Evaluation of Serum Leptin and Androgens Levels in Preeclampsia: Relation with Disease Severity

Naglaa Ghanayem[1], Ashraf Dawood[*1], Rania Azmy[1]and Alaa El Halaby[2]

[1]Medical Biochemistry, and [2] Obstetric and Gynecology Departments, Menofia University
[*]kingashrafdawood@yahoo.com

Abstract: Preeclampsia along with its complications seems to be one of the major causes of maternal morbidity and mortality. Despite numerous studies, the pathology of preeclampsia has not yet been fully elucidated. Serum leptin levels are increased in normal pregnancies and are more elevated in preeclampsia. Also, many studies have concluded that high levels of blood androgens have been observed in preeclamptic women and may implicate the pathogenesis of preeclampsia. This study aims to evaluate total maternal serum leptin and androgen levels in preeclampsia and to evaluate whether these levels are affected by the severity of the disease and if other factors such as BMI and these hormonal factors have a role in the overall regulation of leptin production. The study included a total numbers of 60 cases. Divided into 3 groups: Group I (mild preeclampsia): included 20 pregnant females suffering from mild preeclampsia. Group II (severe preeclampsia): included 20 pregnant females with severe preeclampsia and Group III (controls):- included 20 healthy pregnant females with comparable maternal and gestational age. Total serum Sex hormone binding globulin (SHBG) Dehydroepiandesterone-sulphate(DHEA-S), leptin, Estradiol, free and total testosterone levels were measured in all subjects. The result indicated that Leptin, E2 and testosterone are significantly increased in preeclampsia than control ($p < 0.0001$) and correlates with severity ($p < 0.0001$). SHBG levels are significantly higher ($p < 0.0001$) in preeclampsia while the level of DHEA-S is not statistically different when compared to normal pregnant group (> 0.05). The elevated leptin levels are not associated with preeclampsia independently from BMI and estradiol levels. The study concluded that the levels of serum leptin are higher in women with preeclampsia than controls and that elevation could possibly be related to the underlying relationship between leptin levels and BMI and estradiol level.
[Naglaa Ghanayem, Ashraf Dawood, Rania Azmy and Alaa El Halaby, **Evaluation of Serum Leptin and Androgens Levels in Preeclampsia: Relation with Disease Severity**. Journal of American Science 2011; 7(9): 366-372].(ISSN: 1545-1003). http://www.americanscience.org.

Key words: Leptin, androgens, preeclampsia.

1. Introduction

Preeclampsia is a pregnancy-specific, multisystem disorder that is characterized by the development of hypertension and proteinuria after 20 weeks of gestation in a woman with previously normal blood pressure *(Taghavi, 2007).* Leptin, a16 kda non-glycosylated polypeptide produced by obesity (ob) gene, is mainly produced and secreted by fat cells in proportion to fat mass *(Iftikhar et al., 2008)*, Under the supervision of ob gene, placental trophoblasts also synthesize leptin and this is responsible for the significant increase of plasma leptin during the first 2 trimesters of normal pregnancy *(Sucak et al., 2010).* Also, the prominent alternations of maternal weight, energy expenditure and hormonal status attribute to this increase *(Jenkins et al., 2007).*In preeclampsia, the maternal plasma leptin levels are increased possibly because of the augmented placental production of hormones under hypoxic conditions. There is also evidence that inflammatory mediators increase plasma leptin concentration *(Mihu et al., 2009).*Since several other hormones influence both leptin levels and the development of preeclampsia, the distinct possibility exists that other hormonal factors may be responsible for the higher leptin levels in pregnancies complicated by preeclampsia *(Acromite et al., 2004).*

The aim of this study was to measure total maternal serum leptin and androgen levels in pregnant women with preeclampsia and evaluate whether these levels are affected by severity of the disease and if other factors such as BMI and hormonal factors have a role in the overall regulation of leptin production.

