BIOCHEMICAL MARKERS FOR PREECLAMPSIA

Essay

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In **Obstetric and Gynecology**

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LIST OF ABBREVIATIONS

٢-ME	*Methoxy-estradiol*
ACE	*Angiotensin converting enzyme*
ADAM ١٢	*A disintegrin and metalloprotease ١٢*
AM	*Adrenomedullin*
Ang II	*Angiotensin II*
AT١	*Angiotensin II type ١*
AT١-AA	*AT١R autoantibodies*
AT١R	*Angiotensin type ١ receptor*
ATP	*Adenosine tri-phosphate*
BP	*Blood pressure*
$Ca^{٢+}$	*Calcium*
CffDNA	*Cell-free fetal DNA*
cGMP	*Cyclic guanosine monophosphate*
COMT	*Catechol-O-methyltrasferase*
COX	*Cyclooxygenase*
CRP	*C-reactive protein*
EC	*Endothelial cell*
EDHF	*Endothelial-derived hyperpolarizing factor*

eNOS	*Endothelial NOS*
ER	*Endoplasmic reticulum*
ET-۱	*Endothelin-۱*
ET_AR	*Endothelin ETa RECeptor*
GDP	*Guanosine Di-Phosphate*
GFR	*Glomerular filtrationr ate*
GTP	*Guanosine tri-phosphate*
HELLP	*Hemolysis, elevated liver enzyme and low platelets*
HIFs	*Hypoxia inducible factors*
HTN	*Hypertension*
HTN-preg	*Hypertension in pregnancy*
I/R	*Ischemic-reperfusion*
IgG	*Immunoglobulin G*
IL	*Interleukin*
INF-α	*Tumor necrosis factor-α*
iNOS	*Inducible NOS*
IP۳	*Inositol triphophate*
IUGR	*Intrauterine growth restriction*
L-NAME	*N-nitrol-L-arginine methyl ester*

MMP-۱	*Matrix metallopotease-۱*
MPV	*Mean platelet volume*
NK۱	*Neurokinin receptor*
NKB	*Neurokinin B*
nNOS	*Neuronal NOS*
NO	*Nitric oxide*
Norm-Preg	*Normal pregnancy*
$O_۲$	*Superoxide anion*
PAPP-A	*Pregnancy-associated plasma*
PE	*Preeclampsia*
PET	*Preeclamptic toxemia*
PGF۱α	*٦-Keto-prostaglandin F۱α*
$PGI_۲$	*Prostacyclin*
PHE	*Phenylephrine*
PIGF	*Placental growth factor*
PKC	*VSM protein kinase C*
PP-۱۳	*Placental protein ۱۳*
PTX۳	*Pentraxin ۳*
RIA	*Radioimmunoassay*

RKC	*Protein kinase C*
ROS	*Reactive oxygen species*
RPF	*Renal plasma flow*
SAP	*Serum amyloid P component*
sEng	*Placental derived soluble endoglin*
sFIt-۱	*Soluble FMS-like tyrosine kinase-۱*
SRY	*Sex determining region Y*
TGF-β	*Transforming growth factor- β*
TXA۲	*Thromboxane $A_۲$*
UCA	*Umbilical cord artery*
UPR	*Unfolded protein response*
VEGF	*Vascular endothelial growth factor*
VEGFR-۱	*VEGF receptor-۱*
VSM	*Vascular smooth muscle*
VSMC$^{۲+}$	*Vascular smooth muscle $Ca^{۲+}$ $[Ca^{۲+}]$*
WHO	*World Health Organization*

INTRODUCTION

Preeclampsia (PE) a leading cause of adverse pregnancy outcomes worldwide, remains a major cause of maternal and perinatal mortality ***(Sibai et al., ٢٠٠٥)***.

It is defined as de novo hypertension (>١٤٠/٩٠mmHg) appearing after ٢٠ weeks of gestation accompained by proteinuria (>٠,٣ g/٢٤h) ***(Brown et al., ٢٠٠١).***

An increasing body of evidence indicates that women affected by PE will be at higher risk for cardiovascular disease later in life ***(Forest et al., ٢٠٠٥)***.

