Insights in Obstetrics and Gynaecology

Editorial Open Access

Translational Preeclampsia Research

Juraj Drobny[1] and Vladimira Durmanova[2]

[1]1st Department of Obstetrics and Gynecology, Faculty of Medicine, Comenius University, Bratislava, Slovakia
[2]Institute of Immunology, Faculty of Medicine, Comenius University, Bratislava, Slovakia

[*]**Corresponding author:** Juraj Drobny, 1st Department of Obstetrics and Gynecology, St. Cyril and Method University Hospital, Antolska 11, 85107 Bratislava, Slovakia, Email: drobny715@gmail.com

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Editorial

On the pages of this new Journal, we will certainly meet plenty of scientific articles about translational preeclampsia research. There are some serious, important and, after all, interesting reasons for it. Preeclampsia (PE) is the main cause of perinatal and maternal morbidity and mortality worldwide. Yet, pathophysiology of PE is not well understood. Moreover, this is a unique disease, among all diseases in the whole animated nature it occurs only in pregnant women [1].

In fact, PE is about irregular acceptation of pregnancy conceptus by mother's organism. The reason for this is insufficient communication between conceptus and mother from the time of fertilisation before and during nidation. Of course, maternal and paternal genome variation before fertilisation is of great importance, too. And the disease manifests itself in its fullness.

Hundreds of research teams and thousands of scientists all over the world try to solve the mystery of PE. Multifactorial aetiology and multisystemic disorder in PE [2] caused research diversity. An infinite number of studies with different approaches analyse various aspects of pathological processes. The multi-coloured spectrum of clinical courses, organ, and tissue damages, molecular mechanism deviations in specific cells are studied. This multiplication and certain disintegration seem to be the main difficulty in a complete understanding of etiopathology of PE.

What do we really know about this disease? PE develops in two stages [3,4]. In the first step, shallow nidation of the blastocyst and subsequent insufficient remodeling of spiral arteries lead to decreased uteroplacental perfusion, placental hypoxia, and changes in trophoblast syncytial knots destruction. The result of this alteration is the presentation of altered angiogenic factors and necrotic trophoblast in mother's circulation. As a second step, circulating substances cause an exaggerated inflammatory response and endothelial dysfunction with the presentation of clinical signs of PE in the second half of pregnancy [5]. However, this two stages model seems to be more appropriate in early-onset PE [6]. Six stages model has been presented too [7].

Molecular research of PE is focused on genetic and immunologic aspects of maternal and paternal tissue interaction, as well as a study of metabolic products of impaired placentation, liberated into the maternal circulation.

From the genetic research point of view, it seems that no maternal candidate gene for PE in the maternal genome has been found at this time [8]. However, HLA-G antigen, expressed only in trophoblast, seems to be affected in PE by maternal single nucleotide polymorphism [9,10]. Epigenetic changes may play a role in the development of PE, too [11].

Participation of immunology in PE development has been well known for a long time [12]. In pregnancies with the same partner, PE usually develops only during the first pregnancy, which is on the contrary to the occurrence of PE in successive pregnancy with a new partner. Immunologic changes in PE are mainly connected with trophoblast-decidua interaction. Objects of research in this area are especially helper T lymphocytes [13], regulatory T lymphocytes [14], and integrin in extravillous trophoblast [15] as well as uterine natural killer cells [16] and newly discovered corin [17] in the decidua.

Research tries to find decidual and trophoblastic or placental molecular changes which are the cause of poor placentation. In the uterus, corin was detected as part of a failed spiral artery remodelling [18]. Another new molecule in the process of hypoxia by altered trophoblast invasion is hypoxia-inducible factor-1alpha [19]. Similarly, trophoblast differentiation is damaged by endoglin [20]. Angiotensin through vasoconstriction caused uteroplacental ischemia, too [21]. Placental dysfunction is supported by tumour necrosis factor-alpha [22]. Angiogenesis and vasodilatation are insufficient by the altered enzymatic activity of heme oxygenase-1 [23]. A lot of research studies are connected with a higher placental production of antiangiogenic factors as the cause of clinical signs of PE. The main point of interest is fms-like tyrosine kinase 1 (Flt-1) [24], also endoglin [25] and newly detected semaphorin [26], which have an opposite effect to angiogenic vascular endothelial growth factor [27] and placental growth factor [28]. All these results support the thesis that PE is considered to be an antiangiogenic state [5].

