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Pregnancy preeclampsia: the main stages of pathogenesis. An infuence into fetal organogenesis (literature review)

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Abstract

In the current article there is observed a serious problem of the development of preeclampsia (PE) at a level of severity among women in Ukraine. It is disassembled in the description of the main theories of the development of PE: allergic, hormonal and renal. So that it can be instilled in some types of diseases and the theory of cortical-visceral ailments, which is leading on the pink modern data.

The study of cephalic changes to the pathogenesis of PE made it possible to see and describe the peculiarities of the structure of the placenta's vessels with this pathology with an eye on the development of endothelial dysfunction; hormone-stimulating activity in the mother - placenta - fetus system. Statistically, persons are indicated in a hematoencephalic institution, they are seen in the organisms of fetuses from mothers from the stage of severity. All the above specialties are seen as far as the degree of severity of the PE. It has been shown that in fetuses from mothers and PEs in the later ontogeny, there may be a breakdown of the implementation and the main stages in the development of cells, uterus and uterine tubes. Moreover, there is a trend towards the development of the pathology of the organs of the statutory system in case of women, women of all types of mothers from the moderate and severe stage, as well as a great number of changes in the development of PE at a given birth.

Key words: fetus; preeclampsia; pregnancy; stages of gravity; organogenesis; stage of severity.

Прееклампсія вагітних: основні ланки патогенезу, вплив на органогенез плода (огляд літератури)

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В оглядовій статті вивчено сучасний стан проблеми розвитку прееклампсії (ПЕ) різного ступеню тяжкості у вагітних в Україні. Розглянуто і описано основні теорії розвитку ПЕ, а саме: алергічна, гормональна та ниркова як такі, що можуть бути враховані в деяких випадках та теорія кортико-вісцеральної хвороби, що є ведучою на даному етапі розвитку медичної науки. Багатофакторне дослідження головних ланок патогенезу ПЕ дозволило виділити і описати характерні особливості будови стінки судин плаценти при даній патології з огляду на розвиток ендотеліальної дисфункції; гормон продукуючу активність в системі мати – плацента - плід. В статті наведено зміни в гематоенцефалічному бар'єрі, що відбуваються в організмі плодів від матерів із ПЕ різного ступеню тяжкості. Розглянуто особливості органогенезу плодів та порушення їх формування та дозрівання під впливом стійких судинних та гормональних змін з боку організму вагітної. Всі надані особливості розглянуто відповідно до ступеню тяжкості ПЕ. Показано, що у плодів від матерів із ПЕ у подальшому онтогенезі мають місце порушення закладки і основних етапів розвитку яєчників, матки та маткових труб. Причому відмічається стійка тенденція до розвитку патології органів статевої системи у дівчаток, народжених від матерів із ПЕ середнього та тяжкого ступеню, а також велика ймовірність розвитку ПЕ у подальшому під час вагітності та пологів.

Ключові слова: **плід; прееклампсія; вагітність; ступінь тяжкості; органогенез.**

The problem of preeclampsia (PE) does not lose its relevance. It is determined by a steady increase of maternal and perinatal mortality due to this pathology of pregnancy [11, 15]. During couple of centures scientists from all around the World have been leading

researches with the main aim of finding out main reasons of PE develpment, determing markers of progressing pathologicl changes in vital organs of pregnant, likewise developing prognostic and diagnostic criteria of PE severity [21, 35]. However, strictly up to nowadays there is no single developed concept towards etiology, pathogenesis as well as clear criteria of PE severity [8].

The leading link of pathogenesis in PE development is also a fact, that in most of cases the data of clinical, laboratory as well as instrumental research does not correspond with the stage of severity of pathological changes in the system mother-placenta-fetus [28]. In such clinical cases, when PE of mild or moderate severity could be diagnosed, the severe changes are developing at the same time (premature detachment of normally located placenta or multiorgan failure), which shortens the time interval for determing the scope of medical treatment and providing a necessary care timely and fully [17].

