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Prediction of Preeclampsia – A Workshop Report

Nandor Gabor Than[a,b,*], **Roberto Romero**[b,c], **Renate Hillermann**[d], **Veronica Cozzi**[e], **Guiying Nie**[f], and **Berthold Huppertz**[g]

a*First Department of Obstetrics & Gynecology, Semmelweis University Budapest, Hungary*

b*Perinatology Research Branch, Intramural Division, NICHD/NIH/DHHS, Hutzel Women's Hospital*

c*Wayne State University, Center of Molecular Medicine and Genetics, Detroit, MI, USA*

d*Department of Genetics, University of Stellenbosch, South Africa*

e*Department of Obstetrics & Gynecology, IRCCS PO.MA.RE, University of Milan, Italy*

f*Prince Henry's Institute of Medical Research, Melbourne, Australia*

g*Institute of Cell Biology, Histology and Embryology, Medical University Graz, Austria*

Abstract

Understanding the mechanisms of disease responsible for the syndrome of preeclampsia as well as early risk assessment is still a major challenge. The concentrations of circulating proteins in maternal blood such as placental growth factor, soluble vascular endothelial growth factor receptor-1 and soluble endoglin are altered weeks before the onset of clinical symptoms of the syndrome. Recently, other proteins in maternal serum, such as activin A, inhibin A, PAPP-A, and PP13 have been suggested to be of value in first trimester risk assessment. Since preeclampsia is a syndrome, it seems unlikely that a single test will predict all forms of preeclampsia. This realization has led to the formulation of a new conceptual framework suggesting that a combination of markers (biochemical and/or biophysical) may be required to conduct comprehensive risk assessment for the syndrome.

INTRODUCTION

Early risk assessment for preeclampsia is a major challenge in perinatal medicine. Recently, pro- and anti-angiogenic factors such as placental growth factor (PlGF), soluble vascular endothelial growth factor receptor-1 (sVEGFR-1/sFlt-1) and soluble endoglin were found to be increased in maternal blood a few weeks before the clinical diagnosis of preeclampsia. Other analytes which appear promising include activin A, inhibin A, PAPP-A, and PP13 [1]. Recent studies have also suggested that it may be valuable to combine the results of biochemical tests with uterine artery Doppler velocimetry in the first and second trimesters [1–2]. This workshop was organized to highlight recent discoveries in the field.

*__To whom correspondence should be addressed at:__ Nandor Gabor Than, M.D., PhD, Perinatology Research Branch, NICHD/NIH/DHHS, Wayne State University/Hutzel Women's Hospital, 3990 John R, Box 4, Detroit, MI 48201, USA, Phone: (313) 993-2700; Fax: (313) 993-2694, E-mail: nthan@med.wayne.edu.

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Risk assessment for preeclampsia and microRNAs

Roberto Romero pointed out that there is much enthusiasm about the clinical value of maternal serum/plasma concentrations of PlGF, sVEGF-R1, and endoglin in the prediction of preeclampsia. Recent data from a longitudinal case control study, as well as cohort studies, indicate that even though the odds ratio conferred by changes in these factors is high, the positive predictive value is low. Moreover, these changes are not specific to preeclampsia and have been observed in patients destined to deliver small-for-gestational age (SGA) neonates and in fetal death.

Differential expression of 157 microRNAs was studied in placentas from women with normal pregnancies as well as from patients with preeclampsia and those who delivered SGA neonates [3]. A specific differential expression of microRNAs was found between preeclampsia and SGA when compared to normal pregnancy. The expression of mir-210 was increased in the placenta of patients with preeclampsia, with and without SGA. Gene ontology demonstrated enrichment with targets involved in the immune response, apoptosis and lipid metabolism. The expression of mir-210 was localized to the syncytiotrophoblast. This finding is important because there is a link between over-expression of mir-210 and regulation of VEGF under different oxygen conditions [4]. Collectively, this data implicate microRNAs in the pathophysiology of preeclampsia and possibly other obstetrical syndromes. Efforts are underway to determine if microRNAs can be detected in the circulation and other biological fluids.

Mutations in the *LGALS13* gene and their impact on the use of PP13 as a biomarker

Renate Hillermann reported the identification of single nucleotide polymorphisms (SNPs) in the *LGALS13* gene, which encodes placental protein 13 (PP13), a galectin expressed predominantly by the placenta [5–6]. Recent studies have demonstrated that patients who subsequently developed preeclampsia had lower maternal serum PP13 concentrations in the first trimester than women who had a normal pregnancy outcome [2,6].

