ISBN: 978-93-72322-37-4

PROGNOSIS AND EARLY DIAGNOSIS OF PREECLAMPSIA BASED ON CLINICO-GENETIC AND ENDOTHELIAL PREDICTORS

Authors:

L. R. AGABABYAN,
S.E. MAXMUDOVA

Published by
Novateur Publication
466, Sadashiv Peth, M.S.India-411030
novateurpublication.org

MINISTRY OF HEALTH OF THE REPUBLIC OF UZBEKISTAN
SAMARKAND STATE MEDICAL UNIVERSITY

L. R. AGABABYAN, S.E. MAXMUDOVA

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UDC: 618.3-06-008.6:616-06-037

RECENTS:

1. **Khudoyarova D.R.-** Head of the Department of Obstetrics and Gynecology №1 SamMU Doctor of medical sciences, Professor

2. **Oripov F.S.**- Head of the Department of Histology, Cytology and Embryology SamSMU, Doctor of medical sciences, Professor

3. **Ikhtiyarova G.A.** - Head of the Department of Obstetrics and Gynecology of the Bukhara State Medical Institute, Doctor of medical sciences, professor

The monograph presents the main issues of pathogenesis, diagnosis, prognosis and methods of early treatment of preeclampsia. The results of research by foreign authors, based on evidence-based medicine, summarized over the past 10 years, reflecting modern ideas about etiology, pathogenesis, clinic, diagnostic criteria, prognosis and treatment of preeclampsia. Thanks to advances in molecular genetic studies, as well as advances in the field of experimental and clinical studies have led to new views on the reasons for the formation of abnormalities in the vascular bed in pre-eclampsia. The author's experience on risk factors of pre-eclampsia, as well as early diagnosis and prognosis of preeclampsia. A special chapter is devoted to molecular genetic studies, morphologic structure of the placenta in preeclampsia.

The book is intended for obstetrician-gynecologists, doctors of other specialties interested in this problem

Content

LIST OF ABBREVIATIONS

AH	-	arterial hypertension.
ARVI	-	acute respiratory viral infection.
AGTR1	-	Angiotensin II receptor type 1
AGTR2	-	Angiotensin II receptor type 2
ALAT	-	alanine aminotransferase.
AP	-	umbilical cord arteries.
AsAT	-	aspartate aminotransferase.
ATP	-	antithrombin III.
AtrAT	-	antiplatelet antibodies.
APS	-	antiphospholipid syndrome.
ACTV	-	activated partial thromboplastin time.
BP	-	blood pressure.
BMI	-	body mass index.
C-section	-	cesarean section.
CA	-	spiral arteries.
CNS	-	central nervous system. ECM - extracellular matrix
CTG	-	cardiotocography.
DIC	-	disseminated intravascular coagulation.
DM	-	diabetes mellitus.
ELI-P-Test	-	ELISA-detected Probability of Pathology in Pregnancy.
FGR	-	fetal growth retardation.
FPC	-	fetoplacental complex.
FGTN	-	fetoplacental insufficiency.
FPS	-	feto-placental system
MA	-	uterine arteries.
MI	-	maternal mortality.

MSC	-	uterine-placental complex.
PLGF	-	placental growth factor
PAAP-A	-	Pregnancy-associated plasma protein A
PI	-	pulse index.
PN	-	placental insufficiency.
PS	-	perinatal mortality.
PP	-	perinatal morbidity.
PR	-	prenatal risk.
PE	-	preeclampsia.
s-FLT-1	-	Soluble fms-like tyrosine kinase-1
TTL	-	placental bed.
RDS	-	respiratory distress syndrome.
UGI	-	urogenital infection.
USI	-	ultrasound examination.
VEGF	-	Vascular endothelial growth factor
WHO	-	World Health Organization

CHAPTER I. PREECLAMPSIA – A MODERN VIEW TO THE PROBLEM, METHODS OF PROGNOSIS AND EARLY DIAGNOSIS.

Preeclampsia in modern conditions: epidemiology, risk factors, main clinical manifestations

Despite the annual progress of obstetric science and practice, attempts to find out the causes and methods of early diagnosis and treatment of PE, allowing with a sufficient degree of confidence to determine the severity and prognosis of this terrible complication of pregnancy still do not lead to the expected results. Preeclampsia (PE) remains an important medical and social problem. The importance of this problem is primarily due to the fact that PE, which is a syndrome of multiple organ failure that occurs during pregnancy, continues to be one of the main causes of perinatal and maternal morbidity and mortality worldwide. As indicated by the World Health Organization (WHO), hypertensive entanglements that cause maternal mortality represent up to 30 % of all variables in created nations [11, 17, 22,120, 148].

Every year, about 8.5 million cases of preeclampsia are recorded in the world, which is 2-8% of all pregnancies (14% of women die every year) and this figure does not tend to decrease [115, 129,147]. Approximately 72,000 women die each year from severe preeclampsia / eclampsia. This is about 200 women daily. Thus, preeclampsia / eclampsia is most often the second leading cause of maternal mortality after obstetric bleeding. Simultaneously, the risk of death for women in developing countries is approximately 300 times higher than in developed countries [Balancing the scales: expanding treatment for pregnant women with life-threatening hypertensive conditions in developing countries. A report on barriers and solutions to treat preeclampsia and eclampsia [122]. According to [163] the incidence of severe PE in Western countries is 3-5 % among all pregnant women. Providing antenatal services is important in this case. So, according to [98] 40.98% of women with PE are registered in the second trimester of pregnancy, 46.28% in

the third, and only 12.54% in the first in India, for example: Eclampsia during pregnancy occurs in 76.78% of cases, but 13.72% cases of postpartum eclampsia are also described.

In various countries preeclampsia and complications associated with it occupy 2-4 places in the structure of maternal mortality every year. In Uzbekistan, PE occurs in approximately 11-16% of pregnant women and ranks 3rd among the causes of maternal mortality [2, 11, 28]. According to various data, PE is found in 5-30% of all pregnancies in Russia. It is associated with more than one third of severe obstetric pathology [21].

The effect of PE on the fetal condition is significant. Among children born alive from mothers who suffered PE, every fourth child lags behind in physical development [7]. PE stays one of the essential drivers of perinatal mortality (18-30%) and frightfulness (64-78%) [1, 11]. It should be seen that alongside obstetric depleting and overwhelming intricacies, PE frames the alleged "dangerous arrangement of three", which transforms into the justification the stunning number of maternal deaths. Simultaneously, toxemia stays one of the fundamental driver of neonatal horribleness and perinatal mortality. Finally, preeclampsia is associated with stress and subsequent postpartum depression [7,17,25,67,128]. In some developed countries, in particular in the United States, an increase in the frequency of PE has been noted in recent years. Specialists accept that this is because of an increment in the recurrence of such conditions as diabetes mellitus (DM), stoutness, and persistent blood vessel hypertension (HAH). The expansion in the recurrence of toxemia has been particularly noted since 90s, this might be related with an increment in the recurrence of corpulence [91].

To sum up all the data, the frequency of preeclampsia / eclampsia is 5-10% among all pregnant women [193]. However, in African and Asian countries, preeclampsia / eclampsia is the cause of maternal mortality in 9% of cases, and in the Caribbean and Latin America – up to 25% [106]. Hypertensive disorders in pregnancy occur in 10.08% of pregnant women in India, with eclampsia accounting for 1.9%. In India, severe preeclampsia/eclampsia is mainly associated with

adolescent pregnancy, 17% of which have this pregnancy complication [98]. It is important to note that of all cases of preeclampsia/eclampsia, 81% are primaparal and first-pregnancy women [98].

Long-term consequences for women who had PE during pregnancy are also associated with the development of cardiovascular complications in further life.

It should be indicated that the true frequency of severe PE/E cannot be established. For example, one multicenter study indicates a figure of 26 per 1,000 births [117,118].

Risk factors for this maternal pregnancy entanglement include: age more than 40, past pregnancies with PE, first labor, multiple pregnancies, antiphospholipid condition (AFS), ongoing blood vessel hypertension, immune system sicknesses, diabetes, kidney illnesses , dyslipidemia, and stoutness [118]. The rule clinical danger limits for the execution of PE join the going with factors: race, weight record, negative eccentricities (smoking), prophylactic systems, the presence of steady vein hypertension, diabetes, AFS, and thrombophilia, upset obstetric-gynecological (routine unexpected labor, PE during past pregnancy) and intrinsic (PE in the mother or sister, PE in the mate's previous spouses) anamnesis'. Risk factors for developing PE, in addition to those listed above, include: a history of PE, an intergraviditary interval of 5 years or more, age >35 years, overweight/obesity (BMI>25 kg / m2), family history (PE in the mother or sister), and a DAP of 80 mm Hg. and above, proteinuria when registering for pregnancy, multiple pregnancy, extragenital diseases such as HAG, kidney diseases, systemic diseases, vascular diseases, diabetes mellitus, AFS. [70,115].

It was found that the danger of toxemia creating associates with the seriousness of substantial infection. In this way, ladies with a background marked by hypertension have a 10-25% higher danger of toxemia creating contrasted with everyone and a 31% higher danger for long haul hypertension [193]. In gestational diabetes, the overall risk of preeclampsia developing increases by 21% [193]. With a history of diabetes lasting less than 10 years, the risk is 11-12%, and among women with longer diabetes increases from 36 to 54%. Minor renal dysfunction (serum

creatinine less than 1.5 mg/dl) increases the risk of preeclampsia by 20-25%, and for pregnant women with severe renal insufficiency - by more than 50% [194]. Obesity increases the overall risk of preeclampsia about 2-3 times. It can also be noted that preeclampsia is more common in pregnant women with autoimmune conditions such as systemic lupus erythematosus and antiphospholipid syndrome. Even more than 300 years ago, high rate of preeclampsia in primapregnant women was at the center of consideration [115, 162]. B.M. Sibai and co-authors (2012) found that the rate of preeclampsia varied from 4% to 11% in primapara mothers, while the rate of preeclampsia was lower in women who already had labors, although it also varied widely [99]. In women with an upcoming repeat birth, the risk of preeclampsia is only 1.4-4% [44], but they have an increased risk of antenatal fetal death in PE [91]. Multiple pregnancies are also a risk factor for preeclampsia. Thus, in women with twins, the frequency of preeclampsia is 2.5 times higher, reaching 6-31% [54].

In the UK, the national Institute for Health and Clinical Excellence (NICE) has established criteria for assessing the high risk of developing pre-eclampsia. High-risk factors include: hypertension in past pregnancies, persistent kidney illness, immune system infections, diabetes mellitus, and hypertension. Moderate danger factors include: first pregnancy, age 40 years or more, span between pregnancies over 10 years, body mass index at the first visit of 35 kg / m2, presence of preeclampsia in the family history [236]. Maternal factors also include smoking and race. In the United States, according to the recommendations of the American College of obstetricians and gynecologists (ACOG), consideration of life history and disease to assess risk factors for PE is currently the best and only recommended screening approach for assessing risk factors for preeclampsia.

The classic triad of symptoms of PE (increased blood pressure, edema and proteinuria) is the result of a number of pathogenic factors that are closely related with each other. Edema occurs as a result of oncotic pressure decreasing, increasing of capillary permeability, which leads to the exit of fluid from the vascular bed into interstitial space, and arterial hypertension – due to vascular spasm and hyper dynamic systolic function of the heart [114,175]. PE is characterized by blood

pressure lability. When evaluating arterial hypertension at patients with PE, dynamic changes of blood pressure are taken into account, but not absolute figures. Pregnant women with PE often have blood pressure assimilation. The difference in figures on the hands can be from 15 to 50 mm Hg, the greater the degree of assimilation, the more severe the flow of PE. Among each and every hemodynamic factor, remarkable thought is paid to direct procedures for diagnosing PE — explicitly, the components of circulatory strain figures, starting from the principle trimester of pregnancy, using step by step beat noticing (DBPM). This strategy permits us to check the underlying deviations in the day by day musicality and pulse figures, to indicate the degree and security of its expanding, which assists with distinguishing ladies in danger of creating PE in the beginning phases of incubation and decide the further strategies of pregnancy the board [6, 10, 16]. Special attention should be paid to the average arterial pressure (MAP – Mean Arterial Pressure), calculated by the following formula: (diastolic pressure x 2) + systolic pressure) :3. MAP is significantly increased in pregnant women with PE. According to L. Roop et al., K. Harrington et al., mean blood pressure (MBP), pulse index (PI) in uterine course (MA) in the first and second trimesters of pregnancy in the social event of patients with PE of various reality happen to basically be higher than in patients with physiologically occuring pregnancy ($p < 0.0001$). Consolidated PE screening, including mother's danger factors, dopplerometry in UA, considering the estimation of pulse, has a higher affectability (89.2% - for early PE, 57% - for late PE) at a frequency of 10% false positive results (FPR). Proteinuria occurs as a result of renal glomeruli damage with increasing permeability of the basal membrane of their capillaries. During pregnancy, proteinuria may occur in the absence of arterial hypertension, edema, and previous infectious or systemic kidney disease [26, 42]. Although preeclampsia is usually accompanied by proteinuria, the American College of obstetricians and gynecologists (ACOG) announced in 2017 that the presence of proteinuria is no longer required for the diagnosis of preeclampsia. High blood pressure, accompanied by other signs and symptoms, is sufficient to diagnose preeclampsia. These other signs are also included in the new terminology proposed

by ACOG for detecting cases of preeclampsia. The percentage of women who develop preeclampsia without proteinuria, or who presents proteinuria without hypertension preceding preeclampsia, is unknown. Definitions of these atypical phenomena are contradictory. Very few studies are devoted to the study of these clinical conditions. According to G. M. Saveleva et al. when analyzing the initial blood pressure (IBP) figures, out of 33 patients with moderate arterial hypertension (AH) or normotension the increased mean blood pressure (MBP) by 60 mm Hg or more was found in 1/3 of cases. Edema was significantly more frequent in patients of groups 2 and 3. In the structure of complaints, headache is in the first place [64 (42.1%) patients, $p<0.01$]. In 46% of patients, PE was atypical. All patients have a combination of various additional symptoms, complaints, laboratory changes indicating evidence of vital organ dysfunction. According to magnetic resonance imaging (MRI) data, 47.2% of pregnant women with PE and complaints of headache and/or visual impairment showed changes in the brain, 88% of them were caused by hypertension: posterior reversible encephalopathy syndrome (PRES) (13.9%), acute violation of cerebral circulation (AVCC) (5.6%), foci of vascular genesis (22.2%). PRES and AVCC developed at women with atypical form of the disease. In this regard, the authors recommend to reduce the frequency of complications of PE by considering normal for the patient figures of blood pressure to assess the degree of arterial hypertension (AH), any quantitative measurement of protein in the urine, to distinguish atypical form and a critical phase of PE, and MRI of the brain for objective assessment of central nervous system [21,34].

Critical forms of preeclampsia include: eclampsia (acute brain edema, high intracranial hypertension, violation of cerebral circulation, ischemic and hemorrhagic damage to brain structures) and posteclamptic coma; severe liver damage (HELLP syndrome, acute fatty hepatosis, acute renal-hepatic insufficiency, rupture of the liver capsule); premature abruption of the normally located placenta, developed as a result of preeclampsia, complications of severe eye hypertension (hemorrhage, retinal detachment).

Despite a large number of studies devoted to the problem of PE, there is still a lot of uncertainty about its etiology and pathogenesis [61, 94, 106, 128, 193]. There is no coherent etiologically based tactics for prevention and treatment of this pregnancy complication [60, 189, 190, 191, 192, 193, 194].

The scientific works which are possible to assume the development of PE in a patient before pregnancy or in its early stages [12, 70, 118, 150,193] are of particular interest. Currently there is an intensive search for PE prediction markers [88, 127, 146, 201]. In this regard, the immunological changes at pregnant women and the genetic aspects of the development of this disease deserve special attention [71, 85, 96, 148; 188], as well as the function of the vascular endothelium.

The role of predictive markers in the development of preeclampsia

Summarized data from the world literature indicate that PE is a syndrome of multiple organ failure that occurs as a result of the adaptive response of mother's body to the effects leading to fetal oxygen insufficiency. An increase in the permeability of the vascular wall and, as a result, volemic and hemodynamic disorders at women with PE is occured [45,81,96]. At the same time, there is still no answer to the question whether PE is a genetic disorder. Thus, Chesley et al. [67] in the middle of the last century established that 26% of cases of severe PE are observed in daughters whose mothers had PE, and only 8% - in daughters-in-law.

PE is a multifactor pathology [78]. As it is known, the etiological and pathogenetic basis of multifactorial forms of pathology are functionally weakened variants of certain genes (genes of "predisposition"), the damaging effect of which is realized in certain environmental conditions [161,163]. Modern achievements in the field of molecular biology have now provided wide possibilities to study the structure of genetic predisposition to multifactorial diseases. The success of this type of research can ensure the identification of genes that control the synthesis of products (proteins, enzymes) directly involved in a particular pathological process. The selection of candidate genes is based on awareness of the pathophysiological mechanisms of specific multifactorial diseases [140,141]. Since the most important

manifestation of PE is an increase in blood pressure (BP), the study of the polymorphism of genes that regulate blood pressure presents promising perspectives [140,141].

There are examines showing that the trigger component for the improvement of PE is endothelial brokenness. In any case, there is still no agreement on how and why endothelial cell harm happens in PE [14,18,20].

Alongside unnatural birth cycle, fetal development limitation and untimely placental unexpectedness, PE alludes to the supposed "extraordinary obstetric conditions" (Great Obstetric Syndromes) related with placental pathology, which is brought about by shifting levels of renovating problems and check of the twisting veins in the progress zone and in myometrium. A huge job in the advancement of PE has a place with the placenta. This clarifies why this confusion of pregnancy grows solely after the time of pregnancy when placenta starts to work. This was affirmed histologically: trophoblast cells were identified in the circulatory system, just as in the lungs of pregnant ladies who passed on from PE [43,44]. Elements influencing placentation, implantation, and angiogenesis in PE are given below:

- encroachment of the association between humoral, move safety and immunological opposition;

- endothelial brokenness achieved by disbalance among angiogenic and antiangiogenic factors released by placenta;

- change of characteristics liable for blend of combinations that oversees vascular strain and angiogenesis in the essential trimester (improvement factors (GF)), integrins, angiotensin II);

- encroachment of the rule of extending and non-growing angiogenesis [12, 21];

- insufficiency of cytotrophoblast interruption [9]. Encroachment of GF creation can be a marker of these masochist conditions [12-14].

At present, the clinical act of Doppler investigation of blood stream in the uterine veins in early pregnancy in obstetrics is generally carried out. Most analysts accept that it is generally advocated at 11-14 weeks, when the principal screening

ultrasound is performed. There are different examinations that recommend that uterine corridor dopplerometry (UA) gives a more exact anticipation when acted in the subsequent trimester, as opposed to in the first [19]. As indicated by different creators, variances in the affectability, explicitness, and prescient worth of positive and negative Doppler brings about the main trimester are very wide. As indicated by L. Roop et al., R. Napolitano et al., mathematical upsides of the throb file (PI) in UA in the I and II trimesters of incubation in the social event of patients with exactly on schedule and late PE are in a general sense higher than in patients with physiologically happening pregnancy ($p < 0.0001$). All the while, merged PE screening, including maternal risk parts and dopplerometry of UA, has a higher affectability (80% for early PE, 45% for late PE) at a recurrence of 10% .Currently, four main hypotheses of placenta's role in the development of endothelial dysfunction: placental ischemia, immune maladaptation, the influence of low-density lipoproteins, and oxidative stress have been proposed. Some authors believe that vascular disorders initially occur in placenta, and then their generalization occurs and hemodynamic changes become systemic [35]. Other researchers believe that the primary cause of pathophysiological mechanisms in PE is a violation of adaptation of spiral arteries of the uterus to developing pregnancy, which ultimately leads to placental vascular insufficiency [1]. However, it has been proved that the reliable morphological criteria for PE are signs of delay in the first (6-8 weeks) and, more significantly, the second (14-16 weeks) wave of cytotrophoblast invasion into the walls of utero - placental arteries. The result of these disorders is the lack of adaptation of the spiral arteries to developing pregnancy with the preservation of all the main structures in them (endothelium, muscle membrane, elastic membranes) and the characteristic reaction to the impact of pressor impulses. These data were first published by J. Brosens and co-authors in 1972 and have since been repeatedly confirmed by other authors [1,5]. As pregnancy progresses, these morphofunctional features of spiral vessels predispose to spasm, a decrease in interstitial blood flow, and hypoxia [140].

Damage to the placenta's vascular system increases its permeability. In the conditions of local ischemia of the villous chorion, reduced interstitial blood flow and hypoxia, the ischemic placenta begins to produce factors that have the properties of endothelial toxins into the bloodstream. As pregnancy progresses, the release of cytotoxic factors becomes generalized. Violation of the placental barrier, which leads to increased placental permeability and activation of the processes of transplacental transfer, should be considered as a compensatory and adaptive mechanism for the action of hypoxia. It is shown that in PE, the development of compensation reactions in the placenta is more pronounced compared to the physiological course of pregnancy. These reactions are most expressed in women with severe PE. It is also noted that in this group of pregnant women there are minimal reserves for further development of compensatory and adaptive reactions of the placenta against the background of continuing hypoxia. In conditions of increasing hypoxia, the gap between the intensity of exposure to the pathological factor and the restoration of adequate transplacental exchange also increases [5,127,156].

It is known that maternal factor is also important in the development of PE, namely: arterial hypertension, kidney disease, overweight, diabetes, which are also based on endothelial dysfunction. The consequences of PE, combined with the presence of pre-existing endothelial dysfunction in comparison with those developing in the absence of concomitant extragenital pathology, are more serious. It has been proved that repeated births with a history of PE have a high incidence of arterial hypertension [1].

The outcomes of PE reduce the quality of life of women of reproductive age (high frequency of atherosclerosis, diabetes, cardiovascular diseases), as well as a fairly high frequency of violations of the physical, psychosomatic development of premature children. Thus, it is obvious that in a series of pathophysiological changes in PE, an important role is played by a violation of the function of the complicated vascular system, which provides a full and adequate exchange between fetus and mother. The connection of the maternal and placental pathways of PE pathogenesis

occurs in the final phase of reduced placental perfusion at the level of endothelial dysfunction general mechanism. In recent years, it has been established that much of the activity of this system can also be caused by the activity of angiogenic growth factors [1,97,98]. In addition, since preeclampsia cannot be prevented based only on the analysis of previous obstetric anamnesis, a significant amount of researches have been focused on identifying women at high risk for developing preeclampsia using biomarkers [123]. This will allow to conduct more intensive monitoring of high-risk groups, preventive interventions, and timely diagnosis and treatment [144].

The real meaning of PE research is coordinated to examine the fixation and proportion of proangiogenic and antiangiogenic factors, since it is notable that improvement of this multisystem issue depends on the disbalance of elements influencing angiogenesis [2,147]. Until now, there are two known components of new vessels age: vasculogenesis – the arrangement of the essential vascular organization again (the cardiovascular arrangement of the undeveloped organism) and angiogenesis - the development of new vessels from existing ones. The two cycles happen affected by extremely clear physiological guideline, when triggers and inhibitors work in offset with one another [2,147,24,35]. Ordinarily, angiogenesis inhibitors beat proangiogenic particles, hence forestalling the event of angiogenesis, and the expansion of endothelial cells coating the dividers of vessels is going extremely lethargic. The cycles remembered for the idea of angiogenesis have been concentrated exhaustively and shrouded in various audits [2,109]. The job of tissue hypoxia and expanded nitric oxide creation in the commencement of angiogenesis is additionally broadly known. There is a conviction that investigating of variables assuming a significant part in the advancement of toxemia will assist with anticipating the seriousness and level of obsessive changes. The immediate investigation of endothelial designs, which are one of the first to be harmed during the time spent toxemia happening, is presently not accessible [58]. The issue is that meta-examinations to assess biomarkers anticipating toxemia are adequately not. It is hard to think about investigations of specific biomarkers.

