Urinary Prolactin in Preeclampsia

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First and last, great thanks to ALLAH, without his help, nothing could be done.

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Mohamed Zareef

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List of abbreviations

ACOG	American college of Obstetricians and Gynecologists
ACR	Albumin/Creatinine ratio
AST	Aspartate aminotransferase
AUC	Area under curve
BP	Blood pressure
BMI	Body mass index
BPP	Biophysical profile
CAAT	cytidine-adenosine-adenosine-thymidine
cAMP	Cyclic adenosine monphosphate
CBC	Complete blood count
CI	Confidence interval
DIC	Disseminated intravascular coagulopathy
EBP	Enhancer binding protein
ESRD	End stage renal disease
GFR	Glomerular filtration Rate
GH	growth hormone
GnRH	Gonadotropin releasing hormone
HGH	Human growth hormone
HLA-G	Human leucocyte antigen
HP	Healthy pregnant
HUS	Hemolytic uremic syndrome
IUGR	Intra-uterine growth restriction
KDa	Kilo Daltons
KDR	Kinase insert domain receptors
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LFTs	Liver function tests
MAP	Mitogen-activated protein
MHC	Major histocomptability complex
NHBPEP	National high blood pressure education program
NICU	neonatal intensive care unit

List of abbreviations (Cont.)

NPV	Negative predictive value
NST	Non stress test
PIH	Pregnancy induced hypertension
PLF	Proliferin
PlGF	Placental growth factor
PRL	Prolactin
PRP	Proliferin –related peptide
sEng	Soluble Endoglin
sFlt	Soluble fms-like tyrosine kinase 1
SNRI	Serotonin-norepinephrine reuptake inhibitor
sPE	Severe preeclampsia
SSRI	Selective serotonin reuptake inhibitor
TGF	Transforming growth factor
Tie	Tyrosine kinase with immunoglobulin(Ig) and epidermal growth factor(EGF) homology domain
TTP	Thrombotic thrombocytopenic purpura
UA	Uric acid
uPRL	Urinary Prolactin
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptors
WHO	World health organization
WK	Week

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Introduction

Preeclampsia is amultisystemic pregnancy specific disease characterized by endothelial dysfunction. Preeclampsia is presenting 5–8% of all pregnant women, and remains as a major cause of maternal and perinatal morbidity and mortality worldwide **(NHBPEP, 2000).**

Although the etiology of this pregnancy specific syndrome is unclear, recent evidence suggests that preeclampsia may be the result of an imbalance in angiogenic factors **(Levine et al., 2004),** which damage maternal vascular endothelium, leading to the clinical manifestations of this condition **(Ferrara, 2001).**

Due to its prevalence and seriousness, several angiogenic and antiangiogenic factors in both serum and urine have been assessed as diagnostic markers for this complication of pregnancy or to ascertain its severity **(Levine et al., 2006)**.

Prolactin (PRL) is a polypeptide hormone primarily secreted by the anterior pituitary. A substantial increment in serum PRL levels physiologically occurs during pregnancy. Although the best-known biological functions of PRL are linked to lactation and reproduction, this hormone has been also associated with other physiological processes, including angiogenesis **(Freeman et al., 2000)**.

Prolactin stimulates and inhibits angiogenesis: the intact prolactin molecule is angiogenic and there are two additional PRL isoforms that result from proteolytic cleavage of monomeric PRL (16- and 14-kDa fragments) and that exhibit antiangiogenic effects **(Corbacho et al., 2002)**.

Because abnormal angiogenesis is an essential component of the pathogenesis of preeclampsia and considering that PRL has pro- and antiangiogenic effects, so

that the PRL might be a potential candidate as biomarker for this disease **(Leaños-Miranda et al., 2008)**.

More recently, it is reported that defective placental angiogenesis is a primary event in preeclampsia, and the discovery that PRL is proteolytically processed to fragments (vasoinhibins) with antiangiogenic and vasoconstrictive properties **(Clapp et al., 2006)** strengthened the possibility that PRL is involved in this syndrome **(Parra and Ramirez-Peredo, 2002).**

Aim of The Work

The aim of this work is to assess the effect of preeclampsia on the urinary excretion of prolactin (uPRL) and the using of this marker as a prognostic tool for the disease.

Preeclampsia

Overview:

Preeclampsia, a pregnancy-specific disorder characterized clinically by new onset hypertension and proteinuria after 20 wk of gestation, is the most frequently encountered medical complication during pregnancy, affecting about 3–5% of pregnant women worldwide **(WHO, 2005)**.

The incidence of preeclampsia in the United States is estimated to range from 2% to 6% in healthy nulliparous women. Among all cases of the preeclampsia, 10% occur in pregnancies of less than 34 weeks' gestation **(Vatten and Skjaerven, 2004)**. In the developed world, the burden of this disease falls on the neonate because of premature deliveries performed to preserve the health of the mother. Worldwide, preeclampsia is associated with a perinatal and neonatal mortality rate of 10% **(Altman et al., 2002)**.

