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STUDYING THE FEATURES OF KIDNEY DAMAGE IN PREECLAMPSIA

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Abstract
The growing interest of nephrologists in the problem of kidney injury in preeclampsia is due to its high prevalence (2–14% of all pregnancies) and unpredictable outcome. The pathogenesis of kidney injury in PE is poorly known, however, the role of imbalance of pro- and anti-angiogenic factors – VEGF and sFlt-1 – has been established as one of the most important pathogenetic mechanisms underlying the development of PE. The article presents modern data on the pathogenesis and renal manifestations of PE at different times of its development in comparison with markers of placental angiogenesis. The role of the imbalance of the sFlt-1 / VEGF system in the formation of proteinuria, arterial hypertension and renal dysfunction in PE.

Keywords: Preeclampsia, glomerular injury, vascular endothelium growth factor (VEGF), soluble fms-like tyrosine kinase-1 receptors (sFlt-1), podocyturia, proteinuria, glomerular filtration rate, blood pressure.

Introduction

Preeclampsia (PE), which complicates 5-10% of all pregnancies, is still the main cause of maternal and perinatal mortality [1]. More than 8 million cases of PE are registered annually in the world, claiming the lives of 60 thousand young women. Such a high incidence of PE suggests that it is the most frequent cause of glomerular kidney damage [2, 3]. The pathogenesis of PE is complex and has not been fully deciphered. It has been established that the basis of PE development at the first stage is placentation disruption due to defective remodeling of myometrial vessels, which leads to incomplete invasion of trophoblast in early pregnancy. Subsequently, the damaged ischemic placenta begins to secrete in

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excessive amounts a potent antiangiogenic factor, a soluble receptor for vascular endothelial growth factor (VEGF) identified as soluble fms-like tyrosine kinase-1 (sFlt-1). This factor inhibits both VEGF and placental growth factor (PlGF), which ensure normal development and function of the placenta, and, circulating in the maternal bloodstream, may contribute to the development of systemic endothelial dysfunction underlying all clinical manifestations of PE [3,5]. In addition, renal dysfunction and edema serve as manifestations of PE. Since edema occurs in 60% of women with a physiologically normal pregnancy, isolated edema is no longer considered a sign of PE. However, even today, PE is often manifested by a sudden abrupt weight gain in the pregnant woman with edema of the hands, feet, and face [6]. In 2000, a working group of the National High Blood Pressure Education Program (NHBPEP) confirmed that the criteria for pregnancy AH were considered to be an increase in BP above 140/90 mmHg measured twice or more within 4-6 h, especially in women after 20 weeks of gestation with a previous normal BP. It was also suggested that an increase of 30 mmHg in SAP and 15 mmHg in DAP from baseline, even in the case of BP below 140/90 mmHg, should be observed to exclude the development of pre-eclampsia. The mechanisms of AH development in PE are diverse and include increased peripheral vascular resistance as a result of generalized vasoconstriction, sympathetic nervous system activity, cardiac output, excessive response to various pressor stimuli, including angiotensin II, catecholamines, endothelin [4]. Proteinuria (PU) may precede AH but usually develops concurrently or subsequently. The most important diagnostic criterion of PE is considered to be the level of PU exceeding 0.3 g/day. Another "renal" manifestation of PE is a decrease in glomerular filtration rate (GFR), which, however, is rarely paid attention to not only by obstetricians but also by nephrologists. In physiologic pregnancy, CBF increases by 40-60% already during the first trimester, reaching 140-170 ml/min [6], resulting in a decrease in serum creatinine (SeCr), uric acid, and urea. When PE develops, GFR decreases by 30-40% and sometimes more compared to normal pregnancy, but serum creatinine (SeCr) level almost always corresponds to the reference values of non-pregnant women and rarely exceeds 90-100 μmol/L [5,7], which, in turn, leads to underestimation of the patient's

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condition, especially in case of small PU and absence of severe AH. In rare cases of PE, the decrease in CRP progresses to acute kidney injury (AKI). Another characteristic sign of dysfunction in PE is a progressive increase in serum uric acid levels. The severity of hyperuricemia does not correlate with SCr levels but correlates with PU value, severity of PE, and perinatal mortality. Hyperuricemia often precedes proteinuria and decreased GFR. Increased uric acid levels in PE are not only due to impaired renal perfusion and renal ischemia, as previously thought, but also to decreased renal clearance [6, 7]. In recent years, it has been suggested that hyperuricemia in women with PE may contribute directly to the development of vascular damage and AH [6].

