Serum Androgen Levels as a marker for the severity of preeclampsia

Thesis

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✍ ***Joseph Adel Ibrahim***

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List of Abbreviations

Abbr.	*Title*
ACOG	: American College of Obstetricians and Gynecologists
ADMA	: Asymmetric dimethylarginine
ANOVA	: Analysis of variance
AT1-AA	: Angiotensin II Type I Receptor Activating Autoantibodies
AUC	: Area under curve
BMI	: Body mass index
BP	: Blood pressure
C4bp	: C4 binding protein
CBC	: Complete Blood Count
CI	: Confidence interval
CRP	: C- Reactive protein
DBP	: Diastolic Blood Pressure
DDAH	: Dimethylarginine dimethylaminohydrolase
Df	: Degrees of freedom
DHEA	: Dehydroepiandrosterone
DHEA-S	: Dehydroepiandrosterone sulphate
DNA	: Deoxyribonucleic acid
E2	: Estradiol
ELISA	: Enzyme Linked Immunosorbent Assay
eNOS	: Endothelial nitric oxide
FAI	: Free androgen index
FE3	: Free estriol
Ft	: Free Testosterone
GA	: Gestational age
GH	: Gestational hypertension
HELLP	: Hemolysis, Elevated Liver enzymes and Low Platelet syndrome
HTN	: Hypertension
IBM	: International business machines
IL-6	: Interleukin 6
mGH	: Mild gestational hypertension
MMP-9	: Matrix metalloproteinase-9
mPE	: Mild preeclampsia
NEO	: Neopterin
NGAL	: Neutrophil gelatinase – associated lipocalin

NK : Natural Killer
NO : Nitric oxide
NOS : Nitric oxide synthetase
PCOS : Polycystic ovary syndrome
PE : Preeclampsia
PDGF : Platelet-derived growth factor
Pg : Progesterone
PlGF : Placental Growth Factor
PIH : Pregnancy induced hypertension
PRMTs : Protein arginine methyltransferases
PSU : Pilo-Sebaeous Unit
PV : Predictive value
RNA : Ribonucleic acid
ROC : receiver-operating characteristic
SBP : Systolic Blood Pressure
SD : Standard deviation
SE : Standard error
sEng : Soluble endoglin
sFlt-1 : Soluble fms-like tyrosine kinase I receptor
sGH : Severe gestational hypertension
SHBG : Sex hormones binding globulin
SOGC : Society of Obstetricians and Gynecologists of Canada
sPE : Severe preeclampsia
SPSS : Statistical package for social science
STARD : Updated list of essential items for reporting diagnostic accuracy studies
TNF-alpha : Tumor necrosis factor alpha
TXA2 : Thromboxane A2
VEGF : Vascular endothelial growth factor
VSIG 4 : V-set and immunoglobulin domain-containing protein 4

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Introduction

Hypertensive disorders are one of the most important complications during pregnancy, which in combination with hemorrhage and infections make a dangerous triad, making them the major cause of maternal morbidity and mortality in 3.7–5% of all pregnancies ***(Sharifzadeh et al., 2012).***

Hypertensive disorders during pregnancy are classified into 4 categories, as recommended by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy:

- Chronic hypertension
- Preeclampsia-eclampsia
- Preeclampsia superimposed on chronic hypertension
- Gestational hypertension (transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy). This terminology is preferred over the older but widely used term "pregnancy-induced hypertension" (PIH) because it is more precise ***(Mammaro et al., 2009).***

In 2008, the Society of Obstetricians and Gynecologists of Canada (SOGC) released revised guidelines that simplified the classification of hypertension in pregnancy into 2 categories, preexisting or gestational, with the option to add "with preeclampsia" to either category if additional maternal or fetal symptoms, signs, or test results support this ***(Magee et al., 2008).***

Chronic hypertension is defined as blood pressure exceeding 140/90 mm Hg before pregnancy or before 20 weeks' gestation. When hypertension is first identified during a woman's pregnancy and she is at

less than 20 weeks' gestation, blood pressure elevations usually represent chronic hypertension.

