006

Figure-7 Scatter-Plot showing Correlation between Serum TNF-R2 Level and Diastolic Blood Pressure among Pre-eclamptic women.



r_s=0.445, p=0.002

Figure-8 Scatter-Plot showing Correlation between Serum TNF-R2 Level and Mean Arterial Blood Pressure among Pre-eclamptic women.

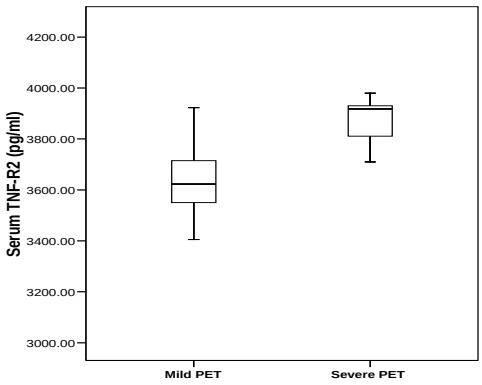


Figure-9: Box-Plot Chart showing Difference between the Mild and Severe Pre-eclamptic Women concerning Serum Level of TNF-R2

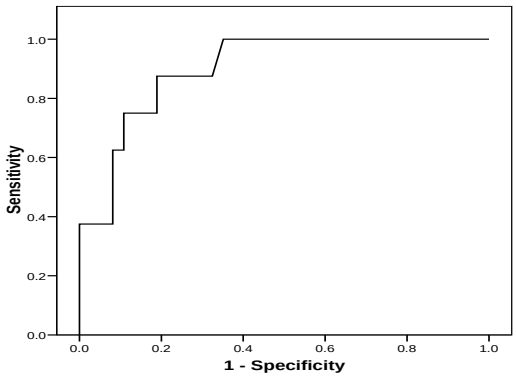


Figure-10: ROC Curve for Serum TNF-R2 as Predictor of Severity of Pre-eclampsia

4. Discussion

The present study revealed a significant elevation in the mean serum TNF-R_2, at 22-26 weeks' gestation in patients subsequently develop preeclampsia at less than 34 weeks gestation. Comparing women who develop severe preeclampsia with those who develop mild preeclampsia, a significant increase in mean serum TNF-R_2 was found in women who develop severe preeclampsia. In addition, there is a significant positive correlation

between serum TNF-R_2 and each of systolic, diastolic and mean arterial blood pressure. These results suggest the presence of an increased systemic inflammatory response early in pregnancy, reflected by increased serum TNF-R_2 concentrations, in patients destined to develop preeclampsia before 34 week's gestation.

Despite the indisputable role of TNF-*a* in the pathophysiology of preeclampsia, this protein is a bad biomarker in blood and its detection is not always reliable because of its high susceptibility to degradation. Thus, TNF-R_2 appears a better biomarker compared with TNF-*a*. It has already demonstrated that the expressions of TNF-R_2 and TNF-*a* were interdependent and follow the same pattern in placentas from women with and without preeclampsia ***(Kharfi et al., 2006).***

The elevated maternal concentrations of serum sTNF-R_2 in the present study, denotes elevation of TNF-alpha which may be a part of the pathogenesis of preeclampsia ***(Kocyigit et al., 2004).*** The strength of this study is that it provides information about sTNF-R_2 concentrations early in pregnancy in a considerable number of women considered at very high risk for development of preeclampsia. The best cutoff point of serum TNF-R_2 as predictor of preeclampsia at gestational age < 34 weeks was ≥ 3586.5 pg/ml [sensitivity 100%, specificity 81.2%, PPV 84.1%, NPV 100%, overall accuracy 90.6%, LR+ 5.3, LR- 0].

The results of the present study came in accordance with ***Sibai et al.*** results; which revealed an increase in serum TNF-R_2 in maternal blood before the clinical manifestation of preeclampsia. Using a cutoff value of the 75th percentile, the authors added that elevated concentrations of TNF-R_2 had poor sensitivity (27.3%) and a limited positive predictive value (23.2%) for subsequent diagnosis of preeclampsia, and so the authors suggested that measurement of s-TNF-R_2 early in pregnancy has limitations ***(Sibai et al., 2009).***

In parallel to the study of Sibai et al., it has been demonstrated increased levels of hydrogen peroxide (H_2O_2) early from the 10th week of gestation in maternal circulation of women with preeclampsia, as well as placentas from preeclamptic women exhibit more H_2O_2 than normotensive women. These results suggested that oxidative stress seen in preeclampsia affects both maternal circulation and the placenta. These findings also proved a potential link between H_2O_2 and TNF-R_2 in preeclampsia, providing two interdependent biomarkers ***(Aris et al., 2009).***

Under normal conditions, cells use their antioxidant defenses, which convert H_2O_2 to oxygen and water, thereby keeping the production of the reactive oxygen species (ROS) system under control. Increased H_2O_2 can result from overproduction of ROS and/or decreased antioxidant capacity. *In vitro* experiments showed that H_2O_2 induces increased release of sTNF-R_2 by cytotrophoblasts, confirming the hypothesis that H_2O_2 is an inductor of sTNF-R_2 synthesis and providing a convincing model of the induction of inflammation by oxidative stress, a phenomenon now called inflammatory stress. Excessive production of ROS and inflammatory factors may occur at certain windows in placental development and in pathologic pregnancies; such as those complicated by preeclampsia and/or intrauterine growth restriction, overpowering antioxidant defenses with deleterious outcome ***(Myatt & Cui, 2004).***

