INTRODUCTION

Preeclampsia refers to the new onset of hypertension and either proteinuria or endorgan dysfunction or both after 20 weeks of gestation in a previously normotensive woman. Severe hypertension and signs/symptoms of endorgan injury are considered the severe spectrum of the disease ***(ACOG, 2013).***

In 2013, the American College of Obstetricians and Gynecologists removed proteinuria as an essential criterion for diagnosis of preeclampsia with severe features. They also removed massive proteinuria (5 grams/24 hours) 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 ***(ACOG, 2013).***

The angiogenic and antiangiogenic factors soluble fms-like tyrosine kinase (sFlt-1) and placental growth factor (PIGF) have been implicated in the mechanisms of disease responsible for preeclampsia ***(Verlohren et al., 2010).***

sFlt-1,VEGF, PIGF- Soluble fms–like tyrosine kinase 1 (sFlt-1 or sVEGFR1) is a naturally occurring, circulating antagonist to vascular endothelial growth factor (VEGF) ***(Dvorak, 2002).***

sFlt-1 antagonizes the proangiogenic biologic activity of circulating VEGF and PlGF by binding to them and preventing their interaction with their endogenous receptors. Increased placental expression and secretion of sFlt1 appear to play a central role in the pathogenesis of preeclampsia based on the following observations ***(Ahmad and Ahmed, 2004):***

- sFlt-1 administered to pregnant rats induces albuminuria, hypertension, and the unique renal pathologic changes of glomerular endotheliosis

- In vitro, removal of sFlt-1from supernatants of preeclamptic tissue culture restores endothelial function and angiogenesis to normal levels. Conversely, exogenous administration of VEGF and PlGF reverses the antiangiogenic state induced by excess sFlt-1 ***(Taylor, 2003).***

A nested case control study using banked sera to measure serum sFlt-1, as well as PlGF and VEGF, across gestation found that changes in sFlt-1 were predictive of the subsequent development of preeclampsia. sFlt-1 levels increased during pregnancy in all women; However, compared to normotensive controls, women who went on to develop preeclampsia began this increase earlier in gestation (at 21 to 24 weeks versus 33 to 36 weeks) and reached higher levels. A significant difference in the serum sFlt-1 concentration between the two groups was apparent five weeks before the onset of clinical disease. PlGF and VEGF levels fell concurrently with the rise in sFlt-1 which may have been related, in part, to binding by sFlt1 ***(ACOG, 2013).***

The sFlt-1/PIGF ratio may be of value in the prediction of PE and in the differential diagnosis of patients with atypical presentations of preeclampsia, and in the differential diagnosis of women with chronic hypertension suspected to develop superimposed preeclampsia ***(Verlohren et al., 2010).***

In women with suspected preeclampsia presenting at 34 weeks, circulating sFlt-1/PlGF ratio predicts adverse outcomes occurring within 2 weeks ***(Rana et al., 2012).***

Studies have shown that sFlt-1, soluble Endoglin (sEng) and PIGF could be suitable biomarkers for preeclampsia prior to the development of the disease. Second trimester sFlt-1/PIGF ratio was found to be useful as an aid in the prediction and diagnosis of preeclampsia. The addition of sFlt-1/PIGF to Doppler ultrasound was found to improve the sensitivity and specificity of Doppler ultrasound alone ***(Verlohren et al., 2012).***

An imbalance of angiogenic markers correlates with the severity of preeclampsia symptoms and can be detected well before clinical signs and symptoms appear. Recent studies on the use of angiogenic markers in preeclampsia prediction have shown that: the sFlt-1/PlGF ratio is a better predictor than either of these parameters alone sequential changes in the concentrations of sFlt-1, PlGF and sEng may be more informative than single measurements the addition of angiogenic marker measurements can improve the predictive value of Doppler ultrasound alone ***(Hagmann et al., 2012).***

There is a more pronounced alteration of angiogenic factors in early-onset compared with late-onset preeclampsia. In the second trimester the sFlt-1/PlGF ratio may be ideal parameter to diagnose early-onset preeclampsia (< 34 weeks) or preterm preeclampsia (< 37 weeks) ***(Hagmann et al., 2012).***

AIM OF THE WORK

The aim of this study is to identify the role of sFlt-1/PIGF ratio as a prognostic marker for cases of Preeclampsia.