WHO has recognized the importance of PE by launching a program specifically dedicated to the study and treatment of this syndrome ***(WHO/OMS, ٢٠٠٣)***.

PE is characterized by a complex pathophysiology and heterogeneous clinical and laboratory findings ***(Broughton, ١٩٩٤)***. Numerous pathophysiological mechanisms alone or in combination have been suggested to be responsible for the diverse subsets of PE. They include impaired vascular remodeling of the maternal-fetal interface, excessive immune response to paternal antigens, systemic inflammatory response, and dysfunctional placental or endothelial response, all of these processes being modulated by genetic and environmental parameters ***(Iiekis et al., ٢٠٠٧)***.

Such heterogenecity of potential processes leading to or resulting from PE has contributed to the lack of diagnostic means for identification of women susceptible to developing PE resulting in delayed recognition and severe complications ***(Lockwood, ٢٠٠٢)*** and impeding evaluation of new preventive intervention. The latter problem holds particular consequences for high- risk women, in whom treatments have shown potential protective effects ***(Duley et al., ٢٠٠٧)***.

A recent metaanalysis suggested that, in high risk women low-dose aspirin started before ١٦ weeks gestation could prevent up to ٥٠٪ of PE, severe PE, and intrauterine growth restriction (IUGR). This reinforces the need for early identification of at risk women with the objective of implementing targeted interventions for improving both perinatal and maternal outcome ***(Bujold et al., ٢٠٠٩)***.

In ٢٠٠٤, after performing a systematic review of screening tests for PE, WHO reaffirmed that "there is no clinically useful screening test to predict the development of preeclampsia in either low-risk or high- risk populations. Further prospective, longitudinal studies are needed ***(Conde-Agudelo et al., ٢٠٠٤)***.

Since this assertion, many groups have identified or studied potential biochemical and/or biophysical markers

based on physiological mechanisms, some of which showing encouraging results. Systematic reviews and/or metaanalyses assessing the clinical utility of, most often, single markers, have recently been published, but so far no markers has demonstrated an appropriately high accuracy level to justify its clinical application ***(Cnossen et al., ٢٠٠٦)***.

AIM OF THE WORK

This review will examine the pathophysiology underlying preclampsia, and will identify and evaluate potential biochemical markers for prediction of PET.

Preeclampsia

Hypertensive disorders of pregnancy such as preeclampsia occur in ٦ to ٨ percent of all pregnancies ***(Sibai and Dekker, ٢٠٠٥)***. Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia are unknown ***(Sibai et al., ٢٠٠٣)***. The hypertension associated with preeclampsia develops during pregnancy and remits after delivery implicating the placenta as a central culprit in this disease ***(Sibai and Dekker, ٢٠٠٥)***. The initiating event in preeclampsia has been postulated to involve reduce placental perfusion which leads to widespread dysfunction of the maternal vascular endothelium. While the mechanisms are not clear, they are likely to involve a delicate balance of vasodilators such as nitric oxide and prostacylin and vasoconstrictors of which the potent vasoactive peptide, endothelin may play an important role ***(Khalil and Granger, ٢٠٠٢)***.

Definition of preeclampsia

Preeclampsia is characterized by hypertension and proteinuria after the ٢٠th week of gestation and results in significant maternal and fetal morbidity and mortality ***(Sibai, ٢٠٠٠)***.

Preeclampsia is a human pregnancy-specific disorder that adversely affects the mother (by vascular dysfunction) and the fetus (by intrauterine growth restriction). The incidence of preeclampsia is between ٦٪ and ٨٪ of pregnancies, and there is no evidence that this has changed appreciably during the last century. Preeclampsia is characterized by vasospasm, increased peripheral vascular resistance, and thus reduced organ perfusion ***(Hauth, ١٩٩٩)***. The syndrome is polymorphic in that virtually every organ system can be affected. Preeclampsia is diagnosed by the new development of hypertension (usually > ١٤٠/٩٠ mm Hg), significant proteinuria, and remission of these signs after delivery ***(Leindheimer et al., ١٩٩٩)***. Eclampsia is the occurrence of seizures in a preeclamptic patient that cannot be attributed to other causes. Even without progression to eclampsia, the syndrome presents substantial risk to mother and baby ***(Leindheimer et al., ١٩٩٩)***.