Until now, a few handfuls talked about factors have been depicted. It is set up that the accompanying substances merit exceptional consideration [5,8,121,175]:

1. Proangiogenic factors, one of the principle delegates of the group of which is vascular endothelial development factor (VEGF);

2. Antiangiogenic factors, including solvent FMS-like tyrosine kinase-1 (sFlt-1 or sVEGFR-1);

3. Solvent attachment atoms: intercellular grip particle 1 (ICAM-1) and vascular cell bond atom 1 (VCAM-1).

Hypoxia is the fundamental trigger of angiogenesis. At the point when the activity of proangiogenic factors surpasses the activity of antiangiogenic factors, endothelial cells go into a functioning state, which is designated "turning on angiogenesis". Endometrium, decidual film, and placenta are the wellsprings of angiogenic development factors that trigger angiogenesis through a mind boggling arrangement of middle people including transmembrane receptors with tyrosine kinase action [83]. It was tracked down that around 20 animating and 30 angiogenesis-repressing variables take an interest during the time spent vascular arrangement [41]. "Endurance" and apoptosis of endothelial cells are inverse, yet fundamental for angiogenesis measures, controlled by an equilibrium of proangiogenic and antiangiogenic factors [64]. Illnesses like coronary illness, diabetes, hypertension, lastly PE are described by deficient angiogenesis [100, 201]. The support of changed creation of various development factors in the advancement of PE has been demonstrated, since they are the primary transporters of the mitogenic sign of cells, and can invigorate or repress the development of tissues and veins [39]. Since solvent variables associated with the arrangement of veins are more accessible to use for research in the maternal circulatory system, and changes in their substance in mother's blood likewise reflect changes in their substance in embryo blood and tissues, the inspection of these elements in the blood of a pregnant lady is of major significance for understanding and anticipating infringement of vascular morphogenesis [49]. The most examined and quite compelling in contemplating the pathogenesis of PE are proangiogenic specialists: vascular endothelial development

factor (VEGF) and placental development factor (PlGF). The job of other development components and dynamic substances in the arrangement of utero-placental blood stream has not been adequately contemplated, since by far most of studies are acted in the late phases of pregnancy, and the basic occasions that decide the further course of pregnancy happen at the earliest reference point [41]. Vascular endothelial advancement factor, as of late known as vascular permeability factor (VPR), was first bound and portrayed in an assessment in 1983 by Senger and has a spot with the gathering of platelet improvement factors, taking into account glycoprotein [135]. The present moment, there are a couple of known sorts of VEGF – A, B, C, D, and E, the most mulled over is VEGF-A [118]. VEGF is the singular express mitogen of endothelial cells, it empowers their turn of events, movement, increase, and proteolytic activity, growing vascular permeability and progressing vasculogenesis and angiogenesis [94, 151, 192]. Along these lines, VEGF accepts a huge part in physiological advancement of placenta and vascular association of the villous stroma, similarly as coordinating the prominent properties of cytotrophoblast [73]. One of the essential components of VEGF in placenta in late pregnancy is to ensure extended sensibility of endothelial cells and to settle the vascular bed. Jojović M. et al. showed that adding VEGF to mouse cell culture strengthens placental tissue progression and extends placental district [152]. VEGF is conveyed by endothelial cells, fibroblasts, smooth muscle cells and provocative cells [131, 140]. It was found that close by the enrollment of angiogenesis, it increases vascular permeability, this limit is around numerous occasions higher than that of histamine [24, 48]. It's effect on cells is intervened by 3 sorts of express layer receptors: VEGF-R1 (FMS-like tyrosine kinase-1, Flt-1), VEGF-R2 (Flk-1/KDR) and VEGF-R3 (Flt-4), and the dissolvable kind of the first of them – sFlt-1 – is considered as an antiangiogenic factor [201]. It is understood that the most exceptional verbalization of VEGF-An and VEGFR-2 is seen in early pregnancy, and the improvement of VEGF-R1 is more genuine closer to full-term [44].

Vascular endothelial advancement factor receptor 1. Vascular endothelial advancement factor receptor 1 (VEGFR1) is a high proclivity tyrosine kinase

receptor. In patients with PE serum levels of sVEGFR1 are extended, a connection between's the centralization of sVEGFR1 and the level of proteinuria, platelet check at mother and clinical guidelines for the request for PE [127] was moreover taken note. Both early and late PE are connected with an extension in sVEGFR1. Regardless, in patients with early PE, the serum centralization of sVEGFR1 increases earlier and to a more significant degree than in the late kind of the ailment. Also, sVEGFR1 can anticipate early PE with more noticeable affectability and identity than late PE.

Solvent FMS-like tyrosine kinase. Thinking about the association of PlGF and VEGF with the development of trophoblast, it very well may be expected that a significant job in the advancement of PE is played by antiangiogenic factors that repress their capacities. PlGF and VEGF are restricting to the FMS-like tyrosine kinase receptor, which goes through elective joining from Flt-1 to dissolvable FMS-like tyrosine kinase (sFlt1), which instigates endothelial brokenness. Placental articulation of sFlt1 expansions in PE, and in certain examinations it is related with the seriousness of the infection [44]. There is verification that immense changes in the level of PlGF in PE are seen viably in the first or close to the beginning of the ensuing trimester. The level of sFlt1 extends 2-3 months before the start of clinical results of PE [9]. Both early and late PE are connected with changes in serum assemblies of sFlt1, with encroachment more expressed in the early headway of the affliction.

Pregnancy-related protein A - PAPP-A (pregnancy related plasma protein A). PAPP-A presentations it's natural worth through an insulin-like development factor. As a controller protein, it expands trophoblast intrusion, influences glucose and amino corrosive vehicle to the chorion and cell development [21, 27]. Decreased creation of RARP-A prompts expanded vascular obstruction in mother – placenta - embryo framework from early pregnancy. Pilalis et al. (2007), Spencer et al. (2008), Poon et al. (2009), just as exploration led by R. I. Shalina et al. (2009) showed decreased PAPP-A levels at 11-14 weeks in pregnant ladies who consequently created PE of different seriousness [9,15, 22, 23, 27, 28]. P. Meloni [21]

demonstrated essentially expanded danger (in each tenth perception) of PE in patients with RARP-A levels in the main trimester inside 0.53—1.08 MoM. Simultaneously, L. C. Poon and co-creators [25] introduced an examination of the course and result of pregnancy in 8061 patients. As per the aftereffects of the investigation, there was no increment in the recurrence of toxemia with a decline in the grouping of RARP-A. The affectability of just decreased PAPP-A levels for the finding of PE differs generally (from 6.5% to 23.1%) and stays at a low level. As per various creators, the blend of PAPP-A with adjusted Doppler boundaries in the uterine conduits at 11-14 weeks is of the best significance and expands the indicative chance of foreseeing the improvement of PE by 3-4 times [9,15, 22, 24, 26-28].

AGTR1 and AGTR2. It is realized that polymorphic variations in qualities encoding a few segments of the renin-angiotensin framework, like AGT (angiotensinogen), kidney (renin), ACE (angiotensin-changing over catalyst), and AGTR1 and 2 (angiotensin II receptors type 1 and 2) are essentially connected with renal cylindrical dysgenesis [25,35]. The main job in the improvement of fundamental hypertension is relegated to the polymorphism of the accompanying qualities: REN (renin quality), ACE (angiotensin changing over protein quality), AGT (angiotensinogen quality), AGTR1 (type 1 receptor quality to angiotensin II), AGTR2 (type 2 receptor quality to angiotensin II), BKR2 (type 2 bradykinin receptor quality), ADRB1 (β1-adrenoreceptor quality), ADRB2 (β2–adrenoreceptor quality), MTHFR (5.10 - methylentetrahydrofolate reductase quality), NOS3 (type 3 NO-cyntase quality) [30,32,33]. Renin-angiotensin-aldosterone, bradykinin and homocysteine frameworks are a mind boggling chain of biochemical responses associated with the guideline of pulse. Cells of the juxtaglomerular device of the kidney discharge into the blood renin compound (a result of the REN quality), which influences angiotensinogen (a result of the AGT quality) and converts it into angiotensin I [33,41,45]. This peptide, in its turn, fills in as a substrate for an angiotensin-changing over catalyst (a result of the ACE quality) that changes over angiotensin I (AT1) to angiotensin II (AT2). Angiotensin II demonstrations through angiotensin receptors of cells and is quite possibly the most impressive

vasoconstrictors. By restricting to angiotensin receptors (AT1 is the result of the AGTR1 quality; AT2 is the result of the AGTR2 quality), angiotensin II causes vasoconstriction, adding to expanded circulatory strain [115,116]. Under the impact of an angiotensin-changing over protein (a result of the ACE quality), the creation of aldosterone builds, it's expands the reabsorption of sodium particles in kidney tubules. What's more, angiotensin changing over catalyst, intervening its activity through type 2 bradykinin receptors (a result of the BKR2 quality), takes part in the inactivation of bradykinin and restrains the arrangement of NO – amazing vasodilatation factor. In this way, results of the renin-angiotensin-aldosterone and bradykinin frameworks, joined in a solitary biochemical chain, all the while partake in the guideline of circulatory strain. The aftereffects of a near investigation of the commonness of angiotensin II receptor qualities (AGTR1 and AGTR2) in the gathering of ladies with PE showed that the pervasiveness of the AA, AC and CC genotypes of the AGTR1 quality (A1166C) among ladies with PE and the benchmark group didn't contrast measurably. Concerning the AGTR2 quality (C4599A), it worked out that in the gathering of ladies with PE, the predominance of the AA genotype is lower than in the benchmark group (22.4% versus 60.4%, separately), however the distinctions are not genuinely huge; the predominance of AC genotype contrasts somewhat (36.7% versus 31.3%, separately); the commonness of CC genotype among ladies with PE is altogether higher than that among ladies in the benchmark group (40.8% versus 12.5%, separately) at p=0.009. Hence, it is set up that the transporter of a homozygous variation of the AGTR2 quality (C4599A) is a danger factor for the improvement of PE [8,10]

Endothelial brokenness is basic in the pathogenesis of blood poisoning [41], which is displayed by a development in "affectability" vascular divider to pressor effects of center individuals with coordinated decrease in the making of vasodilators, as nitric oxide (NO). Nitric oxide is the essential endothelial loosening up factor related with staying aware of vascular divider tone and thrombogenesis [10,14]. Set up endothelial NO synthase type 3 (NOS3, identical Enos) is related with blend of

NO in the endothelium and, along these lines, in the rule of vascular tone, circulatory system and heartbeat) [42].

At this moment, 3 allelic varieties of endothelial NO-synthetase (NOS3) quality are most viably thought of: 4a/4b in intron 5, 894g>T basic replacement in exon 7, and polymorphism of the publicist region of the quality – 786T>C. These polymorphisms are low-helpful, that is, on the off chance that they are accessible in the genotype, the affirmation of NOS3 quality decays. Lessened formation of endothelial NO-synthetase, in its turn, causes a decrease in centralization of nitric oxide in the circulatory framework, achieving diminished vasodilatation, which can be a critical instrument of vein hypertension. Data of relationship of low-utilitarian varieties of the endothelial NO-synthetase quality with various obstetric pathologies, which rely upon changes in vascular tone (PE, placental insufficiency, fetal improvement delay condition) are presented recorded as a hard copy [16,17]. As shown by the eventual outcomes of I. N. Fetisov, I. A. Panova, E. A. Rokotyanskaya, S. Yu. Ratnikova,E. V. Smirnova,N. S. Fetisov analyzes [17,26], women with pre-eclampsia have an extended pace of the allele-786C in the NOS3 quality. This is dependable with the eventual outcomes of different makers procured for different peoples and various ethnic social affairs, where the relationship of low-valuable alleles of the NOS3 quality with the plan of endothelial brokenness in patients with hypertension was set up [8,33]. The presence of polymorphisms of vascular tone-controlling characteristics (renin-angiotensin system and endothelial nitric oxide synthetase) grades to hypertension ensnarements which by and large forms the risk for pre-eclampsia. The perceived affiliations can be used as innate markers of tendency to the plan of pre-eclampsia, which will allow advantageous improvement of a peril assembling and cure of treatment and evasion measures.

Influence of preeclampsia development markers on placental morphological changes

Exploration of the placental bed started in the last part of the 50s of the last century, and was directed by two autonomous gatherings of scientists who utilized

different biopsy methods. Histological affirmation that the biopsy material was taken from the placental bed depended on the presence of trophoblastic cells, villi, or changed twisting corridors. In any case, the shortfall of these morphological segments didn't show that the example was not taken from the placental bed. Essential data about the job of cytotrophoblast intrusion in the utero-placental region (placental site) and deficient gestational rebuilding of the endo - and myometrial winding courses in PE was acquired in the 80's and portrayed in exemplary investigations [95]. There are two sorts of cytotrophoblast-interstitial (ICT) and obtrusive, which enters the lumen of endometrial conduits intravascular CT (IVCT). The greatest obtrusive action of ICT and IVCT is acknowledged at the fifth eighth seven day stretch of development, when their joined activity prompts emerged of the twisting courses and the arrangement of their mouth opening into major since space of placenta. Thus, during the main trimester, a few many utero-placental supply routes are shaped in the endometrium, which builds the progression of oxygen to the seriously developing organs of the undeveloped organism. After a specific decrease in toward the finish of the primary trimester, presumably because of the vanishing of the hypoxic boost, another ascent in intrusive action starts — its subsequent wave, arriving at a most extreme at the sixteenth—eighteenth week. It spreads mostly in the conduits of in the supply route of bordering myometrium. Various creators accept that the fundamental system of endothelium and elastomuscular parts of the dividers of myometrial sections of twisting courses annihilation is intravascular attack, when the CT moves against the progression of maternal blood. Nonattendance of gestational rebuilding of the myometrial portions of the winding courses is a critical connection in the pathogenesis of toxemia. This is expected to the shallow or abbreviated during its subsequent wave. The advancement of biomedical explores has essentially extended our insight into the placental bed. It is realized that in PE there is no physiological recreation (renovating) of winding corridors, which comprises of decidual and trophoblast-subordinate stages. These cycles happen in the decidual and transitive intersection zone (TJZ) of corridors myometrial fragments. In decidua, early vascular rebuilding

is essentially incompletely performed by leukocyte penetration, including uterine NK-cells that show up during early endometrial decidualization in the late luteal period of the cycle and group around winding supply routes toward the start of the renovating interaction [46]. NK-cells assume a significant part in trophoblast attack and renovating of twisting courses. Uterine NK-cells are a significant wellspring of angiogenic development factors and, not at all like fringe blood NK-cells, don't have cytotoxic action, particularly comparable to trophoblast cells, however they produce undeniable degrees of cytokines: γ-interferon (IFN-γ), interleukin (IL)- 10, granulocytmacrophagal province invigorating element (GM-CSF), leukemia-hindering component (LIF), tumor rot factor (TNF-α) [27,133].

Human trophoblast cells don't have the alleged old style human leukocyte antigens of class I of the principle histocompatibility complex (HLA-An and HLA-B), which are focuses for the cytotoxic activity of NK cells of fringe blood. Simultaneously, trophoblast cells express HLA-C, HLA–E, and HLA – G, which associate with NK cells of the endometrium and decidual tissue and are engaged with the advancement of pregnancy. Early vascular smooth muscle disruption likewise happens in PJZ of myometrium, where NK cells are missing. Accordingly, NK cells assume a significant part in trophoblast intrusion and rebuilding of twisting courses. NK cells help supplant endothelial cells in the winding corridors with trophoblast cells, which permits the twisting courses to give always expanding blood stream needs in a physiologically creating pregnancy. In any case, in PE, articulation on decidual NK cells of the AA variation the executioner cell immunoglobulin-like receptors (KIR AA) and on trophoblast cells - HLA – C2 is regularly discovered, which prompts deficient NK cell work, diminished creation of vascular endothelial development factor (VEGF) and IFN-γ, and hindered rebuilding of twisting veins. Rather than decidual tissue, vascular rebuilding in myometrium is upgraded by the presence of interstitial trophoblastic cells and angiogenic development factors confined in them, which add to the cycle of early vascular renovating [75]. Solely after this phase of vascular complication, endovascular trophoblasts show up in the winding veins, trailed by their consideration in the vessel divider. During this

interaction, the endothelium appears to vanish, while the smooth muscle and versatile layers of vessels are additionally divided because of trophoblast-prompted apoptosis of endothelial and smooth muscle cells [148]. In PJZ of myometrium, there are 3 unique sorts of winding corridor change problems: fractional change, no change, and no change with obstructive harm [112]. The depicted highlights of trophoblastic intrusion, taken as a premise, give significant data about the development of damaged placentation in future.

Winding vein redesigning can be portrayed as a multi-stage measure that happens toward the start of pregnancy [112,60]. Two principle factors are being deciding in the blood stream from mother to placenta: the size of placental bed, which depends from the quantity of twisting conduits speaking with interstitial space, and the level of physiological change of winding courses, which is generally communicated in the focal point of the placental bed. Investigations of the placental bed utilizing biopsy affirm that the vast majority of winding conduits go through a total change in PJZ of the myometrial portion, which is reliable with the aftereffects of ultrasound contemplates. Studies in the second trimester of pregnancy utilizing beat Doppler technique with staining showed that the obstruction of blood stream in the focal area of the placental bed is not exactly in the fringe. The consequences of three-dimensional ultrasound Doppler screening concentrate with the assurance of the placental bed vascular file in the main trimester in 4325 pregnant ladies in examination with the information of blood stream in the uterine conduits at 12 and 22 weeks, the volume of placenta and the grouping of PAPP-An uncovered a high prognostic meaning of deciding the placental bed vascular list in the advancement of serious pregnancy intricacies, including PE [84].

In extreme PE, just some of twisting veins in the focal point of the placental bed are totally changed into PJZ of the myometrial portion. Also, obstructive supply route harm (like apoplexy, intense atherosis) can prompt or add to inadequate placentation. The placental bed of patients with PE is described by diminishing the quantity of winding courses with a changed myometrial portion. This portion saves the hypertrophied construction of the smooth muscle layer, in spite of the presence

of interstitial trophoblasts, here and there even in overabundance sum [138]. The decided changes are more articulated in myometrial than in decidual portions. The placental region in patients with PE and fetal development limitation (FGR) is like that portrayed in patients with PE. It is portrayed by countless untransformed twisting myometrial veins, which regularly have obstructive harm, like intense atheroma and apoplexy. Intense atheroma isn't just a trademark harm of little decidual corridors, yet in addition a common harm of winding myometrial veins in PE and FGR. Hindered profound placentation in PE and FGR prompts the presence of focal zones with changed supply routes. The quantity of interstitial extra villous trophoblastic cells is diminished in PE and, on the other hand, expanded in the instances of fetal development restriction(FGR) [76,145]. The degree of the impeded change of twisting supply routes of myometrium and the presence of its obstructive vascular harms clarify the successive blend with placental areas of dead tissue. 90% of twisting veins in PJZ myometrium of the placental region are totally changed in the typical course of pregnancy. Examination of certain clinical circumstances and the level of seriousness of twisting supply route rebuilding problems recommended that the interaction of cyclic decidualization and ensuing period fills in as a component for setting up the uterus for profound placentation. Both period and implantation are fiery conditions that cause certain physiological ischemic-reperfusion tissue pressure. As indicated by the creators, normal feminine cycle can be urgent in shielding the uterine tissue from profound provocative and oxidative pressure related with profound placentation. This interaction is designated "preconditioning" [11]. The absence of satisfactory "preconditioning" may clarify why the first pregnancy in quite a while under 20 years old is related with a critical danger of unfavorable results (preterm birth, FGR and PE), contrasted with the first pregnancy in quite a while following 20 years old who have encountered "preconditioning". Then again, placental irregularities even at preclinical stages are available in patients with PE and FGR. In such conditions, hindered profound placentation is portrayed by the presence of untransformed twisting courses of the PJZ, which can be influenced by obstructive vascular wounds. Blood vessel wounds

like intima hyperplasia, intense atheroma, and apoplexy can create in these supply routes in an exceptionally brief timeframe, even with slight hypertension. The blend of obstetric entanglements and different vascular illnesses in the connective zone of myometrium demonstrates that "preconditioning" in this zone during treatment can be a critical factor for fruitful implantation and typical placentation. At present, there is solid proof that the pathology of the placental bed because of ischemia and immunologically intervened measures prompts different intricacies of pregnancy (PE, FGR, untimely birth, untimely break of fetal films in untimely pregnancy, placenta suddenness). Furthermore, the improvement of one of these complexities relies upon hereditary components, natural elements, pregnancy, length and predominance of the ischemic zone. What's more, the assurance of the clinical aggregate and the seriousness of its appearances rely upon the state and cooperation of mother-placenta-embryo framework [123,97]. The set number of studies and surveys, and the absence of set up models for isolating early and late PE, recommends that extra exploration is expected to decide if these two structures are independent illnesses or phases of a similar interaction. Likewise, the majority of the investigates toward this path has a place with placental exploration, however a couple of studies are given to the investigation of placental site tissues. In such manner, thinking about the cozy relationship of the placenta and placental bed, the absence of definite information on changes in the tissues of the placental bed and placenta's condition, contingent upon various variations of the course of PE, the presence or nonappearance of going with fetal development limitation disorder, further investigates toward this path are required.

Prevention of severe preeclampsia / eclampsia

Researchers of various strengths (cardiologists, obstetricians, gynecologists, geneticists) have been giving a lot of consideration to the issue of PE for a long time, yet notwithstanding the outcomes got, there is still no exact data about the causes and pathogenesis of the infection, solid lab techniques for conclusion have not been grown at this point, so there are no compelling proportions of avoidance and

treatment. Unmistakably mediations ought to be taken as ahead of schedule as could be expected, preferably before pregnancy. Regardless of the way that there is solid information on hazard factors for PE, there is still no data in writing about straightforward, protected, non-intrusive and cheap screening techniques that would be preventive for extreme PE. Previously, such strategies as severe bed rest and a sans salt eating routine were demonstrated, which later end up being insufficient. Then, at that point there were deals with the job of ascorbic corrosive (nutrient C) and different nutrients in the avoidance of PE. It was tracked down that a diminishing in blood plasma of nutrient C, E and β-carotine is related with extreme PE [21,22]. In any case, these wonders were clarified by the body's reaction to oxidative pressure, yet not by an absence of supplements. Enhancements of fish oil or omega-3 polyunsaturated unsaturated fats showed a reduction in prostacyclin levels (an increment of this pointer happens in PE) [45]. Nonetheless, it has not been set up whether gentle or serious PE can be forestalled by these added substances. The supplementation of specific minerals (zinc, magnesium, cadmium, selenium, zinc) in the avoidance of PE has clashing information. For instance, the convergence of zinc in plasma, red platelets and placental tissues in pregnant ladies with PE diminishes. One huge randomized clinical preliminary showed that magnesium supplementation doesn't influence the advancement of PE. This was because of the way that oral magnesium consumption doesn't have a decent ingestion impact [48,52]. Studies have shown that the centralization of calcium in plasma of patients with PE is altogether lower than in plasma of solid ladies. A progression of randomized controlled clinical preliminaries showed the advantages of calcium supplementation in 4500 ladies at okay of PE [47]. Lastly, there is an entire series of studies on PE anticipation with prescription. Preventive remedies of diuretics and hypotensive medications have shown zero viability, yet in addition critical damage to the soundness of pregnant ladies [49,52].

A few randomized fake treatment controlled twofold visually impaired clinical preliminaries have been directed since 1993, including 22,000 ladies, who have demonstrated the advantages of low-portion ibuprofen in PE counteraction and

the shortfall of antagonistic impacts for mother and baby [125,132]. By the by, the writing doesn't uphold utilizing low-portion ibuprofen to forestall PE in generally safe ladies. Preventive utilization of ibuprofen can lessen the advancement of PE by 13% in ladies at high danger of its creating. [132]. Since PE is related with coagulation problems, it was recommended to treat with anticoagulants to forestall PE. Examination results have shown that in a gathering of ladies at high danger of PE, joined organization of ibuprofen and low-sub-atomic weight heparin (LMWH) can further develop pregnancy results (low birth weight and perinatal results) [142] In 2019, a multicenter randomized controlled preliminary was led in Uzbekistan [106,107] showed that ideal therapy of ladies with ongoing infections muddled by placental brokenness and the danger of toxemia with incorporation of L-arginine in the treatment routine in the second and early third trimester of pregnancy works on perinatal results, improves utero-placental blood dissemination, decreases the movement of gentle to serious PE, which permits to delay pregnancy until conveyance.