There are lots of theories about PE development. Each of them consists of different elements of pathogenesis, and are correponding with a level of science's development in a specific period of time. Every of these theories had made a specific contribution to level of understanding of this complication. We are going to dwell briefly on each of these theories in the aim of disclosing main pathogenesis links as well as explaining a necessity of considering this problem on a deeper level [11, 12].

The main point in the development of alergic theory is a connection between an appearance of PE from one side, and an existance of fertiled egg in a woman's organism, which is acting like an antigen from another side. Moreover, in a role of antigen we could also see fetal proteins or placental proteins [20]. The authors of the aforementioned theory (P.F. Belikov, A.E. Manevich, G.M. Shpolianskii) had been drowing an analogy between PE develpment and rhesus conflict [6, 18]. However, the theory was not applied for a large scale, while there were no develped pregnancy complications in case of the same women during following pregnancies.

The proponents of the hormonal theory explained PE development by a so-called plurigrandular genesis, i.e. participation of all endocrine glands in the development of complication [27, 32]. The main role undoubtedly was given to adrenal glands, namely to increase of corticosteroids' production. The disadvatage of the aforementioned theory was once again a lack of same complications' development in case of the same women during following pregnancies. What is more, from time to time there was also a comlete lack of PE symptoms for hormones' administration during an experiment.

The leading link of the renal theory wa so-called “body position theory” [13]. It means, that the PE develpement could be explained by the fact of uterus pressure on kidney and its vessels. However, the aforementioned theory had not gained any wide application, while there were features of complications in case of women with ascites as well as presence of tumors in abdominal cavity.

The modification of the renal theory was a theory of the uterus ischemia, according to which the main condition of the PE development is polyhydramnios, multiple birth and other changes, that lead to increasing an uterine pressure [34]. The theory had not been accepted due to the fact, that it did not come up with explanation on PE development in case of women, who did ot have any features of polyhydramnios or multiple birth.

Each of these theories were relevant under the prism of contributions, which was implemented by them into the whole study on the PE pathogenesis. However, more and more often appeares a question of mowing the perspective of study on complications’ development from the organ level to cellular and molecular ones [9, 16, 33].

One of the generally accepted theories, the main postulates of which are taken into account in a modern science, is the theory of cortico-viscelar nature of PE development [33, 35]. Namely, the developing fetilized egg gives impulses and leads to irritation on nerve endings of the uterus. As a result, patholgical reactions, as a cortico-viscelar disease with features of neurisis are appearing.

By the way, there are disruptions in cooperation between cortex and subcortex, which lead to generalized vasospasm and, as a result, to circulatory disorders [12, 19]. The detailed study on microcirculation in case of this pathology, as well as gaining a convincing data about meaning of intravascular structures in the frame of PE developement (change in hemostasis; disseminated intravascular coagulation syndrome; violation of rheological indexes of blood; blockade of microdynamics in vital organs) became a stimulus for development and deep study on this theory.

In the current step of the science’s develpment there was two-staged model of this complication’s development presented, the leading link of which is a systemic endothelial damage [1, 13, 14], while PE is considered as multifactorial pathology, in the development of which immunological, genetical as well as hemostatic factors are combined.

The basis of the first step are changes in placenta, that are determined by insufficient remodeling of spirl arteries [6, 9]. During the second step the reaction of the maternal organism joins as a multisystem inflammatory process as well as endothelial dysfunction [2, 24].

The changes in placenta are developing as a reaction for presence of immune complexes (IC) and complement in blood vessels and tissues, as well as increase of all immunological indexes [10]. Moreover, the stage of placenta damage is directly connected with a stage of mothers' PE severity [22]. Deposition and fixation of placental barrier of IC on the membrane structures stimulates a development of dystrophic changes as well as destruction of syncytiotrophoblast, the appearance of necrosis' and hemorrhage' areas in the basal plate, as well as thickening of vessels' walls with obliteration of their lumen [17]. The changes, that were described above, are contributing to development of placenta insufficiency. As a result of IC deposition on the endothelial membranes, immunological inflammations and necrosis are developing, consequently, a connection between endothelial cells and basement membrane is disrupting, what leads to exfoliation of endothelial cells into lumen of blood vessels and getting them to the blood circulation [5, 14]. On the place of defect of vascular wall blood clots are creating as well as blood coagulation system is activated [23].

