Introduction

Several hypertensive states of pregnancy exist, these collectively are referred to as Pregnancy Induced hypertension (PIH) .These include Gestational hypertension, mild preeclampsia, severe preeclampsia and eclampsia. Left undiagnosed, the milder forms of the spectrum can easily progress up to the development of eclampsia ***(Al-Jameil et al., 2014).***

About 5-10 % of pregnancies are complicated by hypertensive disorders with pre-eclampsia affecting 3 % of all pregnancies. Such patients are at increased risk of maternal and fetal mortality, and serious fetal morbidity, especially if PE is severe ***(*Hutcheon *et al., 2012).***

Pregnancy induced hypertensive disorders are pregnancy –specific multisystem disorders characterized by abnormal vascular placentation which is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial cell dysfunction with resultant reduced organ perfusion ***(*Staff *et al., 2013).***

Although many studies on the pathogenesis of PE have appeared, the precise pathogenetic mechanism and definitive

preventative treatments remain unknown. One possible pathophysiological mechanism is deficient trophoblastic invasion of the maternal vascular bed, reducing maternal blood flow to the placenta, thus creating a degree of ischemia (**Burton *et al., 2009***).

Placental under perfusion triggers angiogenic-responses causing widespread systemic maternal endothelial dysfunction, vascular permeability and vasoconstriction may increase (**Burton *et al., 2009***).

As part of the normal coagulation physiology, contact of platelets with the injured endothelium may activate the coagulation system, increasing both the consumption and bone marrow production of platelets (**Juan *et al., 2011***).

PIH is associated with changes in platelet indices and recent studies suggest that understanding of these changes is one of the most simple and cost effective methods for prediction of PIH way before organ affection ***(*Hutcheon *et al., 2012).***

The coagulation system may become activated, and microangiopathic hemolysis may develop. In addition, hypertension, proteinuria, and other clinical manifestations of PE become prominent (**Sharon *et al., 2011***).

Abnormal active platelets are involved in the pathogenesis of many diseases with thrombotic components like preeclampsia (**Goshal *et al., 2014***).

The activation of platelets affects their size together with other parameters, these are closely linked as a single system; named the megakaryocyte-platelet-hemostatic axis (MPHA) (**Martin *et al., 1991***).

Activated platelets are larger in size, contain more granules and produce greater amounts of vasoactive and prothrombotic factors, such as thromboxane-A2, serotonin and Adenosine triphosphate (ATP) This complex mechanism is regulated by thrombopoietin (TPO) together with several cytokines and growth factors (**Lewin *et al., 2006***).

Platelet functions are indirectly measured by calculating various indices including the platelet count (PC), mean platelet volume (MPV), the PC to MPV Ratio and platelet distribution width (PDW), which measures platelet size distribution *(***Tzur *et al., 2013)***.

Platelet counts (PC) and MPV have been probably the most studied platelet activation markers associated with preeclampsia (**Martin *et al., 1991* , Coban *et al., 2005* and Dundar *et al., 2008***).

MPV increases during pregnancy and is higher in women with PE. MPV may therefore be a valuable tool for evaluating the severity of PE (**Jaremo *et al., 2006***).

Platelet changes caused by activation have been found to include not only t he number, and size of the platelets, but also the morphology and pseudopodia formation which affects PDW (**Vagdatli *et al., 2010).***

Aim of the Work

This study aims to assess the accuracy of platelets indices (MPV-PDW-PC) and their changes in predicting the development and severity of pregnancy induced hypertensive disorders.

Research Question:

In normal pregnant women, do changes in platelet indices predict the development and severity of PIH accurately?

Research hypothesis:

In pregnant women, changes in platelet indices namely (MPV-PDW-PC) may predict the development and severity of PIH accurately.

Primary outcome:

Sensitivity and specificity of platelet indices in prediction of occurrence of PIH.

Secondary outcome:

Co-rrelation between platelet indices and severity of PIH.

Pregnancy induced hypertensive disorders

Pregnancy induced hypertensive disorders (PIH) are pregnancy –specific multisystem disorders characterized by abnormal vascular placentation which is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial cell dysfunction with resultant reduced organ perfusion ***(*Staff *et al., 2013).***

PIH is defined as hypertension (blood pressure>140/90 mmHg) that occurs in pregnancy for the first time after 20 weeks of gestation and disappears following delivery. Current criteria for diagnosis of pre-eclampsia (PE) require the presence of de novo hypertension, with proteinuria or any of the other multisystem abnormalities ***(*Pennington *et al., 2012)***.

