

Predictive Value of Maternal Serum Markers for Preeclampsia

Sue Hyun Oh¹, Heung Yeol Kim²

¹*Department of Laboratory Medicine, Wonjin Green Hospital, Seoul, Korea*

²*Department of Obstetrics and Gynecology, College of Medicine, Kosin University, Busan, Korea*

The study performed a systematic review of screening for preeclampsia with the combination of vascular parameters and maternal serum markers in the first and early second trimester. We identified eligible studies through a search of Medline, and, for each included study, we focused on the relationship between the maternal serum markers and preeclampsia. In the selected literature, a combination of maternal serum markers was analyzed, also. Several tests suggested moderate or convincing prediction of early preeclampsia, but screening for late preeclampsia was poor. Literatures for serum markers were selected. Each serum marker was identified independently, and where relevant, a combination of these markers was analyzed. Encouraging results for the first trimester screening were observed when it was combined with other markers. Even in the first trimester of pregnancy, we can present the reliable results for the prediction of early preeclampsia. Detection rate for combination markers may yield higher detection rate and be promising to identify patients at high risk of developing preeclampsia.

Key Words: Blood Pressure, Biological Markers, Pre-Eclampsia, Screening

Preeclampsia affects 2–8% of pregnancies and is a major cause of maternal and perinatal complications.¹ Although the presentation is predominantly late term with a mild clinical course, severe complications of preeclampsia occur and include renal failure; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome; liver hemorrhage and rupture; eclampsia; cerebral hemorrhage; and maternal death. In addition, preeclampsia is associated with substantial risk of perinatal morbidity and mortality due to concomitant intrauterine growth restriction, iatrogenic prematurity, placental abruptio, and stillbirth.

Preeclampsia is considered to result from complex interactions between placental factors, maternal constitutional factors, and pregnancy-specific vascular and immunologic adaptation.² These interac-

tions involve the cardiovascular and inflammatory systems, resulting in predominant maternal endothelial dysfunction and organ damage due to vascular compromise.² Preeclampsia is a heterogeneous syndrome that does not always develop by the same pathophysiologic pathway, and the causative complex of interacting factors may differ from patient to patient.² Some authors distinguish 2 types of preeclampsia, maternal and placental preeclampsia. Placental preeclampsia is considered to result from impaired trophoblast invasion into the spiral arteries and their failure to remodel.³ Narrow spiral arteries lead to placental ischemia and generate oxidative stress conditions.⁴ Early-onset preeclampsia, developing relatively early in pregnancy and necessitating delivery before 34 weeks of gestation, is more frequently associated with this defective

Corresponding Author: Heung Yeol Kim, Department of Obstetrics and Gynecology, College of Medicine, Kosin University, 34, Amnamdong, Seo-gu, Busan, 602-702, Korea
TEL: +82-51-990-6226 FAX: +82-51-990-3300 E-mail: hykyale@yahoo.com

Received: October 8, 2012
Revised: October 9, 2012
Accepted: October 17, 2012

placentation than late-onset disease. Conversely, maternal preeclampsia, i.e., resulting predominantly from maternal constitutional factors such as high blood pressure, obesity, impaired glucose tolerance, and dyslipidemia, has been suggested to be the predominant type in late pregnancy.⁴ However, pure placental and maternal preeclampsia may be rare and most cases of preeclampsia are likely to be of mixed etiology, i.e., resulting from interplay between factors of more than 1 of the 3 earlier mentioned categories.

Early risk assessment may allow for more appropriate allocation of resources and increased surveillance for women at high risk for preeclampsia.⁵ As it is generally accepted that a single effective test with sufficient accuracy in the prediction of preeclampsia to be clinically useful is highly unlikely, interest in combining several tests into multi-parametric models has been growing in recent years.³

Many markers have been studied for preeclampsia prediction. Some are based upon patient history and demographic characteristics that can, when used alone, detect about one-third of the women destined to develop preeclampsia, but with an unacceptably high false positive rate.⁶ To improve the prediction of preeclampsia, many authors have combined maternal history with a series of biophysical and biochemical markers that change from as early as the first trimester of pregnancy in cases that subsequently develop preeclampsia. Studied biophysical markers include mean arterial blood pressure, uterine artery, and more complex evaluations such as maternal cardiac output and brain hemodynamic measurements, and more recently pulse wave analysis.⁷ Several biochemical markers have been tested for the prediction of preeclampsia, including products of fetal and placental origin, markers of renal or endothelial

damage, angiogenic and antiangiogenic factors, and markers of oxidative stress as reviewed.⁸ Panels of molecular markers (circulating mRNA) have also been widely studied and associated with preeclampsia.⁹ All of these approaches have been combined with maternal factors to derive a logistic regression-based algorithm by which to calculate the detection rate.

