Second Trimesteric Uterine Artery Doppler Velocimetry and Calcium / Creatinine Ratio as Predictors for Pre-eclampsia in High Risk Population

Thesis

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By

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ABSTRACT

Preeclampsia is one of the most important Disease with pregrency, many theories try to explain the etiology and the pathogenesis of preeclampsia , prediction of preeclampsia in this thesis by detection of the level of calcium / creatinine ratio in urine of patient in second trimester and by Doppler. The result showed that calcium / creatinine ratio decreased, resistant index increased and diastolic notch either unilateral or bilateral are predictable.

Key Words : Preeclampsia - calcium - prediction

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DEDICATION

TO

MY

FAMILY

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INTRODUCTION AND AIM OF THE WORK

Pre-eclampsia is hypertension associated with proteinuria ***(Arias, 1993).*** It occurs in 2% of nulliparous women ***(Hauth et al., 2000).*** It is a serious complication of the second half of pregnancy that can lead to both fetal and maternal morbidity and mortality ***(Wang et al., 1998)***. In a study of maternal mortality in Kasr El-Aini hospital during the period ***(1984 - 1988)*** pre-eclampsia accounted for 40.7% of all maternal deaths ***(Minawi et al., 1989)***. In Scotland, the risk of recurrent pre-eclampsia was reported to be 3.4 % in women who developed pre-eclampsia in their first pregnancy ***(August, 1999).*** The pathophysiologic abnormalities of pre-eclampsia are numerous. Some of the reported abnormalities include placental ischeima, generalized vasospasm, abnormal haemostasis with activation of the coagulation system, vascular endothelial dysfunction, abnormal nitric oxide and lipid metabolism, leukocyte activation and changes in various cytokines as well as insulin resistance ***(Dehker, 1991).***

Several methods have been reported for the prediction of pre-eclampsia including clinical and laboratory investigations which include serum uric acid, serum iron, serum fetoprotein, urinary albumin and calcium excretion ***(Stamilio et al and 2000).*** Changes in plasma and intracellular calcium level have been suggested in the pathogenesis of pre-eclampsia ***(Kosch et al., 2000),*** thus calcium supplementation may prevent high blood pressure ***(Hafmeyr, 2003)***.

Calcium/creatinine ratio decrease in pre-eclampsia ***(Kazerooni, 2003)***.

Doppler velocimetry examination is a non-invasive procedure that permits assessment of uterine blood flow ***(Low, 1991).*** The introduction of this technology had advanced our understanding of pathophysiology and research in fetal and maternal haemodynamics ***(Rotmensch et al., 1991).*** A relation between high resistance uterine artery wave forms in the second half of pregnancy and pre-eclampsia has been established ***(Aguilina and Harrington, 1996),*** hence the abnormal uterine artery velocimetry has been related to lack or incomplete development of physiologic changes in spiral arteries of the placenta bed ***(line et al., 1995).***

Harrington et al., (1997) conducted a study to evaluate the predicative value of Doppler ultrasonography of uterine arteries in early pregnancy in identifying women at risk of pre-eclampsia. Many Doppler indices of the uterine artery were evaluated over time such as resistant index (R.I) pulsatility index (P.I) ***(Poutcelot, 1974),*** systolic/diastolic ratio (S/D) ***(Stuart et al, 1980),*** diastolic/averdge ratio D/A ***(Maulik et al., 1982)*** and diastolic-notch ***(Irion et al., 1998).*** However the results are varient and often conflicting between the different authors. This may be due to the obvious interobserver & intraobserver difference in measuring Doppler indices ***(Gill, 1985).*** So the exact role of Doppler indices is to be explored.

Aim of the study:

The aim of this study is to evaluate the predictive value of early second trimester calcium/creatinine ratio and uterine Doppler velocimetric indecies of uterine arteries for predicting the occurrence of pre-eclampsia in high risk women.

PRE-ECLAMPSIA

Classification and Terminology

There are five types of hypertensive disease that complicate pregnancy according to the National high blood pressure education program, 2000.

1- Gestational hypertension (formerly pregnancy-induced hypertension or transient hypertension).

2- Pre-eclampsia

3- Eclampsia

4- Pre-eclampsia superimposed on chronic hypertension

5- Chronic hypertension.

An important consideration in this classification is differentiating hypertensive disorders that precede pregnancy from pre-eclampsia, which is potentially more ominous disease (Leveno et al., 2003).

1- Gestational hypertension:

- Blood pressure $\geq$ 140/90mmHg diagnosed for first time during pregnancy
- No proteinuria
- BP return to normal within 12 weeks post partum
- Final diagnosis made only post partum.
- May have other manifestations of pre-eclampsia e.g. epigastric discomfort or thrombocytopenia.

2- Pre eclampsia:

Minimum critenia:

- BP $\geq$ 140 /90 mmHg after 20 weeks of gestation.
- Proteinuria $\geq$ 300mg/24hr or $\geq$ 1 + dipstick.

Increased certainty of pre-eclampsia:

- BP $\geq$ 160/110 mmHg.
- Proteinuria 2.0 gm/24h or $\geq$ 2 + distick
- Serum creatinine > 1.2mg/dl unless known to be previousaly elevated
- Platlets < 100, 000/mm^3.
- Microangiopathic haemolysis (increased LDH)
- Elevated ALT and/or AST
- Persistant headache or other cerebral or visual disturbances
- Persistant epigastric pain.

3- Eclampsia:

- Seizures that can not be attributed to other causes in a women with pre-eclampsia.

4- Superimposed pre-eclampsia (on chronic hypertension)

- New –onset proteinuria $\geq$ 300mg/24h in hypertensive women but no proteinuria before 20 weeks gestation.

