Hypertension in Pregnancy

Proceeding of The 3rd Biennial Congress of ISSHP Indonesia
(International Society for The Study of Hypertension in Pregnancy)

Editors
Tono Djuwantono
M. Alamsyah Aziz
Jusuf Sulaeman Effendi
Sofie Rifayani Krisnadi
Dear friends and colleagues,

It is our great honor to have you all participants of the 3rd Biennial Congress of ISSHP (International Society for study of Hypertension in Pregnancy) Indonesia to be held on October 7th to 10th, 2017 at the Hilton Hotel, Bandung Indonesia.

The organizing committee have done their best to prepare everything in order to fulfill your commitment to come by step forwarding the cutting edge scientific information about hypertension in pregnancy delivered first handed by the well-known international and national speakers. From workshop on Emergency Obsetrics and Obstetric intensive Care in the first day followed by workshop on Fetal Echo Cardiography in the second day and then the symposia in the next two days, you will get various topics covering areas of hypertension in pregnancy and its corresponding factors and problems like nutrition, genetic, epigenetic, environment, biomarker,. Herbal and modern medicine, ultrasound, Doppler, emergency obstetrics, long term consequences, as well as epidemiology.

We are persuading you all as well to spare your time here to witness the beautiful of our city Bandung, along with her hospitality, traditional culture, friendly climate and culinary hubs.

We welcome you all participants, friends and colleagues to enjoy your stay in Bandung and have a nice and fruitful congress with us.

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# PROGRAMME MAP

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**Notification:**
All Abstracts & Presentations in this event are in English (Spoken & Writing)

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- 08.30-09.00 am: Keynote Speech III
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- 05.00-05.10 pm: Closing Ceremony

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Early Detection: Biomarkers in Preeclampsia

John J. E. Wantania
Department of Obstetrics & Gynecology, Faculty of Medicine, University of Sam Ratulangi
Prof Dr R D. Kandou General Central Hospital

Abstract

Preeclampsia is often ended with high morbidity and mortality in pregnant women and to the fetus. Their markers to predict the likelihood of preeclampsia is very important matter with regard to early diagnostics, prevention, therapeutic intervention and follow-up. A number of biomarkers have been developed by a number of scientists and researchers, but no one has found a biomarker that can be used singly because of limited accuracy. It also relates to the complexity of the pathogenesis of preeclampsia.

Various models of good combination with other biomarkers and the risk factors and clinical conditions and investigations such as ultrasound have been developed to get a higher accuracy, while taking into account the criteria of an ideal screening methods. Further studies in addition for a new marker, also tried to further explore the markers that have been fairly well established.

Keywords: Biomarkers, Prediction, Preeclampsia

Early this century, more than 63,000 maternal deaths worldwide are associated with preeclampsia (WHO, 2005). The risk of preeclampsia alone is approximately 5 times against morbidity and maternal and neonatal mortality (Bilano et al, 2014).

Preeclampsia is a multisystem impact for the pregnancy, and complicates 3-5% of all pregnancies. Common clinical features such as hypertension and proteinuria occurred after 20 weeks of pregnancy in women with previously unknown to have hypertension. Signs and symptoms include edema and headache, and in severe cases, the condition is associated with seizures (eclampsia), renal and liver dysfunction, and blood clotting disorders, respiratory distress syndrome in adults and intrauterine growth restriction (IUGR) (Cunningham et al, 2014).

In preeclampsia, invasion of trophoblast in the muscle layer of the spiral arteries and surrounding matrix tissue surrounding does not occur completely. The muscle layer of spiral arteries remain rigid and hard, causing limitation to distend and vasodilated. As a result, the spiral arteries are relatively vasoconstricted due to failure of "remodeling of the spiral arteries", lessen uteroplacental blood flow, and lead to placental hypoxia and ischemia. The average diameter of the spiral arteries in preeclamptic women are smaller than normal, resulting higher resistance with limited blood flow. The impact of further deterioration not only fetoplacental function decline, but also spending a number of factors into the maternal circulation resulting in disruption, endothelial dysfunction and damage, and manifested in clinical symptoms of preeclampsia-eclampsia syndrome (Powe et al, 2011; Cunningham et al, 2014).