Preeclampsia is the leading cause of maternal mortality in developed countries and is associated with a five-fold increase in perinatal mortality. The major cause of fetal compromise is reduced uteroplacental perfusion ***(Hauth, ١٩٩٩)***. The only intervention that effectively reverses the syndrome is delivery. A large portion of the perinatal mortality is consequently due to iatrogenic prematurity; as ١٥٪ of preterm births are due to preeclampsia ***(Meis et al., ١٩٩٨)***.

Pre-eclampsia is defined as a syndrome consisting of hypertension and proteinuria that may also be associated with myriad other signs and symptoms, such as edema, visual disturbances, headache and epigastric pain ***(National High Blood Pressure Education Program, ٢٠٠٠)***.

Hypertension is defined as a systolic blood pressure level of ١٤٠mmHg or higher a diastolic blood pressure level of ٩٠mmHg or higher that occurs after ٢٠ weeks of gestation in a women with previously normal blood pressure on at least two occasions six hours apart ***(National High Blood Pressure Education Program, ٢٠٠٠)***.

Proteinuria is defined as the presence of ٠,٣gm or more protein in ٢٤-hour urine specimen. This finding usually correlates with a finding of ١+ or greater but should be confirmed using a random urine dipstick evaluation and a ٢٤-hour or timed collection ***(National High Blood Pressure Education Program, ٢٠٠٠)***.

Terminology and classification

The term gestational hypertension is used now to describe any form of new-onset pregnancy-related hypertension. It was adopted by the working group of the ***National high Blood Pressure Education Program (٢٠٠٠),*** which proposed a classification system based on

clinical simplicity to guide management. There are five types of hypertensive disease:

١. Gestational hypertension (formerly pregnancy-induced hypertension that included transient hypertension).
٢. Pre-eclampsia.
٣. Eclampsia.
٤. Pre-eclampsia superimposed on chronic hyper-tension.
٥. Chronic hypertension.

Diagnosis of hypertensive disorders complicating pregnancy

Gestational hypertension:

BP >١٤٠/٩٠mmHg for first time dining pregnancy No proteinuria.

BP returns to normal <١٢ weeks' postpartum.

Final diagnosis made only postpartum.

May have other signs or symptoms of pre-eclampsia, for example, epigastric discomfort, or thrombocytopenia.

Pre-eclampsia

Minimum criteria

BP >١٤٠/٩٠mmHg after ٢٠ weeks' gestation.

Proteinuria>٣٠٠mg/٢٤hrs

or>١+dipstick

Increased certainty of pre-eclampsia:

BP >١٦٠/١١٠mmHg.

Proteinuria ٢,٠g/٢٤hrs or >٢+ dipstick.

Serum creatinine >١,٢mg/dL unless known to be previously elevated.

Platelet <١٠٠,٠٠٠/$mm^{٣}$.

Microangiopathic hemolysis (increased LDH).

Elevated ALT or AST.

Persistent headache or other cerebral or visual disturbance.

Persistent epigastric pain.

Eclampsia:

Seizure that cannot be attributed to other causes in a women with pre-eclampsia.

Superimposed pre-eclampsia (on chronic hypertension)

New-onset proteinuria >٣٠٠mg/٢٤hrs in hypertensive women but no proteinuria before ٢٠ weeks' gestation.

A sudden increase in proteinuria or blood pressure, platelet count <١٠٠,٠٠٠/$mm^{٣}$ in women with hypertension and proteinuria before ٢٠ weeks' gestation.

Chronic hypertension:

BP >١٤٠/٩٠mmHg before pregnancy or diagnosed before ٢٠ weeks' gestation not attributed to gestational trophoblastic disease.

Or

Hypertension first diagnosed after ٢٠ weeks' gestation and persistent after ١٢ weeks' postpartum.