Summing up the writing audit, it ought to be noticed that there are no clinically huge techniques for anticipating and forestalling PE. The solitary effective strategy for treatment is the convenient end of pregnancy. In such manner, in present day conditions, the lone genuine approach to decrease extreme types of PE and its inconveniences is expectation, early finding, improvement and execution of an unmistakable calculation for checking and treatment, contingent upon the seriousness of PE.

Risk factors for PE

Although preeclampsia occurs primarily in first pregnancies, a woman who had preeclampsia in a previous pregnancy is seven times more likely to develop preeclampsia in a later pregnancy.

Other factors that can increase a woman's risk include:

- Chronic high blood pressure or kidney disease before pregnancy
- High blood pressure or preeclampsia in an earlier pregnancy

- Obesity. Women with overweight or obesity are also more likely to have preeclampsia in more than one pregnancy.
- Age. Women older than 40 are at higher risk.
- Multiple gestation (being pregnant with more than one fetus)
- African American ethnicity. Also, among women who have had preeclampsia before, non-white women are more likely than white women to develop preeclampsia again in a later pregnancy.
- Family history of preeclampsia.

Preeclampsia is also more common among women who have histories of certain health conditions, such as migraines, diabetes, rheumatoid arthritis, scleroderma, urinary tract infections, gum disease, polycystic ovary syndrome, multiple sclerosis, gestational diabetes, and sickle cell disease.

Preeclampsia is also more common in pregnancies resulting from egg donation, donor insemination, or in vitro fertilization.

Table 1.

Risk factors for PE

Risk factors	Main group (n=132); abs (%)	Comparison group (n= 40); abs (%)
First pregnancy/first labor	72(54,5%)	20(50%)
Age <20 years	35(26,5%)	5(12,5%)
Age >35 years	9(6,8%)	-
Multiple pregnancy	2(1,5%)	-
Polyhydramnios	3(2,3%)	-
Preeclampsia during last pregnancy	40(30,3%)	1(2,5%)
Chronic arterial hypertension	7(5,3%)	-
DM	1(0,8%)	-

Obesity	38(28,8%)	-
Urinary tract infection (UTI)	55(41,7%)	3(7,5%)
Chronic inflammatory diseases of the respiratory system	71(53,8%)	-
Chronic hepatitis	5(3,8%)	-
ARVI during this pregnancy	17(12,9%)	3(7,5%)
PCOS	12(9%)	-
Benign tumors/tumor-like formations of the uterus and uterine appendages	27(20,5%)	3(7,5%)
Pregnancy after infertility treatment	25(19%)	2(5%)
Intergenetic interval < 2 years	3(22,7%)	12(30%)
Intergenetic interval >5 years	37(28%)	2(5%)
Spontaneous abortions	17(12,9%)	9(22,5%)
Undeveloped pregnancy	15(11,4%)	-
Mortinatality/neonatal mortality	7(5,3%)	1(2,5%)
Vomiting of pregnant women	29 (22%)	3(7,5%)
Insufficient follow-up in antenatal period	103(78%)	27(67,5%)

CHAPTER III. PROGNOSIS AND EARLY DIAGNOSIS OF PREECLAMPSIA (RESULTS OF OWN RESEARCH)

The course of preeclampsia, endothelial function, gene polymorphism, and the state of the placental bed

The course of PE, pregnancy and delivery outcomes were studied in 132 patients admitted to maternity complex No. 2 in 2017-2020.

Upon admission, 87 women (65.9%) were diagnosed with mild PE, and 45 (34.1%) with severe PE. Thus, the patients were divided into 2 subgroups according to the severity of the main disease – O1 and O2.

The age of pregnant women ranged from 18 to 38 years, the average value was 27.5=0.5 years. At the same time, in the O1 subgroup, the average age was 24.7±1.2 years, and in the O2 subgroup – 28.9 ±0.4 years. By the place of residence, the patients were distributed as follows: O1: city 53 (60.9%), village 34 (39.1%); O2 :city 20 (44.4%), village 25(55.6%)

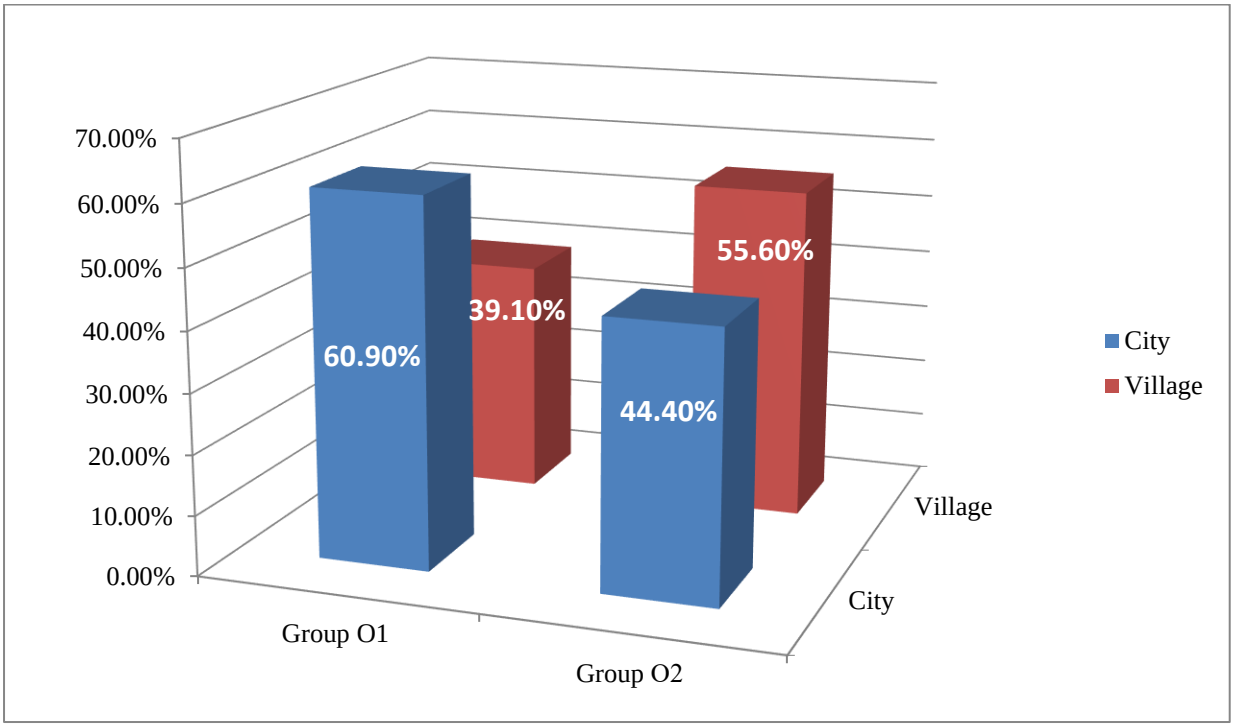

Figure 1. Distribution of patients by place of residence.

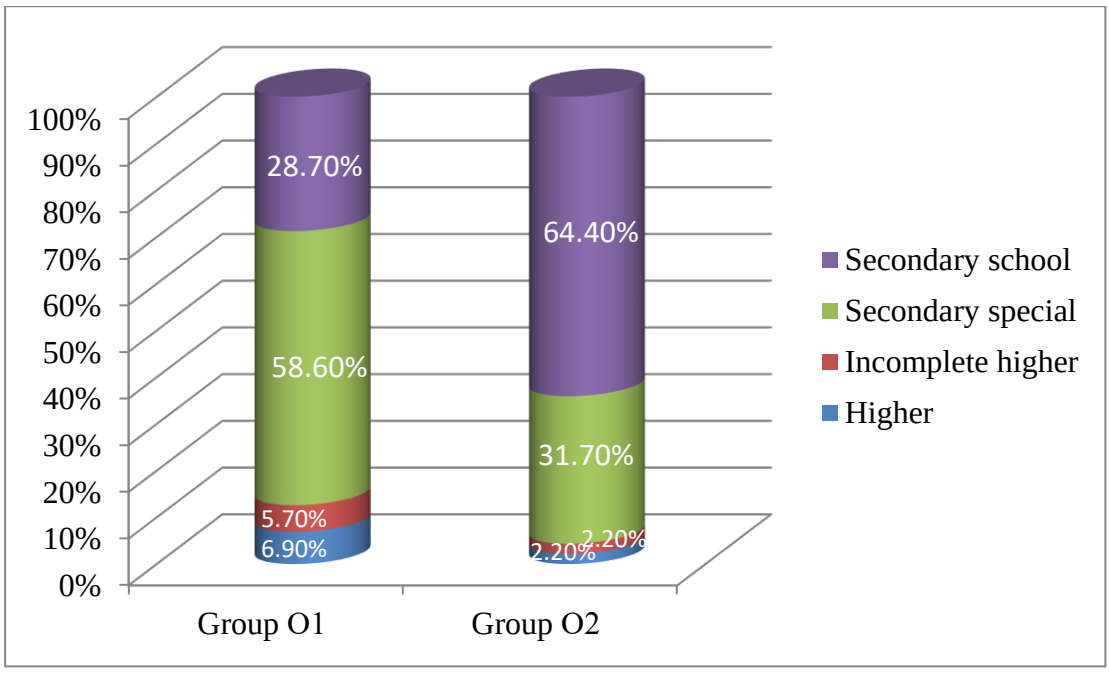

Figure 2. Education of the examined patients with PE.

O1 higher education -6 (6.9%), incomplete higher education - 5 (5.7%), secondary special education – 51 (58.6%), secondary school (9 classes) – 25 (28.7%). O2 higher – 1 (2,2%), incomplete higher - 1 (2,2%), secondary special – 14 (31,7%), secondary school (9 classes) -29(64,4%). Data presented in the figure 2 allow to conclude that incidence of both mild and severe PE increases in women with less education. At the same time, the frequency of severe forms was more frequent in patients without education.

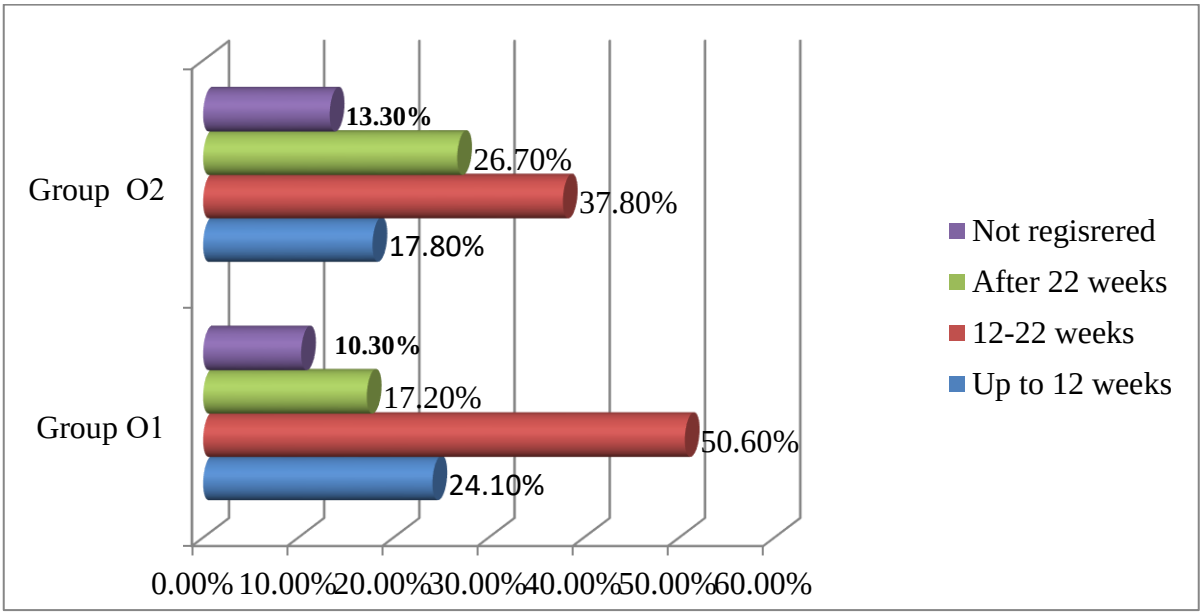

Figure 3. Terms of registration of patients with PE

Figure 3 shows the terms of registration of patients with PE. O1 – up to 12 weeks - 21 (24.1%);12-22 weeks - 44 (50.6%); after 22 weeks – 15 (17.2%); were not registered – 9 (10.3%). O2 up to 12 weeks - 8 (17.8%); 12-22 weeks – 17 (37.8%); after 22 weeks – 12 (26.7%); were not registered – 6 (13.3%). It should be noted that 15 (11.3%) patients with subsequently developed PE were not observed at all during pregnancy. These women were examined for the first time with an already established diagnosis of PE. At the same time, a severe form of the disease developed in 13.3% of women. Table 2 shows the terms of pregnancy during hospitalization of patients with PE diagnosis.

Table 2.

Terms of pregnancy during hospitalization of patients with PE diagnosis.

Term of pregnancy	Subgroup O_1	Subgroup O_2	$\chi 2$	P
Up to 34 weeks	16(18,4%)	22(48,9%)	**13,457**	**0,000**
34-37 weeks	62(71,3%)	20(44,4%)	**9,066**	**0,003**
38 weeks and more	9(10,3%)	3(6,7%)	**0,486**	**0,486**

The table shows that in the early stages of pregnancy severe PE is more often manifested. The mild form in 71.3% of cases was manifested in more favorable for delivery terms of pregnancy. In 9% of cases, PE was diagnosed during full-term pregnancy.

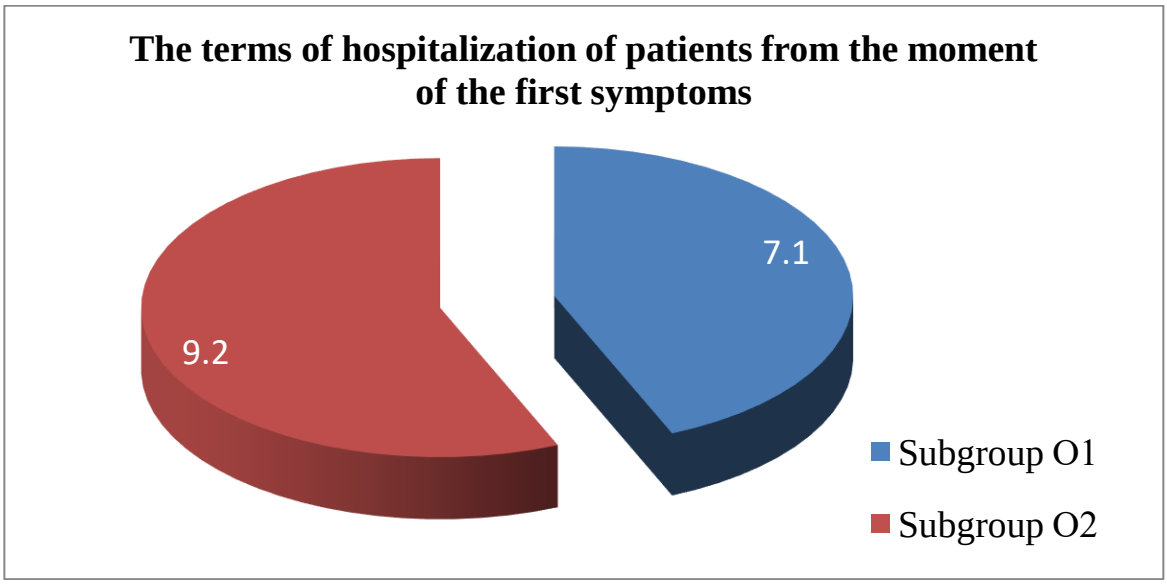

Figure 4. The terms of hospitalization of patients from the moment of the first symptoms of PE.

Accordingly, the condition of the patients of the O1 subgroup at admission was regarded as a moderate condition. The condition of the patients of the O2 subgroup is considered to be severe. The terms of hospitalization of patients from the moment of the first symptoms of PE are shown in Figure 4.

As can be seen, from the moment of the first symptoms of PE to hospitalization, more than 1 week passes, which indicates a late treatment of patients, insufficient careful management of their condition in the level of primary care and, consequently, the manifestation of a more severe form of the disease.

For the clinical diagnosis of PE, the presence of two main symptoms – arterial hypertension and proteinuria-was taken into account. Arterial hypertension was determined by measuring B/P on both hands. If the patient's condition allowed (there were no threatening symptoms – severe headache, nausea, vomiting, convulsive readiness), B/P was measured twice with an interval of 4 hours. The severity of hypertension was assessed on the basis of National Standards for the Management of Pregnancy and Childbirth in various obstetric conditions [1]. The assessment of proteinuria was carried out, diagnosing it at the level of 0.3 g/day or more. In the diagnosis of severe PE, the presence of other dangerous symptoms was taken into account, regardless of B/P level and proteinuria. Table 3 shows the main clinical manifestations of PE.

Table 3.

Main clinical manifestations of PE in observed women.

Symptoms	Subgroup O_1	Subgroup O_2	$\chi 2$	P
AH+proteinuria	87(100%)	45(100%)	-	-
AH+proteinuria+ anasarca±ascites	0 (0%)	16(35,6%)	**35,200**	**0,000**
AH+proteinuria +headaches	0 (0%)	11(24,4%)	**23,200**	**0,000**
AH+proteinuria + hearing/vision impairment	0 (0%)	11(24,4%)	**23,200**	**0,000**
AH+proteinuria + epigastric pains	0 (0%)	6(13,3%)	**12,152**	**0,000**
AH+proteinuria +nausea/vomiting	0 (0%)	4(8,9%)	**7,975**	**0,005**

Table 3

B/P value in both subgroups.

B/P value in both subgroups	Subgroup O_1	Subgroup O_2	P
B/P value	140/90-159/99 mmHg	160/110-180/120 mmHg	-
Average systolic	147,2±8,5 mmHg	167,1±5,2 mmHg	**<0,05**
Average diastolic	89,9±5,1 mmHg	110,5±5,1 mmHg	**<0,01**

While both systolic and diastolic blood pressure indicators are important in themselves, it is also important to know the average blood pressure (MAP –Mean Arterial Pressure) in order to find out how well the organs are supplied with blood. We calculated this value using the following formula: **(2 (DBP)+ SBP)/3**, where DBP is the diastolic blood pressure and SBP is the systolic blood pressure.

Table 4

Average Blood pressure (MAP –Mean Arterial Pressure) in both subgroups.

Average Blood pressure (MAP –Mean Arterial Pressure**) in both subgroups**	Subgroup O_1	Subgroup O_2	P
	109,2±5,4 mmHg	129,4±7,1 mmHg	**<0,02**

It is known that the MAP in healthy people is in the range of 90-100 mm Hg. . If MAP is 105 mm Hg and above, arterial hypertension is diagnosed. In our study, MAP was 109.2± 5.4 mmHg in O1 subgroup and 129.4±7.1 mmHg in the O2 subgroup. One of the manifestations of severe PE, we considered the restriction of fetal growth according to ultrasound data.

Table 5

Matching the correspondence of fetus size to the gestational age.

	Patients with mild PE	**patients with clinical symptoms of mild PE**	**patients with clinical symptoms of severe PE**	$\chi 2$	P1	$\chi 2$	P2

Corresponds to the gestational age	45 (51,7%)	0	15(33,3%)	60,698	0,000	4,046	0,044
FADS I degee	0	22 (25,3%)	0	25,184	0,000	-	-
FADS II degee	0	0	18 (40%)	-	-	40,295	0,000
FADS III degee	0	0	12 (26,7%)	-	-	25,520	0,000

It should be noted that in patients with clinical manifestations of severe PE, we did not find fetal development arrest syndrome (FDAS) I degree. The correspondence of fetal size to gestational age in this subgroup occurred in 15 (33.3%) patients, which is significantly lower than in the O1 subgroup.

In the structure of FDAS in patients with clinical manifestations of severe PE, the asymmetric form prevailed - 83.3% (25) of cases, the symmetrical form was found in 16.7% of cases (5). Mixed form of FDAS was not detected. The development of FDAS accounted for the following periods: up to 30 weeks – in 8 (17.8%); 30 -32 weeks-in 8 (17.8%), 32-34 weeks-in 4 (18, 2%); 34-36 - in 9 (40.9%), 36-38 weeks - in 1 (4.5%) pregnant women.

Ultrasound placentography revealed its premature maturation only in 2 (9%) pregnant women in terms of more than 36 weeks of pregnancy. Low water content was also noted in 9%, in three patients 13.6% polyhydramnios was diagnosed and intrauterine infection of the fetus was confirmed after birth.

Thus, in the majority of FADS I cases, the normal echographic structure of placenta was detected - 90.9% (20) and the normal amount of amniotic fluid – 77.3% (17).

Cardiotocographic examination revealed only signs of initial fetal hypoxia just in 22.7% (5 patients). Doppler study revealed that the indicators were similar to uncomplicated pregnancy. In the structure of FADS II, the asymmetric form prevailed in 75% (6) of the observations, the symmetric and mixed forms occurred in one case each, which was 12.5%. In the group with FADS II degree, its initial diagnosis occurred at periods up to 28-30 weeks of gestation in 2 (25%), 30 - 32 weeks. - in 3 (37.5%), 32-34 - in 2 (25%) and after 36 weeks of gestation in 1 (12.5%) pregnant women. It is noteworthy that ratio of late FADS development (after 36 weeks) decreases up to 12.5%, and the ratio of its early development, up to 32 weeks, increases significantly — 62.5%.

Ultrasound examination of the placenta revealed its "premature" maturation in 3 (37.5%) pregnant women. "Premature" maturation of the placenta, reflecting the involutive-dystrophic processes occurring in it, was detected at 32-35 weeks of pregnancy. Cardiotocographic signs of mild and moderate chronic intrauterine hypoxia was detected in 6 (75%) patients with FADS II degree. It should be emphasized that subcompensation of fetoplacental complex and the fetus is characterized not only by an increase in the frequency of chronic intrauterine fetal hypoxia detection, but also by an increase in its severity. Thus, the initial signs of hypoxia according to cardiotocography were detected in 4 (50%) pregnant women, moderate hypoxia - in 2 (25%) women.

Lack of amniotic fluid was diagnosed in 4 (50%) women. At the same time, all of these patients had pronounced lack of amniotic fluid (the amniotic fluid index is less than 5), all of them had long-term pre-eclampsia. Polyhydramnios with a combination of FADS and intrauterine infection was diagnosed in one pregnant woman. The normal echographic picture of the placenta and the amount of amniotic fluid were detected in 3 (37.5%) cases.

In the case of FADS II, a Doppler study revealed a combination of blood flow disorders in uterine arteries and the umbilical cord artery. Examination of fetal arterial circulation in FADS II revealed violations of blood flow in the fetal aorta and the middle cerebral artery, which indicates the centralization of fetal blood flow

as a universal protective and adaptive mechanism in response to the deterioration of the conditions of its intrauterine existence.

Thus, the combination of PE and several background pathologies is typical for a severe form of FADS, emphasizing the general pathogenetic background of the adaptive capabilities of mother and fetus.

The structure of FADS III in our study is fundamentally different from that of FADS I and FADS II. Thus, mixed form was predominant form in both patients. The initial development of PN occurred before 32 weeks of gestation. Chronic intrauterine hypoxia was detected in all pregnant women with FADS III. At the same time, in both cases, there was an antenatal death of the fetus. It should also be noted that signs of chronic fetal hypoxia according to CTG data appeared early, already up to 34 weeks.

Ultrasound placentography revealed its premature maturation and other signs of degenerative changes in both pregnant women of this subgroup. Normal echographic picture of the placenta and the amount of amniotic fluid at this severity of FADS was not found. The most pronounced changes in FADS III were found both in mother-placenta-fetus system and in the arterial and venous blood flow of fetus.

During the Doppler study of uteroplacental, fetal and intraplacental blood circulation in pregnant women of this subgroup, we found that all patients had disorders in the system of uteroplacental, fetoplacental and intraplacental blood flow. It should be noted that cases of FADS III with impaired venous blood flow occurred on the background of severe pre-eclampsia.

