Introduction

Preeclampsia is a life-threatening multisystem disorder occurring in pregnant women, with wide range of pathological changes and multiple clinical impacts on mother and fetal health. Millions of women risk death to give birth globally each year, almost 300, 000 lose their life in this process and over 500, 000 babies die as a consequence of preeclampsia. Despite decades of research, we still lack pharmacological agents to treat preeclampsia on etiological rather clinical basis ***(Ahmed et al., 2016).***

The current 'gold standard' of preeclampsia diagnosis must be revised in the light of the increasing understanding of the central role of the placenta in the pathophysiology of preeclampsia. Till a few years ago, no biomarker was available to reliably assess the placental function in the clinical setting. Revising the gold standard does not simply mean to change the diagnostic criteria for preeclampsia. Future interest must be directed toward a re-definition of preeclampsia, as hypertension and proteinuria are just arbitrary markers for a syndrome that we did not have the means to previously describe better. It has been shown that patients with 'non angiogenic preeclampsia' are not at risk for adverse outcomes, where those with angiogenic

dysbalance are at risk of adverse pregnancy outcome ***(Llubra et al., 2015).***

There is experimental evidence that supports the hypothesis that interference with Vascular Endothelial Growth Factor (VEGF) and Placental Growth Factor (PlGF) signaling could mediate endothelial dysfunction the core of pathophysiology of preeclampsia. Hence, Study of VEGF in preeclamptic patients gives new era in the future modality of diagnosis, classification and etiology-based management of preeclampsia ***(Malshe and Sibai, 2017).***

Aim of the work

To estimate maternal serum vascular endothelial growth factor (VEGF) level in patients with preeclampsia compared to normotensive pregnant women.

Preeclampsia

Preeclampsia is a multisystemic disorder in pregnancy recognized as a clinical entity since the times of Hippocrates, characterized by hypertension and proteinuria. The condition is associated with a reduced plasma volume, hemoconcentration, and increased vascular resistence. The clinical findings of preeclampsia can manifest either a maternal syndrome (hypertension and proteinuria with or without multisystemic abnormalities) or fetal syndrome (fetal growth restrictiont, reduced amniotic fluid and abnormal oxygenation). The condition may cause serious maternal and fetal complications ***(Kjell Haram et al., 2014).***

The root cause of preeclampsia is thought to be reduced placental perfusion. It has been demonstrated that impaired extravellous trophoblasts (EVTs) invasion in the decidua and the spiral arteries and insufficient spiral a artery remodeling may take place in women preeclampsia. The ischemic placenta liberates bioactive factors like: VEGF, prostaglandins and cytokines into maternal circulation. These factors contribute to the wide range of maternal pathological changes of preeclampsia ***(Sircar et al., 2015).***

Epidemiology:

Preeclampsia is estimated to occur in 4 – 8 % of all deliveries. Chronic hypertension, obesity (body mass index ≥ 35), sever anemia (heamoglobin ≤ 7 g/dl), were the highest risk factors of preeclampsia, where the risk rises three times or more. Other risk factors include maternal age ≥ 30 years), nulliparity, renal or cardiovascular disease, diabetes, and antenatal care less than 8 visits ***(Ver Luanni et al., 2014).***

Terminology:

There are four major hypertensive disorders related to pregnancy ***(American College of Obstetricians and Gynecologists, 2013):***

- **Preeclampsia**:

Preeclampsia refers to the new onset of hypertension and proteinuria or hypertension and end-organ dysfunction with or without proteinuria after 20 weeks of gestation in a previously normotensive woman. It may also develop postpartum. Severe hypertension or signs/symptoms of end-organ injury represent the severe end of the disease spectrum ***(American College of Obstetricians and Gynecologists, 2013).***

- **Eclampsia:**

Refers to the development of grand mal seizures in a woman with preeclampsia, in the absence of other neurologic conditions that could account for the seizure.

HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets) probably represents a severe form of preeclampsia, but this relationship remains controversial; HELLP may be an independent disorder. As many as 15 to 20 percent of affected patients do not have concurrent hypertension or proteinuria, leading some authorities to opine that HELLP syndrome is a separate disorder from preeclampsia.

- **Chronic/pre-existing hypertension**

Chronic/pre-existing hypertension is defined as systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg that antedates pregnancy or is present on at least two occasions before the 20th week of gestation or persists longer than 12 weeks postpartum. It can be primary (primary hypertension, formerly called "essential hypertension") or secondary to a variety of medical disorders.

