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Editorial

In Search of New First Trimester Biomarkers for Ischemic Placental Disease

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Major pregnancy complications, such are: preeclampsia, intrauterine growth restriction, preterm labor, preterm premature rupture of membranes, late spontaneous abortion, and placental abruption, are associated with defective deep placentation [1]. Furthermore, 3 clinical conditions: preeclampsia (PE), placental abruption and intrauterine growth restriction (IUGR) has been recently termed ischemic placental disease (IPD) implying common biological pathways of these conditions: poor placentation in early pregnancy leading to uteroplacental under perfusion and insufficiency along with hypoxia and placental ischemia [2]. According to recent investigations, among term births at least with 1 condition 4.5% present with all 3 conditions, and1.0% has 2 conditions of IPD, whereas in preterm births between 22-36 weeks of gestation, these indices are increased to 12.1% and 4.7%, respectively [3]. Different interesting studies investigated and proposed strategies for first trimester/antenatal suspicion of IPD by using combination of maternal characteristics, Doppler examinations and biomarkers [4-6], but still there is a necessity to search for new highly sensitive and specific reliable biomarkers to detect IPD in the first trimester of pregnancy in order to avoid the risk of perinatal and maternal mortality and long-term morbidity [7,8].

"Omics" family of technologies implies the most contemporary study methodologies proposing a highly reliable and simultaneous analysis of biological molecules. They are important in prediction of diseases by searching for the disease-specific biomarkers. Moreover, there is necessity for the deeper understanding of the diseases pathophysiology and the development of molecularly targeted specific therapies, and "Omics" technologies might have importance in achieving these goals. Any molecule less than 1 kDa in mass can be sorted out by metabolomics technology as a single final product of active/inactive genes in a given condition (genome), its activation (mRNA transcriptome), the setup of enzymatic machineries (proteome), and their actual biological processes [9].

Recent studies have been focused on use of metabolomics (metabonomics) as well as the related metabolic fingerprinting in obstetrics and gynecology with the special emphasize on normal and complicated pregnancies. The first review on this topic had been published in 2009 [10]. Since then, metabolomics were analyzed: in plasma of pregnant women, urine of pregnant women and neonates, amniotic fluid, placenta, vaginal secretion, and cord blood in few studies. Different technologies have been adopted: nuclear magnetic resonance (NMR) spectroscopy, gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-mass spectrometry (LC-MS) [9].

One of recent investigations performed metabolomic analyses in plasma samples between 14-16 weeks of gestation from women who had subsequently developed PE and the control cases. 457 candidate biomarker metabolite peaks has been defined. 70 metabolomics were successfully identified chemically as known metabolites, of which 45 were "unique" in the sense of being defined molecular entities. They belonged to 11 different classes of known metabolites. These were amino acids, carbohydrates, carnitines, eicosanoids, fatty acids, keto or hydroxyl acids, lipids, phospholipids, porphyrins, phosphatidylserine, and steroids. The Genetic Algorithm chose totally 14 metabolites as metabolite signature of PE. At a 90% detection rate, the estimated false positive rate (FRP) of subsequent PE for the discovery data and validation data were 21% and 24%. The predictive power of the 14-metabolite rule is compared highly favorably with that of other proposed first trimester screening tests, including those based on first trimester levels of placental hormones, such as placental protein 13 and pregnancy-associated plasma protein A [11].

According to another investigation, blood samples from women with singleton pregnancies between 11–14 weeks of gestation had been studied. Totally were analyzed 40 acylcarnitine species (C2-C18 saturated, unsaturated, and hydroxylated) and 32 amino acids. In the cases with blood samples from women who had subsequently developed PE compared to the control cases, metabolites identified in first-trimester maternal serum adjusted for maternal BMI, diabetes and ethnicity were: 1 form of acylcarnitine (hydroxyhexanoylcarnitine (C6OH)) and 3 amino acids (phenylalanine, glutamate, alanine), but since the acylcarnitine levels were only weakly significantly different between cases with PE and the control group, attention was focused only on 3 main amino acids. The area under the curves (AUC) for this limited model was 0.81 (95% CI, 0.72–0.88) with a similar detection rate for all PE at the different FPRs. Even though this study had a limitation due to the small sample size, it proved once again a potential role for first-trimester metabolomics in screening for PE [12].