Doppler study changes in hemodynamics in FADS III were revealed in all parts of the fetal and utero-placental blood flow. Signs of fetal blood flow critical condition were seen in this degree of syndrome severity. These hemodynamic changes indicate an extreme tension of the compensatory mechanisms of the fetoplacental complex in severe PE, which do not allow the fetus adequately adapt to progressively deteriorating conditions of intrauterine existence, which is manifested by severe fetal growth retardation with severe hypoxia, which is prognostically unfavorable. Table 6 shows the main biochemical and hemostasiological indicators of patients with PE.

Table 6.

Main biochemical and hemostasiological indicators of patients with PE.

Indicator	Subgroup O_1 n=87	Subgroup O_2 n=45	Control n=35	P_1	P_2
Bilirubin (mcmol/l) Total	18,3±0,6	24,0±0,9	12,3±0,4	**<0,001**	**<0,001**
Direct	5,6±0,3	6,9±0,3	3,1±0,2	**<0,001**	**<0,001**
Indirect	14,6±0,8	17,4±0,9	10,8 ± 0,6	**<0,001**	**<0,001**
ALT un/l	34,7±1,7	64,3±2,3	24,8±1,2	**<0,001**	**<0,001**
AST un/l	32,0±1,7	63,0±3,2	25,2±1,1	**<0,001**	**<0,001**
Residual nitrogen mmol/l	26,5±1,3	29,2±1,4	18,5±0,7	**<0,001**	**<0,001**
Creatinin **mcmol/l**	83,4±4,7	106,6±5,9	64,7±4,9	**<0,01**	**<0,001**
Blood sugar mmol/l	5,9±0,2	6,5±0,3	4,5±0,2	**<0,001**	**<0,001**
Total protein g/l	62,1±3,0	54,6±2,5	73,2±4,0	**<0,02**	**<0,001**
Thrombocytes thousands Un/mcl	226,8±11,1	138,9±7,8	302,9±12,1	**<0,001**	**<0,001**
INR units	0,9±0,1	0,6±0,1	1,0 ± 0,1	**>0,5**	**<0,01**
APTT sec**.**	24,4±0,8	19,8±0,7	27,7±1,0	**<0,01**	**<0,001**
Fibrinogen g/l.	2,5±0,1	2,1±0,1	2,8± 0,1	**<0,05**	**<0,001**
Blood coagulation time min	6,4±0,3	5,5±0,2	8,7±0,5	**<0,001**	**<0,001**

Note: P1 is an indicator of the reliability of the compared values in two subgroups. P2 - an indicator of the reliability of the compared values with the control group

As can be seen from the table, the main biochemical indicators (bilirubin, ALT, AST, total protein) in the group of women with severe PE were significantly higher compared to the control group and the O1 group ($p < 0.001$). When

comparing similar indicators of the O2 group, it was noted that these indicators are somewhat increased, but no significant differences were found. As for the indicators of the hemostatic system – they were significantly higher in both groups than in the control group. From this, it can be concluded that hemostatic parameters can also be a marker of PE development. The outcomes of this pregnancy are presented in table 7.

Table 7.

Outcomes of pregnancy in women with PE.

Pregnancy outcome	Subgroup O_1	Subgroup O_2	$\chi 2$	P
Labor in time	78(70%)	3(6,7%)	**47,803**	**0,000**
Preterm labor	9(10,3%)	42(93,3%)	**12,279**	**0,000**
Labor per vias naturalis	52(59,8%)	2(4,4%)	**14,835**	**0,000**
Cesarean section (CS)	35(40,2%)	43(95,6%)	**3,255**	**0,071**
- uterus atony	3(3,4%)	17(39,5%)	**29,620**	**0,000**
- ligation of the uterine arteries	0(0%)	4(9,3%)	**7,975**	**0,005**
- ligation of the internal iliac arteries	2(2,2%)	7(16,3%)	**8,204**	**0,004**
- uterus extirpation	1(1,1%)	6(14%)	**8,767**	**0,003**
- Kuweler's uterus	0(0%)	2 (4,7%)	**3,926**	**0,048**
Postpartum eclampsia	-	1(2,2%)	**1,948**	**0,163**
Postpartum septic complications	1(1,1%)	4(8,8%)	**4,875**	**0,027**

As can be seen from the presented table, the percentage of iatrogenic preterm labor increased in patients with severe PE – 93.3%. At the same time, in 95.6% of cases, the delivery was completed by caesarean section. The abdominal delivery itself in 3.3% of cases ended with extirpation of the uterus due to premature detachment of the normally located placenta (PDNLP), uncontrolled bleeding on the background of uterine atony and DIC syndrome. Combined spinal-epidural anesthesia (in 33 patients of both groups – 42.3%) and long–term epidural anesthesia (in 26 patients-33.3%) were chosen as the main method of anesthesia during Cesarean section. In 19 patients (24.4%), general anesthesia was performed under

artificial lung ventilation (ALV) due to the severity of the condition, severe blood coagulation disorders, Couveler's uterus, and developed DIC syndrome. All labors were performed per vias naturalis under epidural anesthesia.

The time from the moment of admission to delivery in the O1 subgroup was 6.5±1.7 days. That means that due to enabling condition of mother and fetus, the pregnancy was tried to be prolonged to as close as possible to the full-term period. While in O2 subgroup, the time from the moment of hospitalization to delivery was significantly less ($p< 0.001$) and amounted to 1.3 ±0.5 days. Table 8 shows data on the amount of blood loss in both groups of patients.

Table 8.

Blood loss in labor.

Blood loss amount	Subgroup O_1(n=87)		Subgroup O_2 (n=45)		$\chi_1 2$	P1	$\chi_2 2$	P2
	Natural labor	Cesarean section	Natural labor	Cesarean section				
Up to 350 ml	44 (50,6%)	0	0	0	**34,138**	**0,000**	-	-
350-500 ml	8 (9,2%)	0	2(4,4%)	0	**0,956**	**0,328**	-	-
500-1000 ml	0	32(36,8%)	0	3(6,7%)	-	-	**13,805**	**0,000**
1000-1500 ml	0	2(2,3%)	0	23(51,1%)	-	-	**46,030**	**0,000**
More than 1500 ml	0	1(1,1%)	0	17(37,8%)	-	-	**33,788**	**0,000**

P1 - reliability of differences in the blood loss amount in natural labor in the compared subgroups, P2-the significance of differences in the blood loss amount in Caesarean section in the compared subgroups

The average blood loss in natural childbirth in both subgroups was 315.5±140.5 ml. In abdominal delivery – in subgroup O1 -1100.0± 120.5 ml, in subgroup O2 – 1580.4 ± 220.5 ($p< 0.01$). It should be noted that only in patients with mild PE, physiological blood loss occurred in 50.6% of cases during delivery per vias naturalis. Pathological blood loss occurred in all other cases, which required

transfusion of blood reparations in 88.9% of cases in patients with severe PE. Table 9 shows the morphofunctional parameters of newborns from mothers with PE.

Table 9.

Newborns morphofunctional parameters.

Newborns weight	**Subgroup O_1 (n=87)**	**Subgroup O_2 (n=45)**	$\chi 2$	P
2500,0 gr and more	69 (79,3%)	7(15,6%)	49,355	0,000
1500,0 г – 2499,0 gr	17 (19,5%)	30(66,7%)	28,729	0,000
1000,0г -1499,0 gr	1(1,1%)	5 (11,1%)	6,783	0,009
Less than 1000,0 gr	0	3 (6,7%)	5,935	0,015
Apgar score (by time)				
1 minute	6,3±0,4	5,2±0,3		<0,05
5 minute	7,5±0,4	6,4±0,3		<0,05
Status in points				
10-8	9(10,3%)	-	4,996	0,025
7-5	77(88,5%)	23(51,1%)	22,583	0,000
4-1	1(1,1%)	20(44,4%)	41,557	0,000
Artificial lung ventilation	1(1,1%)	4(8,9%)	4,875	0,027

It ought to be noticed that in two cases, patients with extreme PE had antenatal fetal passing, which was 1.5% in the complete design of patients with PE. Another 5 babies with exceptionally low and incredibly low body weight passed on in the early neonatal period (3.8%). Hence, perinatal mortality in patients with PE in our investigation was 5.3%.

The study of angiogenic status, gene polymorphism and morphological studies in patients with PE

Table 10 presents data on the concentration of PLGF, sFlt-1 and their ratio, as well as concentration of pregnancy-associated protein A (PAAP-A) in patients with PE compared with pregnant women without PE.

Table 10.

Concentration of main endothelial factors in patients of studied groups.

Studied groups	**Mild PE (n=87)**	**Severe PE (n=45)**	**Pregnant without PE (n=40)**	**Non-pregnant (n=35)**	**p_1**	**p_2**	**p_3**
PIGF ng/ml	61,4±3,2	52,7±2,6	265,0±14,0	41,5±2,5	**<0,05**	**<0,001**	**<0,001**
sFlt-1 ng/ml	11151±48	13288±79	4661±31	2204±93	**<0,001**	**<0,001**	**<0,001**
sFlt-1/ PIGF ng/ml	165,4±9,3	643,8±22,7	18,9±0,6	37,4±1,7	**<0,001**	**<0,001**	**<0,001**
PAPP-A mM/ml	2,3±0,1	1,7±0,1	8,4±0,3	1,5±0,1	**<0,001**	**<0,001**	**<0,001**

Note: p1 - significant differences in O1 and O2 subgroups (p< 0.01); p2- statistically significant differences in the indicators of patients with PE from healthy pregnant women (p2< 0.01); p3 - statistically significant differences in the indicators of pregnant and non-pregnant women.

Currently, an important prognostic value as a diagnostic marker of PE is given to the embryo-specific protein PAPP-A (pregnancy-associated protein A). Reduced production of RARP-A leads to an increase in vascular resistance in the mother-placenta-fetus system and thus to the development of placental dysfunction and

FADS, which can be considered as one of PE signs. Only pregnant women with severe PE had a significant decrease in PAPP-A compared to the group of healthy pregnant and non-pregnant women in our study. As for this indicator in the group of patients with mild PE, it did not have a statistically significant difference compared to healthy pregnant and non-pregnant women. This allows us to conclude that PAPP-A can only be a diagnostic criterion for severe PE.

Table 11

The concentration of PLGF, sFlt-1 and dynamics of sFlt-1/ PIGF ratio in patients with preeclampsia of different severity in II and III trimesters of pregnancy

Term of pregnancy Mild PE (n=87)	III trimester			Term of pregnancy Severe PE (n=45)	III trimester			P1	P2	P3
	PIGF ng/ml	sFlt-1 ng/ml	sFlt-1/ PIGF ng/ml		PIGF ng/ml	sFlt-1 ng/ml	sFlt-1/ PIGF ng/ml			
Up to 34 weeks (n=16)	78,8±4,7	7040±54	115,4±6,4	Up to 34 weeks (n=22)	61,7±3,8	11505±70	208,4±11,1	<0,01	<0,001	<0,001
34-37 weeks (n=62)	62,6±3,8	12568±52	147,2±8,0	34-37 weeks (n=20)	59,1±3,0	13621±82	237,3±12,4	>0,5	<0,001	<0,001
38 weeks and more (n=9)	43±2,4	13902±61	242,1±11,5	38 weeks and more (n=3)	38,4±2,0	14502±91	324,9±16,1	>0,1	<0,001	<0,001

Note: p1 - significance of differences in PIGF in group with mild and severe PE; p2 - significance of differences in sFlt-1 in group with mild and severe PE; p3 - significance of differences in sFlt-1/ PIGF in group with mild and severe PE.

The groupings of PlGF and sFlt-1 at about four months didn't essentially vary from the comparing esteems at 17 and 18 weeks of pregnancy. At 19 weeks, the PlFG fixation essentially expanded, and at 20 weeks it fundamentally surpassed that at 19 weeks. The proportion of PlGF and sFlt-1 focuses additionally changed as needs be. At 16-18 weeks of pregnancy, the sFlt-1/PlGF proportion arrived at the midpoint of 13.1±2.6, while at 19-20 weeks it was 6.9±2.1. It ought to be especially noticed that in the primary trimester of pregnancy (11-13 weeks), the normal worth of this marker was 39.3±4.2. Clearly in ladies with PE there is a critical decline in the grouping of PIGF, contingent upon the seriousness of PE. Simultaneously, the serum level of sFlt-1 increments. At 30-32 weeks, the grouping of PlGF was multiple occasions higher than that at 20 weeks of pregnancy, and the convergences of sFlt-1 at these development periods didn't fundamentally contrast. In like manner, the sFlt-1/PlGF proportion at 30-32 weeks was negligible and found the middle value of 1.7±0.8. These pointers mirror the change in the angiogenic status of pregnant ladies with PE toward hostile to angiogenic factor transcendence. This demonstrates endothelial cells brokenness, which is clinically showed by hypertension, proteinuria, and different signs of PE. At 33-36 weeks of pregnancy, the convergence of PlGF was multiple times lower than that at 30-32 weeks, and the centralization of sFlt-1 expanded by multiple times. The proportion of these markers was 10±2.5. In 37-40 weeks of pregnancy, a further lessening in the centralization of PlGF and an expansion in the grouping of sFlt-1 were noted. Their proportion was 17.6±2.4.

Subsequently, because of the led work, information were gotten on the substance of PlGF, sFlt-1 and the upsides of their proportion during pregnancy from 11 to 13 weeks, from 16 to 20 weeks and from 30 to 40 weeks. The pregnancy periods picked for the examination are because of the way that arranged pre-birth conclusion is completed right now in the first and second trimesters, just as powerful observing of the hatchling in the third trimester of pregnancy. It appears to be that the evaluation of the danger of creating toxemia during these times of pregnancy can assist with decreasing the recurrence of intricacies and perinatal misfortunes, since

the reception of proper measures at times permits convenient right the creating obsessive condition and resolve the issue of conveyance time.

While examining qualities polymorphism related with the danger of hypertension in ladies with PE we discovered that the recurrence of low-practical variations in the qualities related with the advancement of blood vessel hypertension (type 1 and type 2 receptor qualities for angiotensin II and nitric oxide synthase) was measurably essentially higher in ladies with toxemia, than in ladies with the physiological course of pregnancy (Table 12).

Table 12.

Genes polymorphism presumably associated with PE.

Gen	Gen location	Polymorphism
AGTR1 (angiotensin II type I receptor)	3q21-q25	A1166C
AGTR2 (angiotensin II type II receptor)	Xq23	G1675A
NOS3 (endothelial nitric oxide synthase)	7q36 NOS3	786T/C
		Glu298Asp
		C774T

It is realized that chemical angiotensin II causes vasoconstriction and is the primary controller of aldosterone amalgamation. The final product of this activity is an increment in the volume of coursing blood and an increment in foundational circulatory strain. Angiotensin II collaborates with two cell angiotensin receptors of types 1 and 2, encoded, separately, by the AGTR1 and AGTR2 qualities. The replacement of adenine (A) for cytosine (C) at position 1166 in the administrative district of AGTR1 quality prompts an increment in its demeanor. Gain instrument is brought about by the accompanying. During the union of the receptor protein, miR155 microRNAs connect with non-coding areas of mRNA interpreted from the AGTR1 1166A allele on the standard of complementarity, which restrains the interpretation cycle and adds to a reduction in protein combination.

MicroRNAs can't tie to the AGTR1 1166C polymorphic allele, which expands the amalgamation of the protein item and changes the practical action of the

receptors [145,152]. The cardiovascular impacts of angiotensin II interceded by AT2-receptors are something contrary to those brought about by AT1-receptors, for example the connection of angiotensin II with type 2 receptors causes a reduction in pulse. Expansion in the quantity of angiotensin II sort 2 receptors on the cell surface is controlled by AGTR2 1675G allele, since it is related with the actuation of quality record. The idea of the guideline of quality articulation changes contrarily with nucleotide replacement of G1675A in the administrative district of the quality. Thus, transporters of this low-useful polymorphism have a lessening in the quantity of type 2 receptors and a fractional loss of their capacity (investment in NO creation, vascular dilatation), which adds to an expanded danger of creating blood vessel hypertension. The current investigation causes to notice the higher recurrence of homozygous transporter of this low-utilitarian polymorphism in ladies with toxemia contrasted with ladies with physiological course of pregnancy. Considering the way that AGTR2 quality is limited in X-chromosome, the phenotypic sign of heterozygous transporter of 1675A allele can be smoothed because of the marvel of allelic avoidance when inactivation in the phone of one of the sex chromosomes happens. In homozygotes, the phenotypic impact isn't evened out by this marvel, which is likely likewise the case deciding the high recurrence of AGTR2 1675A/A genotype in the gathering of ladies with confounded pregnancy.

Endothelial brokenness is vital in the pathogenesis of toxemia [106,108], which is showed by an increment in the "affectability" of the vascular divider to the pressor impacts of arbiters, while decreasing the creation of vasodilators, like nitric oxide (NO). Nitric oxide is the principle endothelial unwinding factor associated with keeping up with vascular divider tone and thrombogenesis.

Established endothelial NO-synthase 3-type (NOS3, equivalent word eNOS) is engaged with NO blend in the endothelium and consequently in the guideline of vascular tone, blood stream and pulse [117,118]. The presence of qualities polymorphisms managing vascular tone (renin-angiotensin framework and

endothelial nitric oxide synthetase), inclining to hypertension inconveniences, essentially builds the danger of toxemia.

Genetic predisposition in women with preeclampsia

Table 12.1

Frequency of alleles and genotypes of Glu298Asp polymorphism in the NOS3 gene distribution in the main group of patients and control group

Allele	Frequency (%)		$\chi 2$	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Pregnant with PE (n=54)	Control (n=35)					
Glu	73,8	77,1	**0,215**	**0,643**	**0,85**	**0,42**	**1,71**
Asp	26,2	22,9	**0,215**	**0,643**	**1,18**	**0,58**	**2,39**
Genotypes							
Glu/Glu	50	60,1	**0,855**	**0,355**	**0,67**	**0,28**	**1,58**
Glu/Asp	40,7	34,2	**0,375**	**0,540**	**1,32**	**0,54**	**3,19**
Asp/ Asp	9,3	5,7	**0,368**	**0,544**	**1,68**	**0,31**	**9,20**

Comparative study of NOS3 gene polymorphism (Table 29.1) revealed that Asp alleles were more common (26.2%) in the group of pregnant women with preeclampsia, while there was no statistically significant difference in comparison with control group ($\chi 2$=0.215; P-value= 0.643; OR=1.18, CI 95% - 0.58-2.39). The study of NOS3 gene polymorphism also showed a greater occurrence of Glu/Asp (40.7%) and Asp/Asp (9.3%) genotypes in patients with preeclampsia compared to patients in control group, but no statically significant confidence was found ($\chi 2$=0.375; P-value= 0.540; OR=1.32, CI 95% - 0.54-3.19; $\chi 2$=0.368; P-value= 0.544; OR=1.68, CI 95% - 0.31-9.20).

Table 12.2

Frequency of alleles and genotypes of Glu298Asp polymorphism in the NOS3 gene distribution in the groups of patients with mild, severe preeclampsia and control group

Allele	Frequency (%)		$\chi 2$	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_1 mild PE (n=36)	Control (n=35)					
Glu	76,4	77,1	**0,004**	**0,949**	**1,04**	**0,34**	**3,16**
Asp	23,6	22,9	**0,004**	**0,949**	**0,96**	**0,32**	**2,94**
Genotypes							
Glu/Glu	55	60,1	**0,144**	**0,705**	**0,83**	**0,32**	**2,14**
Glu/Asp	41,6	34,2	**0,410**	**0,522**	**1,37**	**0,52**	**3,58**
Asp/ Asp	2,7	5,7	**0,378**	**0,539**	**0,47**	**0,04**	**5,45**
Allele	Frequency (%)		$\chi 2$	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_2 severe PE (n=18)	Control (n=35)					
Glu	58,3	77,1	**4,065**	**0,044**	**0,41**	**0,17**	**0,99**
Asp	41,7	22,9	**4,065**	**0,044**	**2,41**	**1,01**	**5,73**
Genotypes							
Glu/Glu	38,8	60,1	**2,126**	**0,145**	**0,42**	**0,13**	**1,36**
Glu/Asp	38,8	34,2	**0,110**	**0,741**	**1,22**	**0,38**	**3,96**
Asp/ Asp	22,3	5,7	**3,227**	**0,072**	**4,71**	**0,77**	**28,77**

Comparative study of the NOS3 gene polymorphism (Table 29.2) also revealed that Asp alleles were more common (23.6%) in the group of pregnant women with mild preeclampsia, while there was no statistically significant difference in comparison with control group ($\chi 2$=0.004; P-value= 0.949; OR=0.96, CI 95% - 0.32-2.94). Comparative study of the NOS3 gene polymorphism in the group with severe preeclampsia revealed that this subgroup of patients with a higher frequency had the presence of the Asp allele (41.7%) in comparison with control group, a statistically significant difference was also revealed ($\chi 2$=4,065; P-value=0.044; OR=2.41, CI 95% - 1.01-5.73).

The study of NOS3 gene polymorphism also showed a greater occurrence of Glu/Asp genotypes in patients with preeclampsia (41.6%) compared to patients in control group, but there was no statistically significant difference ($\chi2$=0.410; P-value= 0.522; OR=1.37, CI 95% - 0.52-3.58). A comparative study of NOS3 gene polymorphism showed a greater occurrence of Glu/Asp (38.8%) and Asp/Asp (22.3%) genotypes in patients with severe preeclampsia compared to patients in control group, but no statistically significant difference was also found ($\chi2$=0.110; P-value=0.741; OR=1.22, CI 95% - 0.38-3.96; $\chi2$=3,227; P-value= 0,072; OR=4,71, CI 95% - 0,77-28,77).

Table 13.1

Frequency of alleles and genotypes of T786C polymorphism in the NOS3 gene distribution in the main group of patients and control group

Allele	Frequency (%)		$\chi2$	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Pregnant with PE (n=54)	Control (n=35)					
T	60,2	84,3	**6,216**	**0,013**	**0,26**	**0,09**	**0,78**
C	39,8	15,7	**6,216**	**0,013**	**3,82**	**1,28**	**11,40**
Genotypes							
T/T	46,3	74,3	**6,800**	**0,009**	**0,30**	**0,12**	**0,75**
T/C	27,8	20,0	**0,690**	**0,406**	**1,54**	**0,55**	**4,27**
C/C	25,9	5,7	**5,883**	**0,015**	**5,78**	**1,22**	**27,25**

A comparative study of the T786C polymorphism in the eNOS gene (Table 30.1) showed that C alleles were more common in the group of pregnant women with preeclampsia (39.8%), which was shown as a statistically significant difference compared to control group ($\chi2$=1.673; p-value= 0.001; OR=3.55, CI 95% - 1.68-7.51).

The study of T786C polymorphism in eNOS gene also showed a greater occurrence of C/C genotypes in patients with preeclampsia (25.9%) compared to patients in control group, which was also expressed as a statically significance ($\chi2$=5.883; p-value= 0.015; OR=5.78, CI 95% - 1.22-27.25).

Table 13.2

Frequency of alleles and genotypes of T786C polymorphism in eNOS gene distribution in the groups of patients with mild, severe preeclampsia and control group

Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_1 mild PE (n=36)	Control (n=35)					
T	61,1	84,3	**9,568**	**0,002**	**0,29**	**0,13**	**0,65**
C	38,9	15,7	**9,568**	**0,002**	**3,41**	**1,53**	**7,59**
Генотипы							
T/T	47,2	74,3	**5,442**	**0,020**	**0,31**	**0,11**	**0,84**
T/C	27,8	20,0	**0,590**	**0,443**	**1,54**	**0,51**	**4,64**
C/C	25,0	5,7	**5,041**	**0,025**	**5,50**	**1,09**	**27,64**
Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_2 severe PE (n=18)	Control (n=35)					
T	58,3	84,3	**8,650**	**0,003**	**0,26**	**0,10**	**0,66**
C	41,7	15,7	**8,650**	**0,003**	**3,83**	**1,52**	**9,65**
Генотипы							
T/T	44,4	74,3	**4,603**	**0,032**	**0,28**	**0,08**	**0,92**
T/C	27,8	20,0	**0,411**	**0,522**	**1,54**	**0,41**	**5,78**
C/C	27,8	5,7	**5,048**	**0,025**	**6,35**	**1,09**	**36,92**

Comparative study of T786C polymorphism in eNOS gene (Table 30.2) revealed that C alleles were more common (38.9%) in the group of pregnant women with mild preeclampsia, which was confirmed by a significant difference in comparison with control group (χ2=9.568; P-value= 0.002; OR=3.41, CI 95% - 1.53-7.59). Comparative study of this gene in the group with severe preeclampsia revealed that there was also a statistically significant frequency of C allele (41.7%) in comparison with control group (χ2=8,650; P-value= 0.003; OR=3.83, CI 95% - 1.52-9.65). The study of the T786C polymorphism in the eNOS gene also showed a statistically significantly higher occurrence of C/C genotypes in pregnant women with mild preeclampsia (25.0%) compared with patients in control group (χ2=5.041;

P-value= 0.025; OR=5.50, CI 95% - 1.09-27.64). A comparative study of T786C polymorphism in eNOS gene also showed a significantly higher occurrence of C/C genotypes in patients with severe preeclampsia (27.8%) compared to patients in the control group ($\chi 2$=5.048; P-value=0.025; OR=6.35, CI 95% - 1.09-36.92).

