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PREECLAMPSIA RENAL INVOLVEMENT: ROLE OF ANGIOGENIC FACTORS

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Abstract. *Kidney damage in preeclampsia (PE) remains a pressing problem in modern obstetrics and nephrology due to its high prevalence (2-14% of all pregnancies) and unpredictability. The pathogenesis of kidney damage in PE has practically not been studied, as has the balance of pro- and antiangiogenic factors, which are considered today as one of the main pathogenetic mechanisms of PE. The article presents modern data on the pathogenesis of kidney damage in preeclampsia, the influence of the sFlt-1/VEGF system imbalance on the clinical manifestations of nephropathy in PE.*

Keywords: *preeclampsia, glomerular lesions, vasculoendothelial growth factor, soluble fms-like tyrosine kinase 1, arterial hypertension, glomerular filtration rate, proteinuria.*

PREEKLAMPSIYADA BUYRAK SHIKASTLANISHI: ANGIOGEN OMILLARNING ROLI

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Annotatsiya. *Preeklampsiyada buyrak shikastlanishi zamonaviy akusherlik va nefrologiyada dolzarb muammo bo‘lib qolmoqda, bu uning yuqori tarqalganlik darajasi (barcha homiladorliklarning 2-4%) va oqibatlarini oldindan aytib bo‘lmasligi bilan bog‘liq. PEda buyrak shikastlanishining patogenezi deyarli o‘rganilmagan, shuningdek pro- va antiangiogen omillarning muvozanati bugungi kunda PEning asosiy patogenetik mexanizmlaridan biri sifatida qaraladi. Maqolada preeklampsiyada buyrak shikastlanishining patogenezi, sFlt-1/VEGF tizimi disbalansining PEda nefropatiyaning klinik ko‘rinishlariga ta’siri haqidagi zamonaviy ma’lumotlar keltirilgan.*

Kalit so‘zlar: *preeklampsiya, glomerulyar zararlanish, vaskuloendotelial o‘sish omili, eruvchan fms-simon tirozinkinaza 1, arterial gipertenziya, koptokchalar filtratsiyasi tezligi, proteinuriya.*

ПОЧЕЧНОЕ ПОРАЖЕНИЕ ПРИ ПРЕЭКЛАМПСИИ: РОЛЬ АНГИОГЕННЫХ ФАКТОРОВ

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Аннотация. *Поражение почек при преэклампсии (ПЭ) остается актуальной проблемой в современном акушерстве и нефрологии, что обусловлено ее высокой распространенностью (2–14% всех беременностей) и непредсказуемостью исхода. Патогенез поражения почек при ПЭ практически не изучен, как и баланс про- и антиангиогенных факторов, которые рассматриваются сегодня как один из основных патогенетических механизмов ПЭ. В статье представлены современные данные о патогенезе почечного поражения при преэклампсии, влияние дисбаланса системы sFlt-1/VEGF на клинические проявления нефропатии при ПЭ.*

Ключевые слово: *преэклампсия, гломерулярное поражения, васкулоэндотелиальный фактор роста, растворимая fms-подобная тирозинкиназа 1, артериальная гипертензия, скорость клубочковой фильтрации, протеинурия.*

In recent years, there has been a steady increase in interest in the study of pre-eclampsia (PE) in nephrology, which can be considered the most common cause of glomerular kidney damage [1, 2]. More than 8 million cases of PE are registered worldwide each year, which is the leading cause of maternal and perinatal mortality, claiming the lives of 60,000 young women annually [3].

Currently, there is widespread discussion of the role of the imbalance between proangiogenic and antiangiogenic factors as an important mechanism in the development of arterial hypertension (AH) and proteinuria in patients with PE. It has been established that at the time of PE, there is a deficiency of vascular endothelial growth factor (VEGF) caused by circulating VEGF receptors identified as soluble fms-like tyrosine kinase-1 – sFlt-1, which the ischaemic placenta begins to synthesise 5–6 weeks before the clinical manifestation of PE. These factors inhibit both VEGF and placental growth factor (PlGF), which ensure normal placental development and function, and, circulating in the mother's bloodstream, may contribute to the development of systemic endothe-

lial dysfunction, which underlies all clinical manifestations of PE [4, 5].