Despite a current lack of effective preventive strategies, risk assessment for preeclampsia early in pregnancy may be of benefit for both pregnancy outcome and optimization of resource utilization in antenatal care.¹⁰ Stratification of women by risk category, as early as the first-trimester of pregnancy, could enable intensified antenatal surveillance, timely intervention and better outcomes in those who are at high risk, and less intensified antenatal care and additional testing in those at low risk. However, so far we have no reliable single screening test to identify women who are at high risk before the clinical manifestation of preeclampsia.¹⁰ In this article, we performed the current systematic review to evaluate first- and second-trimester screening for preeclampsia with tests that combine uterine artery Doppler and maternal serum markers.

MATERNAL SERUM MARKERS

Maternal serum analytes provide minimally invasive tests of fetal and placental endocrine function as well as endothelial dysfunction. The failure of trophoblastic invasion may be related to dysregulated secretory activity of the trophoblasts; whereas, alteration in the surface layer of the syncytiotrophoblast may contribute to leakage of human chorionic gonadotropin (hCG) and alpha-fetoprotein (AFP) into maternal circulation.¹¹ Reduced placental size or defective

syncytiotrophoblast formation may result in reduced production of placenta-derived proteins, such as pregnancy associated plasma protein A (PAPP-A).¹² Hypoxia-reoxygenation may be responsible for the increased secretion of proinflammatory cytokines, such as tumor necrosis factor alpha and interleukin 1b, and antiangiogenic factors, such as the soluble receptor for vascular endothelial growth factor (sFlt-1).¹³ Endothelial cell damage, platelet activation dysfunction, and disturbances in coagulation may be responsible for increased P-selectin and markers of insulin resistance.¹⁴ The use of analytes routinely collected for aneuploidy screening is attractive because results are routinely available. However, they have generally yielded poor predictive characteristics, increasing interest in the development and testing of additional markers.

1. PAPP-A

PAPP-A is produced by the syncytiotrophoblast.¹⁵ It regulates the bioavailability of free insulin-like growth factor at the placental-decidual interface during human implantation.¹⁶ It is thought to play an important role in the autocrine and paracrine regulation of trophoblast invasion into the decidua.⁹ Low concentration of PAPP-A in the first trimester of pregnancy is highly associated with chromosomal aneuploidies. In pregnancies with a normal karyotype, low PAPP-A has been shown to be an indicator of increased risk for various pregnancy complications. The majority of the published studies have shown that low concentrations of PAPP-A are significantly associated with early-onset preeclampsia.¹⁶

2. Free beta subunit of hCG

The free beta subunit of hCG is secreted by the

syncytiotrophoblast cells. Its primary function is to maintain the decidual spiral arteries and the vascular supply of the placenta during pregnancy.¹⁷ In normal pregnancies, the concentration of free beta subunit of hCG increases exponentially until 8 to 10 weeks, decreasing afterward. In the second-trimester, free beta subunit of hCG has been reported to be elevated in women who later develop preeclampsia.¹⁸ Studies that have retrospectively evaluated free beta subunit of hCG have shown no evidence for a predictive value of this marker for hypertensive disorders of pregnancy.¹⁸

3. Inhibin A and Activin A

The fetoplacental unit is an important source of inhibin A and activin A, and it has been suggested that both are involved in a feedback loop regulating hCG levels during pregnancy.¹⁹ Muttukrishna et al have shown that the third trimester maternal serum concentrations of both markers were about 10-fold higher in women with severe preeclampsia as compared with controls.²⁰ Several studies have shown that inhibin A and activin A were significantly elevated in the first trimester in women with preeclampsia.²⁰

4. Placental protein 13 (PP 13)

PP13 is produced predominantly by the syncytiotrophoblast and is thought to play an important role in the implementation of the blastocyst.²¹ PP13 has also been suggested to be involved in the remodeling of the common fetomaternal blood-circulation through binding to proteins between the placenta and endometrium.²² From the first-trimester, levels of PP13 slowly increase in healthy pregnancies. First-trimester concentrations of PP13 have been shown to be significantly lower in the first trimester, but higher

in the second and third trimesters in association with preeclampsia.²² Reasons for this are currently not known.

5. Angiogenic factors

An imbalance between pro- and anti-angiogenic factors before and after the onset of PE is suggested to play a crucial role in its pathogenesis. It is thought that the poorly implanted placenta becomes ischemic and subsequently secretes antiangiogenic factors such as sFlt-1 also known as soluble vascular endothelial growth factor receptor-1 and sEng (soluble endoglin) into the maternal circulation which later antagonize a number of proangiogenic factors, such as PlGF (placenta growth factor) and vascular endothelial growth factor.²³ It is hypothesized that as a consequence, the concentration of important angiogenic and PlGFs in the maternal circulation is reduced, leading to impaired endothelial function and subsequently early-onset preeclampsia. These studies concentrated mostly on the second half of the pregnancy in which a clear difference in the concentrations of both antiangiogenic and proangiogenic factors in preeclampsia pregnancies was shown when compared with controls (antiangiogenic factors elevated, proangiogenic factors decreased).²⁴ Major studies in the first trimester, however, have shown that plasma sFlt-1 and sEng were constant throughout the first-trimester and that their concentrations in normal pregnancy might be equal to or possibly lower than those in pregnancies destined to be complicated by preeclampsia.²⁵ From the perspective of first-trimester screening for preeclampsia, studies on antiangiogenic factors have been indeterminate and so far do not support inclusion of these factors as new markers for risk assessment

for preeclampsia.