2. Material and Methods

The study included 60 pregnant women proven to have a single fetus by US. All the pregnant women participating in this study had given informed written consent before blood sampling. Approval was obtained from the Research Ethics Committee of Menofiya Faculty of Medicine. The pregnant women were enrolled from the Obstetric and Gynecology Department in Menofiya University Hospital. They were divided into 3 groups:-

Group I (mild preeclamptic group):- included 20 pregnant females suffering from mild preeclampsia (gestational age =32-37 weeks) with maternal ages ranging from 19-31 years. Group II (sever preeclamptic group) included 20 pregnant

females suffering from severe preeclampsia (gestational age = 34-40 weeks) with maternal ages ranging from 23-34 years, Group III: included 20 healthy pregnant females (gestational age = 34-39 weeks) of comparable maternal and gestational age.

Preeclampsia was defined according to American College of Obstetricians and Gynaecologists criteria as follow: - blood pressure equal or higher than 140/ 90 mmHg after 20 weeks of gestation (at two different measurements) and proteinuria ≥ 300 mg/dl *(Mihu et al., 2009)*. These criteria applied to women that were normotensive prior to pregnancy. Whereas severe preeclampsia was defined as blood pressure ≥160/ 110 mmHg and proteinuria ≥ 2.0 g/dl *(Sucak et al., 2010).*

Exclusion criteria included:-

1- History of hypertension
2- Hyperandrogenism
3- Polycystic ovarian disease
4- Hormonal treatment

All women participating in this study have been subjected to full history talking, general examination and then anthropometric data as weight, height and body mass index (BMI) were recorded for each subject enrolled in the study.

Laboratory investigation including: Serum uric acid, urea and creatinine, hormonal profile: leptin, E2, total and free testosterone,DHEA-S and SHBG.

Sample preparation:

10ml of peripheral venous blood was collected in plain vacutainer tube for serum separation. The blood samples were centrifuged at 3000g and the serum samples were stored at -20° C until analysis.

Serum uric acid and serum urea are estimated by enzymatic end point method *(Duncan et al., 1982; Taylor and Vadgama, 1992)*. Serum creatinine is estimated by enzymatic fixed rate colorimetric test *(Perrone et al., 1992)*. E2 and total testosterone are estimated by Immulite 2000 *(Ismail, 1986; Kricka, 2006)*.Leptin was estimated by DIA source Leptin-ELISA kit-Belgium *(Ma,1996)*, DHEA-S by APLICO Diagnostic, USA *(Holtzclaw and Gordon,1989)*, SHBG by Immuno-Biological Laboratories (IBL)-America *(Selby, 1990)* and free testosterone by ELISA GenWay Biotech, San Diego *(McCann and Kirkish,1985)*.

Statistical analysis:

The data were analyzed using IBM computer with the aid of Microsoft Excel, SPSS version 11.5 and Epicalc 2000.The quantitative data were expressed in the form of numbers and percentage, qualitative data were represented as mean and standard deviation. Statistical analysis was made with the use of the following tests: Anova (F) test and Chi-square(X2).Pearson correlation was used to identify the direction and power of association between the qualitative variables. Multiple linear regression analysis was used to find out the independent effect of each of the possible predictors after adjustment of the other risk factors included in the model.

3. Results

In this study, concerning the study of the variables between preeclamptic cases and controls, there was no significant statistical difference regarding maternal age and mean gestational age between the two groups whereas, there was significant statistical difference regarding diastolic blood pressure, systolic blood pressure and body mass index (BMI). The serum levels of urea showed significant statistical difference between the preeclamptic subjects and controls ($p<0.001$) while serum creatinine levels did not show statistical difference between the two groups ($p>0.05$). Concerning the leptin levels, leptin levels were significantly higher in preeclamptic cases, whereas the hormonal profile showed that total and free testosterone levels, E2 and SHBG levels were significantly higher in preeclamptic cases while the levels of DHEA-S showed no statistical difference between the two groups (Table 2).