PIH can be categorized into the following categories according to the ACOG practice bulletin ***(*ACOG, *2013)***:

1) ***Gestational hypertension:*** defined as blood pressure elevation of greater than or equals 140 mmHg (systolic) or 90 mmHg (diastolic) in a previously normotensive

woman for the first time after mid pregnancy, but in whom proteinuria is not identified.

2) ***Non severe preeclampsia :*** defined by hypertension (blood pressure greater than or equals 140 mmHg systolic or 90 mmHg diastolic) on more than 2 readings taken 6 hours apart after 20 weeks of gestation, combined with proteinuria more than or equal to 0.3g/24 hours, but not meeting the standards of severe preeclampsia.

3) ***Severe preeclampsia:*** defined as: Arterial blood pressure greater than or equals to 160 mm Hg (systolic) or greater than or equal to 110 mm Hg (diastolic) confirmed within a short interval (minutes).

AND

Proteinuria (greater than or equal to 0.3g/24 hours urine collection or protein/creatinine ratio greater than or equals to 0.3).

OR

In the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

- Thrombocytopenia (platelet count less than 100,000/microliter).

- Renal insufficiency (serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease).
- Impaired liver function (elevated blood concentrations of liver transaminases to twice normal concentration).
- Pulmonary edema.
- Cerebral or visual symptoms.

4) ***Eclampsia:*** defined as the onset of convulsions in women with pre-eclampsia that can't be attributed to other causes.

Despite extensive research, the exact cause of pre-eclampsia and eclampsia is not clearly understood ***(*Pennington *et al., 2012)***.

Preeclampsia is a multi-systemic disorder that originates in early pregnancy and leads to considerable maternal morbidity and mortality ***(*Spencer *et al., 2005,* CEMACH*, 2008* and Duley *et al., 2009).***

Abnormalities in the development of placental vasculature early in pregnancy is considered to be a primary cause of relative placental under-perfusion/hypoxia/ischemia,

which then leads to release of numerous factors into the maternal circulation that alter maternal systemic endothelial function and cause hypertension and other manifestations of the disease ***(*Warrington *et al., 2013).***

Preeclampsia can be classified into early and late onset, and it is widely accepted that these subtypes of preeclampsia represent different forms of the disease. Early onset preeclampsia, requiring delivery before 34 week gestation, is commonly associated with intrauterine growth restriction (IUGR), abnormal uterine and umbilical artery doppler waveforms, and adverse maternal and neonatal outcomes. In contrast, late-onset preeclampsia, with delivery at or after 34 weeks, is mostly associated with mild maternal disease and a low rate of fetal involvement ***(*Witlin *e al., 2000,* Irgens *et al., 2001* and Yu *et al., 2008).***

The definitions and classifications of pre-eclampsia and its severity differ between professional groups such as the Royal College of Obstetrics and Gynaecology (RCOG), the American College of Obstetricians and Gynecologists (ACOG), the Society of Obstetricians and Gynaecologists of Canada (SOGC), the International Society for the Study of Hypertension in Pregnancy (ISSHP) and Society of

Obstetrics Medicine of Australia and New Zealand (SOMANZ).

The RCOG unlike the other institutions does not include uteroplacental insufficiency in their definition. The ACOG necessitates the definition of pre-eclampsia to include proteinuria and use a lower cut off systolic blood pressure (≥160 mmHg) compared to the SOMANZ classification ***(*Von Dadelszen *et al., 2014)***. The former has a clear distinction between mild and severe pre-eclampsia. The ISSHP aimed to clarify the uncertainties involving the definition and classification of pre-eclampsia by the various societies. One of the questions raised was whether the presence of proteinuria was mandatory for the diagnosis, due to the high false positive readings associated with urine dipsticks, as well as the expense and time taken to collect a 24 hour urine sample. ISSHP agreed that in clinical practice it is not mandatory to include proteinuria, but in the academic setting where research will occur, inclusion of proteinuria in the diagnosis of pre-eclampsia would make selection more uniform ***(*Tranquilli *et al., 2014)***

The SOMANZ classification uses the definition of pre-eclampsia as the onset of hypertension typically after 20

weeks, but there are cases that may develop before 20 weeks such as in cases of twin pregnancies and molar pregnancies. Hypertension must be associated with features of end organ damage in relation to the renal, haematological, liver, neurological, respiratory, cardiovascular and uteroplacental systems. The classification does not include proteinuria as mandatory and uses a limit of systolic blood pressure ≥170 mmHg ***(*Lowe *et al., 2014)***.