6. A disintegrin and metalloproteinase 12 (ADAM 12)

ADAM12 is a placenta-derived member of the ADAM protein family.²⁶ It is present in the syncytiotrophoblast and is thought to be involved in placental growth and development. Gack et al demonstrated that ADAM12 was the most upregulated transcript in placental tissues of women with PE.⁵³ This finding led to speculations as to whether ADAM12 could serve as an early biomarker for hypertensive disorders of pregnancy.²⁶ Laigaard et al and Spencer et al have shown reduced ADAM12 levels in pregnancies complicated by PE, and in both studies ADAM12 was suggested to be a potential PE marker (median ADAM12 MoM were 0.86, $P = 0.008$ and 0.49 $P = 0.0001$, respectively).²⁷ In contrast, Poon et al, and Wortelboer et al reported no alteration of first-trimester ADAM12 levels in women developing PE.²⁷ The median MoMs in these studies were not significantly different from controls.

INTEGRATION OF MULTIPLE PARAMETERS

Since none of the current single parameter tests are sufficiently predictive of adverse pregnancy outcomes, many investigators have attempted to improve the predictive value of tests by combining them.²⁸ The use of multiple parameters seeks to increase specificity and sensitivity by exploring the different disease pathways. Combination of maternal serum markers and other markers such as uterine artery Doppler studies for the prediction of adverse pregnancy outcomes has both advantages and

limitations. The studies are divided into first-trimester tests, second-trimester tests, and a combination of first-trimester and second-trimester testing. These studies are heterogeneous with regards to populations studied, biomarkers used, definitions of positive screen, and definitions of outcomes. Despite this heterogeneity, the results illustrate several important features and provide useful insights for future research:

1. Combined screening tests generally produce higher sensitivities and specificities than the individual tests alone.
2. Combined screening is more effective in predicting early than late preeclampsia, reflecting the likely different pathogenesis of late-onset preeclampsia.
3. Some combinations produced no improvements in screening performance, likely secondary to correlation between the markers. Future research should focus on combining independent biochemical and/or Doppler markers.
4. It is important to control for confounders in deriving patient-specific risks for adverse outcomes using multiple markers.
5. Many of the studies are by the same investigators and need to be replicated by others.
6. Some studies, including many in the first trimester, have promising predictive abilities and should be the focus of larger future studies.
7. Any combinations proposed for general use should be cost-effective and have high sensitivity and acceptable false-positive rates.

SUMMARY

Among the various marker combinations studied

during the second trimester, several markers appeared to have promising predictive characteristics. Overall, the addition of uterine artery Doppler data to biochemical marker data improved the predictive performance of biochemical markers alone to a greater extent.

First trimester or early second trimester PAPP-A, inhibin A, and activin A in combination may provide relatively good predictive performance for preeclampsia. Data from recent publications have indicated that these biochemical markers, taken individually, have low power for predicting early preeclampsia, but up to 89% when combined with maternal characteristics (race, body mass index, parity) in a low-risk population. PAPP-A and PIGF were recently found to be significantly decreased during first trimester in women destined to experience early onset preeclampsia, whereas they were only mildly diminished in women who developed late preeclampsia. Therefore, growing evidence suggests that combination of first-trimester biochemical markers may be useful in prediction of preeclampsia.

From the perspective of integrative medicine, there is a clear need for prospective large-scale studies with rigorous study design criteria to determine the clinical usefulness of combinations of biomarkers in different geographic and healthcare environments. In conducting such studies, it will be essential to incorporate a universally agreed-on definition of hypertensive disorders of pregnancy. The ultimate outcome of research efforts like these will be the development of an efficient screening procedure that is evidence based and that uses a multivariate algorithm of selected maternal characteristics and measurements of biochemical markers to identify women at risk for preeclampsia who would benefit

from early targeted preventive interventions.

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Peer Reviewers' Commentary

Preeclampsia affects 2–8% of pregnancies and is a major cause of maternal and perinatal complications. Although the presentation is predominantly late term with a mild clinical course, severe complications of preeclampsia occur and include renal failure; hemolysis, elevated liver enzymes, and low platelets syndrome; liver hemorrhage and rupture; eclampsia; cerebral hemorrhage; and maternal death. The aim of this review was to performed a systematic review of screening for preeclampsia with the combination of vascular parameters and maternal serum markers in the first and early second trimester. Detection rate for combination markers may yield higher detection rate and be promising to identify patients at high risk of developing preeclampsia.

(정리: 편집위원회)