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EDITORIAL

Preeclampsia Screening: Combining All the Right Markers to predict a Wrong Disease?

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ABSTRACT

As preeclampsia is a multisystem disorder associated with high maternal and neonatal morbidity and mortality, several screening strategies have been designed for early detection in order to initiate the prophylactic medication in a critical stage of placentation and short-term prediction for the purpose of closer surveillance in a high-risk population. Even though abundant combinations of clinical history, biophysical, biochemical, and sonographic parameters were proposed in complicated algorithms to predict this serious condition, there has been no convincing approach for outcome improvement.

Keywords: Markers, Preeclampsia, Prediction, Screening.

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RATIONALE OF PREECLAMPSIA SCREENING

The prevalence of preeclampsia in central part of Thailand was 4.34%. This data came from an identification of 2,730 preeclampsia complicating on a cohort of 62,981 deliveries at Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand from the year 1998 to 2003.[1] We used traditional diagnostic criteria to emphasize new onset of proteinuric hypertension after 20 weeks of gestation. Our prevalence did not differ from the previously reported prevalence of preeclampsia between 2 and 7%, depending on the study population.[2] Preeclampsia is associated with serious maternal morbidities, such as seizure or collapse (eclampsia), cerebrovascular accident, placental abruption, and disseminated intravascular coagulation.

Our group at Faculty of Medicine, Siriraj Hospital in Bangkok, Thailand recently published an analysis of 10-year retrospective review (2002–2011) from electronic medical records of 701 women with severe preeclampsia and their corresponding 740 neonates.[3] There has been a clear trend of continuous decline in maternal morbidities. This is likely to be attributed by a rapid technological advancement in critical care medicine. Counterintuitively, neonatal morbidity has remained stable in the study period. An increasing number of iatrogenic prematurity in recent years is the major factor that contributed to this finding.[4]

Prompt detection and timely management are the key elements to reduce maternal and neonatal morbidities. This idea has led to the attempt to "predict" the women that destined to develop preeclampsia. The classic hypothesis, suggested by Rose and Barker in 1978, has been a guidance to implement a screening strategy to particular disease. Table 1 compares how screening and prediction of preeclampsia can fit into this hypothesis.

Table 1: Comparison between the classic hypothesis for screening of a disease and screening for preeclampsia (adapted from Rose G, Barker DJ. Br Med J 1978)

Rose and Barker hypothesis for a disease screening	*Preeclampsia screening*
Screening for a disease will be useful when	
Early treatment of the disease can improve the prognosis	First trimester screening is for risk stratification
Validity and repeatability of the screening test	Second trimester screening is for short-term prediction of early-onset (< 34 menstrual weeks) preeclampsia
Definitive sensitivity and specificity of the screening test	Third trimester screening is for short-term prediction of late-onset (≥ 34 menstrual weeks) preeclampsia
Yield of the screening service	Early diagnosis of preeclampsia is to improve prognostication

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GOALS FOR PREECLAMPSIA SCREENING

Most published studies aimed to address three major goals for presymptomatic screening of preeclampsia.

1. *Early screening* of women that eventually will develop preeclampsia, preferably before 16 weeks of gestation, will allow for an initiation of prophylactic measure, such as aspirin. There is a "window of opportunity," which is hypothesized to be from 12 to 16 gestational weeks. This is a critical stage of placental development, i.e., trophoblastic invasion and remodeling of uterine artery, which can still be modified by administration of aspirin.[5,6]
2. *Short-term prediction*: To identify high-risk population for closer surveillance and more effective resource allocation for critical cases.
3. *For research purposes:* To randomize high-risk group in order to gain more statistical power with a smaller number of research subjects.

PROPOSED PARAMETERS FOR PREECLAMPSIA SCREENING

Accurate prediction or screening of a disease can be achieved only when causative factors can be identified. This is not the case for preeclampsia. Alterations in the hemodynamics and levels of vasoactive biochemical markers are observed in women with preeclampsia. Combination of these markers in multivariate algorithm can detect some women who eventually developed the disease.[7-10] Table 2 showed examples of strategies using various approaches that have been proposed and tested. Thangaratinam et al[11,12] have analyzed the performance of clinical history, biophysical, biochemical, and sonographic parameters that are commonly used in preeclampsia prediction model.