INCIDENCE:

Hypertension is the most common medical problem encountered during pregnancy. About 5-10 % of pregnancies are complicated by hypertensive disorders with pre-eclampsia affecting 3 % of all pregnancies ***(*WHO*, 2003)***.

Variations in incidence reflect, at least in part, differences in the maternal age distribution and proportion of primiparous women among populations ***(*Hutcheon *et al., 2001)***.

Burden of the disease:

Women with PIH are at an increased risk for life-threatening events, including placental abruption, acute renal failure, cerebral hemorrhage, hepatic failure or rupture, pulmonary edema, disseminated intravascular coagulation,

and progression to eclampsia. Worldwide, 10 to 15 percent of direct maternal deaths (i.e., resulting from obstetric complications of pregnancy) are associated with preeclampsia/eclampsia *(***Duley** ***et al., 2009)***.

In the United States, preeclampsia/eclampsia is one of four leading causes of maternal death, along with hemorrhage, cardiovascular conditions, and thrombo-embolism *(***Chang** ***et al., 2003*** **and** ***Main, 2010)***. 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*** **and Livingston** ***et al., 2003)***.

In the Egypt between 2011 and 2013, preeclampsia was the most common cause of maternal death, with 45 maternal deaths per 100, 000 live births ***(WHO, 2013).***

Morbidity and mortality are also increased for the fetus/neonate because of the greater risk of restricted fetal growth and preterm birth in affected pregnancies. The above being stated, identification of pregnant women with increased pre-eclampsia risk is an objective of paramount importance in modern obstetrics *(***Lowe** ***et al., 2014)***.

Patho-physiology:

Pregnancy induced hypertensive disorders are characterized by abnormal vascular placentation which is associated with increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation system and endothelial cell dysfunction with resultant reduced organ perfusion ***(*Staff *et al., 2013).***

Pre-eclampsia is described as the "disease of theories" because although research has been conducted for many years it still remains poorly understood and unpredictable, thus management and classification of the condition is still under debate**.** The disease process, initiated within the placenta and the vascular endothelium, starts early in pregnancy, many weeks before manifestation of clinical disease ***(*Steegers *et al., 2010).***

The common theory that pre-eclampsia is primarily a placental function disorder is further reinforced by cases with molar and an-embryonic pregnancies which develop pre-eclampsia that resolves only after the pregnancy has been terminated. The patho-physiologies of early and late onset pre-eclampsia are believed to differ. Early onset disease, which is clinical onset at less than 34 weeks gestation, is

believed to occur as a result of abnormal adaptation and functioning of the placenta, immunological factors and abnormal endometrial preparation *(***Steegers *et al., 2010)***.

This results in impaired fetal growth. Haemodynamically there is typically a low cardiac output, increased peripheral resistance and small left ventricular size, refer to it as "placental pre-eclampsia" *(***Von Dadelszen *et al., 2014)***.

Late onset disease, the clinical onset of pre-eclampsia after 34 weeks, appears to be more influenced by the underlying maternal condition of chronic hypertension or obesity as well as endothelial dysfunction *(***Sircar *et al., 2015)***. This causes changes in vessels of the decidua, resulting in poor adaption of the spiral arterioles to the pregnancy between 10-15 weeks as well as abnormal cardiovascular response to normal pregnancy**.** Haemo-dynamic studies reveal reduced peripheral resistance, increased cardiac output and left ventricular enlargement *(***Steegers *et al., 2010* and Von Dadelszen *et al., 2014)*** refer to this as "maternal pre-eclampsia". In some patients the early and late onset disease processes may be combined *(***Foo *et al., 2015)***.

a. Abnormal placentation:

The placental insult begins as early as day 11 after fertilization with abnormal formation of the placenta. In normal placental development the first phase of invasion occurs by week 12 where the cytotrophoblast invades the spiral arterioles within the decidua. By week 16 the second invasion occurs where the trophoblasts invade even deeper into the myometrium and radial arteries ***(*Sandler *et al., 2005)***.

Abnormal placental development is believed to be influenced by multiple predisposing factors which include genetics, abnormally functioning natural killer cells, human leukocyte antigen (HLA) types C, D, E (which are the regulators controlling the remodelling of vessels to adapt to pregnancy), reduced levels of CD4+ T regulatory cells and increased levels of T helper 17 (found to be increased in some autoimmune conditions). Decreased release of Notch ligand JAG1, has also been found in placental tissue (notch signals regulate the formation of blood vessels) ***(*Foo *et al., 2015)***. Abnormal placental formation results in narrow and thick walled spiral arterioles, instead of the large-calibre, virtually amuscular vessels seen in normal pregnancy. The