- A sudden increase in proteinuria or BP or platelets count < 100,000/mm^3 in women with hypertension and protenuria before 20 weeks gestation

5- Chronic hypertension:

BP ≥ 140/90mmHg before pregnancy or diagnosed before 20 weeks gestation or hypertension first diagnosed after 20 weeks' gestation and persistent after 12 week's post-parturm.

Indications of severity of pre-eclampsia (Leveno et al., 2003)

Abnormality	Mild	Sever
Diastolic BP	< 100mmHg	> 110mmHg
Proteinuria	Trace- 1+	Presist 2+ or more
Headch	Absent	Present
Visual disturbance	Absent	Present
Abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsions	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia	Absent	Present
Liver enzyme elevation	Minimal	Marked
Fetal growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present

Incidence of pre-eclampsia

Pre-eclampsia is a disease of primigravida and is not usually a recurrent condition. In Scotland, ***August (1999)*** reported a risk of recurrent pre-eclampsia of 3.4% in the second pregnancies of women who developed pre-eclampsia with their first pregnancies. Many factors influence the incidence of pre eclampsia such as parity, age, race, genetic predisposition and environomental factors. The racial and genetic factors are important because they contribute to the incidence of underlying chronic hypertension ***(Cunnningham et al., 1993).***

In China, the rate of pre-eclampsia in urban areas is more than double those of rural area. Incidence appears to be increased in poor populations, and in certain racial ethenic groups, including black in US. Urbancity can also influence the occurrence of pre-eclampsia ***(Innes and Wimsatt, 1999)***.

Ventura and colleagues (2000) estimated that the incidence of eclampsia in united states in 1998 was about 1: 3250 according to the national center for health statistics and gestational hypertension was identified in 150.000 women, or 3.7 percent of pregnancies. ***Martin and colleagues (2003)*** reported that 16 percent of 3201 pregnancy related deaths in the united states from 1991 to 1997 were form complications of pregnancy-related hypertension.

RISK FACTORS OF PRE-ECLAMPSIA

Zhang et al., (2003), found a higher recurrence rate of all hypertensive disorders with earlier onset of hypertension in the first pregnancy. ***Dietl, (2000)*** reported that the etiology of pre-eclampsia, has not yet been clearly established. The most important risk factors are :

1- Age:

There is increase in pre-eclampsia in young primigravidas and pregnant ladies over 30 years of age. In young primiparas the increased incidence may be due to poor immune capacity, whilst the increased incidence with increasing age probably reflect the increasing incidence of essential hypertension or latent hypertension ***(Davey et al., 1995).***

2- Parity:

It is well accepted that pre-eclampsia and eclampsia are essentially diseases of the first pregnancy and even if pre-eclampsia occurs in subsequent pregnancies, it will be much less severe and much less common (1-2%). Many workers reported that the combination of primigravidity and age over 35 years leads to a much higher risk of developing pre-eclampsia ***(Mac-Gillivray, 1983).***

3- Race:

The incidence in white races is 6.2% while it is 8.5% in black races. This variation is mostly due to genetic factors ***(Mac Gillivray et al., 1983).***

4- Family history:

Several studies of World Health Organization (W.H.O) reported that there is a familial tendency for both pre-eclampsia and eclampsia because detailed studies of pregnant sisters, daughters, grand-daughters of pre-eclamptic women showed that the incidence of pre-eclampsia was 2% ***(Chesley, 1984).***

5- Blood grouping:

An early report from U.S.A suggested the role of blood group incompatibility between the mother and the fetus as a predisposing factor for pre-eclampsia. However, most of other studies denied the existence of this relationship. More recently, it was found in the Federal Republic of Germany that pre-eclampsia in blood group A is 14.4% while it is 12% in blood group O and it is 12% in Rh +ve ladies while it is 9% in Rh –ve ones ***(Chesley et al., 1984).***

6- Diet:

Various dietary deficiencies have been suspected as a cause of pre-eclampsia. Calcium deficiency has been implicated by some and calcium supplementation appears to reduce the risk of pre-eclampsia ***(Sanchez-Ramos, 1994).*** After mid pregnancy, dialy dietary supplementation with 2g of calcium reduced the incidence of hypertension. Women who developed pre-celampsia excreted less calcium than healthy pregnant women. Whether this reduction in calcium excretion in women with pre-eclampsia precedes or follow hypertension is unknown. These observations suggest

apathophysiologic role for altered urinary calcium excretion in pre-eclamptic patient ***(Sanchez-Ramos et al., 1994).***

Suarez et al., (1996) stated that in young healthy primigravidas, a low urinary excretion of calcium per kilogram of body weight per 24 hours before the end of the first half of gestation is a risk factor for pre-eclampsia.

7- Obesity and insulin resistance:

The higher risk of pre eclampsia with increasing obesity, in particular abdominal rather than gluteal-femoral is associated with insulin resistance and hypertriglyceridaemia ***(Greer et al., 1996). Thadhani et al., (2004)*** examined the relationship between body mass index (BMI), elevated cholesterol level and the development of hypertensive disorders of pregnancy. The relationship between maternal wieght and the risk of pre eclampsia is progressive.

In the study of pregnant women by ***Wolf and Colleagues (2002)***, c-reactive protein, an inflammatory marker, was shown to be increased in obesity, which in turn was associated with pre-eclampsia.

An investigation of more than 4000 nulliparous women participating in a clinical trial also demonstrated that increased body mass index was a risk factor for pre-eclampsia ***(Sibai, 2003).***

8- Pre existence of medical disease:

Such as cardiovascular disease, glucose intolerance, renal disease and hyperlipidaemia ***(Ness and Roberts, 1996).*** The higher incidence of pre-eclampsia among diabetics may be attributed to the