In contrast, new onset of elevated blood pressure readings after 20 weeks' gestation mandates the consideration and exclusion of preeclampsia ***(Phillips, 2015).***

Chronic Hypertension

Chronic hypertension is a primary disorder in 90-95% of cases and may be either essential (90%) or secondary to some identifiable underlying disorder, such as renal parenchymal disease (eg, polycystic kidneys, glomerular or interstitial disease), renal vascular disease (eg, renal artery stenosis, fibro-muscular dysplasia), endocrine disorders (eg, adreno-corticosteroid or mineralocorticoid excess, pheochromocytoma, hyperthyroidism or hypothyroidism, growth hormone excess, hyperparathyroidism), coarctation of the aorta, or oral contraceptive use. About 20-25% of women with chronic hypertension develop preeclampsia during pregnancy ***(Roberts, 2008).***

Chronic hypertension occurs in up to 22% of women of childbearing age, with the prevalence varying according to age, race, and body mass index. Population-based data indicate that approximately 1% of pregnancies are complicated by chronic hypertension, 5-6% by gestational hypertension without proteinuria, and 1-2% by preeclampsia ***(Roberts, 2008)***

Gestational Hypertension

Gestational hypertension refers to hypertension with onset in the latter part of pregnancy (>20 weeks' gestation) without any other features of preeclampsia, and followed by normalization of the blood pressure postpartum. Of women who initially present with apparent gestational

hypertension, about one third develops the syndrome of preeclampsia. As such, these patients should be observed carefully for this progression. The pathophysiology of gestational hypertension is unknown, but in the absence of features of preeclampsia, the maternal and fetal outcomes are usually normal ***(Hedderson and Ferrara, 2008).***

Gestational hypertension may, however, be a harbinger of chronic hypertension later in life ***(Chang et al., 2003).***

Furthermore, hypertension before pregnancy or during early pregnancy is associated with a twofold increased risk of gestational diabetes mellitus. Transient hypertension of pregnancy (ie, the development of isolated hypertension in a woman in late pregnancy without other manifestations of preeclampsia) is associated strongly with later development of chronic hypertension ***(Hedderson and Ferrara, 2008).***

Although maternal diastolic blood pressure greater than 110 mm Hg is associated with an increased risk for placental abruption and fetal growth restriction, superimposed pre-eclamptic disorders cause most of the morbidity due to chronic hypertension during pregnancy ***(Chang et al., 2003).***

Preeclampsia is defined as the new onset of hypertension and either proteinuria or end organ dysfunction after 20 weeks of gestation in a previously normotensive woman. In 2013, the American College of Obstetricians and Gynecologists removed proteinuria as an essential criterion for diagnosis of preeclampsia. They also removed massive proteinuria (5 grams/24hours) and fetal growth restriction as possible features of severe disease because massive proteinuria has a poor correlation with outcome and fetal growth restriction is managed similarly

whether or not preeclampsia is diagnosed. Oliguria was also removed as a characteristic of severe disease ***(Townsend et al., 2016).***

Hypertension before 20 weeks' gestation is almost always due to chronic hypertension; new-onset or worsening hypertension after 20 weeks' gestation should lead to a careful evaluation for manifestations of preeclampsia ***(Carson and Ramus, 2016).***

Signs suggesting a secondary medical cause of chronic hypertension

Centripetal obesity, "buffalo hump," and/or wide purple abdominal striae suggest glucocorticoid excess; other clinical signs may demonstrate hyperthyroidism, hypothyroidism, or growth hormone excess. In addition, a systolic bruit heard over the abdomen or in the flanks suggests renal artery stenosis, whereas radio femoral delay or diminished pulses in the lower versus upper extremities suggests coarctation of the aorta ***(Carson and Ramus, 2016).***

Aim of the Work

This study aims to assess if serum total and free testosterone could be used as a marker for the severity of preeclampsia when compared to control group.

Hypothesis

In women with preeclampsia, there is an elevated serum total and free testosterone levels which may be implicated in its pathogenesis .

Research question

Will serum total and free testosterone affect the severity of preeclampsia ?

Preeclampsia

Preeclampsia is a common complication of pregnancy associated with high maternal morbidity and mortality and intrauterine fetal growth restriction. There is extensive evidence that the reduction of utero-placental blood flow in this syndrome results from the toxic combination of hypoxia, imbalance of angiogenic and anti-angiogenic factors, inflammation, and deranged immunity ***(Eiland et al., 2012).***

Definition:

Preeclampsia is defined as the presence of a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg, on 2 occasions at least 4 hours apart in a previously normotensive patient. In addition to the blood pressure criteria, proteinuria of ≥ 0.3 grams in a 24-hour urine collection, a protein (mg/dl)/creatinine (mg/dl) ratio of 0.3 or higher, or a urine dipstick protein of 1+ is required to diagnose preeclampsia**. Eclampsia** is defined as seizures that can't be attributable to other causes, in a woman with preeclampsia ***(Jeyabalan et al., 2013).***

Epidemiology

Overall, 10%–15% of maternal deaths are directly associated with preeclampsia and eclampsia. Some epidemio-logical findings support the hypothesis of a genetic and immunological etiology. The risk of preeclampsia is 2 to 5 times higher in pregnant women with a maternal history of this disorder. Depending on ethnicity, the incidence of preeclampsia ranges from 3% to 7% in healthy nulliparous and 1% to 3% in multiparas ***(Uzan et al., 2011).***