The excessive formation of IC, that are represented by neuroantigens and complement, is stimulating a development of neuroimmune process as well as a development of so-called acute immunocomplex endothelisis [3, 25].

The impaired permeability of the blood-brain barrier in case of this pathology explains a development of changes in organs and systems of fetuses and newborns, that are analogical to ones in the mothers' organism [1, 26].

The endothelal disorders are the starting point for a systemic inflammatory reaction development, which could be confirmed by activation of monocytes, granulocytes and leukocytes, components of compliment, blood coagulation system, overexpression of adhesion molecules, increased release of inflammatory cytokines into the bloodstream [4]. The main signs of the systemic endotheliosis are violations of thromboresistant, vasoactive and other endothelium functions, as well as the change of activity and concentration of the endothelial dysfunction factors in the blood [2].

In the present point of the science' development there were the following stages of the endothelial dysfunction development described: NSE – specific marker of damage of the mature differentiated neurons; GFAP – specific marker of damage of the mature differentiated astrocytes; VCAM-1 – mollecules of the cellular adhesion of vessels; VEGF-A – a vascular endothelial factor, which is expressed by the activated endothelial cells; PIGF – placental factor of growth, which indicates pathological activity of endothelium [24]. During pregnancy, which is complicated by PE, the level of factor and antibodies to them is clearly

increased relatively to one in case of healthy women [7]. Moreover, it is known, that the concentration of aforementioned factors in the blood of pregnant women and newborns is directly connected with a stage of PE severity [28].

Thus, we could come up with the conclusion, that the complex disorders, that were described above, are developing with a lack of direct dependance from the PE stage of severity [29]. Moreover, there is a direct connection between a syndrome of the multiorgan failure from one side, and cells' damage from another side, what stimulates the complex of protective and adaptive responses (activation and suppression of the functional state of vital organs and systems) with accumulation of endotoxins and biologically active substabces with formation of aggressive vicious circle and a high frequency of both maternal and newborns' death [30].

The multifactorial study on PE problem by scientists from all over the World allows to consider PE as a result of interaction between maternal pathology and triggers from the fetus [31]. On the basis of the fact, that PE is developing only during the pregnancy period and disaapears after the childbirth, medical scientists had put forward the theory about its genetic etiology [32]. It has been shown, that the predisposition to PE development is inherited through both the female and male lines, i.e. through the fetus, the pregnancy with which was complicated by PE development [34]. Namely, there were the following connections described: women, who were born from mothers with a pregnancy, which was complicated by PE, were suffering from the same pregnancy complication twice as likely during the first pregnancy, while the risk of the PE development was increasing in case, if the mother of the fetus' father also suffered from this pathology [16]. Hereditary connection plays an important role for the PE stage of severity: thus, the complications was developing more often in case of children, whose mothers were suffering from PE of the severe stage [39]. Another specific feature is a fact, that the high level probability of PE development could be observed in case of sisters, while in case of brothers is absent [9].

By comparing an obtained anamnestic data with changes in the antigens' system, researchers had disclosed an existance of associations between the presence of HLA-DR 4 antigen and PE development [7]. Moreover, there was postulated a genes' polymorphism, that had been taking part in the endothelium regulation (PLAT, PAI-1, ACE, eNOS, TNF-α, GSTP), as well as an association with comparable and isolated preeclampsia for genes PLAT, PAI-1, TNF-α. In a comparative study of different pathology models there were disclosed three independent mechanism of the PE development: 1) the line BPH/5 correlates with a borderline of maternal hypertension (here we are speaking about increase of blood pressure

only during pregnancy); 2) renin-angiotensis-transgenic line is connected with an excessive renin production by placenta; 3) p57 Kip2 - a mutant line which is situated in a direct interaction with the development of pathological changes in placenta [17, 23].