The *LGALS13* gene was screened for DNA variants in genomic DNA samples of women with preeclampsia, their offspring and women with normal pregnancy. The genomic mutation screen revealed a deletion frame-shift mutation (222deltT/L74W) in exon 3 in patients with preeclampsia, their newborns and in healthy controls [7]. This mutation is predicted to create a novel terminal region of PP13, which is shorter than and different to the wild-type protein [5]. Existing monoclonal anti-PP13 antibodies do not recognize the shorter PP13 isoform. Furthermore, four intronic SNPs were identified around exon 3, and a promoter variant (−98 A/C) was also described. Women with preeclampsia had a higher rate of homozygosity for this promoter variant allele than those with normal pregnancy.

The existence of SNPs in the *LGALS13* gene and of shorter PP13 isoforms, which are not recognized by the current PP13 ELISA test, might explain the lower values of PP13 in the first trimester of pregnant women who subsequently develop preeclampsia [6].

Long pentraxin (PTX3) as a potential marker for preeclampsia

Veronica Cozzi presented the results of two studies on PTX3 in women with normal pregnancy and in those with preeclampsia or intrauterine growth restriction. PTX3, a soluble pattern recognition receptor [8], is up-regulated in endothelial and immune cells upon inflammation. The plasma concentration of PTX3 increases dramatically during endotoxic shock or sepsis. PTX3 is also implicated as a candidate marker for inflammatory vascular disorders, such as

myocardial infarction. As prominent features of preeclampsia are excessive maternal systemic inflammation and endothelial dysfunction, PTX3 was hypothesized to be involved in this syndrome [8].

A cross-sectional study revealed that plasma PTX3 concentrations of normal pregnant women were higher than those of non-pregnant women but did not change with advancing gestational age. Maternal plasma PTX3 concentrations were higher in patients with intrauterine growth restriction (IUGR) than in normal pregnant women in the third trimester, and higher in women with preeclampsia than in those with IUGR. Among women with preeclampsia, plasma PTX3 concentrations were higher in those with severe preeclampsia than in those with mild preeclampsia. No differences were found in placental and decidual expression of PTX3 between women with normal pregnancies or preeclampsia; however, PTX3 immunopositivity was stronger in peritoneal vessel endothelium in preeclampsia than in normal pregnancy. A preliminary second study revealed that between 11–14 weeks of gestation, maternal plasma concentrations of PTX3 were higher in women who subsequently developed preeclampsia than in women with normal pregnancy or IUGR. Thus, PTX3 might be involved in the excessive inflammatory response and altered endothelial function in preeclampsia, and it might be implicated as a new candidate early marker for preeclampsia.

Importance of HtrA3 during early pregnancy

Guiying Nie had cloned alternatively spliced members of the high-temperature requirement factor A (HtrA) protein family and characterized the newly identified genes in humans and mice [9]. HtrA3 is a pregnancy-related serine protease differentially expressed in uterine tissues at the time of implantation.

HtrA3 expression was increased in endometrial glands and stromal cells in the late secretory phase of the menstrual cycle, and a further increase in HtrA3 expression was observed in the first trimester of human pregnancy [10]. The villous syncytiotrophoblast, the distal region of the trophoblast cell columns, and the endovascular extravillous trophoblasts strongly stained for HtrA3. While its decidual expression was maintained during gestation, placental expression of HtrA3 was down-regulated during the second and third trimesters, when it was only detectable in the syncytiotrophoblast [10]. This dynamic expression of HtrA3 in the placenta throughout gestation was reflected by a similar change in its maternal serum concentrations. HtrA3 concentrations were higher in pregnant women than in non-pregnant women, and the highest concentrations were measured during the first trimester [10]. In the 13th–14th week of pregnancy, increased concentrations of HtrA3 were found in the sera of women who later developed preeclampsia compared to those who had a normal pregnancy. Hence, the placental production of HtrA3 is well reflected by its maternal serum concentrations, and therefore, it might have potential implications in the prediction of preeclampsia.

Conclusions

Placental microRNA profiling may help in the classification of preeclampsia. The candidate biomarkers presented here all have altered maternal serum concentrations in the first trimester in women who subsequently developed preeclampsia and have potential as predictive markers. The biological information obtained from these studies can further enhance our understanding of the underlying mechanisms of the preeclampsia syndrome.

Preeclampsia is not a single disorder but rather a syndrome. It has become increasingly clear that it is unlikely a single test will be able to predict all forms of preeclampsia early in pregnancy. Hence a new strategy is needed that focuses on the identification of women at high risk of developing preeclampsia, based on a combination of biochemical markers and even,

perhaps, biophysical markers such as uterine artery Doppler velocimetry. This effort may also help in unraveling the underlying mechanisms of the various subtypes of this syndrome.

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