Concerning the severity of the disease, serum urea and uric acid were significantly higher in severe preeclamptic cases compared to mild cases while there was no significant statistical difference between the two groups regarding serum creatinine levels ($p>0.05$). The levels of free and total testosterone also showed significant statistical difference between mild and severe cases while the levels of E2, DHEA-S and SHBG showed no statistical difference between the two groups (Table 2).

Concerning the correlation between leptin levels and other anthropometric and hormonal factors, the spearman correlation coefficient showed that the leptin levels are significantly associated with BMI and estradiol levels in preeclamptic cases while it was associated with BMI only in control group (Tables 3, 4).

A multiple linear regression analysis for the possible risk factors for increased leptin levels was made. After adjustment for all potentially confounding variables, it was found that the study group, BMI and estradiol levels were significant predictors for leptin levels while age, gestational age, total and free testosterone, DHEA- S and SHBG were not independent predictors for leptin levels and this indicates that elevated leptin levels by univariant analysis could possibly be related to the underlying

relationship between leptin levels and BMI and E2 levels.

Table (1): Clinical characteristics of the studied groups

Parameters	Studied groups (n=60)			Test of significance	p-value
	Mild preeclampsia (n=20) ($\bar{X}$± SD)	Severe preeclampsia (n=20) ($\bar{X}$± SD)	Control (n=20) ($\bar{X}$± SD)		
Age (years)	27.0±3.7	29.7±2.9	28.1±2.4	**Anova (F) test=** 3.98	P1 >0.05 P2 >0.05 P3 >0.05
Gest. age (wks)	35.0±1.5	36.1±1.6	37.0±1.3	**Anova (F) test=** 8.88	P1 >0.05 P2 >0.05 P3 >0.05
DBP (mm/Hg)	100.0±0.01	111.0±8.5	77.0±8.0	**Anova (F) test=** 131.98	P1 **<0.0001*** P2 **<0.0001*** P3 **<0.0001***
SBP (mm/Hg)	142.0±5.2	169.5±11.5	115.0±7.6	**Anova (F) test=** 205.70	P1 **<0.0001*** P2 **<0.0001*** P3 **<0.0001***
Body mass index (BMI) (Kg/m²)	31.1±2.3	32.6±2.2	27.7±1.3	**Anova (F) test=** 30.66	P1 **<0.0001*** P2 **<0.0001*** P3 **<0.0001***

Insignificant = P >0.05 * highly significant = P <0.001 P1= Mild preeclampsia Vs control
P2= Severe preeclampsia Vs control P3= Mild preeclampsia Vs Severe preeclampsia

Table (2): Statistical comparison of studied parameters between studied groups

Parameters	Studied groups (n=60)			Anova (F) test	p-value
	Mild preeclampsia (n=20) ($\bar{X}$± SD)	Severe preeclampsia (n=20) ($\bar{X}$± SD)	Control (n=20) ($\bar{X}$± SD)		
Blood urea (mg/dl)	30.9±8.1	42.9±11.5	27.0±2.5	20.3	P1 >0.05 P2 **<0.0001***** P3 **<0.0001*****
S. creatinine (mg/dl)	0.81±0.15	0.79±0.14	0.78±0.11	0.38	P1 >0.05 P2 >0.05 P3 >0.05
Uric acid (mg/dl)	4.3±0.9	6.7±1.2	3.2±0.7	68.9	P1 **<0.0001***** P2 **<0.0001***** P3 **<0.0001*****
Leptin (ng/ml)	43.5±4.8	71.1±8.7	26.9±2.7	281.2	P1 **<0.0001***** P2 **<0.0001***** P3 **<0.0001*****
E2 (Pg/ml)	7673.3±672.5	7349.4±726.2	5206.2±488.6	88.5	P1 **<0.0001***** P2 **<0.0001***** P3 >0.05
Total test. (ng/ml)	0.92±0.16	1.05±0.22	0.62±0.11	33.7	P1 **<0.0001***** P2 **<0.0001***** P3 **<0.0001*****
Free test. (Pg/ml)	2.0±0.4	2.3±0.4	1.3±0.2	53.6	P1 **<0.0001***** P2 **<0.0001***** P3 **<0.0001*****
DHEA-S (µg/dl)	161.8±20.3	161.7±21.8	158.5±19.4	0.2	P1 >0.05 P2 >0.05 P3 >0.05
SHBG (nmol/L)	257.4±18.8	263.2±17.2	355.5±42.0	75.2	P1 **<0.0001***** P2 **<0.0001***** P3 >0.05