Thus, the accumulated data about genetic predisposition of PE development are indicating a polygenic determinism of this pathology, as well as genetic heterogeneity of mild and severe stage of PE. There is no doubts, that there are specific features of interactions between genotypes of mother and fetus on the basis of this pathology' development.

Changes in the mother-placenta-fetus system in case of pregnant with PE of different stages of severity.

Feto-placental complex is a specific system, which provides conditions, that are necessary for a normal fetus' development [17, 35]. Such complications of pregnancy, as PE of different stages of severity contribute to the formation of primary and secondary placental dysfunction, what leads to the systemic and structural changes in the main components of this system, as well as is manifested by the syndrome of fetal growth retardation {SFGR} [15, 27]. According to the data of the modern literature, the development of feto-placental dysfunction could be observed in 70% of pregnancies [7, 35]. The severity of structural changes in this case depends on a direct proportion towards the stage of severity of maternal pathology [19, 23]. Let us consider an influence of PE of different stage of severity on a function of single mother-placenta-fetus system.

PE of different severity stage leads to the microcirculation disorder, which is determined, primarily, by the insufficient gestational reorganization of uterine-placental arteries, and entails also a violation of the second wave of cytotrophoblast invasion (namely: keeping of narrow lumens, endothelial lining as well as elastometrial components of endo- and miometrioid segments of spiral arteris, likewise delaying of its reorganization into uterine-placental arteries) [26, 33]. In placenta due to this condition general pathological changes are taking place, that are characteristic for hypertension [7], likewise some specific features, that are characteristic for PE of different stages of severity [22, 36].

Among general changes we could name the following: massive fibrinoid deposits in the intervillous spaces, immaturity of the chorionic villi, microcirculation disorders, sclerosis, obliteration and narrowing of the lumen of blood vessels [3]. The specific features of placenta are: deposition of immune complexes, that consist of antibodies to NSE classes IgA, IgG, IgM in chorionic villi, in fibrinoid, as well as along the uterine-placental arteries, decrease of intervillous circulation, violation of transformation of the muscular layer of spiral arteries [16, 29, 31].

Both general, likewise specific changes are leading to disorder of condition of the endothelial system as well as uteroplacental circulation, which is manifested by placental dysfunction [2]. As a result of placetal dysfunction, there is formation of the syndrome of fetal growth retardation {SFGR}, which, according to the literatural data, takes place in 5-10% of pregnancies in case of PE with a mild stage of severity, 18-25 % - in case of moderate stage of PE severity, as well as 80% - in case of severe stage of PE severity [33].

The hormonal function of placenta is also disturbed, what could be confirmed by an increased consentration of soluble vascular - endothelial growth factor receptor in the blood of pregnant women as well as by decrease of the placental growth factor [4]. In addition, there is a described increase of Willebrand factor in the blood of pregnant women, while the concentration of placental lactogen and estriol was decreased [28].

In the literature there are specific described structural changes in the mother-placenta-fetus system, that could be characteristic as for PE of different stages of severity, likewise for chronic infection of lower genital tract [34]. It means, for compatible pathology. In 50% of observations we could notice formation of syncytial nodes, thrombosis of the intervillous space and retroplacental hematomas in placenta. Moreover, there is a disorder in a biological barrier between maternal and fetal blood, which is determined by changes in proportions of placental proteins in the mother's serum [19].

The pathological changes, that are developing in placenta due to the aforementioned disorder, cause a premature maturation of placenta, which, in turn, is a morphological feature of placental pathological immaturity, as well as ultrasound feature of the placental insufficiency [5]. The main equivalents of insufficiency are: dissociated development of villous chorion, inflammatory changes, involutive-dystrophic process and circulatory disorders, changes of proportion of stromal component and vascular bed of villi, significant fibrosis of the villous stroma, fibrosis changes in muscular layer of arteries, presence of great number of small villi with necrotic and dystrophic chabges, syncytiotrophoblast proliferation, focal thickening of the basement membrane [19].