Nephrological manifestations of PE

The main nephrological manifestations of PE are AH, PU and/or renal dysfunction. Since oedema occurs in 60% of women with physiologically normal pregnancies, oedema alone is no longer considered a sign of PE.

In 2000, the National High Blood Pressure Education Program Research Working Group (NHBPER) confirmed that the criteria for hypertension in pregnant women are considered to be an increase in blood pressure above 140/90 mm Hg, measured two or more times within 4-6 hours, especially in women after 20 weeks of gestation with previously normal blood pressure. It was also suggested that an increase in systolic blood pressure of 30 mm Hg and diastolic blood pressure of 15 mm Hg from baseline, even in cases of blood pressure below 140/90 mm Hg, requires monitoring of the woman to rule out the development of PE.

PU may precede hypertension, but usually develops simultaneously or following it. The most important diagnostic criterion for PE is considered to be a PU level of 0.3 g/day or more. PU is characterised by a rapid (sometimes hourly) increase. As a result, hypoproteinemia (in pregnant women, albumin in the blood less than 25 g/l) and nephrotic edema may be absent in the early days of PE development [6]. PE is considered the leading cause of nephrotic syndrome (NS) during pregnancy [5,6], although this fact is virtually unknown to nephrologists. However, it was confirmed as early as 1977 by K.A. Fisher et al., who performed kidney biopsies on pregnant women with PE in connection with the development of NS and found only its histological signs in 67% of cases [7]. In general, NS is a fairly rare complication of pregnancy, with a frequency of less than 0.0025%, but to date, there are no studies comparing the frequency of NS depending on the timing of PE development.

In recent years, the role of damage to podocytes — epithelial cells of the renal glomeruli responsible for glomerular permeability — in the genesis of massive PU, including in the development of PE, has been discussed. When studying podocyturia as a marker of podocytopathy, high specificity and sensitivity of the indicator were noted. According to V.D. Garovic et al., podocyturia was detected in 15 out of 15 women with PE, was absent in 16 out of 16 women with uncomplicated pregnancies, and was also absent in 7 women with other causes of AH, PU, or kidney disease. In addition to podocin, other podocyte proteins can also serve as indicators of podocytopathy: nephrin, podocalyxin, and synaptopodin. However, it is podocin that has the highest specificity and sensitivity and rightly claims to be an early predictor of PE [8].

In a physiological pregnancy, the glomerular filtration rate (GFR) increases by 40–60% during the first trimester, reaching 140–170 ml/min, resulting in a decrease in the concentration of creatinine, uric acid, and urea in the blood serum. With the development of PE, GFR decreases by 30–40% compared to normal pregnancy, but serum creatinine levels almost always correspond to the reference values for non-pregnant women and rarely exceed 90–100 μmol/L, which, in turn, leads to an underestimation of renal damage. In this regard, the "gold standard" for determining renal function during pregnancy is considered to be the determination of GFR using the Reberg-Tareev method. Calculation formulas are not acceptable for use in pregnant women, since, for example, GFR calculated using the MDRD formula significantly underestimates the values, while the Cockcroft-Gault formula, on the contrary, overestimates them [9].

Another characteristic feature of reduced renal function in PE is a progressive increase in serum uric acid levels – more than 500 μmol/L. Hyperuricaemia often precedes proteinuria and is caused by impaired renal perfusion [10].

The role of VEGF in the development of renal pathology. VEGF is a signalling protein produced by cells to stimulate vasculogenesis (the formation of the embryonic vascular system) and angiogenesis (the growth of new vessels in the existing vascular system). The most important role in the human body is played by a protein of the VEGF family called VEGF-A. This family also includes placental growth factor (PlGF) and the proteins VEGF-B (embryonic angiogenesis of myocardial tissue), VEGF-C (angiogenesis of lymphatic vessels), VEGF-D (development of lymphatic vessels in the lungs). All members of the VEGF protein family function by binding to two structurally similar membrane tyrosine kinase receptors: VEGF receptor-1 (VEGFR1 or Flt-1) and VEGF receptor-2 (VEGFR2 or Flk-1) and activating them. These receptors are expressed by endothelial cells [11].