Table 14.1

Frequency of alleles and genotypes of C774T polymorphism in NOS3 gene distribution in the main group of patients and control group

Allele	Frequency (%)		$\chi 2$	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Pregnant with PE (n=54)	Control (n=35)					
C	69,4	78,6	**1,421**	**0,233**	**0,54**	**0,20**	**1,49**
T	30,6	21,4	**1,421**	**0,233**	**1,84**	**0,67**	**5,04**
Genotypes							
C/C	48,1	60,0	**1,197**	**0,274**	**0,62**	**0,26**	**1,47**
C/T	42,6	37,1	**0,262**	**0,609**	**1,26**	**0,52**	**3,00**
T/T	9,3	2,9	**1,384**	**0,239**	**3,47**	**0,39**	**31,04**

Comparative study of C774T polymorphism in the eNOS gene (Table 31.1) revealed that T alleles were more common in the group of pregnant women with preeclampsia (30.6%), while there was no statistically significant difference in comparison with control group ($\chi 2$=1.796; p-value= 0.180; or=1.61, 95% Ci - 0.80-3.26).

The study of polymorphism in C774T eNOS gene also showed a greater occurrence in patients with preeclampsia of C/T (42.6%) and T/T (9.3%) genotypes compared to patients in control group, but there was no statistically significance ($\chi 2$=0.262; p-value= 0.609; OR=1.26, CI 95% - 0.52-3.00; $\chi 2$=1.384; p-value= 0.239; or=3.47, Ci 95% - 0.39-31.04).

Table 14.2

Frequency of alleles and genotypes of C774T polymorphism in the eNOS gene distribution in the groups of patients with mild, severe preeclampsia and control group

Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_1 mild PE (n=36)	Control (n=35)					
C	76,6	78,6	**0,053**	**0,819**	**0,88**	**0,28**	**2,74**
T	23,4	21,4	**0,053**	**0,819**	**1,14**	**0,36**	**3,58**
Genotypes							
C/C	47,2	60,0	**1,165**	**0,280**	**0,60**	**0,23**	**1,53**
C/T	41,7	37,1	**0,152**	**0,697**	**1,21**	**0,47**	**3,14**
T/T	11,1	2,9	**1,847**	**0,174**	**4,25**	**0,45**	**40,08**
Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_2 severe PE (n=18)	Control (n=35)					
C	59,1	78,6	**4,799**	**0,028**	**0,38**	**0,16**	**0,92**
T	40,9	21,4	**4,799**	**0,028**	**2,62**	**1,09**	**6,28**
Genotypes							
C/C	50	60,0	**0,484**	**0,487**	**0,67**	**0,21**	**2,09**
C/T	44,4	37,1	**0,265**	**0,607**	**1,35**	**0,43**	**4,30**
T/T	5,6	2,9	**0,238**	**0,625**	**2,00**	**0,12**	**33,97**

Comparative study of C774T polymorphism in the eNOS gene (Table 31.2) revealed that T alleles were more common in the group of pregnant women with mild preeclampsia (23.4%), while no statistically significant difference was found in comparison with control group (χ2=0.053; P-value= 0.819; OR=1.14, CI 95% - 0.36-3.58). In a comparative study of NOS3 gene polymorphism in the group with severe preeclampsia it was noted that this subgroup of patients with a higher frequency had the presence of T allele (40.9%) in comparison with the control group, while no statistically significant difference was also revealed (χ2=4,799; P-value= 0.028; OR=2.62, CI 95% - 1.09-6.28). The study of C774T polymorphism in eNOS gene also showed a greater occurrence of C/T (41.6%) and T/T (11.1%) genotypes

in patients with preeclampsia compared to patients in control group, but there was no statistically significant difference (χ2=0.152; P-value= 0.697; OR=1.21, CI 95% - 0.47-3.14; χ2=1.847; P-value= 0.174; OR=4.25, CI 95% - 0.45-40.08). The study also showed a greater occurrence of C/T (44.4%) and T/T (5.6%) genotypes in patients with severe preeclampsia compared to patients in the control group, but there was no statistically significant difference (χ2=0.265; P-value=0,607; OR=1,35, CI 95% - 0,43-4,30; χ2=0,238; P-value= 0,625; OR=2,00, CI 95% - 0,12-33,97).

Table 15.1

Frequency of alleles and genotypes of A1166C polymorphism in AGTR1 gene distribution in the main group of patients and control group

Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Pregnant with PE (n=54)	Control (n=35)					
A	74,1	72,9	**0,000**	**0,982**	**0,99**	**0,37**	**2,61**
C	25,9	27,1	**0,000**	**0,982**	**1,01**	**0,38**	**2,67**
Genotypes							
A/A	57,4	57,1	**0,001**	**0,980**	**1,01**	**0,43**	**2,39**
A/C	33,3	31,4	**0,035**	**0,851**	**1,09**	**0,44**	**2,71**
C/C	9,3	11,4	**0,110**	**0,740**	**0,79**	**0,20**	**3,17**

Comparative study of A1166C polymorphism in AGTR1 gene (Table 32.1) revealed that alleles A were more common (74.1%) in the group of pregnant women with preeclampsia, while there was no statistically significant difference in comparison with control group (χ2=0.032; p-value= 0.857; or=0.94, Ci 95% - 0.48-1.85).

The study of A1166C polymorphism in the AGTR1 gene also showed a slightly higher occurrence of C/C genotypes in patients with preeclampsia (33.3%) compared to patients in control group, while no statistically significance was revealed (χ2=0.035; p-value= 0.851; Or=1.09, Ci 95% - 0.44-2.71).

Table 15.2

Frequency of alleles and genotypes of A1166C polymorphism in AGTR1 gene distribution in the groups of patients with mild, severe preeclampsia and control group

Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_1 mild PE (n=36)	Control (n=35)					
A	74,1	72,9	**0,010**	**0,919**	**1,04**	**0,49**	**2,18**
C	25,9	27,1	**0,010**	**0,919**	**0,96**	**0,46**	**2,02**
Genotypes							
A/A	66,7	57,1	**0,683**	**0,409**	**1,50**	**0,57**	**3,93**
A/C	19,4	31,4	**1,347**	**0,246**	**0,53**	**0,18**	**1,57**
C/C	5,6	11,4	**0,791**	**0,374**	**0,46**	**0,08**	**2,67**
Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_2 severe PE (n=18)	Control (n=35)					
A	59,5	72,9	**2,302**	**0,129**	**0,52**	**0,22**	**1,22**
C	40,5	27,1	**2,302**	**0,129**	**1,92**	**0,82**	**4,47**
Genotypes							
A/A	38,9	57,1	**1,585**	**0,208**	**0,48**	**0,15**	**1,52**
A/C	61,1	31,4	**4,314**	**0,038**	**3,43**	**1,05**	**11,23**
C/C	0	11,4	**2,225**	**0,136**	**0,00**	-	-

Comparative study of A1166C polymorphism in AGTR1 gene (Table 32.2) revealed that A alleles were more common in the group of pregnant women with mild preeclampsia (74.1%), while no statistically significant difference was found in comparison with control group (χ2=0.010; P-value= 0.919; OR=0.96, CI 95% - 0.49-2.18). A comparative study of A1166C polymorphism in AGTR1 gene in the group with severe preeclampsia showed that this subgroup had a higher frequency of C allele (40.5%) compared to control group, while no statistically significant difference was also revealed (χ2=2.302; P-value= 0.129; OR=1.92, CI 95% - 0.82-4.47). The study of A1166C polymorphism in AGTR1 gene showed a greater occurrence of A/A genotypes in patients with preeclampsia (66.7%) compared to

patients in control group, but there was no statistically significant difference ($\chi 2$=0.683; P-value= 0.409; OR=1.50, CI 95% - 0.57-3.93). The study also showed a greater occurrence of A/C genotypes in patients with severe preeclampsia (61.1%), which was displayed as a statically significant difference ($\chi 2$=4.314; P-value=0.038; OR=3.43, CI 95% - 1.05-11.23).

Table 16.1

Frequency of alleles and genotypes of G1675A polymorphism in AGTR2 distribution in the main group of patients and control group

Allele	Frequency (%)		$\chi 2$	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Pregnant with PE (n=54)	Control (n=35)					
A	60,2	85,7	**6,216**	**0,013**	**0,26**	**0,09**	**0,78**
G	39,8	14,3	**6,216**	**0,013**	**3,82**	**1,28**	**11,40**
Genotypes							
A/A	44,4	74,3	**7,682**	**0,006**	**0,28**	**0,11**	**0,70**
A/G	27,8	22,8	**0,268**	**0,604**	**1,30**	**0,48**	**3,49**
G/G	24,1	2,9	**7,212**	**0,007**	**10,78**	**1,34**	**86,65**

A comparative study of polymorphism in AGTR2 gene G1675A (Table 33.1) revealed that G alleles were more common (39.8%) in the group of pregnant women with preeclampsia, which was displayed as a statistically significant difference compared to control group ($\chi 2$=13.238; p-value= 0.000; OR=3.97, CI 95% - 1.83-8.59).

The study of polymorphism in AGTR2 gene G1675A also showed a greater occurrence of G/G genotypes in patients with preeclampsia (24.1%) compared to patients in control group, which was also expressed as a statistical significance ($\chi 2$=7,212; p-value= 0.007; OR=10.78, CI 95% - 1.34-86.65).

Table 16.2

Frequency of alleles and genotypes of G1675A polymorphism in AGTR2 distribution in the groups of patients with mild, severe preeclampsia and control group

Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_1 mild PE (n=36)	Control (n=35)					
A	62,5	85,7	**9,927**	**0,002**	**0,28**	**0,12**	**0,63**
G	37,5	14,3	**9,927**	**0,002**	**3,60**	**1,58**	**8,19**
Генотипы							
A/A	47,2	74,3	**5,442**	**0,020**	**0,31**	**0,11**	**0,84**
A/G	30,6	22,8	**0,537**	**0,464**	**1,49**	**0,51**	**4,29**
G/G	22,2	2,9	**6,012**	**0,014**	**9,71**	**1,14**	**82,42**
Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	O_2 severe PE (n=18)	Control (n=35)					
A	55,6	85,7	**11,681**	**0,001**	**0,21**	**0,08**	**0,53**
G	44,4	14,3	**11,681**	**0,001**	**4,80**	**1,88**	**12,27**
Генотипы							
A/A	38,9	74,3	**6,339**	**0,012**	**0,22**	**0,07**	**0,74**
A/G	33,3	22,8	**0,671**	**0,413**	**1,69**	**0,48**	**5,94**
G/G	27,8	2,9	**7,353**	**0,007**	**13,08**	**1,39**	**122,86**

Near investigation of polymorphism in AGTR2 quality G1675A (Table 33.2) uncovered that G alleles were more normal (37.5%) in the gathering of pregnant ladies with gentle toxemia, which was affirmed by a critical contrast in examination with control bunch (χ2=9.927; p-value=0.002; OR=3.60, CI 95% - 1.58-8.19). Near investigation of this quality in bunch with serious toxemia showed that there was likewise a measurably critical recurrence of P allele (44.4%) in correlation with control bunch (χ2 = 11.681; P-esteem = 0.001; OR = 4.80, CI 95% - 1.88 - 12.27).

The investigation of polymorphism in AGTR2 quality G1675A likewise showed a measurably altogether higher event of G/G genotypes in pregnant ladies with gentle toxemia (22.2%) contrasted and patients in control bunch (χ2=6.012; p-

value= 0.014; Or=9.71, Ci 95% - 1.14-82.42). The relative examination likewise showed a fundamentally higher frequency of G/G genotypes in patients with extreme toxemia (27.8%) contrasted and patients in control bunch ($\chi 2$=7,353; p-value=0.007; OR=13.08, CI 95% - 1.39-122.86).

Investigation of qualities polymorphism related with the danger of hypertension in ladies with PE uncovered that in ladies with toxemia, the recurrence of low-practical variations in the qualities related with the improvement of blood vessel hypertension (qualities of the receptors of the first and second sorts for angiotensin II and nitric oxide synthase), genuinely fundamentally surpassed that in ladies with the physiological course of pregnancy.

Consequently, the distinguished relationship in the examination can be utilized as hereditary markers of inclination to toxemia development, which will permit us to frame a danger bunch in an opportune way and change remedial and preventive measures.

Morphological studies of placental bed

The objects of the morphological study were placentas and biopsies from the placental site area obtained during surgical delivery and comprised 35 observations of patients with a clinical picture of severe PE, 15 observations in patients with mild PE, and 15 observations of women without PE.

In the group of patients with severe PE, the average placental mass was 254.5±10.9 g, small placentas with thinned edges and multiple infarcts, vascular thrombosis prevailed, while in the group with mild PE, a higher placental mass of 426.35±12.1 g was noted and they were regular rounded or oval in shape. Central (36-72 %) or paracentral (9-18 %) umbilical cord attachment prevailed in both groups. Marginal and shell attachment of the umbilical cord was observed in 5-10% cases in the main group with severe PE.

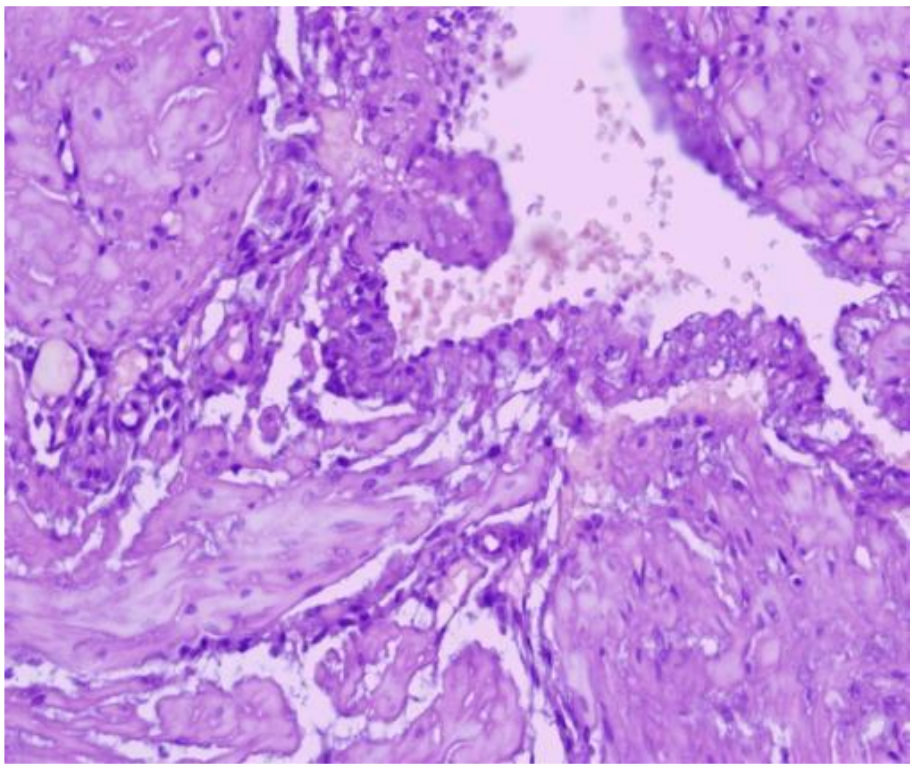

Figure 5. Surface invasion of extra-dorsal cytotrophoblast in endometrium in severe PE, (hematoxylin and eosin staining), x200. (Patient B. 22 years old with mild preeclampsia)

The study of placental bed biopsies from the group with severe PE revealed a superficial location of the extra-dorsal trophoblast at the d. basalis level of the endometrial tissue (Figure 5).

Violation of invasion in severe PE was observed in 33 cases (94.3%) and was also characterized by the presence of sharply sclerotic deformed vessels, as well as decidualization and dystrophic changes of smooth muscle cells in myometrium. In addition, there was no complete gestational reconstruction of the spiral arteries. There was a pronounced thickening of the muscular-elastic wall of the spiral arteries with almost complete obliteration, the absence of opening ostii, sclerosis and hyalinosis of the basement membrane, and areas of hemorrhage.

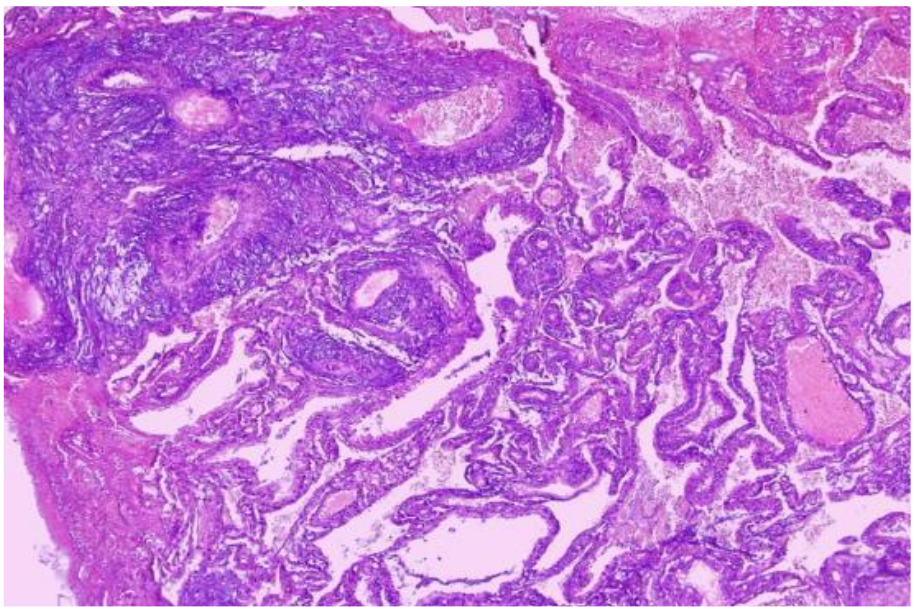

Figure 6. Remodeling disorder and spiral artery sclerosis in severe PE, stained with hematoxylin and eosin. (Patient S. 25 years old with severe PE)

Thus, the results of morphological study of the placental bed spiral arteries in PE allowed us to reveal the invasion of the extra-dorsal trophoblast in endo-and myometrium, the presence of non-remodeled sclerotic vessels. Comparison with similar studies of patients without PE, operated because of the scar on the uterus revealed that in the samples of the placental site of the uterus during delivery at 38-40 weeks of pregnancy, only the long-term consequences of two waves of cytotrophoblastic invasion were noted according to the degree of gestational rearrangement of the endometrial and myometrial segments of the utero-placental arteries. In addition, until the end of pregnancy, multinucleated giant cells remain in the placental bed, which are fused isolated cells of the interstitial cytotrophoblast, as an outcome of cytotrophoblastic invasion. The detected multinucleated giant cells (MGC) in the biopsies make it possible to assess the depth of their penetration into the adjoining myometrial bundles, that is, to indirectly imagine the adequacy or failure of the second wave of cytotrophoblast invasion. In the control group of women, cellular markers of cytotrophoblast invasion were constantly encountered. Thus, there is an adequate correlation between the rates of development and maturation of the placental villous tree and the constant increase in the volume of utero-placental blood flow during physiological pregnancy, which is provided by

successive waves of cytotrophoblast invasion, destruction of the elastic-muscular framework of the spiral and radial uterine arteries, their replacement with fibrinoid masses, and, most importantly, a significant expansion of the lumen of the utero-placental arteries, in particular, their endo - and myometrial segments. This, in turn, leads to a permanent decrease in the vascular resistance to the maternal blood flow in the placental bed of the uterus. The presence of utero-placental blood bypass is the main hemodynamic feature of the systemic circulation of a healthy pregnant woman.

Features of PE course in the context of COVID-19 pandemic

Due to the fact that a new coronavirus pandemic developed at one of the stages of this study, pregnant patients who sought medical help with symptoms of PE were included.

In many countries, including Uzbekistan, a strict self-isolation regime is recommended for pregnant women to reduce the chances of coronavirus infecting. However, in the case of coronavirus infection, pregnant women do not show more severe symptoms compared to other healthy adults. As Christoph Lees, professor of obstetrics and gynecology at Imperial College London, says, "If the risk level was very high, we would already know about it."

But at the same time, pregnancy is a special time, full of excitement and expectations. But for future mothers, fear, anxiety and uncertainty overshadow this happy time due to the current situation with coronavirus infection (COVID-19). In the context of pandemic, many pregnant women, like all healthy people, experience feelings of fear, anxiety, increased blood pressure, palpitations due to limited space and being in quarantine conditions, as well as increased anxiety for their relatives and their health. In such conditions pregnant women began to complain more often about headaches, high blood pressure, anxiety disorders, palpitations, a feeling of lack of air, fear of losing control of themselves, fear of losing consciousness, heart failure, a feeling of heat or cold, difficulty breathing, non-systemic dizziness. All of

the above was the object of our research to identify severe pre-eclampsia or anxiety disorder of the neurotic level associated with stress, occurring in the type of panic attack. A panic attack is an intense attack of fear, and it is always accompanied by physical, bodily manifestations. These symptoms include rapid heartbeat, weakness, sweating, nausea, chills, chest pain, shortness of breath, dizziness, tingling sensation in the fingers, and a person's limbs may become numb. As a rule, a panic attack lasts from 5 to 20 minutes, but sometimes its duration can reach up to an hour.

During the SARS-CoV-2 pandemic and self-isolation, the number of pregnant women admitted to the maternity complex No. 2 in Samarkand with a preliminary diagnosis of severe preeclampsia for the period March – July 2020 increased by 6% compared to the same period in 2019. A total of 46 women were admitted. The symptoms of preeclampsia in some pregnant women have shifted towards a vegetative-vascular, neurogenic anxiety state with a hypertensive and hypotensive state, but without proteinuria. In order to study the features of PE course and neurotic anxiety disorder associated with stress in the context of the SARS-CoV-2 pandemic, a survey was conducted among 68 women in Samarkand: 26 women with severe preeclampsia (the main group), and 42 pregnant women with neurotic anxiety disorder, i.e. panic attack (the comparison group).

When selecting the control group and the comparison group, a guideline was made to ensure that this group did not differ from the main one in a number of important social and hygienic parameters. Statistical processing was performed using the applied statistical utility Excel 7.0. The age of the respondents ranged from 19 to 38 years, the average age was 26.9 years and 27.3 years in the main, control and comparison groups, respectively. There were no significant differences in age among women of both groups ($p>0.05$).

Table 17.

Distribution of respondents by age

Age	Main (PCR, COVID+), n= 26	Comparison group, n=42	$\chi 2$	P
18-24	12 (46,1%)	18(42,8%)	**0,071**	**0,790**
25-34	6 (23,1%)	17(40,4%)	**2,172**	**0,141**
35-38	8(30,8%)	7(16,6%)	**1,858**	**0,173**

Among the respondents of all groups, women of the most important age from the point of reproductive significance – 18-34 years (90% and 96%, respectively) prevailed.