Risk factors

- Null parity (3.1)
- Age more than 35 or less than 20 years old (3:1)
- Black race (1.5:1)
- Family history (5:1)
- Chronic renal disease (20:1)
- Chronic hypertension (10:1)
- Anti-phospholipid syndrome (10:1)
- Diabetes mellitus (2:1)
- Twin gestation but unaffected by zygosity (4:1), triplet gestation carries a greater risk than twin, suggesting that increased placental mass plays some role.
- Obesity (3:1)
- Genetic factors: there may be several genes. Associations have been described between risk for preeclampsia and polymorphisms of the genes or factor V Leiden, angiotensinogen (homozygosity for angiotensinogen gene T235 (20:1) heterozygosity for angiotensinogen gene T235 (4:1)) and endothelial nitric oxide synthetase, although these associations have not been confirmed consistently in other populations
- History of preeclampsia in the previous pregnancies (7:1)
- Smoking during pregnancy protects against preeclampsia
- Molar pregnancy
- High altitude has also been shown to increase the incidence of preeclampsia, and is attributed to greater placental hypoxia
- Smaller uterine artery diameter and lower uterine artery blood flow.
- Collagen vascular disease ***(Yogev et al., 2010).***

Pathophysiology

The mechanisms by which preeclampsia occurs is not certain, and numerous maternal, paternal, and fetal factors have been implicated in its development.

The factors currently considered to be the most important include the following: Maternal immunologic intolerance, abnormal placental implantation, genetic, nutritional, environmental factors, cardiovascular and inflammatory changes ***(Cunningham et al., 2010).***

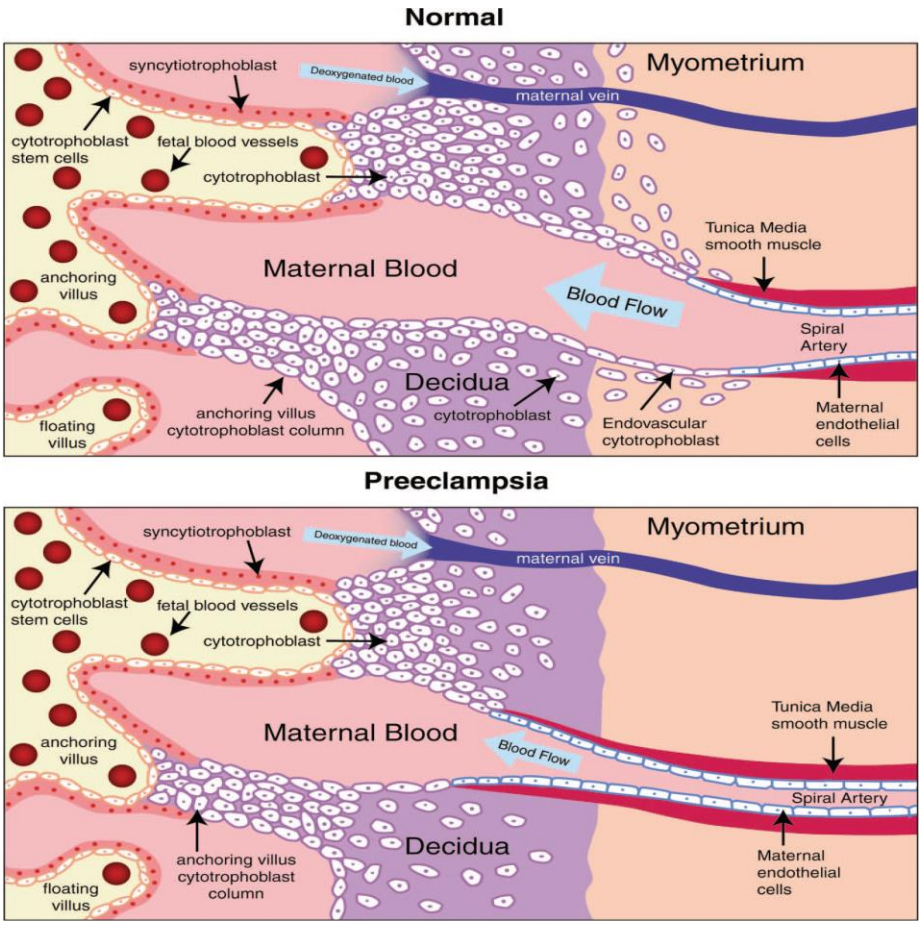

Figure 2: Abnormal placentation in pre-eclampsia ***(Lam et al., 2005).***