In terms of clinical history, history of thrombophilia [relative risk (RR) 9.7, 4.3–22; 95% CI], preeclampsia in previous pregnancy (RR 7.2, 5.9–8.8; 95% CI), and history of autoimmune disease (RR 6.9, 4.3–42; 95% CI) are the strongest predictors for development of preeclampsia. However, it is also important to know that the majority (>70%) of women who have preeclampsia did not have a suggestive history.[13] Clinical history alone can detect only 33% of early-onset (delivery at less than 34 weeks), 27.8% of intermediate-onset (delivery at 34 to 37 weeks), and 24.5% of late-onset (delivery after 37 weeks) preeclampsia, compared to the detection rate from combined screening of 91, 79.4, and 64.9% respectively.[7]

In terms of biophysical parameters, a body mass index (BMI) over 35 kg/m^2 has poor sensitivity of only 21% (12–31; 95% CI) with 92% specificity (89–95; 95% CI) for predicting preeclampsia. Our group at Faculty of Medicine, Siriraj Hospital recently showed that BMI may not be useful as a prognostication factor for preeclampsia in our population.[14]

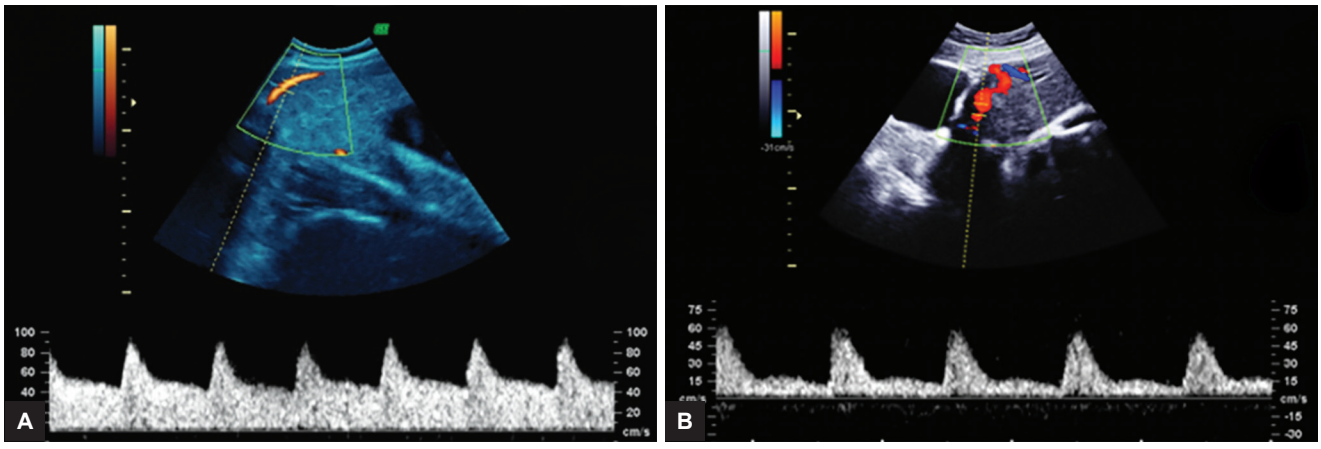
Mean arterial pressure at or over 90 mm Hg has a better sensitivity of 62% (35–89; 95% CI) with 82% specificity (72–92; 95% CI). Abnormal pulse-wave Doppler studies of the uterine artery, including high pulsatility index and prediastolic notching, are predictive for subsequent development of preeclampsia. When implemented in high-risk population (according to clinical history), the sensitivity of uterine artery Doppler can be as high as 83% (36–100; 95% CI) with 96% (90–99; 95% CI) specificity.[11] The normal and abnormal Doppler waveforms of uterine artery are shown in Figures 1A and B.

In normal pregnancy, loss of muscular layer in the vessel wall, so-called "remodeling," allows for a continuous forward perfusion throughout the pregnant uterus, as shown in Figure 2. Inadequate remodeling of uterine artery is believed to play an important role in the pathogenesis of preeclampsia. Accurate interrogation of the uterine artery (Fig. 3) to put in the algorithmic risk calculation requires a standardized protocol and proper training.[15] The adoption of uterine artery Doppler screening may be more difficult in certain cultures, particularly if transvaginal approach is implemented.