Table 18

Distribution of respondents depending on postpartum interval

Postpartum interval in years abs. (%)	Main (PCR, COVID+) n= 26	Comparison group n=42	$\chi 2$	P
0,25-0,5	3 (11,5%)	8 (19,0%)	**0,668**	**0,414**
0,5- 1	10 (38,5%)	3 (7,1%)	**10,187**	**0,001**
1,1 - 3	4 (15,4%)	15 (35,7%)	**3,296**	**0,069**
3,1 - 5	3 (11,5%)	11 (26,1%)	**2,109**	**0,146**
5,1 – 7	4 (15,4%)	3 (7,1%)	**1,181**	**0,277**
7,1 - 10	2 (7,7%)	2 (4,8%)	**0,249**	**0,618**

At the time of the survey, the average postpartum interval in the main group was 2.3 ± 1.7 years, and in the comparison group 2.2 ± 1.8 years.

The distribution of the respondents of the main and the comparison group did not have significant differences in age, parity, and duration of birth ($p > 0.05$), which allowed them to be considered homogeneous in these parameters and to make appropriate comparisons.

According to the marital status, all groups of respondents were identical ($p > 0.05$). There were 23 (93.4%) married women in the main group and 41(97.6%) in the comparison group, respectively. There were 3 (6.5%) women in the main group who were not married, and 1(2.4%) in the comparison group.

The main venue for interviews with pregnant women were maternity complexes. From the history of somatic pathology, it was revealed that the most

common diseases of the gastrointestinal tract were 19 (73.1%) in the main group, 28 (66.7%) in the comparison group, and diseases of the urinary system, 20 (77%) in the main group and 32 (76.2%) in the comparison group. The most significant point was the detection in the comparison group of a large number of women with diseases of the nervous system 32 (76.1%).

The distribution of respondents in the main and comparison groups did not have significant differences in anemia ($p>0.05$), i.e., mild and moderate anemia was most common in all groups.

When interviewing pregnant women in all groups about SARS-CoV-2 pandemic, the majority of pregnant women - 61 (90%) - were informed about the dangerous signs that occur in pregnant women and whether they know where they should immediately go when dangerous signs appear, such as increased blood pressure, headaches, hearing and vision disorders, increased body temperature, abdominal pain, the appearance of bloody discharge, and termination of fetus movement sensation.

The distribution of respondents in the main and comparison groups did not have significant differences in compliance with quarantine measures, i.e. 65 (95.6%) observed wearing a mask, 66 (97%) observed self-isolation, and 62 (91.2%) washing their hands with soap at least 10 times during the day.

Table 19.

Distribution of respondents by question - Did they experience feelings of anxiety or fear about pregnancy during coronavirus pandemic

Answer	**Main (PCR, COVID+), n= 26**	**Comparison group, n=42**	**$\chi 2$**	**P**
YES	18 (69,2%)	39(92,8%)	**6,611**	**0,010**
NO	8 (30,8%)	3 (7,1%)	**6,611**	**0,010**

As can be seen from this table, 39 (92.8%) pregnant women from the comparison group experienced the most frequent feelings of anxiety and fear in connection with pregnancy during coronavirus pandemic. The survey of these pregnant women revealed that panic attacks can occur during the day or at night, mainly at night, and were accompanied by an increase in blood pressure.

Distribution of patients by blood pressure level: an increase in blood pressure of 160/110 mmHg or more was most often observed in the main group -18 (69.2%) and was stopped by antihypertensive drugs for 4 hours. An increase in blood pressure of 160/110 mmHg or more was observed in 39 (92.8%) in the comparison group. At the same time, there were no significant changes in the urine tests (there was no proteinuria), but the increase in blood pressure was not stopped by antihypertensive therapy for 4 hours. The attack often began with the feeling that the throat is blocked, it becomes difficult to breathe, there is not enough air, and every breath is given with difficulty. But most often, the first signal of a panic attack is a push in the heart, from which it is taken to count a frenzied rhythm (140 beats per minute). At the same time, there is a pounding in the temples, a severe headache, and chills. Sometimes there is numbness of the limbs, the body is covered with "goose bumps", and the temperature rises to 38~39°C.

Differential diagnostic criteria of panic disorder according to ICD-10:

1. Repeated occurrence of panic attacks. Diagnosis requires at least 2 spontaneous panic attacks within one month. Patients with panic disorders may experience situational panic attacks.

2. Panic attacks are observed for a month or more and are accompanied by the following symptoms:

- constant anxiety about the recurrence of attacks,
- anxiety about the complications of attacks or their consequences (loss of self-control, severe organic pathology)
- significant changes in behavior due to the occurrence of attacks

The occurrence of attacks is not caused by somatic diseases, the action of any substances and other mental illnesses. The main tool for dealing with panic attacks in pregnant women is psychotherapy. Working with a psychotherapist will help to identify the hidden causes that caused the panic disorder. Treatment is carried out on the basis of these reasons - negative attitudes are worked out and replaced with positive ones, hidden fears are revealed, self-esteem and self-confidence are established. Huge role in the formation of fear in pregnant woman is played by her

subjective perception and mental processing of incoming information, which is accompanied by appropriate emotions. We conducted phone and video conversations.

Thus, long-term emotional stress caused the development of mental disorders in pregnant women, which is fraught with stimulation of somatoform and psychosomatic disorders. Most likely, the number of patients who become ill and suffer from the increase and aggravation of psychosomatic pathology will be much greater than the number of patients who have suffered a coronavirus infection. Prevention of psychosomatic disorders in case of possible repeated outbreaks of infectious diseases requires further study and analysis to make adjustments in the organization and provision of psychiatric care to pregnant women. At the same time, the number of women with true PE was not significantly increased in our study.

Conclusion. Examining patients of 2 groups, comparing their anamnestic data, clinic and laboratory tests revealed that pregnant women with panic attacks, against the background of severe anxiety, have from 4 to 2 physical sensations, an emotional surge, while objective data may vary within the practical norm, and there are also asymptomatic light intervals, spontaneous panic attacks can occur in the morning with hypotension and at night with hypertension. Psychoemotional symptoms in pregnant women with preeclampsia are possible because of hormonal changes, and objective data have pathology, repeated urine tests tend to increase proteinuria. We did not note this in the study group. During coronavirus infection pandemic, we have chosen not only the most popular, but also the still rare methods of conducting research and evaluation. The latter can be useful both now and after the end of the quarantine. In addition, the introduction of such methods is a qualitatively new step in the management of pregnant women. These methods can be used in the future to collect data in difficult-to-reach places or to contact pregnant women when they do not have the opportunity to visit a medical facility, as well as to draw attention to the problem and the results achieved.

The state of the vascular endothelium, gene polymorphism and specific changes in pregnant women from risk groups in the early stages of pregnancy

Based on the risk factors identified in chapter II, a group of patients was formed to dynamically monitor the course of pregnancy, starting at 11-13 weeks. A total of 70 women were examined at this stage. The criteria for inclusion in this group were (the presence of at least one of these features):

- Age 18 years
- Age over 30 years
- Burdened obstetric history (habitual pregnancy loss, fetal loss syndrome, preterm labor, a history of PE/eclampsia, PDNLP, uterine scar)
- Intergravidar interval of 5 years or more
- Intergravidar interval up to 2 years
- Pregnancy after treatment of PCOS/infertility in anamnesis
- Multiple pregnancy
- Related somatic diseases (hypertension, diabetes, urinary tract infections, obesity, varicose veins of the lower extremities, chronic inflammatory diseases of the respiratory system, chronic hepatitis)

All patients in this group were registered during current pregnancy at 11-13 weeks. The patients received a voluntary written informed consent to participate in the study. All the mandatory and additional methods of examination were carried out for the first time at the time of registration.

The average age of the patients in this group was 29.7±1.9 years. At the same time, patients aged 18 years were 15.7% (11 women); 30-35 years-70% (49 women); over 35 years-14.3% (10 women). All women were residents of the city of Samarkand. 2 patients were in an unregistered marriage, the remaining 97.1% were in a stable official marriage.

Violations in the formation and development of menstrual function in this group of patients were not found. However, 9 women (12.9%) became pregnant after infertility treatment. The causes of infertility in 4 patients – polycystic ovary syndrome, of which two women became pregnant after IVF, and two others- after ovulation stimulation. 5 women have secondary infertility after a previous Cesarean section. Pregnancy occurred after HSG, hysteroscopy, removal of suture material

from the uterine cavity and complex anti-inflammatory treatment. The duration of infertility was from 3 to 5 years. Other gynecological diseases in this group are shown in Figure 7.

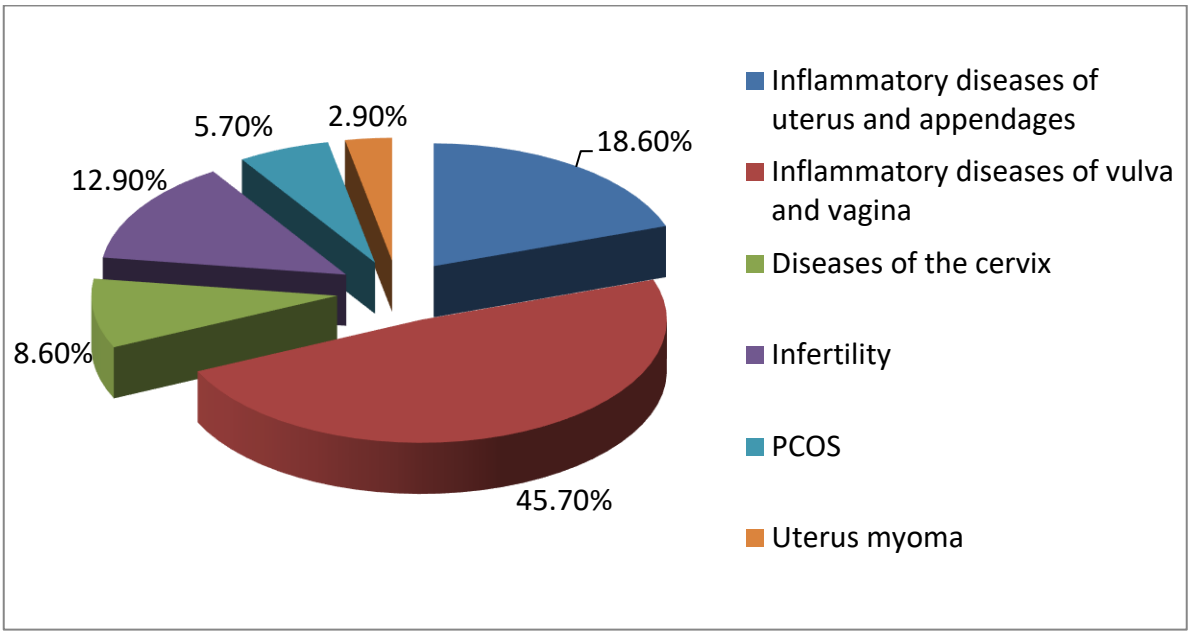

Figure 7. Gynecological diseases in patients of the second stage (II-s) of the examination.

From the presented diagram, it can be seen that the main place in the structure of gynecological pathology of patients of that group is occupied by inflammatory diseases of the female reproductive system – from vulva to uterus and the appendages of the uterus.

Table 20

Endured gynecological diseases in patients of the second stage of the study

Nosological form	II stage of study group (n=70); abs (%)	Control group (n= 35); abs (%)	χ2	P
Inflammatory diseases of uterus and appendages	13(18,6%)	9(25,7%)	**0,719**	**0,397**
Inflammatory diseases of vulva and vagina	32 (45,7%)	13(37,1%)	**0,700**	**0,403**
Uterus cervix pathology	16(8,6%)	6 (17,1%)	**1,694**	**0,193**
Infertility	9(12,9%)	1 (2,9%)	**2,708**	**0,100**
Uterus myoma	2(2,9%)	1(2,9%)	**0,000**	**1,000**
PCOS	4(5,7%)	5 (14,3%)	**2,188**	**0,139**

Related somatic pathology is shown in figure 8.

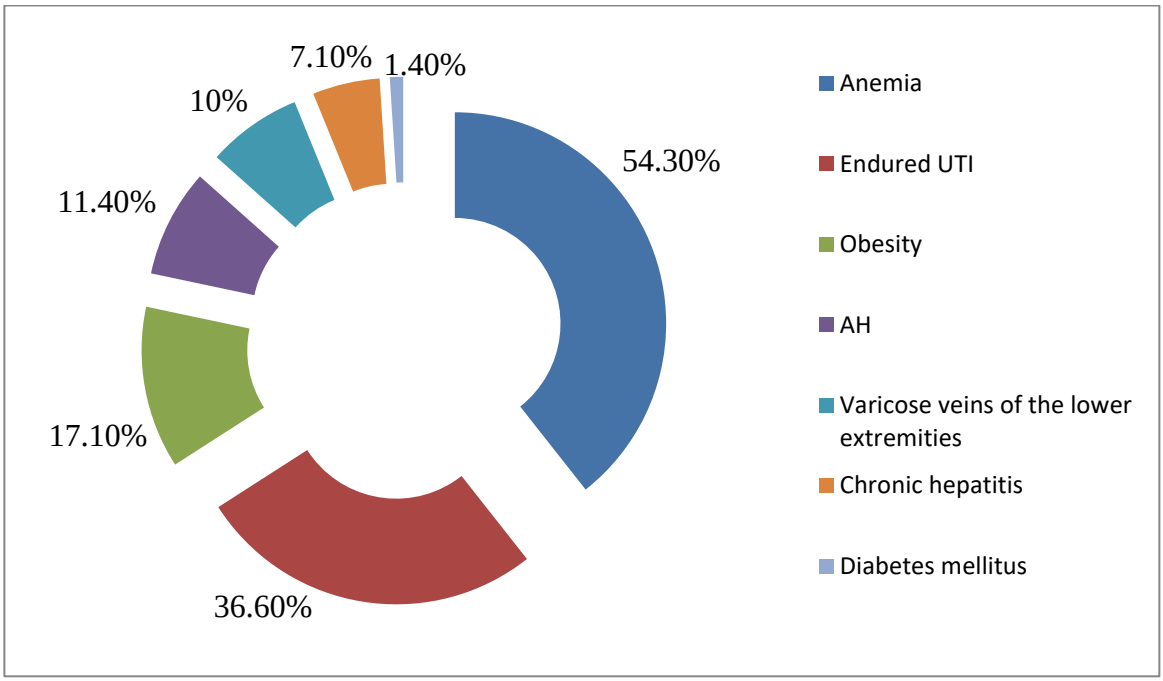

Figure 8. Related somatic pathology in patients of stage 2 study.

As it shown in this table, 28 women out of 70 (40%) had a combination of several somatic diseases. Most often, it was a combination of anemia and other extragenital pathology.

Table 21

Endured / concomitant somatic diseases of patients of the second stage of the study

Nosological form	**II stage of study group (n=70); abs (%)**	**Control group (n= 35); abs (%)**	**χ2**	**P**
Anemia	38(54,3%)	21 (60%)	**0,310**	**0,578**
UTI	27 (36,6%)	3 (8,6%)	**9,528**	**0,002**
AH	8 (11,4%)	0	**4,330**	**0,037**
Obesity	12 (17,1%)	5(14,2%)	**0,140**	**0,708**
Varicose veins	7 (10%)	3 (8,6%)	**0,055**	**0,814**
Chronic hepatitis	5 (7,1%)	3(8,6%)	**0,068**	**0,795**
Diabetes mellitus	1 (1,4%)	0	**0,505**	**0,477**
Myopia	0	3 (8,6%)	**6,176**	**0,013**

Table 21 shows reproductive function of patients in this group

Table 22.

Reproductive function of patients of II stage of study.

Indicator	II-s (n-70)	II-s %
Eclampsia/PE	6	8,6
Infertility: Primary Secondary	9 4 5	12,9
First pregnancy	21	30
3 and more labors	10	14,3
Repeated pregnancy I labor	18	25,7
Abortion: Spontaneous Artificial	16 13 3	22,9
Non-developing pregnancy	7	10
Ectopic pregnancy	2	2,9
Molar pregnancy	1	1,4
Cesarean section	31	44,3
PDNLP/PP	26	37,1
Antenatal fetal death	11	15,7
Stillbirth	2	2,9
Intergenetic interval before the onset of this pregnancy < 2 years 5 and more	5 22	7,1 31,4

Analyzing the data in the table, it is necessary to draw a conclusion about a large number of factors that aggravate the course of this pregnancy, such as cesarean section in history, PDNLP/PP, stillbirth, eclampsia/PE, intergenetic interval of 5 years or more, multipara, etc. However, it should be noted that the patients in this group were selected specifically as women of high risk for PE developing. Table 23 shows the main biochemical and hemostasiological parameters of patients in the comparison groups.

Table 23.

The main biochemical and hemostasiological parameters in patients of the second stage of examination at the moment of registration.

Indicator	Subgroup O_1 n=87	Subgroup O_2 n=45	Control n=35	II – э n=70	P1	P2	P3
Bilirubin (mcmol/l) Total	18,1±0,6	24,2±1,0	12,5±0,5	16,1±0,7	**<0,05**	**<0,001**	**<0,001**
Direct	5,7±0,3	6,9±0,3	3,1±0,2	4,2±0,2	**<0,001**	**<0,001**	**<0,001**
Indirect	14,3±0,7	17,3±0,9	10,7 ± 0,5	12,3±0,7	**<0,05**	**<0,001**	**>0,1**
ALT un/l	34,5±1,8	65,1±2,5	24,3±1,1	28,3±1,1	**<0,01**	**<0,001**	**<0,01**
AST un/l	32,1±1,6	62±2,9	25,1±0,9	27,4±1,0	**<0,02**	**<0,001**	**>0,1**

Residual nitrogen mmol/l	26,5±1,2	29,3±1,6	18,3±0,7	22,3±0,9	**<0,01**	**<0,001**	**<0,001**
Creatinin **mcmol/l**	82±5,4	109±6,1	63,5±4,7	68,2±3,8	**<0,05**	**<0,001**	**>0,5**
Blood sugar mmol/l	5,8±0,2	6,5±0,3	4,5±0,2	4,8±0,2	**<0,001**	**<0,001**	**>0,2**
Total protein g/l	61,5±3,1	54,3±2,7	74,6±4,3	70,2±3,8	**>0,1**	**<0,001**	**>0,5**
Thrombocytes thousands Un/mcl	220±9,4	140±7,5	298,9±11,5	230,6±10,5	**>0,5**	**<0,001**	**<0,001**
INR units	0,9±0,1	0,6±0,1	1,0 ± 0,1	1,0±0,1	**>0,5**	**<0,01**	**>0,5**
APTT sec**.**	24,0±0,7	20,1±0,5	27,5±1,1	25,4±0,9	**>0,2**	**<0,001**	**>0,1**
Fibrinogen g/l.	2,5±0,1	2,1±0,1	2,8± 0,1	2,6±0,1	**>0,5**	**<0,001**	**>0,2**
Blood clotting time, min	6,4±0,3	5,6±0,2	8,4±0,4	7,2±0,4	**>0,1**	**<0,001**	**<0,05**

Note: P1 - indicator of the reliability of the compared values with O1 group; P2 - indicator of the reliability of the compared values with O2 group; P3 - indicator of the reliability of the compared values of the control group

The table shows that already at the moment of registration, i.e. in the short term of pregnancy, women at risk for developing PE have a strained functioning of hemostatic system, which is manifested by an increase in fibrinogen, platelets and shortening of APTT, which go beyond the normal parameters during pregnancy.

Table 24.

The concentration of the main endothelial factors in patients of the examined groups.

Studied groups of women	II - s	Mild PE (n=87)	Severe PE (n=45)	Pregnant without PE (n=40)	Non-pregnant (n=35)	p_1	p_2	p_3	p_4
PIGF ng/ml	43,6±1,5	61,4±3,2	52,6±2,6	269±14	42,3±2,4	**<0,001**	**<0,01**	**<0,001**	**>0,5**
sFlt-1 ng/ml	1415±62,4	11190±50	13217±60,7	4652±41	2191±45	**<0,001**	**<0,001**	**<0,001**	**<0,001**
sFlt-1/ PIGF ng/ml	189±8,1	168,7±9,2	638,7±23,9	18,7±0,7	37,7±1,7	**>0,1**	**<0,001**	**<0,001**	**<0,001**
PAPP-A mM/ml	2,6±0,10	2,34±0,10	1,64±0,08	8,54±0,31	1,54±0,06	**>0,1**	**<0,001**	**<0,001**	**<0,001**

Note: p1 - significant differences in subgroups II-s, O1 and O2 (p< 0.01); p2- statistically significant differences in the indicators of patients II-s from healthy pregnant women (p2< 0.01); p3 - statistically significant differences in the indicators of pregnant women II-s and non-pregnant women.

It can be seen from this table, that a decrease in the concentration of PLGF and an increase in the concentration of sFlt -1 are recorded long before the clinical signs of preeclampsia appear and can be used as screening tests at the end of the first trimester of pregnancy. The analysis of the obtained data indicates the presence of significant differences in PLGF concentrations and sFlt-1\ PLGF ratios in pregnant women with preeclampsia and the corresponding reference indicators already in the first trimester of pregnancy. Only pregnant women with severe PE in our study had a significant decrease in PAPP-A compared to the group of healthy pregnant women and women of the second stage of the study. As for this indicator in the group of patients of the second stage of the study, it did not have a statistically significant difference compared to healthy pregnant and non-pregnant women.

Genetic predisposition in women with risk factors for preeclampsia

Table 25

Frequency of Glu298Asp polymorphism in NOS3 gene alleles and genotypes distribution in the group of women with risk factors for preeclampsia and control group

Allele	Frequency (%)		$\chi 2$	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Group of pregnant with PE risk factors (n=43)	Control (n=35)					
Glu	72	77,1	**0,516**	**0,472**	**0,77**	**0,37**	**1,59**
Asp	28	22,9	**0,516**	**0,472**	**1,31**	**0,63**	**2,71**
Genotypes							
Glu/Glu	51,2	60,1	**0,609**	**0,435**	**0,70**	**0,28**	**1,72**
Glu/Asp	41,9	34,2	**0,468**	**0,494**	**1,38**	**0,55**	**3,48**
Asp/ Asp	7,1	5,7	**0,051**	**0,821**	**1,24**	**0,20**	**7,85**

A comparative analysis of the frequency of alleles of the **Glu298Asp** polymorphism in the **NOS3 gene** (Table 42) distribution in the group of women with risk factors for preeclampsia and control group showed that there was no statistically significant difference between compared groups ($\chi 2$=0.516; P-value= 0.472;

OR=0.77, CI 95% - 0.37-1.59; χ2=0.516; P-value= 0.472; OR=1.31, CI 95% - 0.63-2.71). Analysis of the frequency of Glu298Asp polymorphism genotypes in the NOS3 gene distribution also showed that there was no statistically significant difference between the compared groups, despite the relatively frequent occurrence of the Glu/Asp genotype (41.9%) in pregnant women with risk factors for preeclampsia (χ2=0.468; P-value= 0.494; OR=1.38, CI 95% - 0.55-3.48).

Table 26

Frequency of T786C polymorphism in eNOS gene alleles and genotypes distribution in the group of women with risk factors for preeclampsia and control group

Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Group of pregnant with PE risk factors (n=43)	Control (n=35)					
T	61,6	84,3	**9,783**	**0,002**	**0,30**	**0,14**	**0,65**
C	38,4	15,7	**9,783**	**0,002**	**3,34**	**1,54**	**7,26**
Genotypes							
T/T	51,2	74,3	**4,359**	**0,037**	**0,36**	**0,14**	**0,95**
T/C	20,9	20,0	**0,010**	**0,919**	**1,06**	**0,35**	**3,20**
C/C	27,9	5,7	**6,453**	**0,011**	**6,39**	**1,32**	**30,86**

A comparative analysis of the frequency of alleles of **T786C** polymorphism in the **eNOS gene** (Table 43) distribution in the group of women with risk factors for preeclampsia and control group showed the predominance of C allele (38.4%) in the group of pregnant women with risk factors for preeclampsia, which was reflected by a statistically significant difference (χ2=9.783; P-value= 0.002; OR=3.34, CI 95% - 1.54-7.26). Analysis of the frequency of distribution of T786C polymorphism genotypes in the eNOS gene showed that pregnant women with risk factors for preeclampsia were significantly less likely to have T/T genotype (51.2%) and significantly more likely to have C/C genotype (27.9%) compared to control group (74.3% and 5.7%), which was statistically reflected (χ2=4.359; P-value=0.037;

OR=0.36, CI 95% - 0.14-0.95; χ2=6.453; P-value=0.011; OR=6.39, CI 95% - 1.32-30.86).