By applying an immunohistochemical method, by using MCAT to different types of collagens, the disorder in distribution of collagens of the I, III and IV types in central, paracentral and lateral areas of placenta was presented [29, 33]. The specific features of the collagen-synthesizing funtion indicate clear sclerotic changes in placenta and could be one of the links in the development of chronic placental dysfunction [21].

By taking into account everything, what was mentioned above, we could come up with a conclusion, that the formation of primary or secondary placenal dysfunction on the surface

of PE contributes to the development of deep strucutral and functional disorders of placental complex, what is manifested by circulation' disorder, changes in the endotheline-producing activity, decrease of the placental hormonal function as well as formation of features of the connective tissue dysplasia. The aforementioned changes are leading to formation of the SFGR, early termination of the pregnancy, stillborn pregnancy in the third trimester.

Modern ideas about influence of the PE of different stage of severity on the fetuses' organogenesis

The data of WHO indicates the fact, that there disorders of physical psycho-emotional development, as well as increased level of morbidity during infancy and early childhood observed, in case of children, who were born from mothers with PE of different severity [6]. During leading a study on a condition of newborns, their physical development as well as morbidity, it was shown, that at birth, children, who were born from mothers with PE are estimated in 8-10 points on the Apgar scale only in 12% of cases; in other observations - in 5-7 points; the average indexes of body's weight and length of newborns are clearly decreased in 75% of cases comparing to such indexes in case of children, who were born from healthy mothers [4]; the course of the early neonatal period is complicated by development of hypoglycemia condition, respiratory failure; after birth though the pathological weight loss is admited, the index of which exceeds in 1,5 times comparing to physiological one; the period of staying in the hospital is prolonging for newborns, as well as rehabilitation is carried out in two stages [13, 21].

Moreover, generally, the stage of PE severity does not correspond with a harmful effect on the fetus [31, 34]. It means, that PE of mild or moderate severity are not leading to less gross violations in implementation and formation of internal organs of the fetuses, comparing to those, which could be observed in case of PE of severe stage [33, 35]. As an explanation we could provide here a fact, that the clinical manifestations of PE are developing in the second half od pregnancy [29, 35]. At that time, vascular and metabolic disorders could be noticed, as well as affect the fetus already on the early stages of its in utero development. It means, that the main stages of organogenesis are taking place on the background of the overstrain of compensatory-adaptive mechanism of the mother's body, namely, in the period, when an appropriate medical treatment is not provided, as well as unformed fetal organs are taking part in stabilization of the condition of pregnant woman [11, 18, 30]. The process of the further stabilization and formation of the functional activity, in turn, is taking place on the background of the disruption of mother's organism adaptation, as well as accession of hormone therapy.

Vascular, hormonal and metabolic disorders in the mother-placenta-fetus system are leading to the formation of SFGR [15, 20]. What is more, it was disclosed, that the level of severity of this syndrome is directly connected with duration of PE, and not with the stage of the disease's severity [22, 29]. SFGR is manifested by violation of implementation and formation of fetuses' internal organs and systems. Thus, the hypoxic brain damage is characterized by decrease of the content of neurotrophic and growth factors, with increase of proapoptotic factors at the same time [12, 26]. The aforementioned features are indicating a lack of protective mechanisms, reducing of neurons' and vascular system' resistance towards ischemia, a low ability for reparative processes [27].

The data of a modern literature indicates the fact, that by comparing cardiorgythms of the mother and fetus in case of PE, their distinction could be noticed [12, 31]. It is known, that the index of cardiorhythms in case of physiological pregnancy indicates a balanced regulatory effects on a heart rate, an enough level of protective and adaptive reactions as well as high anti-stress resistance [15]. In case of presence of an extragenital pathology we could notice the following changes: in case of fetuses, who were born from mothers with a PE of a mild stage of severity, there were postulated signs of a compensatory stress of the cardiovascular system of fetus, that are directed into stabilization of intensity of the fetal metabolic and regulatory processes [17, 27]. In case of PE of the moderate stage of severity a yperadaptive condition prevails, the main characteristic features of which are: the violation of adaptive and compensatory processes, as well as functioning of the system in an autonomous regime [6, 9]. In case of PE of the severe stage, we could notice a hypoadaptive condition, which indicates low reserves of metabolic processes, as well as depletion of the protective and adaptive capacity of cardiovascular system of fetus [34, 35]. The changes, that were described above, are contributing further to development of cardiovascular insufficiency in case of increase of the needs of growing organism [11, 26].