Insignificant = P >0.05 * highly significant = P <0.001 P1= Mild preeclampsia Vs control
P2= Severe preeclampsia Vs control P3= Mild preeclampsia Vs Severe preeclampsia

Table (3): Pearson's correlation between the levels of leptin and each of maternal age, gestational age, BMI and studied chemical and hormonal profile in preeclamptic group (n=40).

Parameters	Leptin	
	(r)	p-value
Age (years)	- 0.34	P >0.05
Gest.age (weeks)	0.17	P >0.05
BMI (Kg/m²)	**0.58****	P **<0.001**
Urea (mg/dl)	0.31	P >0.05
Creatinine (mg/dl)	- 0.01	P >0.05
Uric acid (mg/dl)	0.04	P >0.05
E2 (Pg/ml)	**- 0.61****	P **<0.001**
Total testosterone (ng/ml)	- 0.01	P >0.05
Free testosterone (Pg/ml)	0.08	P >0.05
DHEA-S (µg/dl)	- 0.01	P >0.05
SHBG (nmol/L)	- 0.12	P >0.05

Insignificant = P >0.05 ** highly significant = P <0.001

Table (4): Pearson's correlation between the levels of leptin and each of maternal age, gestational age, BMI and studied chemical and hormonal profile in control group (n=20).

Parameters	Leptin	
	(r)	p-value
Age	- 0.10	P >0.05
Gest.age	- 0.29	P >0.05
BMI	**0.71****	P **<0.001**
Urea	- 0.34	P >0.05
Creatinine	- 0.04	P >0.05
Uric acid	0.18	P >0.05
E2	- 0.28	P >0.05
Total test.	- 0.04	P >0.05
Free test.	0.08	P >0.05
DHEA-S	- 0.21	P >0.05
SHBG	- 0.13	P >0.05

Insignificant = P >0.05 * highly significant = P <0.001

Table (5): Multiple linear regression analysis for the possible risk factors of increased leptin levels in the preeclamptic cases.

Independent variables	S.E*	Standardized coefficients (β)	Odds ratio	p-value	Confidence intervals (95% level)	
					Lower bound	Upper bound
Group	**9.10**	**- 0.80**	**0.45**	**0.001****	**- 50.91**	**- 14.37**
Age	**0.41**	**0.08**	**1.05**	0.27	**- 0.48**	**2.12**
Gest.age	**0.92**	**0.09**	**1.09**	0.25	**- 0.77**	**2.92**
BMI	**0.70**	**0.45**	**1.57**	**0.0001****	**1.67**	**4.47**
E2	**0.002**	**- 0.38**	**0.68**	**0.011***	**- 0.01**	**- 0.001**
Total test.	**1.43**	**0.05**	**1.05**	0.81	**-25.24**	**32.23**
Free test.	**0.76**	**0.06**	**1.06**	0.78	**- 13.24**	**17.45**
DHEA-S	**0.006**	**- 0.07**	**0.93**	0.32	**- 0.19**	**0.06**
SHBG	**0.05**	**0.10**	**1.11**	0.45	**- 0.06**	**0.13**