Table 27

Frequency of alleles and genotypes of C774T polymorphism in the eNOS gene distribution in the group of women with risk factors for preeclampsia and control group

Allele	Frequency (%)		χ2	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Group of pregnant with PE risk factors (n=43)	Control (n=35)					
C	72,1	78,6	**0,864**	**0,353**	**0,70**	**0,34**	**1,48**
T	27,9	21,4	**0,864**	**0,353**	**1,42**	**0,68**	**2,98**
Genotypes							
C/C	53,5	60,0	**0,333**	**0,564**	**0,77**	**0,31**	**1,89**
C/T	37,2	37,1	**0,000**	**0,995**	**1,00**	**0,40**	**2,52**
T/T	9,3	2,9	**1,336**	**0,248**	**3,49**	**0,37**	**32,73**

A comparative analysis of the frequency of alleles of polymorphism in the **C774T eNOS gene** (Table 44) distribution in the group of women with risk factors for preeclampsia and control group showed that there was no statistically significant difference between the compared groups (χ2=0.864; p-value= 0.353; HR=0.70, Ci 95% - 0.34-1.48; χ2=0.864; p-value= 0.353; Or=1.42, Ci 95% - 0.68-2.98).

Analysis of the frequency of genotypes polymorphism in the C774T eNOS gene distribution also showed that there was no statistically significant difference between the compared groups, despite the relatively frequent occurrence of T/T genotype (9.3%) in pregnant women with risk factors for preeclampsia (χ2=1.336; p-value=0.248; or=3.49, Ci 95% - 0.37-32.73).

Table 28

Frequency of alleles and genotypes of A1166C polymorphism in AGTR1 gene distribution in the group of women with risk factors for preeclampsia and control group

Allele	Frequency (%)		$\chi 2$	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Group of pregnant with PE risk factors (n=43)	Control (n=35)					
A	72,1	72,9	**0,011**	**0,915**	**0,96**	**0,47**	**1,95**
C	27,9	27,1	**0,011**	**0,915**	**1,04**	**0,51**	**2,11**
Genotypes							
A/A	55,8	57,1	**0,014**	**0,906**	**0,95**	**0,39**	**2,33**
A/C	32,5	31,4	**0,011**	**0,915**	**1,05**	**0,40**	**2,74**
C/C	11,6	11,4	**0,001**	**0,978**	**1,02**	**0,25**	**4,13**

A comparative analysis of the frequency alleles polymorphism of A1166C gene AGTR1 (table 48) distribution in the group of women with risk factors for the development of preeclampsia and control groups showed that a statistically significant difference was not detected between the compared groups ($\chi 2$=0,011; P-value= 0,915; OR=0,96, CI 95% - 0,47-1,95; $\chi 2$=0,011; P-value= 0,915; OR=1,04, CI 95% - 0,51-2,11).

The analysis of the frequency distribution of genotypes polymorphism of A1166C gene AGTR1 also showed that a statistically significant difference was not detected between the compared groups ($\chi 2$=0,001-0,014; P-value=0,906-0,978).

A comparative analysis of the frequency of G1675A alleles polymorphism in the AGTR2 gene (Table 49) distribution showed the predominance of the G allele (39.5%) in the group of pregnant women with risk factors for preeclampsia in comparison with control group, which was reflected by a statistically significant difference ($\chi 2$=12.149; P-value= 0.000; OR=3.92, CI 95% - 1.77-8.70).

Table 29

Frequency of alleles and genotypes of G1675A polymorphism in AGTR2 gene in the group of women with risk factors for preeclampsia and control group

Allele	Frequency (%)		$\chi 2$	P-value	OR	Lower limit 95% CI	Upper limit 95% CI
	Group of pregnant with PE risk factors (n=43)	Control (n=35)					
A	60,5	85,7	**12,149**	**0,000**	**0,25**	**0,11**	**0,57**
G	39,5	14,3	**12,149**	**0,000**	**3,92**	**1,77**	**8,70**
Genotypes							
A/A	46,5	74,3	**6,152**	**0,013**	**0,30**	**0,11**	**0,79**
A/G	27,9	22,8	**0,258**	**0,611**	**1,31**	**0,47**	**3,67**
G/G	25,6	2,9	**7,654**	**0,006**	**11,69**	**1,43**	**95,76**

Analysis of the frequency of G1675A genotypes polymorphism in AGTR2 gene distribution also showed that pregnant women with risk factors for preeclampsia were significantly less likely to have A/A genotype (46.5%) and significantly more likely to have G/G genotype (25.6%) compared with control group (74.3% and 2.9%), which was statistically reflected ($\chi 2$=6,152; P-value=0.013; OR=0.30, CI 95% - 0.11-0.79; $\chi 2$=7,654; P-value=0.006; OR=11.69, CI 95% - 1.43-95.76).

Thus, the study allowed us to establish both the alleles of the genes predisposing to the development of preeclampsia: T786C eNOS *allele C, G1675A AGTR2 * allele G, and the alleles of the genes that are protective to the development of preeclampsia: T786C eNOS *allele T, G1675A AGTR2 * allele A.

The study also revealed a number of alleles of genes predisposing to the development of severe preeclampsia: Glu298Asp NOS3* allele Asp, T786C eNOS *allele C, C774T eNOS* allele T, G1675A AGTR2* allele G and alleles protective to the development of severe preeclampsia: Glu298Asp NOS3* allele Glu, T786C eNOS *allele T, C774T eNOS* allele C, G1675A AGTR2* allele A.

The study of various genotypes frequency occurrence showed that a number of them contribute to the development of preeclampsia in pregnant women: T786C

eNOS *C/ C, G1675A AGTR2*G/G), while it was found that the detection of T786C eNOS *T/T, G1675A AGTR2*A/A in pregnant women reduces the likelihood of preeclampsia developing, which will allow timely prevent this pathology in women.

Thus, our study revealed a link between interacting genes involved in the regulation of angiogenesis and the development of PE in pregnant women. There was a high correlation between the number of unfavorable genotypes of genes with the clinical form of mild and severe preeclampsia.

These data allow us to develop a prognostic algorithm for the risk of developing preeclampsia in early pregnancy in women with risk factors for PE developing and to carry out effective therapeutic and preventive measures in a timely manner, taking into account genetic characteristics.

Computer program for improving forecasting and risk methods of PE development

Statistically significant differences between the main indicators that characterize the risk of PE developing in women at risk and healthy groups were established. Based on the obtained information base, a computer program was developed using the method of logistic regression to diagnose factors and identify markers that diagnose predisposition to PE, which was tested on an independent sample. The sensitivity of this method for the risk of PE developing was 70.9%, and the specificity was 75.7%. The computer program "Improvement of forecasting and risk methods of PE development" was developed and registered (certificate of state registration in the register of computer programs No. 09025 24.08.20, Federal Service for Intellectual Property, Tashkent).

The program Improvement of forecasting and risk methods of PE development, based on the determination of clinical and anamnestic factors and laboratory markers, can be recommended for routine use for early diagnosis and prediction of PE and a more differentiated approach to the implementation of therapeutic/preventive measures.

The program is designed to improve the methods of predicting and early diagnosis of preeclampsia. The use of this program allowed us to develop an algorithm for predicting and early diagnosis of preeclampsia and management tactics for this cohort of pregnant women, as well as to improve the treatment algorithm for preeclampsia in order to preserve health of mother and child.

Functional features of the program: registration of pregnant woman's card, collection, input, and storage of data on clinical, instrumental, anamnestic, genetic, and laboratory research methods. The program allows you to develop a diagnostic algorithm for determining the risk of preeclampsia developing and tactics for managing such pregnant women and work out methodological recommendations of screening for timely identification of a risk group for preeclampsia development.

The program can be used in practical medicine, in particular, in obstetrics, genetics, and neonatology. Using modern diagnostic methods, the program will assess the effect of FMS-like tyrosine kinase (sLIt-1), placental growth factor (PIGF) and AGTR types 1 and 2 on the course of pregnancy and the risk of preeclampsia. The use and inclusion of modern diagnostic methods in program will allow timely detect pregnancy complications-preeclampsia and develop a differentiated approach to its treatment. The main program parameters are included in Table 30.

Table 30.

Parameters of a computer program for PE predicting and early diagnosis.

№	***Indicators***	***Main characteristics***	***Scores***
1	**Severity**	Satisfactory condition	0
		Moderately severe condition	1
		Severe condition	2
2	**Burdened anamnesis**	0-1 risk factors	0
		2-4 risk factors	1
		5 and more risk factors	2
3	**Related somatic diseases**	No	0
		Chronic kidney disease	1
		Chronic arterial hypertension	2
4	**Thrombocytes**	$180\text{-}310 \times 10^9$ /l	0

		179-101 × 10^9 /l	1
		Less than 100 × 10^9 /l	2
5	**AST/ALT**	Up to 31 Un/l	0
		32-69 Un/l	1
		70 Un/l	2
6	**INR**	85-115%	0
		114-101%	1
		Менее 100 %	2
7	**FMS-like tyrosine kinase (sFlt-1)**	1357 Pg/ml	0
		1357-1458 Pg/ml	1
		Более 1458 Pg/ml	2
8	**Endothelial nitric oxide synthetase gene NOS3**	Genotype G/G	0
		Genotype G/T и T/T	1
9	**AGTR 1 and 2 types**	Genotype G/G	0
		Genotype G/A и A/A	1
10	**Serum creatinine**	39-72 mkmol/l	0
		71-68 mkmol/l	1
		Less than 67 mkmol/l	2
11	**Total bilirubin**	8,5-17,2 mkmol/l	0
		17,1-15,1 mkmol/l	1
		Less than 15,0 mkmol/l	2
12	**Fibrinogen**	2,6-5,6 gr/l	0
		2,5-2,1 gr/l	1
		Less than 2,0 gr/l	2
13	**Residual nitrogen**	14,3 up to 28,6 mmol/l	0
		28,7-30,1 mmol/l	1
		More than 30,2 mmol/l	2
14	**Placental growth factor**	42,8-80,58 pg/ml	0
		40,2-42,7 Pg/ml	1
		Less than 40,1 Pg/ml	2
15	**sFlt-1 / PlGF ratio Pg / ml**	4,2- 18,3 Pg/ml	0
		18,2-27,0 Pg/ml	1
		More than 27,1 Pg/ml	2
16	**Pregnancy-associated placental protein A (PAPP-A)**	1,47 - 8,54 MME/ml	0
		1,30-1,46 MME/ml	1
		Less than 1,29 MME/ml	2

Based on the data obtained, a score assessment of preeclampsia developing risk, followed by the choice of treatment tactics, was performed in 45 pregnant women up to 20 weeks of pregnancy:

0-5 points - pregnant women without risk of preeclampsia appearing. They require routine standard monitoring, carried out during the physiological course of pregnancy.

5-17 points - the risk of mild preeclampsia developing. The revealed changes in the study can be the basis for detailed monitoring of mild PE development, conducting detailed counseling, advice on nutrition, lifestyle, and after its manifestation – appropriate management tactics for the duration of pregnancy.

18-40 points – the risk of severe preeclampsia developing. The revealed changes during examination in risk groups may be basis for the using drugs that improve the rheological properties of blood and utero-fetal-placental blood flow, additional examinations by an obstetrician-gynecologist and a general practitioner in order to control blood pressure, correct hypertension, choose the method and time of delivery before the clinical manifestation of severe preeclampsia appear.

CHAPTER III. COURSE AND OUTCOMES OF PREGNANCY AND CHILDBIRTH IN PATIENTS WITH PREDICTED PREECLAMPSIA

The course and outcomes of pregnancy and childbirth in women of the second stage of study

Observations were made for 70 pregnant women, selected for the presence of clinical risk factors, from the first trimester of pregnancy at this stage of the study. All patients were registered for pregnancy up to 13 weeks. The entire range of studies indicated as markers of PE were performed to them. It was found from these studies, that already in the first trimester of pregnancy, 11 women (15.7%) have a tense functioning of hemostatic system, 7 (10%) have significant changes in the concentration of main endothelial factors, 3 patients (4.3%) had changes in gene and genotypic frequencies of polymorphisms AGTR1 A1166>C, AGTR2 G1675A, NOS3-786T/C, NOS3 - Glu298Asp, NOS3-C774T. Thus, 30% of women at risk for developing PE already had changes in some predictors of PE at an early stage. These patients were prescribed: aspirin 75 mg/day, tivortin 2 scoops x 4 times/day for 4 weeks, continue to take Elevit 1 tab. after breakfast.

All patients with diagnosed anemia were additionally prescribed oral iron medications at a dose of 60 -120 mg/day, depending on the severity of anemia.

The course of the first and second trimester of pregnancy in the group of patients of the second stage of the study in comparison with the main group of the first stage is presented in Table 31.

Table 31.

The course of I and II trimester of pregnancy in the group of patients of the second stage of the study.

Pregnancy complications		Main n=132	Main %	Second stage n=70	Second stage, %	$\chi 2$	P
I trimester	Vomiting of pregnant	29	22	14	20	**0,106**	**0,745**
	Threat of termination	10	7,6	5	7,1	**0,012**	**0,911**
	Anemia	52	39,4	27	38,6	**0,013**	**0,909**
	ARI (acute respiratory infection)	17	12,9	8	11,4	**0,089**	**0,766**
	No complications	26	19,7	12	17,1	**0,195**	**0,658**
	Combined pathology	2	1,5	3	4,3	**1,455**	**0,228**
II trimester	Threat of termination	17	12,9	7	10	**0,362**	**0,547**
	Anemia	78	59	31	44,3	**4,036**	**0,045**
	Preeclampsia	7	5,3	2	2,9	**0,643**	**0,423**
	ARI	6	4,5	3	4,3	**0,007**	**0,932**
	Placenta previa	1	0,8	1	1,4	**0,210**	**0,647**
	No complications	25	18,9	20	28,6	**2,451**	**0,117**
	Combined pathology	2	1,5	3	4,3	**1,455**	**0,228**

Analyzing data presented in Table 48, it can be concluded that in the first trimester of pregnancy in patients with developed PE and at risk of developing PE, such indicators as anemia, vomiting of pregnant women, and the threat of termination did not differ. However, combined complications of the first trimester in group of the second stage were 3 times more common than in main group. Special

attention should be paid to the fact that there is no significant progression of such disease as anemia in the group of the second stage compared to the main group (5.7% vs. 19.6%, respectively). This has to affect the development of PE, which was 2 times more common in patients of the main group in the second trimester. At the same time, the absence of complications in the second trimester in patients of the second stage was 1.5 times more often than in the main group, which indicates a positive effect of the preventive measures in patients at risk of PE.

Table 32 provides information on the course of the third trimester of pregnancy in two groups of examined women.

Table 32.

Course of the III trimester of pregnancy in groups of examined women.

Complications of pregnancy	Main n=132	Main %	Second stage, n=70	Второго этапа, %	χ2	P
Preeclampsia	132	100	14	20	**146,104**	**0,000**
Threat of termination	2	1,5	0	0	**1,071**	**0,301**
Placenta previa	1	0,8	1	1,4	**0,210**	**0,647**
Anemia	82	62,1	34	48,6	**3,435**	**0,064**
FADS	19	14,4	2	2,9	**6,536**	**0,011**
No complications	0	0	19	27	**39,548**	**0,000**

As can be seen from the table, the preventive measures carried out led to the fact that PE in patients at risk developed only in 20% of cases. At the same time, absence of third trimester complications revealed in 27% of women in this group.

The dynamic study of PE markers – biochemical, hemostasiological and endothelial - during pregnancy in patients of the second stage is presented in Table 33-34.

Table 33.

Dynamics of some biochemical and hemostasiological parameters in patients of the second stage of the study.

Indicator	Term of pregnancy				
	11-13 weeks	**20-21 weeks**	**28-32 weeks**	**34-37 weeks**	**38 weeks and more**
Bilirubin (mcmol/l) Total Direct Indirect	12,5±4,1 3,1±1,4 10,7 ± 2,9	16,1±4,1 4,2±1,4 12,3±2,9	15,8±4,1 4,2±1,4 11,2±2,9	18,1±4,1 5,7±1,4 14,3±2,9	18,7±4,1 5,8±1,4 15,5±2,9
ALT un/l	24,3±5,2	28,3±5,2	29,3±5,2	34,5±5,2	32,5±5,2
AST un/l	25,1±2,9	27,4±2,9	28,4±2,9	32,1±2,9	31,6±2,9
Residual nitrogen mmol/l	18,3±4,6	22,3±4,6	24,3±4,6	26,5±4,6	29,5±4,6
Creatinin **mcmol/l**	63,5±15,7	68,2±15,7	72,2±15,7	82±15,7	88,4±15,7
Blood sugar mmol/l	4,5±0,5	4,8±0,5	5,0±0,5	5,8±0,5	5,9±0,5
Total protein g/l	74,6± 8,3	70,2±8,3	68,2±8,3	61,5±8,3	60,5±8,3
Thrombocytes thousands Un/mcl	298,9±22,5	230,6±22,5	210,6±22,5	220±22,5	195±22,5
INR units	1,0 ± 0,15	1,0±0,15	0,9±0,15	0,9±0,15	0,9±0,15
APTT sec**.**	**27,5± 6,0**	25,4±6,0	24,4±6,0	24±6,0	23,2±6,0
Fibrinogen g/l.	2,8± 0,5	2,6±0,5	2,7±0,5	2,5±0,5	2,3±0,5
Blood coagulation time, min	8,4±1,0	7,2±1,0	**7,6±1,0**	6,4±1,0	**6,2±1,0**

It can be seen from this table, that with an increase in the duration of pregnancy, 20% of women experience gradual changes in hemostasis and liver tests, especially after 32 weeks of pregnancy.

Table 34.

Concentration of main endothelial factors in patients of the second stage.

Indicator	Term of pregnancy				
	11-13 weeks	**20-21 weeks**	**28-32 weeks**	**34-37 weeks**	**38 weeks and more**
sFlt-1 pg/ml	1582±121,4	2020±107,3	11543±103,4	12696±110,2	3779±90,3
PIGF pg/ml	40,4±11,2	30±10,9	31,1±9,8	63,3±12,5	43,0±11,6
PIGF/ sFlt-1 pg/ml	39,2±12,4	67,2±13,3	371,2±17,7	204,9±21,3	87,9±14,2
PAPP-A	0,17	1,47	8,54	6,52	9,6

It tends to be finished up from this table that a lessening in convergence of PlGF and an increment in grouping of sFlt-1 are recorded well before the clinical signs (around 5 weeks) of toxemia and can be utilized as screening tests toward the finish of the principal trimester of pregnancy. In the principal trimester of pregnancy, grouping of PlGF is essentially lower than that in the second trimester of pregnancy, and convergences of sFlt-1 are not fundamentally contrasted. The proportion of PlGF and sFlt-1 fixations at about four months are not altogether contrasted from the comparing markers at 17 and 18 weeks of pregnancy. At 19 weeks, the PlFG fixation altogether expanded, and at 20 weeks, it fundamentally surpassed that at 19 weeks . The proportion of PlGF and sFlt-1 fixations likewise changed as needs be. At 16-18 weeks of pregnancy, the sFlt-1/PlGF proportion found the middle value of 13.1±2.6, while at 19-20 weeks it was 6.9±2.1. It ought to be especially noticed that in the main trimester of pregnancy (11-13 weeks), the normal worth of this pointer was 39.3±4.2. Next we broke down the circumstance of the first manifestations of PE in quite a while in danger (Table 35).

Table 35.

Timing of the first symptoms of PE in patients at risk

Term of pregnancy	Symptoms					
	AH+ proteinuria	AH+ proteinuria + anasarca/ascites	AH+ proteinuria +headaches	AH+ proteinuria + epigastric pains	AH+ proteinuria + FADS	AH+ proteinuria + nausea, vomiting
24-28	1-1,4%					
28-32	3- 4,3%	1-1,4%		1-1,4%		1-1,4%
33-34					1- 1,4%	
35-38				1-1,4%		

This table shows that in 8 (11.4%) patients, clinical manifestations of PE in the form of arterial hypertension in combination with proteinuria occurred already at the time of 24-34 weeks. Another three women from the risk group at 28-32 weeks had symptoms of severe PE (anasarca, epigastric pain, headaches, nausea, vomiting), which required early termination of pregnancy. At 33-34 weeks these symptoms were observed in 1 (1.4%) patient, and at 35-38 weeks – in another 1 (1.4%). Thus, the appropriate examination and treatment carried out in the first trimester of pregnancy allowed to prolong pregnancies in patients from the risk group in 87.1% of cases with a relatively satisfactory condition of mother to a safe gestational age of fetus.

At the same time, special attention should be paid to the fact that changes in the studied endothelial factors appeared almost 5 (M±m) weeks earlier before the appearance of clinical symptoms of PE in 20 women (28.6%). And changes in hemostatic system and some biochemical parameters are observed in 20% of women at risk already in the early stages, and they progress with an increase in the duration

of pregnancy, especially after 32 weeks. Timely diagnosis of these conditions and conducted therapy allowed to avoid the development of severe PE in these pregnant women.

Outcomes of pregnancy and childbirth in women of the second stage of study

The outcomes of the present pregnancy in patients of the second stage of the study are presented in figure 9.

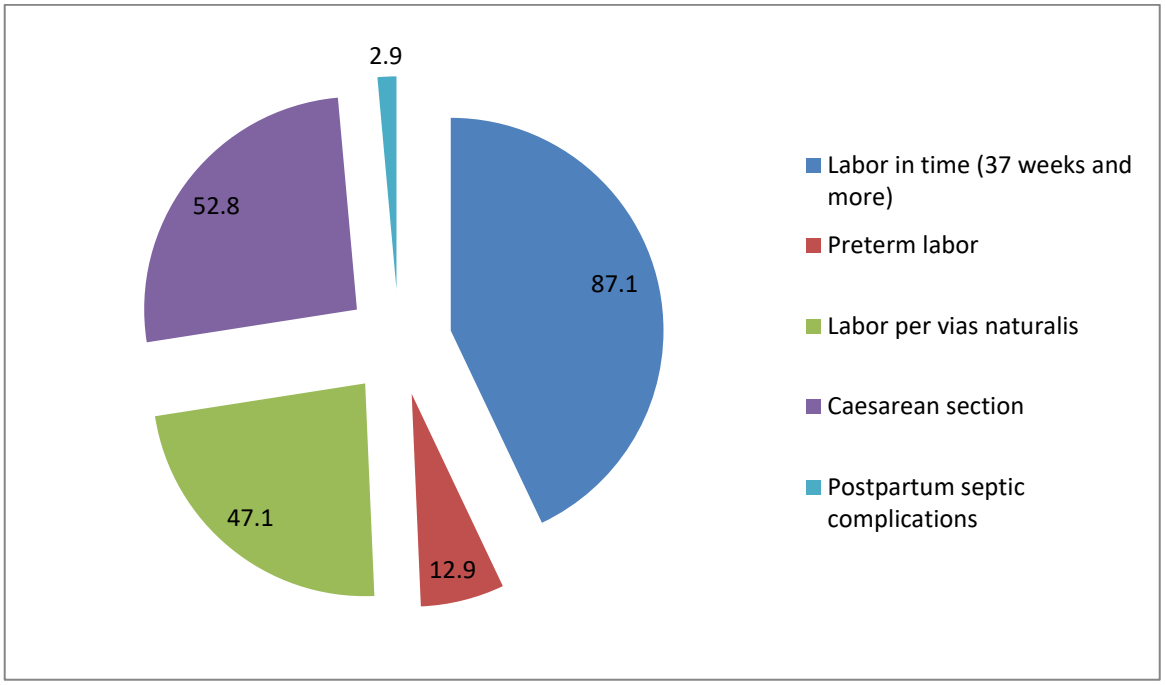

Figure 9.The pregnancy outcomes in patients of the second stage.