There are described changes in a structure of fetuses' internal organs, in case of this patholgy of pregnancy (thymus, pancreas, liver, thyroid) [21, 29]. In the aforementioned organs we could notice unilaterally directed changes. Namely: there are clear sclerotic and atrophic changes in parenchyma and stroma of organs, change in a structure of main components of the organ, as well as a violation of the functional activity as hyperplastic changes in case of fetuses from mothers with PE of a moderate stage of severity; hypoplastic ones - in case of fetuses from mothers with a secere stage of PE [17, 18]. The strucutral and functional changes in internal organs are described as a syndrome of multiorganic insufficiency.

The functional disorder of vital organs could be also determined by specific features of the rehabiitation period of newborns and children from mothers with PE [33, 34]. The improvement as well as modern equipment of intensive care units allow a preterm birth and reduce mortality among newborns [27, 30]. The set of resuscitation measures by the way is directed into saving lives, that is why one of the most important componets of it are hormonal treatments. However, neonatologists and therapists are still not dealing with issues of the further rehabilitation, which is directed to preventing complications of the hormonal therapy [4, 30]. In the meanwhile, children from mothers with PE of different stages of severity, who suffered critical conditions during a period of being newborns, are becoming a "risk group" because of development of central nervous system' complications, diabetes, liver insufficiency, hypothyroidism, respiratory distress syndrome, as well as genital dysfunction in case of girls [9, 26, 33]. Primarily, it is determined by immaturity of the newborn's organism, as well as inferiority of its adaptation' mechanisms for extrauterine life [7, 25].

The study on mother's PE affect on implementation and stabilization of the female genital organs, as one of the links in a single endocrine system, has been leaded by couple of generations of scientists as well as is relevant for a current stage of the medical science [25, 29]. Thus, it was disclosed, that girls, who were born from mothers with PE, as well as such girls, who were suffered from critical conditions while being newborns, lag behind their peers in the main parameters of the physiological development. They also have a difference in three pelvic sizes [14, 25]}. In 50% of cases we could notice a violation of the physiological development of these adolescents; in 25% of cases the asthenic morphotype is being formed; in 15% of cases - an infantile one [31, 36]. In case of girls, whose birthweight was less, than 2000g, the pathology' development of organs of the genital system is oberved in 30% of cases, while in case of adolescents, who were born prematurely - in 45% of observations [28, 32]. Moreover, in case of girls adolescents, who were born from mothers with PE, the violations of the hormonal status could be noticed: namely, a decrease of somatotropic hormone, an increase of the progesterone and testosterone level, decrease of an extrogen production [16, 19]; decrease of folliculin-producing hormone level as well as level of luteinotropic hormone [2]. All changes, that were mentioned above, are primarily manifested by the development of a secondary amenorrhea, pubertal uterine bleeding, oligoamenorrhea and conditions, that are close to hyperpolymenorrhea [16, 25].

In the development of pathology of a female reproductive system a leading role is taken by the imbalance of the concentration of cytokines in the serum, which occurs in case of PE [33, 34, 35]. Thus, it was postulated, that in case of pregnant women with PE, a

concentration of pro-inflammatory cytokines is clearily increased (IL-1ß, IL-2, IL-6, IL-8, TNFα), as well as the ratio among pools of pro-inflammatory cytokines (IL-4, IL-10) is dusrupted [15]. The changes of this type are aggravating an endothelial damage, as well as could further lead to formation of the ovarian hyperstimulation syndrome [22].

The changes, that were described above, are indicating discordance of individual parts of the reproductive system and could further contribute to development of gross disorders of puberty, anovulation, as well as infetility.

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