- **Preeclampsia superimposed upon chronic/pre-existing hypertension**

Superimposed preeclampsia is defined by the new onset of proteinuria, end-organ dysfunction, or both after 20 weeks of gestation in a woman with chronic/pre-existing hypertension. For women with chronic/pre-existing hypertension who have proteinuria prior to or in early pregnancy, superimposed preeclampsia is defined by worsening or resistant hypertension (especially acutely) in the last half of pregnancy or development of signs/symptoms of the severe end of the disease spectrum.

- **Gestational hypertension**

Gestational hypertension refers to hypertension without proteinuria or other signs/symptoms of preeclampsia that develops after 20 weeks of gestation. Some women (10 to 25 percent) with gestational hypertension may ultimately develop signs and symptoms of preeclampsia. It should resolve by 12 weeks postpartum. If hypertension persists beyond 12 weeks postpartum, the diagnosis is "revised" to chronic/pre-existing hypertension that was masked by the physiologic decrease in blood pressure that occurs in early pregnancy. If hypertension resolves postpartum, and if signs and symptoms of

preeclampsia have not developed, the diagnosis can be "revised" to transient hypertension of pregnancy.

Burden of disease

Women with preeclampsia are at an increased risk for life-threatening obstetric or medical complications. Worldwide, 10 to 15 percent of direct maternal deaths (ie, resulting from obstetric complications of pregnancy) are associated with preeclampsia/eclampsia ***(Duley, 2009).*** In the United States, preeclampsia/eclampsia is one of the four leading causes of maternal death, along with hemorrhage, cardiovascular conditions, and thromboembolism ***(MacKAy et al., 2011).*** There is approximately one maternal death due to preeclampsia-eclampsia per 100, 000 live births, with a case-fatality rate of 6.4 deaths per 10, 000 cases ***(MacKay et al., 2001).*** For the fetus, preeclampsia can lead to intrauterine growth restriction and oligohydramnios, as well as medically or obstetrically indicated preterm birth. As a result, perinatal morbidity and mortality are increased.

- A **past history of preeclampsia**

Increases the risk of developing preeclampsia in a subsequent pregnancy sevenfold compared with women without this history

The severity of preeclampsia strongly impacts this risk. Women with severe features of preeclampsia in the second trimester are at greatest risk of developing preeclampsia in a subsequent pregnancy: Rates of 25 to 65 percent have been reported ***(MacKay et al., 2001).*** By comparison, women without severe features of preeclampsia in their first pregnancy develop preeclampsia in 5 to 7 percent of second pregnancies ***(Xiong et al., 2002)***. Women who had a normotensive first pregnancy develop preeclampsia in less than 1 percent of second pregnancies.

- **First pregnancy (nulliparity):**

It is unclear why the nulliparous state is consistently found to be a significant predisposing factor for preeclampsia. One theory is that the immune system of nulliparous women has had limited exposure to paternal antigens, and this lack of desensitization may play a role in the pathogenesis of the disease. Epidemiologic data support this theory: Protection from preeclampsia in subsequent pregnancies is either reduced or eliminated if there is a change in paternity, women using barrier methods of contraception are at increased risk, and risk is reduced with increased duration of sexual activity before pregnancy.

However, the notion that the risk of preeclampsia is increased in a second pregnancy with a new partner has been challenged by data suggesting that a longer interval between pregnancies may be the reason for the increased risk with a new partner ***(Rich-Edwards et al., 2014).***

- **A family history of preeclampsia:**

In a first-degree relative suggesting a heritable mechanism in some cases ***(Nilsson et al., 2004).*** The occurrence and severity of the disease appears to be influenced primarily by maternal factors, but the paternal contribution to fetal genes may have a role in defective placentation and subsequent preeclampsia.

- **Pre-existing medical conditions:**
  - **Pregestational diabetes** ***(Dekker and Sibai, 1998)***
  - **Blood pressure ≥130/80 mmHg** at the first prenatal visit. The risk of superimposed preeclampsia is highest in women with diastolic blood pressure ≥110 mmHg and ≥100 mmHg before 20 weeks of gestation ***(Bartsch et al., 2016).***
  - **Antiphospholipid antibodies** ***(Bartsch et al., 2016).***
  - **Body mass index ≥26.1** ***(Bartsch et al., 2016).***
  - **Chronic kidney disease (CKD)** ***(Nevis et al., 2011).***

- **Twin pregnancy**: Preeclampsia is even more frequent with multi-order gestations (triplets, quadruplets) ***(Cassell et al., 2001)***
- **Advanced maternal age**: Older women tend to have additional risk factors, such as diabetes mellitus and chronic hypertension, that predispose them to developing preeclampsia.

