INTRODUCTION

Preeclampsia is a multi-system disorder which was classically characterized by the new onset of hypertension and proteinuria or end organ dysfunction or both in the last half of pregnancy ***(Sibai et al., 2003).***

Although most affected pregnancies deliver at term or near term with good maternal and fetal outcomes, these pregnancies are at increased risk for maternal and/or fetal mortality or serious morbidity ***(Hutcheon et al., 2011).***

Women with preeclampsia are at an increased risk for life-threatening events, including placental abruption, acute kidney injury, cerebral hemorrhage, hepatic failure or rupture, pulmonary edema, disseminated intravascular coagulation, and progression to eclampsia. Worldwide, 10 to 15 percent of direct maternal deaths (ie, resulting from obstetric complications of pregnancy) are associated with preeclampsia/ eclampsia. Although outcome is often good, preeclampsia can be devastating and life threatening, where maternal mortality is high, most of deaths are attributable to eclampsia, rather than preeclampsia ***(Duley et al., 2009).***

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 ***(American College of Obstetricians and Gynecologists, 2013).***

These abnormalities can result in placental under perfusion, and possibly hypoxia and ischemia. Observational data support the hypothesis that placental under perfusion, hypoxia, and/or ischemia may lead to release of circulating antiangiogenic factors (soluble fms–like tyrosine kinase [sFlt-1], soluble endoglin [sEng]) and other substances that can cause widespread maternal systemic endothelial dysfunction (increased vascular permeability, vasoconstriction, activation of coagulation system, microangiopathic hemolysis), resulting in hypertension, proteinuria, and the other clinical manifestations of preeclampsia ***(Maynard and Karumanchi, 2011).***

Recently, various screening tests have been published, some of them even reporting a sensitivity and specificity >90% for the detection of early pre-eclampsia ***(Harrington et al., 2004).*** However, the vast majority of them have been described in general populations and have not been validated in high-risk groups**.**

Deterioration of Doppler velocimetry in the umbilical artery (UA) reflects progressive obliteration of placental tertiary villi with compromise of placental oxygen and nutritive exchanges ***(Vedmedovska et al., 2011).***

The cerebroplacental ratio (CPR), i.e. the ratio of the pulsatility index (PI) of the middle cerebral artery (MCA) to that of the umbilical artery (UA), can detect fetal hypoxemia occurring via two different mechanisms: reduced resistance in the MCA (brainsparing effect) and increasing placental resistance ***(Baschat and Gembruch, 2003).***

Recent studies have shown that combining these two parameters in the cerebroplacental ratio (CPR) further improves the prediction ***(Khalil, et al., 2016).***

A ratio of MCA to UA, the cerebroplacental ratio (CPR), has been proposed as a better predictor of fetal compromise than either vessel considered alone, even when umbilical resistance index is within normal range ***(Hershkovitz et al., 2000).***

However, a major screening study at 32 weeks' gestation reported that the performance of low cerebroplacental ratio in screening for adverse perinatal outcomes is poor, with detection rates (DRs) of 5–11%, at false-positive rate (FPR) of about 5 percent .The study

reported that the prediction of adverse outcome by low cerebroplacental ratio was better if the time interval between assessment and delivery was ≤2 weeks rather than >2 weeks and, consequently, suggested that the performance of screening by cerebroplacental ratio at 36 weeks may be superior to that at 32 weeks ***(Bakalis et al., 2015).***

Aim of the Work

Research hypothesis

In women with severe preeclampsia, the middle cerebral artery/umbilical artery pulsatility index ratio Doppler during third trimester may predicte neonatal acidemia and low Apgar score at 5 minutes after birth accurately.

Research question

In women with severe preeclampsia, does middle cerebral artery/umbilical artery pulsatility index ratio during third trimester predicte neonatal acidemia and low Apgar score at 5 minutes after birth accurately?

Aim of the Work

The aim of this prospective observational study is to assess the accuracy of fetal middle cerebral artery/umbilical artery pulsatility index ratio during third trimester in predicting acidemia and low Apgar score at 5 minutes after birth in neonates of women with severe preeclampsia.