Insignificant = P >0.05 * significant = P <0.01 ** highly significant = P <0.00

4. Discussion

Leptin, an adipocyte-derived peptide that binds to receptors to initiate a cascade of biological processes involved in regulating food intake and energy expenditure, has been implicated in the pathogenesis of preeclampsia *(Muy- Rivera et al., 2005).*

Preeclampsia which is a hypertensive disorder of pregnancy caused by placental hypoxemia secondary to shallow endovascular cytotrophoblast invasion of spiral arteries, is one of the major causes of maternal morbidity and mortality and known to affect approximately 5-10% of all pregnant women *(Young et al., 2010)*

Although the pathogenesis of preeclampsia has not been yet fully understood, several mechanisms have been studied in relation to increase in serum androgens. It has a relation with alternations in the vascular sensitivity to some endogenous hormones such as angotensin II, catecholamines and vasopressin which have important role in the increase in blood pressure

observed in preeclampsia *(Ghorashi and Sheikhvaton, 2008)*

Inspite of the fact that a number at cross sectional studies have found a significantly higher concentrations of leptin in preeclamptic pregnancies when compared to normal pregnancies, the exact role of leptin in the pathogenesis of preeclampsia is still undetermined *(Sucak et al.,2010).*

It was also found that leptin secretion is influenced by many hormonal and metabolic factors. In humans, insulin, glucocortcoides, thyroid hormones, estradiol and testosterone have been claimed to stimulate leptin secretion *(Henson and Castracane, 2006).*

So, a major question has been raised. Does the elevation of leptin levels in preeclamptic cases relate to the pathogenesis of the disorder itself only or it relates to the changes in hormonal and metabolic factors that accompany preeclampsia *(Atamer et al., 2004).*

The aim of this study was to evaluate leptin levels in preeclamptic pregnancies compared to controls, and to determine whether these levels are affected by severity of the disease and whether the elevation in leptin levels is independent from other confounding factors such as BMI and hormonal element.

In this study, there was no statistical difference between preeclamptic cases and controls regarding maternal age and gestational age while there was significant difference between the two groups regarding diastolic blood pressure, systolic blood pressure and BMI. This agrees with *Ghorashi and sheikhvatan (2008)* who showed the same results however BMI didn't differ between the two groups.

The present study showed that the levels of urea and uric acid were significantly higher in preeclamptic group compared to controls and were higher in severe cases compared to mid cases while serum creatinine showed no significant difference neither between preeclamptic cases and controls nor between severe and mild cases. This agrees with Larn *et al.* (2005) and Bainbridge and Roberts *et al.* (2008).

Makuyana et al. (2002) showed that all the renal indices: creatinine, uric acid and urea were significantly raised in preeclampsia.

In this study, serum levels of total and free testosterone, E2 and SHBG were significantly higher in preeclamptic group compared to controls while DHEA-S levels showed no statistical difference between the two groups. Only the levels of free and total testosterone showed relation to severity. These results are in line with Acromite *et al.* (2004) , Baksu *et al.* (2004), Valadan *et al.* (2006), Ghorashi and Sheikhvatan (2008).

Mohamed *et al.* (2009) found higher levels at free and total testosterone in preeclamptic group while SHBG levels were lower in preeclamptic group.

In the current study, leptin levels were significantly higher in preeclamptic group compared to controls and its levels were related to severity. This comes in line with Acromite *et al.* (2004); Atamer *et al.* (2004); Kocygit *et al.* (2004), Haugen *et al.* (2006) and Mihu *et al.* (2009).

Martinez – Abundis *et al.* (2000) and Celik *et al.* (2004) did not report statistical difference between circulating leptin in preeclamptic pregnancies and normal pregnancy inspite of a slight increase of leptin levels in preeclamptic women.