Further case-control studies in this direction revealed a possibility to use the first trimester metabolomic analyses alone or in combination with maternal characteristics and first-trimester uterine artery Doppler pulsatility index (PI) to predict the risk of early-onset PE. Comparisons of blood samples at 11-13 weeks of gestation, between women who had subsequently developed early-onset preeclampsia (requiring delivery before 34 weeks of gestation) and

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the control cases, revealed significant differences for 20 metabolites. A combination of four of these metabolites (citrate, glycerol, hydroxyisovalerate, and methionine) appeared highly predictive of PE with an estimated detection rate of 75.9%, at a FRP of 4.9%. After the addition of uterine artery Doppler PI and fetal crown-rump length (CRL) the predictive performance was improved by with an estimated detection rate of 82.6%, at a FPR of 1.6% [13]. In another study the same group performed metabolomics analyses on first-trimester maternal serum between 11-14 weeks of gestation from women who had developed late-onset PE in indexed pregnancies and requiring delivery beyond 37 weeks of gestation. The concentrations of 40 metabolites were compared between PE and control groups as well as early-onset and the late-onset PE groups. Study results showed that a total of 14 metabolites were significantly elevated and 3 metabolites were significantly reduced in first-trimester serum of late-onset PE patients. After adjustment for maternal demographic characteristics the first-trimester metabolomic markers (pyruvate, hydroxybutirate 3, 1-methylhistidine, glycerol, try methylamine and valine) showed 76.6% sensitivity at 100% specificity for PE detection. Significant differences in the first-trimester metabolites were detected between women who went on to develop early- and late-onset PE [14]. Two metabolites were notable for their differences between preeclamptic and normal pregnant women: glycerol and carnitine. Glycerol and carnitine are both important for lipid metabolism, and mitochondrial energy production is based on lipids. More significantly, carnitine inhibits oxidative stress. All these metabolic pathways are over expressed in metabolic syndrome and in PE [9].

The most recent investigation of multivariate metabolomic analysis was performed on blood serum as well as on urine samples between 17-20 weeks of gestation from women who had subsequently developed PE, women with uncomplicated pregnancies and non pregnant controls. A trend of metabolite profiles showing a continuous change from non-pregnant women through healthy pregnant women to women with PE was found mainly based on increasing total serum lipid content. All pregnant women had higher serum lipid content than the non-pregnant women, and women with PE had even higher serum lipid content. The distribution of lipoproteins was also different between groups, with the PE group expressing higher signals originating from v*ery-low-density lipoprotein (*VLDL) and *low-density lipoprotein (*LDL), and lower signals from high-density lipoprotein (HDL). The lipoprotein distribution was explored further. PE cases were discriminated from healthy pregnant controls by the lipoprotein profile alone, with increased signal in the LDL-VLDL region (the leftmost part of the lipid signal) and decreased signal in the HDL region of the serum spectra. Serum from women with PE had significantly lower concentrations of histidine than the healthy pregnant women, and non-significant lower levels of format and higher levels of glycerol. Healthy pregnant women had higher alanine and lactate than the non-pregnant women.

Results from the urine analyses showed that both the PE and healthy pregnant groups were significantly different from the non-pregnant group based on a combination of higher creatinine and trim ethylamine-N-oxide (TMAO) levels, and lower glycine levels for the non-pregnant group. Creatinine levels were similar between preeclamptic and healthy pregnant women. The groups were separated based on a combination of higher choline and creatine levels, and lower glycine levels for preeclamptic women compared to healthy pregnant women. Urine samples from women with early onset PE (<34 weeks) had lower scores on loading variables (LV2) than the late onset women. These had higher TMAO and creatinine, and lower choline and creatine compared to the late onset PE group. 21 metabolites were significantly different between all three groups at $p<0.05$, with nine metabolite concentrations significantly different between women with PE and healthy pregnant women, and 15 between healthy pregnant women and non-pregnant women. Women with PE showed increased choline and decreased glycine, p-cresol sulfate and hippurate in urine, which may be related to increased oxidative stress and kidney dysfunction. The urinary metabolic profile from the PE group was clearly different from that of healthy pregnant women. Healthy pregnant women also showed a different urinary metabolic profile than non-pregnant women, with higher excretion of amino acids [15]. A difference in urine metabolic profile between women with early and late onset PE also might exist.

High sensitivity and specificity of metabolomic analyzes received in different studies focused on preeclampsia will open new horizons for development of new first trimester biomarkers for early detection of PE. If we take into account that PE is an ischemic placental disease, studies of metabolite profiles of the maternal serum and urine must be further continued in PE alone and/or in combination with IUGR and placental abruption.

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