Table 2: Examples of multivariate screening strategies for preeclampsia

Timing	*Target*	*Tools*	*Performance*	*References*
Early prediction				
First trimester	Universal	Clinical history Mean arterial pressure Serum PAPP-A and PlGF Uterine artery Doppler	95% DR with 10% FPR	Poon and Nicolaides 2014
Short-term prediction				
Second trimester, asymptomatic	Prior risk	NICE guidelines	30% DR with 5% FPR for early-onset preeclampsia	Akolekar et al 2011
Late second to third trimester with borderline signs and symptoms of preeclampsia	Borderline signs and symptoms of preeclampsia	Clinical history Serum or plasma PlGF	>95% sensitivity >95% NPV	Sibiude et al 2012 Chappel et al 2013

Remarks: DR: Detection rate, FPR: False positive rate, NPV: Negative predictive value, PAPP-A: Pregnancy-associated plasma protein A, NICE: The National Institute for Health and Care Excellence, UK



Figs 1A and B: Pulse-wave Doppler studies of uterine artery in the 1st trimester of pregnancy: (A) Apparently, normal Doppler waveform of uterine artery, showing low pulsatility index and absence of prediastolic notching; and (B) abnormal Doppler wave form of uterine artery, showing high pulsatility index and presence of prediastolic notching in every cardiac cycle

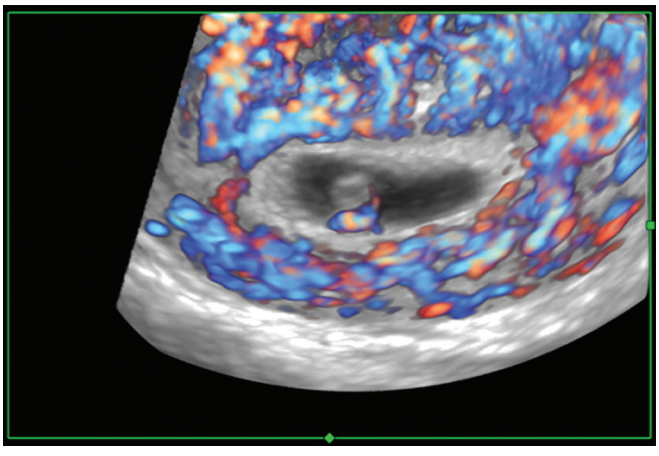


Fig. 2: Three-dimensional, high-definition sonoangiogram of a seven gestational weeks' pregnancy. Note the proliferation of intramural vascularity, especially at the placental bed, to enhance the placentation. The process is facilitated by loss of muscular layer of the uterine arteries, so-called "remodeling." Suboptimal vascular remodeling and abnormal placentation may be detected by abnormal pulse-wave Doppler studies of the uterine artery in the 1st trimester of pregnancy

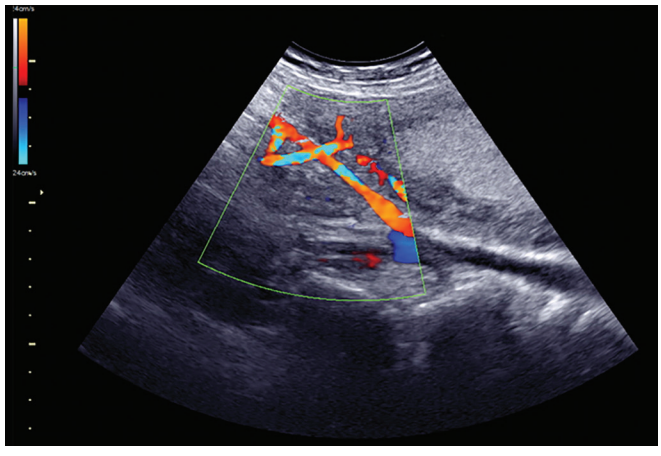


Fig. 3: Color Doppler mapping of the uterine artery. This smaller artery is crossing over larger vessels, which are iliac artery and vein

A number of serum vasoactive biochemical markers have been studied for its usefulness in prediction of preeclampsia. Alterations in the levels of these markers are observed within weeks before the women develop clinical symptoms of preeclampsia.[16] Automated quantitative platforms have been developed for the most promising markers, such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1). This has led to a robust generation of data on biomarker prediction of preeclampsia. However, there are some concerns about widespread clinical adoption of these biomarkers.