Research question:

In women with Preeclampsia, Is there a prognostic role of sFlt-1/PIGF ratio regarding time of delivery, maternal and fetal outcomes?

Research hypothesis:

In women with Preeclampsia the level of sFlt-1/PIGF ratio may be a good prognostic marker regarding time of delivery, maternal and fetal outcomes.

Chapter One

PREECLAMPSIA

Classification and Terminology

Based on the guideline ***(Hypertension in Pregnancy)*** released by the ***American College of Obstetricians and Gynecologists (2013)*** which considers hypertension during pregnancy in four categories:

1- Preeclampsia - Eclampsia.

2- Chronic hypertension (of any cause).

3- Chronic hypertension with superimposed preeclampsia.

4- Gestational hypertension.

Preeclampsia - Eclampsia

Preeclampsia is a pregnancy-specific hypertensive disease with multisystem involvement. It usually occurs after 20 weeks of gestation, most often near term, and can be superimposed on another hypertensive disorder.

Preeclampsia, the most common form of high blood pressure (BP) that complicates pregnancy is primarily defined by the occurrence of new-onset hypertension plus new-onset proteinuria. However, although these two criteria are considered the classic definition of preeclampsia, some women present with hypertension and multi-systemic signs usually

indicative of disease severity in the absence of proteinuria. In the absence of proteinuria, preeclampsia is diagnosed as hypertension in association with thrombocytopenia (platelet count less than 100,000/microliter), impaired liver function (elevated blood levels of liver transaminases to twice the normal concentration), the new development of renal insufficiency (elevated serum creatinine greater than 1.1 mg/dL or a doubling of serum creatinine in the absence of other renal disease), pulmonary edema, or new-onset cerebral or visual disturbances ***(ACOG, 2013).***

A. Hypertension

Hypertension is defined as either a systolic BP of 140 mm Hg or greater, a diastolic BP of 90 mm Hg or greater, or both. Hypertension is considered mild until diastolic or systolic levels reach or exceed 110 mm Hg and 160 mm Hg, respectively.

It is recommended that a diagnosis of hypertension requires at least two determinations at least 4 hours apart, although on occasion, especially when faced with severe hypertension, the diagnosis can be confirmed within a shorter interval (even minutes) to facilitate timely antihypertensive therapy ***(ACOG, 2013).***

B. Proteinuria:

Proteinuria is diagnosed when 24-hour excretion equals or exceeds 300 mg in 24 hours or the ratio of measured protein to creatinine in a single voided urine measures or exceeds 0.3

(each measured as mg/dL). Qualitative dipstick readings of 1+ suggest proteinuria but have many false-positive and false-negative results and should be reserved for use when quantitative methods are not available or rapid decisions are required ***(ACOG, 2013).***

C. Eclampsia:

Eclampsia is the convulsive phase of the disorder and is among the more severe manifestations of the disease. It is often preceded by premonitory events, such as severe headaches and hyperreflexia, but it can occur in the absence of warning signs or symptoms.

Chronic hypertension

During pregnancy, chronic hypertension is defined as high BP≥ 140/90 mm Hg known to predate conception or detected before 20 weeks of gestation.