Clinical presentation:

Most patients are nulliparous and present with new-onset hypertension and proteinuria at ≥34 weeks of gestation, sometimes during labor. Approximately 10 percent of affected women develop these signs and symptoms at <34 weeks of gestation (ie, early-onset preeclampsia) and rarely as early as 20 to 22 weeks. In approximately 5 percent, the signs and symptoms are first recognized postpartum (ie, postpartum preeclampsia), usually within 48 hours of delivery ***(Al-Safi et al., 2011).***

The degree of maternal hypertension and proteinuria, and the presence/absence of other clinical manifestations of the disease (described below) are highly variable ***(Sibai, 2008).*** Approximately 25 percent of affected women develop one or more of the following nonspecific

symptoms, which characterize the severe spectrum of the disease and signify the need for urgent evaluation and possible delivery:

- Persistent and/or severe headache
- Visual abnormalities (scotomata, photophobia, blurred vision, or temporary blindness [rare])
- Upper abdominal or epigastric pain
- Altered mental status
- Dyspnea, retrosternal chest pain

Epigastric pain may be the presenting symptom of preeclampsia; thus, a high index of suspicion is important to make the diagnosis of preeclampsia rather than gastroesophageal reflux, which is common in pregnant women, especially at night.

Spectrum of disease:

Clinical findings:

Hypertension: All patients with preeclampsia have hypertension (but in patients with HELLP, elevations in blood pressure may be minimal or even absent). It is generally the earliest clinical finding of preeclampsia and the most common clinical clue to the presence of the

disease. The blood pressure usually rises gradually, reaching the hypertensive range (≥140/90 mmHg) sometime in the third trimester, often after the 37th week of gestation ***(Cunningham and Lindheimer, 1992).*** Blood pressures are often around 135/85 mmHg in the one to two weeks before reaching the hypertensive range. However, in some women, hypertension develops rapidly or before 34 weeks of gestation or postpartum.

Epigastric pain: Epigastric pain, when present, is a cardinal symptom of the severe end of the disease spectrum. It is characterized by severe constant pain that often begins at night, usually maximal in the low retrosternum or epigastrium, but may radiate to the right hypochondrium or back ***(Walters, 2011).*** Nausea and vomiting sometimes also occur. On examination, the liver may be tender to palpation due to stretching of Glisson's capsule from hepatic swelling or bleeding.

Liver rupture or hemorrhage is rare, but should be suspected when there is sudden onset of right upper quadrant pain associated with a decrease in blood pressure.

Acute pancreatitis is a rare complication of preeclampsia and can mimic the epigastric pain of preeclampsia ***(Lynch and Dexter, 2015).***

Headache: Headache, when present, is a cardinal symptoms of the severe end of the disease spectrum. It may be temporal, frontal, occipital, or diffuse ***(Shah et al., 2008).*** The pain usually has a throbbing or pounding quality, but may be piercing. Although not pathognomonic, a feature that suggests preeclampsia-related headache rather than another type of headache is that it persists despite administration of over-the-counter analgesics and it may become severe (ie, incapacitating, "the worst headache of my life").

The mechanism for headache, as well as other cerebrovascular symptoms of preeclampsia, is poorly understood. Cerebral edema and ischemic/hemorrhagic changes in the posterior hemispheres observed on computed tomography and magnetic resonance imaging help to explain, but do not fully account for, the clinical findings. These findings may result from generalized endothelial cell dysfunction, leading to vasospasm of the cerebral vasculature in response to severe hypertension, or may result from loss of cerebrovascular autoregulation, leading to areas of both vasoconstriction and forced vasodilation, and thus represent a form of posterior reversible leukoencephalopathy syndrome (PRES). PRES is

typically associated with severe hypertension but can occur with rapid increases in blood pressure in patients with endothelial damage ***(Eastabrook et al., 2011).***

Visual symptoms: Visual symptoms, when present, are cardinal symptoms of the severe end of the disease spectrum. They are caused, at least in part, by retinal arteriolar spasm. Symptoms include blurred vision, flashing lights or sparks (photopsia), and scotomata (dark areas or gaps in the visual field). Diplopia or amaurosis fugax (blindness in one eye) may also occur. Visual disturbances in preeclampsia may also be manifestations of PRES ***(Errera et al., 2013).***

Cortical blindness is rare and typically transient. Blindness related to retinal pathology, such as retinal artery or vein occlusion, retinal detachment, optic nerve damage, retinal artery spasm, and retinal ischemia, may be permanent ***(Cunningham et al., 1995).***

Generalized hyperreflexia: Hyperreflexia is a common finding. Sustained ankle clonus may be present.

Peripheral edema: Many pregnant women have edema, whether or not they have preeclampsia. However, sudden and rapid weight gain (eg, >5 lb/week [2.3 kg]) and facial edema are more common in women who develop