Variety contribution such as genetic susceptibility, environment/maternal characteristic, and inflammatory changes are affecting vascular remodelling during early pregnancy. Furthermore it will induced oxidative stress and placental perfusion which will lead to placental dysfunction. The next events will be the release of placental mediators and other biomarkers in maternal circulation. This biomarkers will give us opportunities to predict preeclampsia much earlier.

Most of the factors resulting from the Maternal Fetal Interface can be found in the maternal circulation and it seems no only have
the potential to detect early, but also expected to be used as a theoretical basis to find ways to manage or to prevent preeclampsia evenmore. A number of early biomarkers associated with trophoblast or decidual can describe placental dysfunction which is an important aspect in the early pathogenesis of preeclampsia, whereas other products that arise later better reflect maternal systemic response of the maternal system against abnormal pregnancy as a result of inflammation or metabolic disorders.

An ideal biomarkers are expected to meet the following matters:
- Play a central role n the pathogenesis and the specific
- Appear early or before the clinical manifestation
- Be easy and cheap to measure in maternal blood or urine
- Show a high sensitivity and specificity
- Correlate with the severity
- Be non-detected or very low in normotensive

Until now, a variety of tests to assess the factors of biological, biochemical and biophysical markers demonstrated low sensitivity and specificity to show the abnormality of development process of placenta, concluded no special markers that can be used as an absolute predictor of preeclampsia (Cunningham et al, 2014). Efforts for early detection is needed as one approach to preserve early pregnancy, and to predict and prevent complications.

Biomarkers that quite important in the pathogenesis of preeclampsia are angiogenic factors, composed of pro-angiogenic and antiangiogenic. Due to ischemia of the placenta, there is release of soluble factors into the maternal circulation which plays an important role in the occurrence of endothelial dysfunction (Mikat et al, 2012). There are two antiangiogenic proteins produced in excessively and increases in maternal circulation, responsible for the phenotype of pre-eclampsia, such as soluble FMS-like tyrosine kinase-1 (sFlt-1) and soluble Endoglin (zinc), while another proangiogenic factors are Vascular Endothelial Growth factor (VEGF), Placental Growth factor (PIGF) and Transforming Growth factor - β 1 (TGFβ-1) (Kleinrouweeler et al, 2012).

Endothelial dysfunction in preeclampsia is associated with an imbalance of these angiogenic factors. It is characterized by high levels of Soluble FMS-Like Tyrosine Kinase-1 (sFlt-1) and soluble endoglin, and low levels of placental growth factor (PIGF) and vascular endothelial growth factor (VEGF). (Eiland et al, 2012).

This antiangiogenic factors that are "soluble receptor" and circulating in the maternal circulation can bind proangiogenic factors that normally should be bound to its receptor on the blood vessel wall. As a result, the pro-angiogenic factors cannot maintain the normal function of blood vessels.

Although quite promising for the early detection, but the n angiogenic factors commonly reflected in the second trimester of pregnancy to around 5-7 weeks prior to the onset of preeclampsia. It remains pose limitations in prediction and early detection of preeclampsia. It is expected that early detection which detected from laboratory finding can be monitored and managed early before complications occur so that the outcome could have been better and result minimal complications.

Another limitation is that preeclampsia does not develop in all women with high levels of sFlt-1 or low levels of PIGF, and preeclampsia may also occur in some women with high levels of sFlt-1 and low level of PIGF (Kanasaki et al, 2008). Reyes study (2012) also get a variation of higher levels of sFlt1 in the group of early-onset preeclampsia than normotensive, while soluble Endoglin appear to have higher levels of late-onset preeclampsia or severe preeclampsia (Reyes et al, 2012). Kleinrouweeler reported that PIGF, VEGF, sFlt1 and zinc have poor accuracy for prediction of preeclampsia. (Kleinrouweeler 2012) Zeisler et al in a study in 2016 found high sFlt1/PIGF ratio (> 38) could not be used as prediction of preeclampsia, but low sFlt1/PIGF ratio (<38) can be described as short-term absence of preeclampsia in women with suspected preeclampsia clinically (Zeisler et al, 2016)

Many biomarkers have been proposed but almost all of them have limitations as a single marker. As a result of the existing limitations, the use of combinations of other markers such as a clinical and ultrasound increase the detection rate of markers.