The VEGF-A protein binds to VEGFR-1 and VEGFR-2 receptors, with VEGFR-2 acting as an intermediary in almost all known cell responses to VEGF. VEGFR-1 can also act as a "dummy" receptor, isolating the VEGF protein from the VEGFR-2 receptor (which appears to be particularly important in embryonic vasculogenesis).

VEGF expression is stimulated by a variety of proangiogenic factors, including epidermal growth factor, fibroblast growth factor, platelet-derived growth factor, and interleukin-1. In addition, VEGF levels are directly regulated by environmental factors such as pH, pressure, and oxygen concentrations. The overall effect of these various factors is the VEGF-mediated stimulation of factors important for angiogenesis, including anti-apoptotic proteins, cell adhesion molecules, and metalloproteinases. However, the main stimulus for VEGF expression and/or production is hypoxia [12].

Under physiological conditions, the main functions of VEGF-A are:

- stimulation of endothelial cell proliferation and differentiation;
- increased vascular permeability;

• mediated endothelium-dependent vasodilation;

• maintaining endothelial viability by preventing endothelial cell apoptosis;

• participation in the remodelling of the extracellular matrix by inducing the expression of plasminogen activator and PAI;

• enhancement of adhesion molecule expression on the surface of endothelial cells [11,12].

VEGF is expressed in the kidney by podocytes and also plays a crucial local renal role, namely: regulation of glomerular permeability, formation and maintenance of glomerular capillary endothelial fenestration, and maintenance of the podocyte cytoskeleton. Today, there is convincing evidence that in PE, glomerular VEGF deficiency plays a key role not only in the genesis of renal dysfunction, but also in PU and AH. As it turns out, podocyte VEGF has not only a paracrine function in relation to endothelial cells, but also an autocrine function in relation to the podocytes themselves [13]. In this regard, there is reason to believe that VEGF deficiency leads to damage to podocytes, flattening of their feet, which results in PU [14].

Pathogenesis of renal pathology in PE. At the beginning of the 21st century, a number of epidemiological studies convincingly demonstrated that women who had PE during pregnancy subsequently had a high risk of developing hypertension, ischaemic heart disease, and stroke, and therefore PE was classified as a risk factor for cardiovascular disease [15].

Given the similarity of risk factors for cardiovascular complications and chronic kidney disease (CKD), PE can also be considered a risk factor for CKD. Meanwhile, the mechanisms of chronic kidney damage in PE, especially in its early stages (up to 34 weeks of pregnancy), are virtually unknown to nephrologists.

In 2008, scientists from Norway published a major study showing that the birth of low birth weight babies is associated with a risk of developing CKD in mothers in subsequent years [16]. This unique study, conducted over a period of almost 40 years, made it possible to analyse the relationship between the incidence of end-stage renal failure and a history of PE. Unfortunately, it did not take into account the timing of PE development. It turned out that the risk of developing chronic renal failure in women who had experienced PE was four times higher than in the general population. In 20–40% of women who had no kidney disease before pregnancy, microalbuminuria and elevated blood pressure persisted for several years after delivery. The fact that microalbuminuria persists in 20–40% of patients after PE indicates the possibility of irreversible glomerular damage [10]. In addition, PE, including microalbuminuria, itself causes progressive renal dysfunction by increasing interstitial inflammation. According to the literature, up to 20% of women who have had PE show signs of CKD after delivery [17].

Of course, it is legitimate to ask whether the development of nephropathy in the postpartum period is a consequence of PE or of kidney disease that was not diagnosed before pregnancy. In a number of cases, it is not possible to obtain a definitive answer.