Iftikhar *et al.* (2008) explained the raised level of leptin in preeclamptic women by increased BMI however it suggested that it plays a minor role since BMI in this case doesn't accurately reflect fat because the fetus, placenta, amniotic fluid, increased plasma volume and available degree of extra-vascular fluid all increase maternal weight. Impaired renal function which is a pathophysiology component of preeclampsia may reflect reduced renal clearance of leptin. Another factor is the increased level of inflammatory mediators such as TNF- α and IL- 6 in preeclampsia which proved to be important factors for elevation of plasma leptin levels. Moreover, direct evidence supporting the hypothesis that hyperleptinemia in preeclampsia is mainly due to synthesis at placental level.

Concerning the correlation between leptin levels and other anthropometric and hormonal factors in preeclamptic group the current study showed that leptin levels were significantly positively associated with BMI and negatively associated with oestrogen levels.

Kafulafula *et al.* (2002) found that maternal age, parity and gestational age didn't show correlation with serum leptin levels while BMI and all anthropometric parameters showed a positive correlation with serum leptin levels. Acromite *et al.* (2004) found that leptin levels were significantly associated with estrogen and SHBG levels.

In this study, by multivariante analysis using multiple linear regression model, it was found that study group, BMI and estradiol are significant predictors for leptin levels while maternal age, gestational age, total and free testosterone, SHBG and DHEA-S are not. These results come in line with those of Atamer *et al.* (2004) who found that estradiol could be an independent significant predictor for leptin levels. Acromite *et al.* (2004) stated that BMI, estrogen and SHBG could be independent predictors for leptin levels

Conclusion

It can be concluded that leptin levels are higher in preeclamptic women compared to normal pregnancy and that these levels are related to severity of the disease. BMI and estradiol are independent significant predictors of leptin levels in preeeclpmtic cases.

Corresponding author
Ashraf Dawood
Medical Biochemistry Departments, Menofia University
kingashrafdawood@yahoo.com

References

Acromite M, Ziotopoulou M, Orlova C and Mantzoros C (2004): Increased leptin levels in preeclampsia: association with BMI, estrogen and SHBG. Hormones; 3:46-52.

Atamer Y, Erden A, De Mir B, Kolyigit Y and Atamer A. (2004): the relationship between plasma levels of leptin and androgen in heatlthy and preeclamptic pregnant women. Acta Obstet Gynecol Scand.;83:426-30.

Baksu A, Gurarslan H and Goker N. (2004): Androgen levels in preeclamptic pregnant women. Int J Gynaecol obstet.; 84:247-248.

Banbridge S, Roberts J. (2008): Uric acid as pathogenic factor in preeclampsia. Placenta.;29:567-72.

Celik O, Hascalik S, Ozerol E, Hascalit M and Yologlu S (2004): Cerebrospinal fluid leptin levels in preeclampsia: relation to maternal serum leptin levels. Acta obstet Gynecol Scand.; 83: 519- 523.

Duncan P, Gochman N, Cooper T, Smith E and Bayse D (1982): A candidate reference method for uric acid in serum: optimization and evaluation. Clin Chem.; 28: 284 – 90.

Ghorashi V, Sheikhovaton M (2008): The relationship between serum concentration of free testosterone and preeclampsia. Endo Polska; 59: 390 – 392.

Haugen F, Ranheim T, Harsem N, Lips E, Staff A and Dervone C (2006): Increased plasma adipokines in preeclampsia. Relationship to placenta and adipose tissue gene expression. Am J Physiol Endocrinol Metab., 290: E 326-E333.

Henson M and Castracan V (2006): Leptin in pregnancy: an update Biol Reprod., 74: 218-229.

Holtzclaw, W.D. and Gordon, G.B. (1989): Measurement of serum levels of dehydroepiandrosterone sulfate: A comparison of Elisa and enzymatic analysis. Steroids, 54: 355-371.

Iftikhar U, khoya A, Iqbal A and Karira K (2008): Evaluation of serum leptin levels during normal pregnancy and preeclampsia. J .Ayub. Med. Coll. Abbott., 20:137-140.