Chapter (1): Basic Doppler Ultrasound Physics

The Doppler, named after Austrian physicist Christian Doppler (1803-53), was developed after he discovered that the frequency of sound waves varied according to the distance that the source and observer were in relation to each other. As they moved closer the frequency increased, and decreased when they moved away. This became known as 'the Doppler effect' ***(Hale, 2008).***

In obstetrics, the 'Doppler effect' is used to evaluate changes in sound waves caused by the direction and velocity of blood flowing through vessels and the heart. Electronic fetal monitoring (EFM) technology became commercially available in 1968, and was introduced in the UK in the early 1970s ***(Blincoe, 2005).***

The change in the frequency is called the **Doppler shift** and is described by the Doppler equation:

$\Delta = (2 \times f \times V \times \cos 0/c)$

Where;

$\Delta =$ Doppler shift frequency

$f =$ The frequency of the ultrasound

$V =$ The velocity of the moving reflector

$0 =$ The angel between the sound beam and the velocity vector of the moving reflectors, and

$c =$ The velocity of sound in tissue

(Dewbury et al., 2001)

The Doppler ultrasound was first developed in the 1960s and uses a continuous or pulsed electronic wave that is transmitted into the body. The change in reflected frequency caused by the blood flow velocity in underlying vessels is converted into a signal ***(Mainstone, 2004).***

In blood flow velocity measurement ultrasound is transmitted by piezoelectric crystal into the tissue at a given frequency, reflected by the moving red cells within the vessel and received at a different frequency. The velocity of the blood flow can be calculated when the angel of insonation is known. The ultrasound frequency is typically 1-10 MHz; the Doppler shift caused by the blood flow is then within the audible range. The detected Doppler shift is a spectrum of frequencies rather than a single frequency, as it originates from red cells moving at various velocities within the lumen of the vessel ***(Dewbury et al., 2001).***

Doppler ultrasound instruments:

Types of diagnostic Doppler instrument which are usually distinguished include**)**:

- ***The continuous wave Doppler technique:***

The (CW) system has no depth resolution so that the measurement results of all flows along the line of sight add together and mix. On the other hand this system measures well all (fast and slow) velocities. If there is only one blood

vessel along the line-of- sight or one flow is dominant the (CW) system is very good for practice ***(Kurjak et al., 2004)***.

There are two piezoelectric crystals in a continuous-wave (CW) Doppler flowmeter, one continuously transmitting ultrasound signals, the other functioning as a receiver. The recorded spectrum of Doppler frequencies contains information on the movements of all interfaces traversed by the ultrasound beam, and the sampling is thus non-discriminative ***(Dewbury et al., 2001).***

The main disadvantage is that the vessel being studied cannot be simultaneously visualized. However, this can usually be overcome because the umbilical and uteroplacental vessels both in health and disease have characteristic signals, which are easily recognized ***(Baschat et al., 2006).***

- ***The pulsed wave Doppler technique:***

The sequence of transmitting and then receiving signals needs to be repeated to build up the Doppler signal. The rate at which pulses of ultrasound are emitted is known as the *pulse repetition frequency (PRF).* The higher the PRF the more pulses will be available per cycle, thus giving a better quality signal. However, the PRF is limited, as there must be sufficient time to collect all echoes from one pulse prior to emitting a further pulse ***(Fahemi et al., 2001).***

In the PW technique, a single piezoelectric crystal is used alternately as a transmitter and receiver. The ultrasound is transmitted in a short pulse; then the transducer gate is closed for a period corresponding to the time required for the pulse to travel to the vessel of interest and back. The gate then opens again to receive the ultrasound echoes returning from a defined region within the tissue, the so-called sample volume ***(Dewbury et al., 2001).***

Duplex method:

In duplex system, the transmitted ultrasound frequency in the Doppler mode is often lower than that for B-mode. The low Doppler beam frequency is to enable higher velocities to be handled before aliasing occurs, while the high B-scan frequency is to optimize resolution in the image ***(McDicken et al., 2002)***.