Chronic Hypertension with Super-imposed Preeclampsia

Preeclampsia may complicate all other hypertensive disorders, and in fact the incidence is four to five times that in non-hypertensive pregnant women. In such cases, prognosis for the woman and her fetus is worse than either condition alone. Although evidence from renal biopsy studies suggests that the diagnosis of superimposed preeclampsia may be often erroneous,

the diagnosis is more likely in the following seven scenarios: women with hypertension only in early gestation who develop proteinuria after 20 weeks of gestation. Women with proteinuria before 20 weeks of gestation who:

1. Experience a sudden exacerbation of hypertension, or a need to escalate the antihypertensive drug dose especially when previously well controlled with these medications.

2. Suddenly manifest other signs and symptoms, such as an increase in liver enzymes to abnormal levels.

3. Present with a decrement in their platelet levels to below 100,000/microliter.

4. Manifest symptoms such as tight upper quadrant pain and severe headaches.

5. Develop pulmonary congestion or edema.

6. Develop renal insufficiency (creatinine level doubling or increasing to or above 1.1 mg/dL in women without other renal disease).

7. Have sudden, substantial, and sustained increases in protein excretion ***(ACOG, 2013).***

If the only manifestation is elevation in BP to levels less than 160 mmHg systolic and 110 mmHg diastolic and proteinuria, this is considered to be superimposed preeclampsia without

severe features. The presence of organ dysfunction is considered to be superimposed preeclampsia with severe features.

Gestational hypertension:

Gestational hypertension is characterized most often by new-onset elevations of BP after 20 weeks of gestation, often near term, in the absence of accompanying proteinuria. The failure of BP to normalize postpartum requires changing the diagnosis to chronic hypertension.

Gestational hypertension, although transient in nature, may also be a sign of future chronic hypertension. Thus, even when benign, it is an important marker regarding follow-up and preventive medicine decisions ***(Williams, 2011).***

Postpartum Hypertension

It is important to remember that preeclampsia—including preeclampsia with severe systemic organ involvement and seizures—can first develop in the postpartum period. Because early hospital discharge is the current practice in the United States, this mandates instruction of women at discharge from the hospital to be aware of symptoms (e.g., severe headache, visual disturbances, or epigastric pain) that should be reported to a health care provider.

Although not recommended in this classification schema, there is a phenomenon once labeled "late postpartum hypertension,"

a disorder that was more frequently diagnosed when women in the postpartum period routinely remained hospitalized for as long as 2 weeks. It was defined as women with normotensive gestations who develop hypertension (usually mild) in a period that ranges from two weeks to six months postpartum.

Incidence of Preeclampsia

Preeclampsia often affects young and nulliparous women, whereas older women are at greater risk for chronic hypertension with superimposed preeclampsia. Also, the incidence is markedly influenced by race and ethnicity and thus by genetic predisposition. Other factors include environmental, socioeconomic, and even seasonal influences ***(Lawlor et al., 2005; Spencer et al., 2009).***

With consideration for these vicissitudes, in a number of worldwide studies reviewed by ***Sibai and Cunningham (2009),*** the incidence of preeclampsia in nulliparous populations ranges from 3 to 10 percent. The incidence of preeclampsia in multiparas is also variable but is less than that for nulliparas.

Preeclampsia and related hypertensive disorders of pregnancy impact 5-8% of all births in the United States. Incidence rates for preeclampsia alone in the United States, Canada and Western Europe, range from 2-5% ***(Ronsmans et al., 2006).***

In the developing world, severe forms of preeclampsia and eclampsia are more common, ranging from 4% of all deliveries to as high as 18% in parts of Africa ***(Villar et al., 2003)***. The variation in incidence rates is driven by the diversity of definitions and other criteria (including procedures, tests and their methodologies). In Latin America, preeclampsia is the number (1) cause of maternal death ***(Preeclampsia Foundation, 2010).***

Ten million women develop preeclampsia each year around the world. Worldwide about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders. And, the number of babies who die from these disorders is thought to be on the order of 500,000 per annum ***(Kuklina, 2009).***