Ismail A, Astley P, Burr W, Cawood M,Short F,Wakelin K and Wheeler M (1986): The role of testosterone measurement in the investigation of androgen disorders . Ann.Clin.Biochem., 23:113-134.

Jenkins L, Powers R, Adotey M and Gallaher M(2007): Maternal leptin concentration are similar in African Americans and Caucasians in normal pregnancy, Preeclampsia and small for gestational age infants. Hypetens Pregnan., 26:101-109.

Kafulafula G, Moodley J, Ojwang P and Kagoro H(2002): Leptin and preeclampsia in black African parturients. BJOG.,109:1256-1261.

Kocygit Y, Atamen Y, Atamer A, Tuzau A and Akkus Z (2004): Changes in serum levels of leptin, Cytokines and lipoproteins in preeclamptic and normotensive pregnant women. Gynecol Endocrinal., 19:267-73.

Kricka L.J (2006): Principles of immunochemical techniques. In: Tietz Textbook of Clinical Chemistry and molecular diagnostics. Bruit C , Ashwood E and Bruns D (eds.). 4th edition. Chapter 9. pp. 219-243.

Larn C, Limk Kang D and Karumaschi S (2005): Uric acid and preeclampsia. Semin Nephrol., 25:56-60.

Ma.Z.,Ginderich.R.L.andSantiago,J.V.(1996):Radioimmunoassay of leptin in human plasma. Clin.Chem.,42:942-946.

Makuyana D, Mohamed K, Shukusho F, and Majoko F (2002): liver and kidney function tests in normal and preeclamptic gestation.cont. Afr. J.Med., 48: 55-59.

Martinez-Abundis E, Gonzalez-Ortiz M, Pascoe-Gonzalez (2000): Serum leptin levels and severity of preeclampsia. Arch Gynecol Obstet., 264: 71-73.

McCann D, Kirkish L (1985): Evaluation of free testosterone in serum. Journal of Clinical Immunoassay,8:234-236.

Mihu D, Georgescu C, Mihu C, Costin N, Blaga L and pop R (2009): High maternal serum leptin and IL-6 levels in preeclampsia and relations with clinical and metabolic parameters of disease severity and pregnancy outcome. Acta Endocrinologica (Buc),1:49-60.

Mohammed S, El-Maghawry I, Ibrahim M and Moustafa A (2009): Adiponectin and sex hormone-binding globulin in preeclampsia: Relationship to insulin resistance. EJBM, 27: 47-57.

Muy- Rivera, Ning Y, Frederick I, Vadachkoria S, Luthy D and Williams M (2005): Leptin, soluble

leptin receptor and leptin gene polymorphism in relation to preeclampsia risk. Physiol Res., 54: 167-174.

Perrone RD, Madia ME and Levey AS (1992): Serum creatinine as an index of renal function: New insights into old concepts. Clin Chem.; 38: 1933 – 53.

Selby, C. (1990): Sex hormone binding globulin: origin, function and clinical significance. Ann. Clin. Biochem., 27: 532 - 541.

Sucak A, Kanat- Pektas M, Gungor T and Mollamahmutoglu L (2010): Leptin levels and antihypertensive treatement in Preeclampsia. Singapore Med J., 61: 39-43.

Taghavi S (2007): Serum androgens in preeclamptic women Res. J. Biol. Sci., 2:773-776.

Taylor AJ and Vadgama P (1992): Analytical reviews in clinical biochemistry: The estimation of urea. Ann Clin Biochem.; 29:245-64.

Valdan M, Qadrdoost-Nakhchee N and Davari-Tanha F (2006): Androgen levels in preeclampsia. Acta Medica Iranica., 44: 241-245.

Young BC, Levine RJ and Karumanchi SA (2010): Pathogenesis of Preeclampsia. Annu Rev Pathol., 5:173-92.

8/20/2011