- ***Color Doppler imaging:***

This is the most recently developed method utilizing Doppler ultrasound. Conventional real-time images are superimposed with blood flow information, coded in color to indicate the direction and velocity of flow. Color flow mapping displays the direction of blood flow, in three different formats: blue, indicating flow away from the transducer, red-orange, indicating flow towards the transducers; and a mosaic pattern of red-orange or blue-green which represents flow in several directions, suggesting turbulence ***(Zhang et al., 2006).***

- ***Power Doppler imaging:***

It is another modality in which it displays areas with moving structures in colors. The color means that, there is flow in the area and the brightness of the color qualitatively indicates the quantity of moving erythrocytes, it does not define the direction of blood flow. The virtue of that display mode is that, it shows about equally fast and slow flow, so that we can get the idea about general blood perfusion in some area ***(Chen et al., 1996).***

One advantage of power Doppler imaging is that, as it does not utilize the velocity information, aliasing does not occur. A most important advantage of using power Doppler imaging is its increased sensitivity to flow compared to color Doppler imaging ***(Dewbury et al., 2001).***

Measurement techniques:

- ***Doppler indices:***

1. The Systolic / Diastolic ratio (S/D) ratio.

The S/D ratio is the simplest but it is irrelevant when diastolic velocities are absent, and the ratio becomes indefinite, Values above 8.0 are considered extremely high ***(Kurjak et al., 2004)***.

2. The Pulsatility index (PI), also called the impedance index. (S-D/MEAN)

The pulsatility Index (PI) requires computer -assisted calculation of mean velocity, which still may be subjected to very large experimental error. So, (RI) is considered the ideal parameter as a Doppler index ***(Kurjak et al., 2004)***.

3. The Resistance Index (RI), also called the Pourcelot ratio (S-D/S).

The resistance index (RI) approaches 1.00 when diastolic velocities are abnormally low and, therefore it reflects the relative impairment of flow by its high values ***(Kurjak et al., 2004)***.

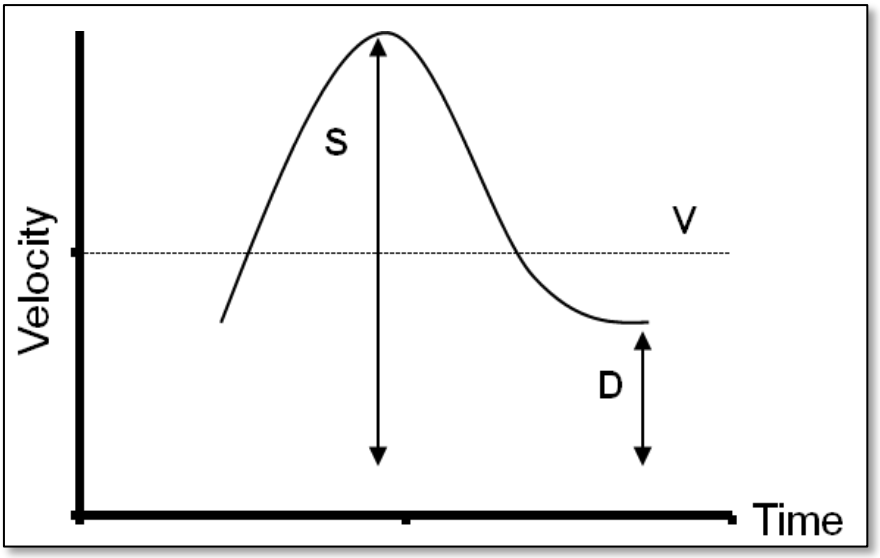

Fig. (1): Resistance index
S-peak systolic velocity
D-minimum diastolic velocity
V-mean of the maximum velocity over the heart cycle
Resistance and pulsatility indices (S/D ratio, RI and PI)

These indices are ratios, independent of the angle between the ultrasound beam and the insonated blood vessel, and therefore not dependent on absolute measurement of true velocity. However, when the angle approaches 90, the measurement error increases rapidly.

- ***Velocity waveform analysis:***

The early reports on Doppler studies in fetuses showed an association between unfavorable fetal outcome and some typical changes of the velocity waveforms recorded from the fetal aorta or umbilical artery. Experience from the diagnostic use of Doppler ultrasound in peripheral vessels indicated that important information on circulation might be gained by analyzing the maximum velocity waveforms ***(Dewbury et al., 2001)***.