Endothelial dysfunction is a major hallmark of preeclampsia. Generalized endotheliosis in the systemic circulation as a second step in PE development could decrease endothelium-derived vasodilators and increase vasoconstrictors, leading to increased vasoconstriction and hypertension [29]. PE research is focused particularly on nitric oxide [30], prostacyclin [31], endothelin-1 [32] and thromboxane A2 [33].

The main clinical symptoms of PE are hypertension, proteinuria, and oedema, respectively as a generalised effect of vasoactive substances of endothelium and subsequent kidney damage. Besides cardiovascular alteration, nephrological, cerebrovascular, ophthalmological and gastrointestinal (especially hepatological) symptoms, as well as coagulopathy, can occur.

Translational preeclampsia research in its clinical part relates to all topics of medical management of this disease. This involves not only diagnosis and therapy. Accordingly, PE prediction or early detection, prevention and the detection of late consequences are involved.

As the results of these investigations, the main proposed clinical prediction of PE in the first trimester of pregnancy is the evaluation of the relationship between anti-angiogenic factors as a soluble fms-like tyrosine kinase 1 (sFlt-1) or endoglin and angiogenic factors vascular - endothelial growth factor or placental growth factor, respectively. Other presented factors are e.g. inhibin [34], adipsin [35] and meteorin [36]. In the routine clinical prediction of PE, evaluation of maternal serum PAPP-A and PlGF, mean arterial pressure and uterine artery Doppler

flow measurements, as well as antiangiogenic maternal risk factors assessment, are appropriate at this time. Moreover, implementation of tailored antenatal surveillance is needed [37].

The latest research recommends a lot of substances as early diagnosis factors, e.g. copeptin [38], resistin [39], pleckstrin homology-like domain, family a, member 2 (Phlda2) [40], microparticles [41], miRNA [42] and recently Smartphone-based diagnosis by the Congo Red Dot (CRD) test [43].

New insight into the clinical course of PE distinguished maternal syndrome and fetal syndrome of PE. In maternal syndrome, early onset PE [44] and late onset PE [45] are established. Other forms of preeclampsia are HELLP syndrome (46) and metabolic syndrome [47,48]. In fetal syndrome, intrauterine growth restriction [49] and/or premature labour [50] can occur.

Measurement of vascular stiffness [51], capillary diameters [52], flow-mediated dilation of the brachial artery [53] and serum level of cardiac troponin [54] as a mirror of the cardiovascular system changes are newly proposed diagnostic tools in PE. Kidney and glomerular changes in PE are detectable by the evaluation of nephrin [55] and/or podocytes [56]. Of course, changes in other organs, e.g. encephalopathy [57], hepatopathy [58], coagulopathy [59], and optic neuropathy [60] are possible, too.

The recent research allowed us to extend our capabilities in the therapy of PE. Certainly, caesarean section, i.e. fetus and placenta removing, still remain to be the only adequate therapy of PE, while antihypertensive drugs and low-dose aspirin are symptomatic therapy. New therapeutic approaches with substances such as angiogenic factors, agents that increase vasodilation, anti-inflammatory drugs, substances that reduce oxidative stress, and statins [61] seem to be quite promising.

During the recent years, some late consequences of PE have been studied. Indeed, a higher incidence of cardiovascular diseases [62] in this group of patients was found out. The newest systematic review and meta-analysis demonstrated changes in the carotid-femoral pulse wave velocity, carotid intima-media thickness, augmentation index and sFlt-1 level. These data suggest persistent vascular dysfunction after PE [63].

In actual fact, PE is a fascinating disease indeed. Thus, it is surprising that the efforts of a huge number of scientists still have not brought fruit in the form of revelation of the nature of PE till now. Hopefully, studies in this Journal will contribute to the successful campaign in this struggle.

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