Concerns of precipitous adoption of serum biomarkers in prediction of preeclampsia can be partially addressed by the statement released by World Health Organization (WHO) in 1968 on the issue of mass screening.[17] This practice can be acceptable because preeclampsia is a "medically important disorder for which there is an effective and socially accepted remedy," and the screening protocol by single blood draw is simple and safe. However, serum screening for preeclampsia should not be used liberally without knowledge attached to it. The screening cannot be perfect because preeclampsia is not a well-defined disorder, the prevalence is not clearly known, the assay is still considerably expensive and cost-effectiveness of the screening is unknown, there is no follow-up or confirmation test, and suitable cut-off has not been established.[17]

IS PREECLAMPSIA A WRONG DISEASE TO SCREEN AND PREDICT?

In 2004, WHO published a list of suggested criteria to help guiding the development and implementation of prediction test in broader scale.[18] According to WHO criteria, the parameters currently used for preeclampsia prediction are rapid, noninvasive, easy to carry out early in gestation, and impose minimal discomfort or risk to the women.

Table 3: A comparison of theoretical advantages and disadvantages between the approaches of "early screening" and "short-term prediction" to reduce maternal and fetal morbidities related to preeclampsia

	Early screening	*Short-term prediction*
Advantages	Most preeclampsia patients do not have clinical risk factors Preventive therapy with aspirin is available	Economical use of medical resources Limit the number of women being tested Implementation in low-income setting Targeted therapy, i.e., selective removal of sFlt-1 with plasmapheresis
Disadvantages	Complex multivariate algorithm may not be easily implemented in larger scale Challenges in translation into low-income settings, where the majority of maternal and perinatal deaths occur Optimal dosage and efficacy of aspirin in screen-positive individuals remain to be proven Psychological issues after positive screening (i.e., anxiety, depression, insufficiency, guilt, relationship problem) The right to know *vs* the right not-to know	Positive only weeks before the disease develop No effective preventive therapy Early intervention (steroids, early delivery) results in reduction of perinatal morbidity but remains to be proven Psychological issues after positive screening (i.e., anxiety, depression, insufficiency, guilt, relationship problem) The right to know *vs* the right not-to know

However, biochemical markers can be expensive, Doppler studies of the uterine artery required training and are not particularly simple, and the technology are not widely available. The most important thing is that these multivariate algorithms have to be properly validated in scientific fashion that they are valid, reliable, reproducible, high likelihood ratio for a positive result (>10), and low likelihood ratio for a negative result (<0.1).[18]

These theoretical hindrances have now been put to a test by international multicenter trials, such as the study "prediction of short-term outcome in pregnant women with suspected preeclampsia," also known as PROGNOSIS trial, and the study "aspirin for evidence-based preeclampsia prevention," also known as ASPRE trial, which also combines validation for multiple markers preeclampsia screening. These two megatrials are, in fact, addressing the ultimate goal of preeclampsia screening, i.e., a significant reduction of preeclampsia-related maternal and fetal morbidities.

The ASPRE trial uses the strategy of early screening in the 1st trimester with multiple markers and complex risk categorization algorithms. Screen-positive individuals receive daily administration of 150 mg of aspirin individual to reduce the chance of early-onset preeclampsia. The PROGNOSIS trial uses the strategy of short-term prediction and/or exclusion of imminent preeclampsia in women with signs and symptoms suggestive for the disease.[19] The trial adopts a very simple risk stratification protocol, which is an angiogenic ratio (serum levels of sFlt-1/PlGF) of over 38. Closer surveillance are selectively offered in screen-positive (sFlt-1/PlGF>38), for the purpose of timely intervention, such as steroids, fetal monitoring, and planned delivery in suitable medical facilities. A comparison of theoretical advantages and drawbacks between the approaches of "early screening" and "short-term prediction" is shown in Table 3.

After all these years of researches, today it is still premature to address the question: "Is preeclampsia a wrong disease to screen and predict?" in a unanimous tone. One of the important developments in preeclampsia research is that the primary objective of preeclampsia screening and prediction has been evolving from an attempt to increase detection rate and reduce false positive rate, in an attempt to reduce preeclampsia-related maternal and fetal morbidities. In the past, more and more potential biochemical and sonographic parameters were put into the risk stratification algorithm. It made the algorithmic calculation even more complicated, and yet it was not translated into a significant improvement in screening performance. The quest for a perfect preeclampsia screening strategy has failed because the pathogenesis of preeclampsia is not known. Now that the paradigm has shifted, elaborated screening strategy can be less meaningful. At the end of the day, any strategy, with simple or complex algorithm, that can save the mother's and the baby's life will be the winner, and deserving an adoption in a broader scale.

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