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A review of hypertensive disorders of pregnancy

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Summary
The detection and clinical management of hypertension in pregnant women are complicated by the concern for fetal development and survival as well as for the health of the mother. Preeclampsia describes a common syndrome that occurs in the second half of pregnancy and often manifesting with hypertension and proteinuria. It occurs in up to 10% of all pregnancies. The factors that initiate preeclampsia are unknown and still a subject of intense clinical research by both Obstetricians and Physicians. The blue print for the development of preeclampsia is probably laid down early in pregnancy, and delivery of the fetus and placenta remains the only effective treatment. Severaclinical, biophysical and biochemical tests have been reported in the world literature to predict the development of preeclampsia. Also, numerous reports have described the predictive value of every possible substance that can be measured in maternal blood or urine. However, the presence of microalbuminuria is an important clinical finding in pregnant women. Indeed, urinary albumin excretion when used as a single test has shown that albumin excretion was higher at booking in those that later developed hypertensive disorders of pregnancy than those that did not have the condition. It had a higher sensitivity and poor predictive value. In conclusion, the factors that are responsible for hypertensive disorders of pregnancy remain unknown and treatment is still difficult. The search for an ideal predictive test or tests should therefore be a continuous exercise.

Keywords: *Hypertension; pregnancy, disorder*

Résumé
La détection et le ménagement de l'hypertension aux femmes anciente sont compliqués par le developement et la survie du fétus et la santé de la mére. La pré-eclampsie décrit un syndrome commun dans la 2iéme miotie de la grossesse et souvent se manifestant par l'hypertension et la protéinurie chez plus de 10% des grossesses. Les facteurs qui initient la pré-eclampsie sont inconnus et demeurent l'object des recherches intense des medecins et des obstétriciens. L'apogée de cette maladie est pendant la grossesse et l'accouchement du fétus , et le placenta reste sous traitement. Plusieurs examens cliniques , biophysiques et biochémiques ont rapportés siur des valeurs des paramétres predictives de cette maladie dans le sang et l'urine maternelle. La presence de l'albuminurie est un facteur clinique important aux femmes enceinte. Le taux d'excretion d'albumine dans les urines était plus élevé aux visites chez celles qui developaient des désordres d'hypertension en grossesse avec une sensitivité élevée et de valeur faible que celles normale. En conclusion, les faceturs responsable des désordres d'hypertension en grossesse restent inconnus rendant le traitement difficile. Ainsi la recherche des tests de prediction ideal pourrait etre valeureux.

Pregnancy induced hypertension

Hypertensive disorders of pregnancy are common and are major complications of pregnancy. They are responsible for significant morbidity and mortality in the fetus, newborn infant and mother in both developed and developing countries [1,2,3]. Hypertension is the second commonest medical condition in pregnancy and it occurs in up to 10% of all pregnancies. It is responsible for several cardiovascular events and accounts for about 12% of all maternal deaths, which is about 1500/100, 000 live birth in Nigeria [4]. Ordinarily, blood pressure falls during the first trimester and increases during the third trimester to about pre-pregnancy levels. Hypertension is therefore established when blood pressure has reached 140/90mmHg cut off or recorded an increase of 30mmHg in systolic or 15mmHg in diastolic pressures. Hypertension in pregnancy may have three possible aetiologies, it may be caused by pregnancy as an isolated event i.e. pregnancy induced hypertension (PIH) or as a syndrome of preeclampsia. Secondly, it may represent chronic hypertension in the woman, which sometime may be revealed for the first time in pregnancy. Lastly, it may be a new entity, which coincides with pregnancy. This becomes more significant when it is associated with proteinuria. Although, distinction between essential hypertension and preeclampsia may be difficult to make especially in patients who book late, it is well know that women with hypertension in pregnancy run an increased risk of chronic hypertension later in life and preeclampsia may also superimpose on chronic hypertension [5]. The detection and clinical management of hypertension in pregnant women are complicated by the concern for fetal development and survival as well as for the health of the mother. In a previous study the authors found out that the incidence of pregnancy induced hypertension without preeclampsia/ eclampsia was noted to be 5.4% [6]. The study also found out that the prevalence of hypertension was significantly higher in the immediate post partum period than at booking. Previous history and family history

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of hypertension were also found to be strong determinants of hypertension in pregnancy in the population studied.