Undoubtedly, one of the achievements of recent years has been the assumption that an imbalance of placental proangiogenic and antiangiogenic factors plays an important role as one of the main mechanisms in the development of PE.

The prerequisites for studying the factors of angiogenesis in PE were the similarity of the clinical manifestations of the latter and the side effects of anti-VEGF therapy in the treatment of malignant tumours, which, as it turned out, can induce the development of renal thrombotic microangiopathy (TMA). In 2002, data from clinical trials of bevacizumab, a VEGF inhibitor, were published for the first time, showing that its use led to hypertension and PE in patients with malignant tumours of various locations [18]. In 2008, Patel T.V. et al. presented six clinical observations of patients with malignant neoplasms receiving bevacizumab therapy. The authors assessed renal function and daily PU levels before treatment and shortly after the drug was prescribed. All patients showed deterioration in renal function with an increase in PU and the onset of hypertension in the months following the start of therapy, which was an indication for renal biopsy. All six nephrobiopsies revealed a picture of TMA, with a combination of TMA and flattening of the small podocyte processes, which was more pronounced in patients with massive PU. After discontinuation of bevacizumab, renal function normalised in all patients. The authors suggested that a decrease in VEGF levels in the kidney as a result of its blockade by anti-antibodies could lead to local renal endothelial dysfunction (all patients had only renal manifestations of TMA and no systemic manifestations) due to impaired interaction of VEGF with its receptors, expressed by glomerular endothelial cells. The similarity of the clinical manifestations of the side effects of anti-VEGF therapy and PE has led some authors to refer to the renal consequences of angiogenesis inhibitor therapy as “preeclampsia-like syndrome” [19].

In 2003, S.E. Maynard et al. established the presence of VEGF deficiency in patients at the time of PE. However, in this case, VEGF inhibition was caused by soluble VEGF receptors – VEGFR1, identified as soluble fms-like tyrosine kinase-1 (sFlt-1), which is synthesized by the ischemic placenta. It has been established that excessive synthesis of sFlt-1 begins 5–6 weeks before the clinical manifestation of PE. This factor inhibits both VEGF and PIGF, which promote vasculogenesis, and, circulating in the mother's bloodstream, may contribute to the development of systemic endothelial dysfunction, which underlies all clinical manifestations of PE. At the same time, the authors consider the leading role of placental dysfunction in the pathogenesis of PE to be debatable, since excess sFlt-1 is an independent fac-

tor in the development of all clinical manifestations of PE underlying the so-called "maternal syndrome" [13].

In the kidneys, endothelial damage is represented by a picture of glomerular capillary endotheliosis with oedema of endothelial cells, loss of fenestrae and detachment from the basement membrane, leading to occlusion of the capillary lumen, which allows us to consider kidney damage in PE as a special type of TMA, despite the rarity of glomerular capillary loop thrombosis [7, 13].

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 in nature [19,20]. The mechanisms of FSGS development in PE are thought to include glomerular endotheliosis, intraglomerular hypertension, and hypercoagulation. In 20–30% of patients with FSGS detected after PE, AH persists, while PU is absent or minimal. In these women, nephrobioscopy shows that the histological manifestations of FSGS persist even in the absence of progression of clinical signs, although the phenomena of endotheliosis gradually disappear. In contrast to the double contour of the glomerular basement membrane (GBM) in type 1 membranoproliferative glomerulonephritis, which is formed by the interposition of mesangial cells between the endothelium and the basement membrane, in TMA, the double contour of the BM is due to its splitting due to fibrin deposition in the subendothelial space. The course of FSGS in women who have undergone PE is more favourable than the course of primary FSGS. Another morphological finding observed in severe nephropathy of pregnancy is fibrinoid necrosis and sclerosis of the interlobular arteries of the kidneys. 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 distant postpartum period, 75% of women with sclerosis of the interlobular arteries have persistent hypertension, often with signs of malignancy. It is evident that it is FSGG and sclerosis of the intrarenal arteries that underlie the "residual changes" after nephropathy in pregnant women, usually masked by "hypertensive disease" or "hypertensive nephritis".