Risk Factors of Preeclampsia

1) Age

Lamminpää et al. 2012 found that women of advanced maternal age (more than 35 years) exhibited more preeclampsia (9.4%) than younger women (6.4%). Other studies also conclude that a maternal age above 40 years doubles the risk of preeclampsia independently of parity ***(Duckitt and Harrington, 2005; Trogstad et al., 2011).***

2) Ethnicity

The incidence of preeclampsia is more common in African-American women than in Caucasian women ***(Trogstad et al., 2011).***

3) Parity

Nulliparity increases the risk of preeclampsia approximately 3-fold as compared to multiparity ***(Skjaerven et al., 2005; Luo et al., 2007).*** It is assumed that immune tolerance against the fetus is not as well developed in the first as in later pregnancies, which could, through immunological maladaptation, associate with preeclampsia. Other theories suggest that differences in the profiles of angiogenic factors or in insulin resistance between nulliparous and multiparous women may be related to preeclampsia ***(Luo et al., 2007).***

In a large prospective study including more than 760.000 primiparous women performed at Swedish Medical Birth Register, ***Hernández-Díaz et al. 2009*** concluded that the risk of preeclampsia was 4.1% in the first pregnancy and 1.7% in later pregnancies overall. However, the risk was 14.7% in the second pregnancy for women who had had preeclampsia in their first pregnancy and 31.9% for women who had had preeclampsia in the previous two pregnancies. The risk for multiparous women without a history of preeclampsia was around 1%.

4) History of preeclampsia

This is considered to be the best predictor for the development of preeclampsia in the next pregnancy, particularly if the preeclampsia was of early-onset (< 34 weeks) or severe. This risk is about seven-fold in a second pregnancy, with higher risk in women with underlying medical condition, such as diabetes mellitus or renal disease ***(Hjartardottir et al., 2006).***

5) Genetic or familial factors

Researches concluded that women whose mothers had a history of hypertension, preeclampsia, or eclampsia were at increased risk of severe preeclampsia. The risk of preeclampsia was greater when the woman had a sister with a history of hypertension (OR 2.60), preeclampsia (OR 2.33), or eclampsia (OR 2.57). The risk of preeclampsia was also higher for women who had both a mother and sister with a history of hypertension (OR 3.65) ***(Bezerra et al., 2010)***.

6) Multiple Pregnancies

Multiple pregnancies increase the risk of preeclampsia. The risk is 3-fold when comparing twin to singleton pregnancies, and 3-fold when comparing triplet to twin pregnancies ***(Duckitt and Harrington, 2005).*** Here, the risk increment could be related to the increased placental mass, which releases high amounts of placental cytokines and antiangiogenic factors into the circulation causing a systemic

inflammatory response ***(Bdolah et al., 2008).*** Also, exposure to paternal genetic material may be increased in multiple pregnancies ***(Trogstad et al., 2011).***

7) Obesity

WHO (2011) estimates the prevalence of obese and overweight women (BMI ≥25 kg/m2) to be 77% in the United States, 73% in Mexico, 37% in France, 32% in China, 18% in India, and 69% in South Africa, with wide variation within each continent.

Obesity increases the risk of preeclampsia. A pre-pregnancy body mass index (BMI) of more than 35 kg/m^2 increases the risk 3- to 5 –fold as compared to those with a pre-pregnancy BMI of less than 24 kg/m^2 ***(Duckitt and Harrington, 2005).*** Importantly, it is not only the risk of late or mild forms of preeclampsia that is increased, but also the risk of early and severe forms of preeclampsia, which are associated with greater perinatal morbidity and mortality ***(Catov et al., 2007).*** Some studies suggest that excessive maternal weight gain is associated with the risk of preeclampsia, although these may be confounded by the increase in fluid retention that occurs with preeclampsia, thereby contributing to higher weight ***(Fortner et al., 2009).*** Although weight loss is discouraged in pregnancy, obesity is a potentially modifiable risk factor for preeclampsia. Weight loss prior to pregnancy is encouraged in overweight and