Histopathologic changes of kidneys in preeclampsia. The morphologic basis of PE is glomerular capillary endotheliosis. Its characteristic features are edema of endothelial cells of tubules, their loss of fenestrae and detachment from the basal membrane, which leads to narrowing of capillary lumen, sometimes up to complete occlusion. These changes allow us to consider renal damage in PE as a special type of thrombotic microangiopathy (TMA), despite the rarity of thrombosis of capillary loops of the tubules at light microscopy [6,8]. In severe or prolonged PE, however, thrombi are found not only in glomerular capillaries but also in small extraglomerular vessels. The most frequent findings in immunofluorescence study are fibrin deposits in the capillaries of the tubules, which are most often detected in early or severe PE [9]. It should be noted that in recent years the data have been obtained that moderately expressed endotheliosis, previously considered as a pathognomonic sign of PE, is detected in 1/3 of patients with gestational AH even in the absence of signs of PE. In patients with early and severe forms of PE, renal biopsy in the postpartum period reveals focal segmental glomerulosclerosis (FSGS) in 35 71% of cases, which is usually secondary [8,10]. Among the causes of FSGS development in these cases glomerular endotheliosis, intracellular hypertension and hypercoagulability are discussed. More recently, it has been suggested that secondary FSGS may be a consequence of podocytopenia found in women with PE [10]. The course of secondary FSGS in the outcome of PE is more favorable than that of primary FSGS. In 20-30% of patients with post-PE FSGS, AH persists, whereas PU is

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absent or minimally expressed. These changes are the result of the direct damaging effect of fulminant development of severe or malignant hypertension at the time of PE. In the remote postpartum period, 75% of women with sclerosis of interval arteries have persistent AH, often with signs of malignancy.

Obviously, it is FSGS and sclerosis of intrarenal arteries that are the basis of "residual changes" after PE, usually under the mask of "hypertension". The pathogenesis of renal damage in preeclampsia is no longer in doubt today that the "maternal syndrome" in PE is based on systemic endothelial dysfunction resulting from an imbalance of angiogenesis factors - deficiency of proangiogenic VEGF and PlGF with an excess of soluble receptors for VEGF - VEGFR-1, identified as soluble fms-like tyrosine kinase-1 (sFlt-1). VEGF is a signaling protein produced by cells to stimulate vasculogenesis (formation of embryonic vasculature) and angiogenesis (growth of new vessels in an existing vasculature). The most important role in the human body is played by a VEGF family protein called VEGF-A. This family also includes placental growth factor PlGF and proteins VEGF-B (embryonic angiogenesis of myocardial tissues), VEGF-C (angiogenesis of lymphatic vessels), VEGF-D (development of lymphatic vessels in lungs). All members of the VEGF protein family function by binding to and activating two closely related membrane tyrosine kinase receptors, VEGF receptor-1 (VEGFR-1 or Flt-1) and VEGF receptor-2 (VEGFR-2 or Flk-1). These receptors are expressed by endothelial cells [24]. VEGF-A protein binds to VEGFR-1 and VEGFR-2 receptors, with the VEGFR-2 receptor acting as a mediator in almost all known cellular responses to VEGF. VEGFR-1 can also act as an "empty" receptor, isolating VEGF protein from the VEGFR-2 receptor (which seems to be particularly important in embryonic vasculogenesis). VEGF expression is stimulated by a variety of proangiogenic factors, including epidermal growth factor, basic fibroblast growth factor, platelet-derived growth factor, and interleukin-1. In addition, VEGF levels are directly regulated by homeostasis factors such as pH, pressure, and oxygen concentration. The overall effect of the above factors is the VEGF-mediated stimulation of substances important for angiogenesis, including anti-apoptotic proteins, cell adhesion

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molecules, and metalloproteinases. However, the main stimulus of VEGF expression and/or production is hypoxia [11, 13].

In 2003, S.E. Maynard et al. established the presence of VEGF deficiency in patients with PE. It turned out that in this case VEGF inhibition was caused by soluble receptors to VEGF - VEGFR-1 or soluble fms-like tyrosine kinase-1 (sFlt-1), which is synthesized by ischemic placenta [5]. It has been found that excessive synthesis of sFlt-1 begins 5-6 weeks before the clinical manifestation of PE. This factor inhibits both VEGF and PlGF, providing vasculogenesis, and, circulating in the maternal bloodstream, may contribute to the development of systemic endothelial dysfunction underlying all clinical manifestations of PE [4, 5]. In the kidney, VEGF is expressed by podocytes and its receptors are expressed by endothelial cells of the tubules, which determines the most important local renal significance of VEGF. Its paracrine function in relation to endothelial cells provides regulation of the tubular permeability, formation and maintenance of fenestration of the endothelium of the capillaries of the tubules [31]. It also appeared that podocyte VEGF has not only paracrine, but also autocrine function - in relation to podocytes themselves, providing maintenance of their cytoskeleton [12,13]. The authors evaluated renal function and daily PU level before and during treatment with the drug. All patients who had no previous signs of renal damage and AH were found to have impaired renal function, increasing PU and development of AH in the next months from the beginning of therapy, which was an indication for kidney biopsy.