Preeclampsia/eclampsia

Preeclampsia describes a common syndrome that occurs in the second half of pregnancy and often manifesting with hypertension and proteinuria [7]. It occurs in up to 10% of all pregnancies [8] and it is one of the most serious complications of pregnancy [9,10]. It is the second leading cause of maternal mortality worldwide, constituting 12 – 18% of pregnancy related maternal deaths[11]. Black women have as much as twice the relative risk of developing it than whites with a prevalence of 15.7% in the author's environment [11,12]. The higher rate of preeclampsia in black women compared to other racial groups is probably because they have a greater prevalence of underlying chronic hypertension.

In the more severe forms, patients may develop seizures and coma (eclampsia). In a study among pregnant women in Ibadan, the incidence of preeclampsia was found to be 9.7% with the incidence increasing with the degree of microalbuminuria at booking [12]. Although not directly comparable, this incidence is slightly higher than the world value of between 2-8% [10]. The factors that initiate preeclampsia are unknown [7] and still a subject of intense clinical research by both Obstetricians and Physicians. The blue print for the development of preeclampsia is probably laid down early in pregnancy, and delivery of the fetus and placenta remains the only effective treatment[13]. It has been postulated that abnormal placentation believed to be due to failure of the second wave of trophoblastic invasion of the spiral arteries from the 20th week of pregnancy is the primary insult [14,15,16]. A second hypothesis proposes that the placenta releases certain cytotoxic substances leading to widespread endothelial damage. However, such cytotoxic substances are yet to be isolated.

Another hypothesis seeks to explain the vasospasm that characterizes the disease [16]. Among the many factors influencing vascular reactivity and which are possibly implicated are: the renin - angiotensin system, prostaglandins, progesterone and its metabolites, calcium, magnesium, digoxin – like immunoreactive substance(s), and substances secreted by platelets, leukotrienes and atria natriuretic factor [16]. Circulating atria natriuretic peptide and renin - angiotensin system seem to be suppressed presumably as secondary compensatory changes, however some of the reports concerning this hypothesis are inconsistent with each other.

Another model suggests that the increased cardiac output observed during pregnancy causes preeclampsia [11]. The increased blood flow and pressure is felt to lead to capillary dilatation, which damages end organ sites, leading to hypertension, proteinuria and oedema. Additional theories have arisen from epidemiologic research, suggesting the important role of genetic and immunologic factors [17,18]. Moreover, the duration of time the woman is exposed to the male antigens prior to conception is inversely related to the risk of developing preeclampsia [19].

The increased incidence observed in patients using barrier contraception, in multiparous women conceiving with a new partner and in nulliparous women suggests an immunologic role. Also, inheritance pattern analysis supports the hypothesis of transmission of preeclampsia from mother to fetus by a recessive gene [11].

There is increased incidence of pregnancy-induced hypertension in association with diabetes mellitus, polyhydramnios, multiple pregnancy, rhesus incompatibility and in cases of hydatidiform mole [20]. It is suggested that the presence of proteinuric hypertension prior to 20 weeks gestation should initiate a search for molar pregnancy because it raises the possibility of increased placental tissue for a given gestational age, which could cause the symptoms. Other causes include drug withdrawal or chromosomal abnormality in the fetus e.g., trisomy [11].

Preeclampsia is regarded primarily as a disease of primigravidae but may occur in subsequent pregnancies and tends to run in families [20]. It is not associated with an increased incidence of hypertension later in life except where it develops in a woman with pre-existing hypertenison. Newer research suggests that primapaternity plays a larger role than primagravidity as a risk factor for the development of preecalmpsia [11]. It is also more common at the extremes of maternal age (<18 years or >35 years) [21,22].

Pathophysiology of preeclampsia/eclampsia

The pathophysiology of eclamptic seizures is not understood. These events are believed to arise from the same preeclamptic effects observed in other areas of the body [11]. In the brain, cerebral vasospasm, oedema, ischaemia, and ionic shifts between intracellular and extracellular compartments are believed to incite eclamptic seizures [23]. Hypertension occurring in preeclampsia is due to vasospasm, with arterial constriction and relatively reduced intravascular volume compared to normal pregnancy [21]. Usually, the vasculature of pregnant women demonstrates decreased responsiveness to vasoactive substance such as angiotensin II and epinephrine [22].

Women who develop preeclampsia may show a hyperesponsivenss to these hormones, their blood pressures are labile, and their normal circadian blood pressure rhythms may be blunted or reversed [22]. The signs and symptoms of preeclampsia become apparent at a relatively late stage in pregnancy, usually in the third trimester. However, the underlying causes of the pathophysiologic mechanisms that are thought to be responsible for the disease process appears to occur much earlier in pregnancy [24]. For this reason, it seems logical to search for earlier indicators for the disorder.