The most important possible error in clinical application is obtaining false positive findings of missing end-diastolic velocities ***(Dewbury et al., 2001).***

Factors affecting flow velocity waveform:

- ***Maternal position:***

For obstetric Doppler examinations, the patient assumes a supine slightly left lateral tilted position. It is important to avoid the supine hypotension syndrome, since it has been associated with alternation in S/D ratios of uterine and umbilical vessels ***(Sanders and James, 2005).***

- ***Maternal exercise:***

The fetal circulatory response to maternal hemodynamic stress secondary to maternal exercise may be an important consideration when timing a fetal Doppler investigation. Several investigators have addressed this issue. All of these studies, which employed some form of bicycle ergometry, demonstrated an exercise-induced response in the maternal cardiovascular system. The fetal cardiac chronotropic response was variable. Often the response was tachycardia, although a lack of variation was also noted. Most studies failed to show changes in the umbilical artery Doppler indices. When such changes were noted, they were associated with fetal heart rate alteration. From these investigations it appears that mild to moderate exercise does not affect flow impedance in the umbilical artery independent of changes in the fetal heart rate ***(Maulik, 2005).***

- ***Diurnal effect (short-term temporal variations):***

It appears that after 30 weeks' gestation diurnal variations in the umbilical arterial Doppler indices have a range of daily variability acceptable for clinical or research applications ***(Maulik, 2005).***

- ***Gestational age effect (long-term temporal variations):***

As gestation advances, umbilical arterial Doppler waveforms demonstrate a progressive rise in end diastolic velocity. This phenomenon was first described by Stuart and associates ***(Maulik, 2005).***

- ***Fetal heart rate:***

In maternal and fetal vessels waveform indices (S/D ratio, RI and PI) have been found to be inversely correlated to the heart rate. With increasing heart rate, the beat-to-beat interval shortens and the diastolic flow velocity increases relative to the peak velocity. An opposite effect is seen in bradycardia. For both the fetal descending aorta and the umbilical artery this effect has been found to be not to pronounced provided the fetal heart rate (FHR) is within normal limits (120-160 beats/min) ***(Dewbury et al., 2001).***

- ***Fetal breathing:***
  - Assessment of fetal activity is an important component of the Doppler
  - Examination. Fetal movement and breathing can have a significant effect on
  - Flow velocity waveforms and produce spurious ratios. High amplitude fetal
  - Breathing movements, for example, may modulate the pulsatility index of the
  - Fetal internal carotid artery from -25% to +20% ***(Baschat et al., 2006)***.

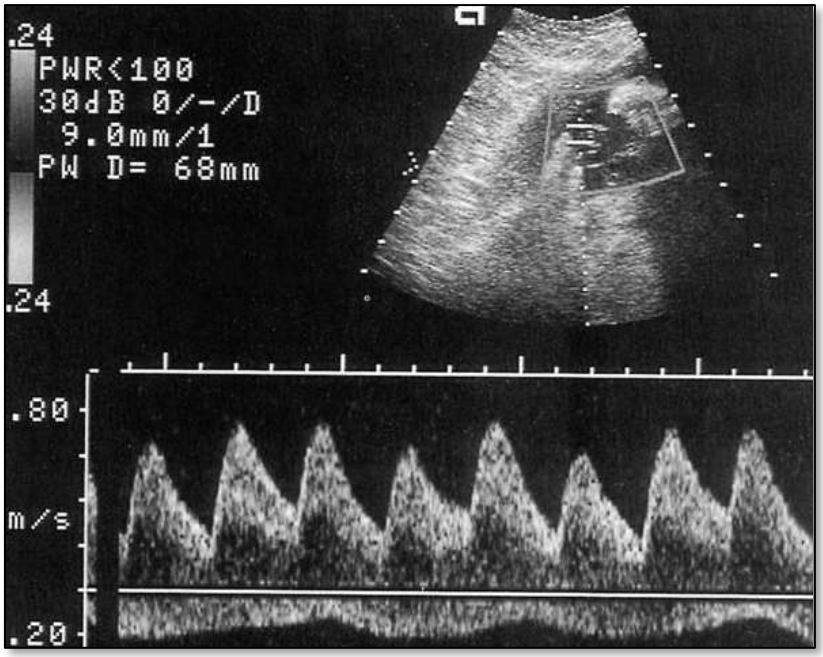

Fig. (2): Fetal breathing and umbilical artery Doppler waveform. Observe the dynamic variations in the arterial and venous Doppler tracings ***(Maulik, 2005).***

Physiology of fetoplacental circulation:

Pregnancy is a high-flow, low-resistance state of cardiovascular homeostasis associated with remarkable hemodynamic changes. Interference with the normal growth and development of the uteroplacental and fetoplacental circulations may result in disruption of the oxygen and nutrient supply to the fetus, leading to reprogramming of fetal development ***(Itskovitz-Eldor and Thaler, 2005).***