The use of the combination of early and late onset preeclampsia studied by many researchers suggested that MAP endomark ADAM12 in the first-trimester maternal characteristics is in assessing the risk of preeclampsia, early-onset preeclampsia small for gestational age infants.

Another problem is that risk population also see the outcome. For example, in low risk population is also used the combination of PP13 in the first trimester showed that a sensitivity of 90% in control, and in severe preeclampsia (Giguere et al, 2010). In low-risk populations, the combination of characteristics and biomarkers is expected to be used in determining the level of preeclampsia, very varied so that the results can be compared.

The use of combination of ultrasound markers and angiogenic factors, especially those level are also accounted. The other angiogenic factors are very useful as a biomarker still be used, including in early prediction (Giguere et al, 2010).

The combination of first trimester is expected to have complementary combinations, including with the use of angiogenic factors. Studies by Stovall et al 2013, shows a moderate to good screening using materi
Preeclampsia is a condition characterized by high levels of angiogenic factors and low levels of anti-angiogenic factors that pose a risk of adverse outcomes such as fetal growth restriction, placental abruption, and maternal hypertension.

The use of combinations of biomarkers with other markers such as angiogenic factors, or with clinical and ultrasound are expected to increase the detection rate compared to single markers.

The use of the combination of both the early and late onset preeclampsia has been studied by many researchers. Kuc et al (2013) suggested that MAP (mean arterial pressure) and PAPP-A, PIGF ADAM12 in the first-trimester combined with maternal characteristics is a promising marker in assessing the risk of preeclampsia, particularly early-onset preeclampsia accompanied by a small for gestational age infants. (Kuc et al, 2013)

Another problem is the different level of risk population also seems to influence the outcome. For example, in high-risk populations, the combination of PP13 and pulsatile index in the first trimester showed a sensitivity of 97% and a specificity of 90% in a study limited to severe preeclampsia (Giguere et al, 2010).

In the low-risk populations, the combination of Placental protein 13 (PP13), pregnancy-associated plasma protein (PAPP-A), disintegrin and metalloproteinases-12 (ADAM12), activin A, or inhibit A measured in the first trimester or early second trimester and uterine artery doppler in the second trimester looks promising (sensitivity of 66% - 80%, specificity of 80%) (Giguere et al, 2010).

Nevertheless, in low-risk populations, the combination of clinical characteristics and biomarkers are not good enough to be used in clinical screening. Determining the level of population risk is also very varied so that the results are also difficult to compare.

The use of combinations of biochemical and ultrasound markers can better predict preeclampsia, especially when patient's risk level are also accounted. The involvement of angiogenic factors are very important, so its use as a biomarker still be promising in various ways, including in early pregnancy (Giguere et al, 2010).

The combination of biomarkers since first trimester is expected to get the best combinations, including with the involvement of angiogenic factors. Study from Akolekar et al, 2013 shows a model for first-trimester screening using maternal characteristics, and biophysical and biochemical markers. In pregnancy with preeclampsia, there is a linear correlation between the MoM value of uterine artery PI, MAP, PAPP-A and PI GF with a gestational age at delivery and the deviation from the normal seem higher in early-onset preeclampsia compared with late-onset. Most of the cases were detected eventually require termination before the age of 34 weeks (Akolekar et al, 2013).

Another breakthrough that has been studied at the beginning of pregnancy is looking at gene expression of angiogenic factors through chorionic villous sampling in the first trimester. Farina (2008) examined the direct alteration of mRNA expression in villi chorialis samples from pregnant women at 11 weeks of gestation with subsequent preeclampsia in late pregnancy. All specimens of mRNA that included in this study, were significantly altered compared to the control, in which the mRNA for Eng and TGF-beta1 are the marker with the highest degree of aberration in preeclampsia compared to the control group.

Pregnancy can be considered as the car with the accelerator and brake. Inflammation, oxidative stress, and imbalance in angiogenic act as an 'accelerator'. 'Braking system' including a track patron of heme oxygenase I (also referred to as Hmox1 or HO-1) and cystathionine-γ-lyase (also known as CSE or Cth), which produces carbon monoxide (CO) and hydrogen sulfide (H2S). Failure at this point (brakes) result in altered pregnancy outcome. Preeclampsia is a disorder of disability of accelerator-brake. CO and H2S also seems to be quite promising because of their unique ability to suppress the anti-angiogenic factor sFlt1 and soluble Endoglin as well as to promote PIGF and eNOS. It is expected that the study developed through this pathway could find the key to find more accurate detection and treatment. (Ahmed et al, 2015).