Management of preeclampsia

Pre-eclampsia is unpredictable in onset and progression. It is incurable except by termination of pregnancy. Generally, where hypertension is mild and there is no significant proteinuria, the basic approach to management is expectant, with the patient being put on sedatives and encouraged to rest in bed [25]. Although the use of antihypertensive drugs is not the first line of management in pregnancy induced hypertension, these drugs can be used to keep the blood pressure from reaching levels that can trigger off cerebrovascular accidents and other cardiovascular events until delivery can be effected [25]. Quite a number of anti-hypertensives have been employed in the treatment of pregnancy-induced hypertension. This includes alpha methyldopa vasodilators like hydralazine, nitroprusside, diazoxide and of late calcium channel blockers are being increasingly used. It would appear however that hydralazine has been preferred over the years. Nitroprusside and diazoxide should be avoided because of their severe side effects especially hypotension and toxic effects on the fetus. Recently, parenteral magnesium sulphate has become increasingly useful in the treatment of preeclampsia and eclamptic seizures [26]. Anecdotal reports have also suggested the usefulness of anti- platelets especially aspirin in the prevention of preeclampsia but the results have been rather inconsistent [27].

Predicting preeclampsia

More than 100 clinical, biophysical and biochemical tests have been reported in the world literature to predict the development of preeclampsia [28]. Also, numerous reports describe the predictive value of every possible substance that can be measured in maternal blood or urine [29]. The wide scatter of results and the lack of agreement between serial tests prevent the use of any individual test for such purpose. In addition, results of pooled data for various tests suggest that none of these tests are sufficiently reliable, sensitive, or specific for use as a screening test in clinical practice. Some of these tests include the use of angiotensin II pressor response [30, 31], the roll over test [32], the isometric handgrip exercise test [33], mean arterial test [34,35] and twenty-four hour automated blood pressure monitoring [36]. These tests, however, have had limitations as screening tools in the clinical setting because of their complexity, high incidence of false-positive results, or the subjective nature of result interpretation.

Many biochemical markers of pre-eclampsia have been recognized in maternal serum. These include uric acid, creatinine, and albumin amongst others. Renal function changes in preeclampsia have been documented and several prospective studies indicate that at least some of these changes present before the clinical diagnosis of preeclampsia [37]. Proteinuria has classically been an important sign in the diagnosis of preeclampsia/eclampsia. However, conventional dipstick methods for detecting proteinuria fail to detect minimal elevation in urinary excretion of albumin that may be present before other clinical signs and symptoms of preeclampsia. However, with radioimmunoassay and other sensitive methodology for detection of microalbuminuria, it is now possible to detect minimal elevations in albumin excretion that may go unnoticed.

Microalbuminuria refers to sub-clinical elevation of urinary albumin excretion usually in the range of 30-300mg/24hrs [38]. It has been shown to be increased significantly in hypertension [39] and to precede the development of chronic renal failure in patients with insulin-dependent diabetes mellitus [40,41,42], and may predict preeclampsia [43,44]. It has also been shown that healthy pregnant women do not excrete albumin in amounts detectable by a screening test [45]. Therefore, the presence of microalbuminuria is an important clinical finding in pregnant women. In a previous study it was shown that up to 24% of pregnant mothers in the booking clinic present with microalbuminuria [12]. Urinary albumin excretion when used as a single test showed that albumin excretion was higher at booking in those that later developed hypertensive disorders of pregnancy than those that did not have the condition. It had a higher sensitivity 88.9% but poor predictive value 22.2% and did not appear to predict outcome of pregnancy too [12]. Assessment of urinary microalbumin excretion early in pregnancy in addition to other tests may therefore be considered as a routine test in the antenatal clinic.

In conclusion, the prediction and treatment of hypertensive disorders of pregnancy have hitherto remained elusive and difficult. Microalbuminuria assessed early in pregnancy appears promising as a predictor of hypertensive disorders of pregnancy. The routine detection of microalbuminuria in at risk patients may predict the disease in some subset of patients who may later develop it. As at this moment there is no one test that fulfils all the criteria of the ideal desired test and until we develop such tests, morbidity and mortality due to hypertensive disorders of pregnancy will continue to remain high the world over.

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