The main reason for the decrease in GFR was found to be the loss of fenestrae by glomerular endothelial cells. Since VEGF is required for fenestration formation and maintenance, it is obvious that the deficiency of the latter will result in endothelial structure and function disorder (glomerular endotheliosis) with a subsequent decrease in GFR [14, 15]. Endothelial damage induced by VEGF blockade may also be the cause of arterial hypertension.

The mechanism of proteinuria in PE has remained a mystery until recently. Like decreased CKF, PU was associated with glomerular endotheliosis, which was considered a pathognomonic morphologic sign of PE. However, the finding of signs of endotheliosis in pregnant women with gestational AH without proteinuria

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and even in healthy pregnant women has led to a different explanation. Studies undertaken in recent years have established that in patients with PE, VEGF deficiency caused by sFlt-1 excess impairs its autocrine function with respect to podocytes. A physiologic concentration of VEGF is necessary to maintain podocyte homeostasis and survival, and to maintain slit diaphragm function through regulation of nephrin expression. The increased concentration of sFlt-1 reduces the expression of slit diaphragm proteins, primarily nephrin, which leads to proteinuria [16, 18, 20, 21].

In our study, we aimed to investigate the effect of PE on the formation of CKD in "early" and "late" development of complications. It turned out that in women who underwent "late" PE, BP normalized and PU decreased to the minimum already on the day after delivery, renal function was normal. These parameters did not change during the next 12 months. On the contrary, after the "early" PE, during this time AG requiring the use of antihypertensive drugs persisted, daily PU was 0.5 g, and GFR was 71-74 ml/min. Thus, a part of patients already in the outcome of early PE formed CKD. When analyzing the monitored parameters 5 years after delivery, AH was observed in both groups of patients, urinary syndrome was represented by a small isolated PU, and GFR corresponded to CKD of the 2nd degree irrespective of the term of PE development. The obtained results indicate that the formation of CKD occurs after both "early" and "late" PE, but at different times [17, 19]. The clinical picture of nephropathy in "early" PE differs from "late" PE. The excessively high level of sFlt-1 in the group of patients with "early" PE confirms the contribution of VEGF inhibition to the formation of severe kidney damage in "early" PE (in "late" PE the level of sFlt-1 did not differ from that in healthy pregnant women). Therefore, we assumed that "early" and "late" PE are separate clinical situations that have not only different obstetric outcomes but also different renal prognosis [20,22,23].

Conclusion

PE is a pathology of the second half of pregnancy based on systemic endothelial dysfunction caused by an imbalance of angiogenic and antiangiogenic factors produced by the placenta. The main manifestation of the "maternal syndrome" in

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PE is the kidneys. Their damage, represented by a combination of glomerular endotheliosis and podocyte damage, is based on VEGF deficiency, caused by excessive content of sFlt-1 in circulation, which blocks autocrine and paracrine effects of VEGF aimed at maintaining structural and functional integrity of the tubules. Its disruption results in AH, PU and decreased GFR. PE is a risk factor for cardiovascular disease (CVD) and CKD in the distant future, and the birth of "low birth weight" children is associated with the development of chronic kidney failure (CKF) in their mothers many years after delivery. Given that early PE is characterized by more severe clinical manifestations and is associated with adverse outcome for both mother and fetus, it should probably be considered as a severe disease of pregnant women, primarily affecting the placenta and acquiring a systemic character due to the generalization of vascular endothelial damage. "Late" PE, in contrast to "early" PE, is rather a syndrome, the clinical manifestations of which are expressed to a much lesser extent, despite the common mechanisms of development. The legitimacy of this assumption is justified by recent information that glomerular endotheliosis is a morphological phenomenon caused by pregnancy as such, and in localized forms does not manifest itself clinically, which is confirmed by the detection of its histological signs in renal biopsy specimens not only in patients with pregnancy-induced AH, but also in healthy women in the III trimester of pregnancy [24, 25]. From this position, PE is an extremely pronounced manifestation of endotheliosis [25], and "early" PE, from our point of view, can probably be considered as its catastrophic variant characterized by a severe course and unfavorable prognosis for mother and fetus.

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