The etiology of preeclampsia is still open to debate, but oxidative stress and inflammation have been shown to be associated with shallow placentation in preeclamptic pregnancies. It is now postulated that these associations may result from a combination of immunologic, environmental, and genetic factors leading to the failure of normal trophoblastic invasion and remodeling of the uterine spiral arteries ***(Kharfi et al., 2003).*** These defects may cause underperfusion, ischemia, and hypoxia in placenta ***(Lyall & Myatt, 2002),*** which is then thought to release in maternal circulation a variety of mediators including proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-*a*), interleukins (IL-1 and IL-6), interferon gamma (INF-χ), and reactive oxygen species (ROS) such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2) ***(Kharfi et al., 2005).*** Such mediators are thought to cause endothelial dysfunction and permanent systemic vasoconstriction characterizing preeclampsia ***(Myatt & Webster, 2009).***

Several lines of evidence support the hypothesis that the ischemic placenta contributes to endothelial cell activation/dysfunction of the maternal circulation by enhancing the synthesis of cytokines such as TNF-α, which has been shown to induced structural as well as functional alterations in endothelial cells, as well as it enhances the formation of a number of endothelial cell substances such as endothelin and reduces acetylcholine-induced vasodilatation ***(Alexander et al., 2001).*** Some studies have found higher endothelin plasma concentrations of ≈2- to 3-fold in women with preeclampsia ***(Dekker et al., 1991).*** Typically, plasma levels of endothelin are highest during the latter stage of the disease, suggesting that endothelin may not be involved in the initiation of preeclampsia, but rather in the progression of disease into a malignant phase ***(Wang et al., 1994).***

It has also reported that the hypertension in response to chronic reductions in utero-placental perfusion pressure in the pregnant rat is associated with significant increases in renal expression of preproendothelin and serum levels of TNF-α ***(LaMarca et al., 2005).***

Moreover, there is considerable evidence linking angiotensin II to the regulation of TNF-α. TNF-α can be increased via angiotensin II–induced angiotensin type-1 receptor activation in endothelial cells (***Arenas et al., 2004)*** and can result in end-organ damage in both the heart ***(Kalra et al., 2002)*** and kidney ***(Ruiz-Ortega et al., 2002).*** In addition, apoptosis by TNF-α was found to require functional angiotensin type-1 receptor activation by angiotensin II in target cells ***(Wang et al., 1999 and Papp et al., 2002).*** Taken together, these and other reports suggest that angiotensin type-1 receptor signaling and the release of TNF-α are closely related. Therefore, in the setting of preeclampsia, excessive activation of the angiotensin type-1 receptor by the autoantibody may lead to deleterious increases in TNF-α, resulting in maternal symptoms ***(Irani et al., 2010).***

Considerable clinical evidence has accumulated that preeclampsia is strongly linked to an imbalance between proangiogenic and antiangiogenic factors in the maternal circulation. Also, plasma and amniotic fluid concentrations as well as placental soluble fms like tyrosine kinase-1 (sFlt-1) mRNA are increased in preeclamptic patients ***(Lam et al., 2005 and Lindheimer & Romero, 2007).*** Moreover, inhibition of vascular endothelial growth factor (VEGF-A) and placenta growth factor (PlGF) action through over-expression of soluble fms-like tyrosine kinase-1 (sFlt-1) causes a pre-eclampsia-like syndrome in pregnant rats was reported in the study of ***Maynard et al. (2003).*** Soluble fms-like tyrosine kinase-1 (sFlt-1) is formed by alternative splicing of the pre-mRNA encoding the full-length-signalling VEGF-R1 receptor, and lacks the cytoplasmic and transmembrane domains ***(Kendall & Thomas, 1993).*** Recently, Herse et al. in their study have reported that increased sFlt-1 may have a predictive value in diagnosing preeclampsia as concentrations seem to increase before manifestation of overt symptoms (e.g., hypertension, proteinuria) ***(Herse et al., 2009).*** These same clinical findings and imbalances in angiogenic factors were found to be reproducible in the rat model via lentiviral overexpression of sFlt-1 ***(Maynard et al., 2003; Gilbert et al., 2007).*** Following this discovery, other investigators revealed that infusion of a proangiogenic factor (e.g., vascular endothelial growth factor) into pregnant rats would attenuate blood pressure elevations and renal damage observed in pregnant rats overexpressing sFlt-1 ***(Li et al., 2007).***

In summary, our results reveal that among women at high risk for preeclampsia, the serum concentrations of TNF-R_2 at 22-26 weeks' gestation are higher in women later diagnosed with preeclampsia than in women not diagnosed with preeclampsia. This finding provides support that level of serum TNF- α receptor 2 should be taken into consideration as a predictor of preeclampsia and may act as a pathophysiological relevant factor in the development of preeclampsia.

In conclusion, the results of the present study should be verified in a prospectively designed study with serial measurements of sTNF-R_2 concentrations. Further studies however are to be recommended that will involve larger study population.

Corresponding author
Gehane M. Hamed
Department of Physiology, Faculty of Medicine, Ain Shams University, Cairo, Egypt

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