In developing nations, the incidence of the disease is reported to be 4-18% ***(Villar et al., 2001)***, with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths in these countries ***(Ngoc et al., 2006).***In developing countries where access to health care is limited, preeclampsia is a leading cause of maternal mortality, with estimates of >60, 000 maternal deaths/yr **(WHO, 2005)**.

Delivery of the placenta results in resolution of the condition, implicating the placenta as a central culprit in the pathogenesis of preeclampsia. This has led to a two-stage theory whose proponents hypothesize preeclampsia to be a systemic syndrome that originates in the placenta and is characterized by maternal widespread endothelial dysfunction **(Walsh et al., 2000).**

Epidemiology and Risk Factors:

The worldwide incidence of preeclampsia is 3–4% of all pregnancies **(WHO, 2005)**. Most cases of preeclampsia occur in healthy nulliparous women, in whom the incidence of preeclampsia may be as high as 7.5% **(WHO, 2003)**. Multiparous women pregnant with a new partner have a similar preeclampsia risk as nulliparous women **(Tuffnell et al., 2005)**; this has been ascribed to factors associated with a change in paternity or increased interpregnancy interval **(Skjaerven et al., 2002)**.

In addition, women with preeclampsia in a prior pregnancy continue to have a high risk of preeclampsia in subsequent pregnancies. Although most cases of preeclampsia occur in the absence of a family history, the presence of preeclampsia in a first-degree relative increases a woman's risk of severe preeclampsia two- to fourfold **(Carr et al., 2005)**. A history of preeclampsia in the father's mother also confers an increased risk **(Esplin et al., 2001).**

Several medical conditions are associated with increased preeclampsia risk, including chronic hypertension, diabetes mellitus, renal disease, obesity, and hypercoagulable states, such as antiphospholipid syndrome and factor V Leiden. Advanced maternal age is also an independent risk factor for preeclampsia **(Duckitt and Harrington, 2005).** Conditions associated with increased placental mass, such as multifetal gestations and hydatidiform mole also predispose women to preeclampsia. There seems to be no clear association between consanguinity and the incidence or severity of preeclampsia **(Badria et al., 2001)**; however, there are reports of familial aggregation of preeclampsia and intrauterine growth restriction in a genetically isolated population **(Berends et al., 2008).**

Interestingly, smoking during pregnancy appears to reduce the risk of preeclampsia. Although none of these

epidemiological risk factors are well understood, they have helped to provide insight into the pathogenesis of preeclampsia **(England et al., 2002)**.

In addition, **Lykke et al**. found that preeclampsia, spontaneous preterm delivery, or fetal growth deviation in a first singleton pregnancy predisposes women to those complications in their second pregnancy, especially if the complications were severe **(Lykke et al., 2009).**

One literature review suggests that maternal vitamin D deficiency may increase the risk of preeclampsia and fetal growth restriction. Another study determined that vitamin D deficiency/insufficiency was common in a group of women at high risk for preeclampsia. However, it was not associated with the subsequent risk of an adverse pregnancy outcome **(Shand et al., 2010).**

Studies have suggested that smoking during pregnancy is associated with a reduced risk of gestational hypertension and preeclampsia; however, this is controversial **(Lim et al., 1997).**

Body weight is strongly correlated with progressively increased preeclampsia risk, ranging from 4.3% for women with a body mass index (BMI) < 20 kg/m2 to 13.3% in those with a BMI >35 kg/m2. A United Kingdom study on obesity showed that 9% of extremely obese women were preeclamptic, compared with 2% of matched controls **(Knight et al., 2010).**

Table (1) lists the risk factors and their odds ratios for preeclampsia ***(ACOG, 1996).***

Table (1): Risk Factors for Preeclampsia.

Nulliparity	3:1
Age >40 y	3:1
Black race	1.5:1
Family history	5:1
Chronic renal disease	20:1
Chronic hypertension	10:1
Antiphospholipid syndrome	10:1
Diabetes mellitus	2:1
Twin gestation (but unaffected by zygosity)	4:1
High body mass index	3:1
Homozygous	20:1
Heterozygous	4:1

*Adapted from ACOG Technical Bulletin 219, Washington, DC 1996 ***(ACOG, 2001).***

Clinical Features:

The cardinal features of preeclampsia are de novo onset of hypertension (defined as systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg, and proteinuria (0.3 g in a 24-h urine specimen and/or protein to creatinine ratio of >0.30). Historically, edema was part of the diagnostic triad for preeclampsia; however, edema was too nonspecific to be disease defining. Still, the sudden onset of severe edema, especially edema of the hands and face, is often the only change detectable by the patient in this otherwise insidious disease. Preeclampsia develops from 20 wk of gestation onward until term, although most cases are diagnosed preterm. In some cases, preeclampsia may even first present after delivery. The spectrum of preeclampsia varies widely. For clinical purposes, it is classified as mild or severe, but such classifications may be misleading. Although the classification of severe preeclampsia serves to emphasize the more ominous features of the syndrome, some have suggested a more nuanced disease categorization **(Lindheimer et al., 2008)** or a