In recent years, data have been obtained showing that moderate endotheliosis, previously considered a pathognomonic sign of PE, is detected in 1/3 of patients with gestational hypertension even in the absence of signs of PE. Moreover, minimal histological signs of endotheliosis in the form of focal oedema of endothelial cells are found in healthy pregnant women, suggesting that minimal pathology of glomerular endothelial cells may be characteristic of pregnancy in general [21].

In 2007, Stillman I.E. et al. published data obtained from experimental models of pregnant and non-pregnant rats in which PE was induced by intravenous administration of sFlt-1. Elevated concentrations of sFlt-1 in the bloodstream of both pregnant and non-pregnant animals caused AH and PU, which resembled "human" PE. Histological studies of the kidney tissue of these animals indicated the presence of glomerular endotheliosis, characteristic of PE. When recombinant VEGF121 was administered to rats with clinical signs of PE, the latter rapidly regressed, demonstrating a dose-dependent effect [22].

Thus, VEGF blockade is one of the most important pathogenetic mechanisms of glomerular damage underlying the "nephrological" component of PE.

A study by E. Robinson et al. demonstrated that inhibition of VEGF with cediranib, a potent VEGFR-2 inhibitor, induces an increase in blood pressure in patients within three days. The authors suggested VEGF blockade as an explanation for this phenomenon. The exact mechanism of AH in VEGF deficiency is unknown, but it has been shown that VEGFR-2 is the main mediator for the hypotensive effect of VEGF (vasodilation through the release of nitric oxide and prostacyclin by endothelial cells) and that VEGF inhibition can lead to AH. A reduction in the microcirculatory bed area due to VEGF deficiency is also being discussed as a possible cause of AH. A decrease in microvascular blood flow leads to an increase in peripheral vascular resistance and a decrease in nitric oxide concentration. Regardless of this, VEGF has a hypotensive effect by acting on the baroreceptors of endothelial cells [20].

In addition, VEGF blockade can cause an imbalance with endothelin, which is a potent vasoconstrictor [24].

Since VEGF is necessary for maintaining podocyte function and regulating glomerular filtration, its deficiency can cause podocytopathy and, as a result, PU, decreased renal filtration function, and glomerular endotheliosis [7] – a pathognomonic morphological feature of PE. It has been established that inactivation of one allele of the VEGF gene leads to the development of severe glomerulosclerosis with damage to podocytes and endothelial cells and, as a result, terminal renal failure in rat embryos at approximately 9 weeks of gestation [24].

A few studies have demonstrated a decrease in the expression of nephrin and synaptopodin in the glomeruli of women who died from PE, and in experimental animals when administered sFlt-1 or anti-VEGF antibodies, as well as the presence of podocytes in the urine of women with PE, confirming the assumption about the role of podocyte damage in the genesis of preeclampsia-induced PU. Thus, to date, there is considerable evidence that inhibition of VEGF by sFlt-1 receptors or anti-VEGF drugs can cause glomerular damage. In relation to PE, it can be assumed that this damage combines glomerular endotheliosis and podocytopathy [25].

Conclusion. Significant progress has been made in studying the pathogenesis of PE, including the mechanisms of renal damage: it has been proven that the ischaemic placenta synthesises excessive amounts of sFlt-1, soluble receptors for VEGF. VEGF deficiency may underlie systemic endothelial dys-

function, renal TMA, podocyte damage with flattening of their feet and, as a result, the development of AH, renal dysfunction and PU.

There is evidence that PE contributes to the development of cardiovascular disease in the distant future, and that the birth of low-birth-weight babies is associated with the development of end-stage renal failure many years after delivery in their mothers. Given that low birth weight babies are usually born when preeclampsia develops early, it is likely that early-onset preeclampsia can also be considered a risk factor for CKD. However, despite the high interest of nephrologists in the problem of PE in recent years, data on the effect of PE on renal damage and the prognostic significance of the timing of PE development are extremely scarce and require further study.

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