Various studies have been conducted but the results are inconsistent and difficult to compare because of heterogeneity. ACOG Task Force stated that screening to predict preeclampsia beyond obtaining an appropriate medical history to evaluate for risk factors is not recommended. FIGO states that screening using...
biomarkers or Doppler ultrasound velocimetry of the uteroplacental circulation cannot be recommended routinely at present for women at low or increased risk of preeclampsia until such screening has been shown to improve pregnancy outcome. (II-2C)

In conclusion, there's no individual biomarkers have met the criteria for a screening test. Combination with other biomarkers, risk factors, biophysical & ultrasound (UtA Doppler) may useful for early screening but increase the cost.

References


Effect of Lyphocele on FMS-like Tyrosine Kinase-1 in Preeclampsia Cells

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Abstract

Preeclampsia is a major cause of maternal and perinatal morbidity and mortality. Its pathophysiology is still largely unknown. Many studies have implicated a genetic factor, immunological disease, and conditions involving the trophoblast were unable to be identified. There is evidence that a decrease in the oxygen supply to the placenta due to a decreased blood flow is the main cause of pre-eclampsia.

Keywords: lycopene, sFlt-1, Preeclampsia, placenta, trophoblast

Introduction

Preeclampsia is a major cause of maternal and perinatal morbidity and mortality. The etiology and pathophysiology of preeclampsia is still largely unknown. It is one of the leading causes of maternal death worldwide. Preeclampsia is a pregnancy-specific hypertensive disorder characterized by elevated blood pressure and proteinuria in the second or third trimester of pregnancy [1]. Preeclampsia can lead to serious complications such as eclampsia, which is a seizure disorder caused by preeclampsia. The incidence of preeclampsia worldwide is reported to be between 0.5% and 10% [2]. The pathogenesis of preeclampsia is complex and multifactorial, involving both genetic and environmental factors. The underlying mechanism of preeclampsia involves the interplay of multiple factors, including genetic susceptibility, immunological responses, and placental dysfunction. The placenta is a key player in the pathogenesis of preeclampsia, as it is the site of exchange between the mother and the fetus [3]. The placenta is a complex organ that plays a crucial role in fetal development and nutrient transport. It is composed of two parts: the maternal component, which is derived from the endometrium, and the fetal component, which is derived from the placental stem cells. The placenta is a major source of growth factors, such as placental growth factor (PIGF), which is a key player in the regulation of fetal growth and development. The PIGF level in the maternal circulation is a useful marker of preeclampsia risk [4]. In addition, the placenta is the site of synthesis of the fms-like tyrosine kinase-1 (FLT1), which is a receptor for the PIGF. The FLT1 is important for the regulation of angiogenesis and placental growth [5]. In preeclampsia, the FLT1 levels are decreased, which results in a decrease in PIGF levels, leading to placental dysfunction and the development of preeclampsia [6]. The role of lycopene, a carotenoid found in many fruits and vegetables, in the prevention of preeclampsia is also under investigation. Lycopene has been shown to have antioxidant properties and may help to reduce oxidative stress, which is implicated in the pathogenesis of preeclampsia. A recent study showed that supplementation with lycopene in pregnant women with a high risk of preeclampsia was associated with a decrease in blood pressure and proteinuria, suggesting a potential role for lycopene in the prevention of preeclampsia [7]. In conclusion, preeclampsia is a complex and multifactorial disorder that involves the interplay of multiple factors, including genetic susceptibility, immunological responses, and placental dysfunction. The pathogenesis of preeclampsia involves the interplay of multiple factors, including genetic susceptibility, immunological responses, and placental dysfunction. The placenta is a key player in the pathogenesis of preeclampsia, as it is the site of exchange between the mother and the fetus. The PIGF level in the maternal circulation is a useful marker of preeclampsia risk, and lycopene has been shown to have antioxidant properties and may help to reduce oxidative stress, which is implicated in the pathogenesis of preeclampsia.