Analyzing the data in figure 9, it can be concluded that the early formation of the clinical risk group for PE, the appropriate examination and correction of changes in hemostatic system and vascular endothelial function, as well as dynamic monitoring of pregnant women, allowed to bring pregnancy to the delivery date in 87.1% of cases, 47.1% of cases to deliver per vias naturalis. Although abdominal delivery was performed in 52.8% of cases, 83.8% of operations were planned, which resulted in a significant reduction in complications, both intraoperative and postoperative. In all cases, a typical retrovesical Caesarean section was performed. The average blood loss during the operation was 780.0±50.5 ml, which is significantly lower than in the main group. We did not observe blood loss of more than 1000 ml in this group of examined patients. In this regard, blood transfusions

in patients of this group were not required. Combined spinal-epidural anesthesia was chosen as the main method of anesthesia during Cesarean section.

Table 36.

Newborns morphofunctional parameters.

Newborns weight	**Abs (%)**
2500,0 gr and more	61 (87,1%)
1500,0 г – 2499,0 gr	5 (7,1%)
1000,0г -1499,0 gr	3 (4,3%)
Less than 1000,0 gr	1 (1,4%)
Apgar score	
Time	
1 minute	7,5±1,5
5 minute	8,4±1,2
Status in points	
10-8	57(81,4%)
7-5	11(15,7%)
4-1	1(1,4%)
Artificial lung ventilation	1(1,4%)

At the same time, perinatal mortality in this group occurred only in one case – early onset of severe PE, Cesarean section at 27-28 weeks, a newborn weighing 970.0 was extracted in a state of severe asphyxia, intubated. However, resuscitation measures were ineffective. Perinatal mortality in this group was 1.4%, which is almost 4 times less than in main group.

CONCLUSION

Continuous search for diagnostic markers of PE is undergoing currently. In the context of practical obstetrics, the most important measures remain a carefully collected medical history, the identification of reliably associated with PE risk factors, as well as adequate laboratory diagnostics. Special attention is paid to modern methods of studying the parameters of hemostatic system and indicators of biochemical and clinical blood tests in laboratory diagnostics. Great importance is attached to the isolation of molecular genetic markers of PE. Among the most objective studies of hemostatic system for the purpose of predicting PE, we attributed a progressive decrease in the number of platelets throughout pregnancy, hypercoagulation, as well as markers of endothelial damage - the protein sLIt-1 and placental growth factor(PIGF). As a prognostic marker of PE, we considered pregnancy-associated plasma protein-A (PPAP-1), a highly glycolized protein complex synthesized by trophoblast. According to our data, a decrease in the level of PPAP-1 in the first trimester of pregnancy is associated with the development of severe PE and FADS. Many researchers have shown that angiogenesis in the formation of vessels of the placental system is of particular importance. Placental growth factor, vascular endothelial growth factor and their antagonists – soluble fms-bound tyrosine kinase and soluble endoglin-are associated with the development of PE [43,109]. Preeclampsia can be predicted at 12-14 weeks in the presence of the following signs: a history of PE in previous pregnancies, the presence of chronic arterial hypertension and diseases of the urinary system, obesity, as well as the first pregnancy and childbirth. These patients can be classified as a risk group according to clinical criteria. To predict PE for high – risk women based on clinical signs, the following markers are indicated: placental growth factor (PIGF), as well as its antagonist, soluble fms – like tyrosine kinase (sFlt-1), and their ratio. The introduction of the proposed method of forecasting allows you to identify high-risk groups for the development of PE, conduct weight correction, monitor overall weight gain and blood pressure, timely resolve the issue of hospitalization and

delivery, as well as conduct drug correction of changes in platelet hemostasis and prescribe nitric oxide donors.

We have proved that from the early stages of pregnancy in some patients from the clinical risk group, long before the appearance of clinical signs of PE, the level of soluble fms-like tyrosine kinase (sFlt-1) begins to increase, and the concentration of placental growth factor (PIGF) decreases. In future, the increase in the level of soluble fms-like tyrosine kinase (sFlt-1) continues and signs of PE are attaching. This section of our work is consistent with the conclusions of Stepan H. et al. that changes in some angiogenic factors occur on average 5 weeks before the onset of clinical symptoms of PE [182].

Thus, in modern conditions, the main task of obstetric science and practice is to reduce maternal and perinatal morbidity and mortality. PE/eclampsia makes a huge contribution to maternal morbidity and mortality. Every year, more than 50,000 women worldwide die from complications associated with PE/eclampsia [150,188]. Over the past decades, there has been an increase in this indicator, both in developed and developing countries, which can be explained by an increase in the number of age-related pregnant women, an increase in intergenetic interval, overweight, and deterioration of somatic health [188]. In this regard, in modern practical and scientific obstetrics, the most important measures for the early diagnosis and prognosis of PE are a set of studies: a carefully collected anamnesis, the identification of risk factors reliably associated with PE, early and adequate laboratory diagnostics, including the study of hemostatic system and molecular genetic predictors, as well as, if possible, timely drug correction of these changes.

Practical recommendations:

1. To assess the individual prognosis of PE development at the stage of pregnancy planning and its early stages, a developed prognostic test based on a multivariate analysis of clinical, anamnestic and genetic predictors of this complication should be used.

2. The determination of markers of preeclampsia in the third trimester of pregnancy can serve as a basis for final diagnosis and decision on the timing of delivery in order to preserve the life of woman and fetus.

3. The proposed computer program "Improvement of forecasting and risk methods of PE development" (certificate of state registration in the register of computer programs No. 09025 24.08.20 of the Federal Service for Intellectual Property, Tashkent) allows to identify risk groups for women with preeclampsia, timely correction of endothelial disorders with L-arginine aspirin 75 mg, as well as antianemic treatment and the appointment of vitamin-mineral complex.

4. The proposed diagram allows the practitioner to screen for preeclampsia in all pregnant women with early pregnancy according to main endothelial predictors (pregnancy-associated plasma protein –A (PPAP-1), placental growth factor (PLGF) as well as its antagonist – soluble fms-like tyrosine kinase)

LIST OF REFERENCES

1. Национальный стандарт по ведению беременности и родов при различных акушерских состояниях для акушер-гинекологов, смежных специалистов и акушерок родильных отделений. Министерство Здравоохранения Республика Узбекистан. 2017 г.

2. Аксенова А.С., Козиолова Н.А., Падруль М.М. Особенности течения гипертензивного синдрома и поражение органов-мишеней в зависимости от формы артериальной гипертензии у беременных //Уральский медицинский журнал, 2017.-N 6.-С.59-65

3. Айламазян, Э.К. Гестоз: теория и практика [Текст]: монография / Э.К. Айламазян, Е.В. Мозговая. - М.: «МЕДпресс-информ», 2008.- 272с. - Библиогр.: с.23 -189.

4. Ахметшин Р.З., Нургалиева А.Х., Миронов П.И. Полиморфизм генов ренин-ангиотензивной системы у детей с пороками развития мочевыводящей системы. //Экспериментальная и клиническая урология. – 2019. - №2.-стр.140-145

5. Богданов А.Р., Дербенева С.А., Черняк О.О., Богданова А.А., Гаппарова К.М., Григорьян О.Н. Генетические предикторы хронической сердечной недостаточности у больных ожирением// Ожирение и метаболизм. – 2019.- №1 (том 16) DOI: https://doi.org/10.14341/omet9667

6. Бурлев, В.А. Клинико-диагностическое значение определения фактора роста плаценты у беременных с хронической плацентарной недостаточностью [Текст] / В.А. Бурлев, З.С. Зайдиева, В.JI. Тютюнник // Проблемы репродукции.-2001.-№5.- С. 31 -34.

7. Ворожищева, А. Ю. Генетические факторы развития преэклампсии в популяциях различного этнического происхождения : автореф. дис. ... канд. мед. наук : 03.02.07 / Ворожищева Анна Юрьевна. –Томск, 2014. – 24 с

8. Временное клиническое руководство по ведению COVID 19 при беременности, в родах и послеродовом периоде. Минздрав Руз. Ташкент 2020

9. Головченко Ю.И., Трещинская М.А. Обзор современных представлений об эндотелиальной дисфункции// Consilium Medicum Ukraina.- 2008.- 11:38-40;

10. А.В. Дзансолова, А.М. Торчинов, Л.В. Акуленко, С.Г. Цахилова, Ф.Б. Кокоева, А.Ю. Скобейников, Д.Х. Сарахова. Возможная роль полиморфизма генов рецепторов ангиотензина II в развитии преэклампсии// Проблемы репродукции, 6, 2015.- стр. 134-136

11. Медведев Б.И. Клинико-биохимические предикторы развития пре-эклампсии/ Б.И.Медведев,Е.Г. Сюндюкова, nС.Л.Сашенков //Акушерство и гинекология.- 2013.- №5.-с.0-35

12. Методические рекомендации. Организация оказания медицинской помощи беременным, роженицам, родильницам и новорожденным при новой коронавирусной инфекции COVID 19. Версия 1 (24.04.2020). Мз Российской Федерации

13. Мозговая, Е.В. Диагностика и медикаментозная коррекция эндотелиальной дисфункции при гестозе [Текст]: афтореф. дис. д-ра мед. наук: 14.00.01./ Мозговая Елена Борисовна;[Санкт-Питер. мед. инс-т.].- Спб, 2004.-30с.-Библиогра.: с. 10-22.

14. Молекулярные маркеры в оценке степени тяжести гестоза [Текст] / И.С. Сидорова [и др.] // Акушерство и гинекология.- 2008.-№4.-С.6-11.

15. Мурашко, JI.E. Роль эндотелия в патогенезе гипертензии при беременности [Текст] /JI.E. Мурашко, И.В. Тумбаев, О.Н. Ткачёва // Проблемы беременности-2006.-№11.-С.49-54.

16. Оценка степени тяжести гестоза [Текст] / Сидорова И.С [и др.] // Акушерство и гинекология.-2008.-№3.-С.40-43.

17. Патогенез гестоза как проявление иммунокомплексной патологии эндотелия [Текст] / Сидорова И.С [и др.] // Акушерство и гинекология.-2008.-№6.- С.13-18

18. Прогностическая значимость молекул адгезии клеток сосудов в оценке степени тяжести гестоза [Текст] / Шеманаева Т.В. [и др.] // Акушерство и ги- некология.-2008.-№2.-С. 16-19.

19. Савельева Г.М., Шалина Р.И., Коноплянникова А.Г.,Симухина М.А. Преэклампсия и эклампсия: новые подходы к диагностике и оценке степени тяжести// Акушерство и гинекология: новости, мнения, обучение. 2018. Т. 6, № 4. С. 25–30. doi: 10.24411/2303-9698-2018-14002.

20. Седашкина О.А., Маковецкая Т.А., Печкуров Д.В. Роль некоторых генетических факторов в прогрессировании хронической болезни почек у детей. Практическая медицина 2015, (7):72-77.;

21. Скворцова, В.И. Синдром задней обратимой энцефалопатии / В.И. Скворцова, Л.В. Губский, Е.А. Мельникова // Журнал неврологии и психиатрии им. С.С. Корсакова. — 2010. — № 5. — С.104—109

22. Соболева, Г.М. Активность матриксных металлопротеиназ -2 и -9 в сыворотке крови [Текст] / Г.М. Соболева, А.В. Шуршалина, Г.Т. Сухих // Бюллетень экспериментальной биологии и медицины. -2006.- Т. 141.

23. Ушакова, Г.А. Регуляторные и адаптационные процессы в системе мать-плацента-плод при гестозе различной степени тяжести [Текст] / Г.А. Ушакова, Ю.В. Рец // Акушерство и гинекология.-2008.-№4.-С.11-15.

24. Халфорд-Князева И.П. Генетические маркеры прогнозирования преэклампсии : автореф. дис. ...канд. мед. наук : 14.01.01 : 03.01.04 / Халфорд-Князева Инесса Павловна. – М., 2013. – 16 с

25. Хасисов, П.З. Металлопротеиназы матрикса нормальных тканей человека [Текст] /. П.З. Хасисов // Биохимия.- 2001. -Т.66- Вып.2.- С. 167-179.

26. Шалина, Р.И. Состояние здоровья женщин после перенесенного гестоза [Текст] / Р.И. Шалина // Вопросы гинекологии, акушерства и перинатологии. - 2004.-Т.№5,- С. 59-63.

27. Шифман, Е.М. Преэклампсия, эклампсия, HELLP- синдром [Текст] / Е.М. Шифман.- Петрозаводск.:«ИнтелТек», 2003.-429с.-Библиогр.: с. 80-127.

28. Aggarwal, P.K. Low urinary placental growth factor is a marker of preeclampsia. [Текст] / P.K. Aggarwal, V. Jain, V. Sakhuja // J. Kidney Int. - 2006.-Vol.69.-№3.-P.621-624.

29. Ahmad, S. Elevated placental soluble vascular endothelial growth factor receptor-1 inhibits angiogenesis in preeclampsia [Текст] / S. Ahmad, A. Ahmed // J. Circ. Res. - 2004.-Vol.29.-№9.-P.884-891.

30. Aksenova A. S., Koziolova N. A., Padrul M. M. Features of hypertensive syndrome course and target organ damage depends on the form of arterial hypertension in pregnant women //Ural Medical Journal, 2017. - N 6. - p. 59-65

31. Akulenko A.V., Tsakhilova S. G., Dzansolova A.V., Sarakhova D. H., Kokoeva F. B., Kravtsova M. E. The role of renin-angiotensin system gene polymorphism in the etiology and pathogenesis of preeclampsia //Problems of reproduction, 2015. - N 1. - p. 8-11

32. Allaire, A.D. Placental apoptosis in preeclampsia [Текст] / A.D. Allaire, K.A. Ballenger, S.R. Wells // J. Obstet. Gynecol. - 2000,-Vol. 96.-№2.- P.271-276.

33. Anand S., Bench Alvarez T. M., Johnson W. E. et al. Serum biomarkers predictiuve of preeclampsia. Biomark Med., 2015; 9(6):563-575. DOI:10.2217/bmm.15.21;

34. Anthony, R.V. Transcriptional regulation in the placenta during normal andcompromised fetal growth factor [Текст] / R.V. Anthony, S.W. Limesand, K.M. Jeckel // J. Biochem. Soc. Trans.-2001.-Vol.29.-№2.-P.42- 48.

35. Banzola, I. Performance of a panel of maternal serum markers in predicting preeclampsia at 11-15 weeks' gestation [Текст] / I. Banzola, A. Farina, M. Concu // J. Prenat Diagn.- 2007.-Vol.27.-№11.-P. 1005-1010.

36. Baranov V. S. Genetic passport-the basis of individual and predictive medicine. Saint Petersburg: publishing house N-L. 2009; 528.

37. Bass, K. N. Tissue inhibitor of metalloproteinase-3 expression is upregulated during human cytotrophoblast invasion in vitro [Текст] / K. N. Bass, E. Haward, S. P. Hawkes //J. Dev. Genet-1997.-Vol.21.-№1.-P.61-67.

38. Baumann, M.U. Serum markers for predicting pre-eclampsia [Текст] / M.U. Baumann, N.A. Bersinger, D.V. Surbek // J. Mol. Aspects Med. -2007.-Vol.28.-№2.-P.227-244.

39. Bdolah, Y. Recent advances in understanding of preeclampsia [Текст] / Y. Bdolah, S.A. Karumanchi, B.P. Sachs // J. Croat Med- 2005.-Vol.46.-№5.-P.728-736.

40. Bdolah, Y. Twin pregnancy and the risk of preeclampsia: bigger placenta or relative ischemia? [Текст] / Y. Bdolah, C. Lam, A. Rajakumar // J. Obstet Gynecol.-2008.-Vol.l98.-№4.-P.428.-435.

41. Berkane, N. Angiogenic factors in preeclampsia: so complex, so simple? [Текст] / N. Berkane, G. Lefevre, A. Hertig // J. Nephrol Dial Transplant.-2007.-Vol.22.-№10.-P.2753-2756.

42. Borkakoti, N. Structural studies of matrix metalloproteinases [Текст] / N. Borkakoti // J. Mol. Med.-2001 .-Vol.78.-P.261-268.

43. Boulanger, H. New insights in the pathophysiology of preeclampsia and potential therapeutic implications[TeKCT] / H. Boulanger, M. Flamant //J. Nephrol Ther.-2007.-Vol.3.-№7.-P.43 7-348.

44. Brew, K. Tissue inhibitors of metalloproteinases: evolution, structure and function [Текст] / K. Brew, D. Dinakarpandian, H. Nagase // J. Biochim. Biophys. Acta.-2000.- Vol. 1477.-P.267-283

45. Buhimschi, C.S. Fractional excretion of angiogenic factors in women with severe preeclampsia [Текст] / C.S. Buhimschi, L. Magloire, E. Funai // J. Obstet. Gynecol.- 2006.-Vol.l07.-№5.-P.l 103-1113.

46. Buhimschi, C.S. Urinaiy angiogenic factors cluster hypertensive disorders and identify women with severe preeclampsia [Текст] / C.S. Buhimschi, E.R. Norwitz, E. Funai // J. Obstet. Gynecol.- 2005.- Vol.l93.-№6.-P.2181-2182.

47. Burton, G.J. Placental vascular morphodenesis [Текст] / G.J. Burton, D.S. Charnock-Jones // Best practice&research.-2000.-Vol.l4.-№6.-P.953-968.

48. Campbell, S. Chorionic villus sampling as a source of trophoblasts [Текст] / S. Campbell, J.H. Park, J. Rowe // J. Placenta.- 2007.-Vol.28.-№11.-P.ll 18-1122.

49. Campbell, S. Interaction of Cocultured Decidual Endotelial Cells and Cytotrophoblasts in Preeclampsia [Текст] / S. Campbell, J. Rowe, C.J. Jackson //J. Biol. Reprod.-2004.-Vol.71.-P.244-252.

50. Carmeliet, P. Mechanisms of angiogenesis and arteriogenesis [Текст] / P. Carmeliet //J. Nat. Med.-2000.-Vol.6. -№4.- P.389-395.

51. CDC. 2019 Novel Coronavirus URL: https://www.cdc.gov/coronavirus/2019-ncov/index.html

52. Chaiworapongsa, T. Plasma soluble vascular endothelial growth factor receptor-1 concentration is elevated prior to the clinical diagnosis of pre-eclampsia [Текст] / T. Chaiworapongsa, R. Romero, Y.M. Kim // J. Matern. Fetal Neonatal Med.-2005.-Vol.l7.-P.13-18.

53. Chaiworapongsa, T. Evidence supporting a role for blockade of the vascular endothelial growth factor system in the pathophysiology of preeclampsia [Текст] / T. Chaiworapongsa, R. Romero, J. Espinoza // J. Obstet. Gynecol.-2004.-Vol. 190.- P.1541-1547.

54. Chesley LC, Annitto JE, Cosgrove RA. The familial factor in toxemia of pregnancy. Obstet Gynccol 1968;32:30-3-11; Chesley LC, Cooper DW. Genetics of hypertension in hypertension: Possible single gene control pre-eclarnpsia and eclamp sia in the descendents of eclamptic women. Br J Obstet Gyn-accol 1986;93:898-908.

55. Chiro, R. Novel functions of TIMPs in cell signaling [Текст] / R. Chiro, X.W. Liu, K.K. Jung // J. Cancer Metastasis. -2006.-Vol. 25.-№l.-P.99-l 13.

56. Chung, I. B. Expression and regulation of vascular endothelial growth factor in a first trimester trophoblast all line [Текст] / I.B. Chung, F.D. Yelian, F.M. Zaher // J. Placenta.-2000.-Vol.21,- №4.- P.320-324.

57. Cockle, J.V. Matrix metalloproteinases and their tisse inhibitors in preterm perinatal complications [Текст] / J.V. Cockle, N. Gopichandran, J.J. Walker //J. Re- prod. Sci. -2007.-Vol. 14.-№7.-P.629-645.

58. Coolman, M. Matrix metalloproteinase-9 gene - 1562CVT polymorphism mitigates preeclampsia [Текст] / M. Coolman, M. Maat. W.L. Van Heerde // J. Placenta.-2007.-Vol.28.-№7.-P.709-713.

59. Cooper, J. VEGF mRNA levels in placentae from pregnancies complicated by preeclampsia [Текст] / J. Cooper //J. Obstet. Gynaecol.-1999.-Vol. 103.-P. 11911196.

60. COVID-19 бўйича миллий қўлланма. Ўзбекистон Республикаси Соғлиқни Сақлаш Вазирлиги Жаҳон соғлиқни сақлаш ташкилоти. Тошкент, 2020

61. Crispi, F. Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction [Текст] / F. Crispi. C. Domínguez, E. Llurba //J. Obstet. Gynecol.- 2006.-Vol.l95.-№1.-P.201-207.

62. Cross, J. C. The genetics of pre-eclampsia: a feto-placental or maternal problem? [Текст] / J. C. Cross // J. Clin. Genet. - 2003.-Vol.64.-№2.-P.96-103.

63. Davison, J.V. New aspects in the pathophysiology of preeclampsia [Текст] / J.V. Davison, V. Homuth, A. Jeyabalan // J. Soc. Nephrol.-2004.-Vol. 15.-P.2440-2448.

64. De Jager, C.A. MMP-9, placental syncytiotrophoblast and the endothelial dysfunction of preeclampsia [Текст] / C.A. De Jager, E.A. Linton, I.Spyropoulou // J.Placenta.-2003.-Vol.24.-№l.-P.84-91.

65. Dekker G, Sibai B. Primary, secondary, and tertiary prevention of pre-eclampsia. Lancet. 2001;357:209-215. 7. Jin JJ, Nakura J, Wu Z, Yamamoto M, Abe M, Chen Y, et al. Association of angiotensin II type 2 receptor gene variant with hypertension. Hypertens Res. 2003; 26:547-552.

66. Erez, O. The change in concentrations of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters in risk assessment

for the subsequent development of preeclampsia and small-for-gestational age. [Текст] / O. Erez, R. Romero, J. Espinoza //J. Matern. Fetal Neonatal Med.-2008.-Vol.21.№5.-P.279-87.

67. Espinoza , J. Identification of patients at risk for early onset and/or severe preeclampsia with the use of uterine artery Doppler velocimetry and placental growth factor [Текст] / J. Espinoza, R. Romero, J.K. Nien // J. Obstet. Gynecol.-2007.- Vol.l96.-№4.-P.326-333.

68. Fatini C, Abbate R, Pepe G, Battaglini B, Gensini F, Ruggiano G, et al. Searching for a better assessment of the individual coronary risk profile. The role of angiotensin-converting enzyme, angiotensin II type 1 receptor and angiotensinogen gene polymorphisms. Eur Heart J. 2000;21:633-638.

69. FDA. Novel coronavirus (2019-nCoV) URL: https://www.fda.gov/emergency-preparedness-andresponse/mcm-issues/novel-coronavirus-2019-ncov

70. Fedele, A.O. Regulation of gene expression by the hypoxia-induciblefactors [Текст] /A.O. Fedele, L.W. Murray, D.J. Peet //J. Molecular Interventions.-2002.-Vol.2.-P.229-243.

71. Fetisov, I. A. Panova, E. A. Rokotyanskaya, S. Yu. Ratnikova,E. V. Smirnova,N. S. Fetisov studies (ГЕНЕТИЧЕСКИЕ ФАКТОРЫ РАЗВИТИЯ ПРЕЭКЛАМПСИИ. Вестник Ивановской медицинской академии Т. 20, № 3, 2015

72. Fisher, S.J. The placental problem: linking abnormal cytotrophoblast diffentia-tion to the maternal symptoms of preeclampsia [Текст] / S.J. Fisher //J. Reprod. Biol. Endocrinol.-2004.-Vol.2.-P.53-68.

73. Foyouzi, N. Placental growth factor in the cerebrospinal fluid of women with preeclampsia [Текст] / N. Foyouzi, E.R. Norwitz, L.C.Tsen //J. Gynaecol. Obstet.-2006.-Vol.92.-№l.P.32-37.

74. Fraser, R. Interleukin-4 -590 (OT), toll-like receptor-2 +2258 (G>A) and matrix metalloproteinase-9 -1562 (OT) polymorphisms in pre-eclampsia [Текст] / R. Fraser, J.J. Walker, U.V. Ekbote // BJOG.-2008.-Vol.l 15.-№8.-P.1052-1056

75. Furruck S., Malik M. Renin-angiotensin system: genes to bedside // Am. Heart. J. 2007. Vol. 134, № 3. P. 514-527.

76. Galewska, Z. Gelatinase matrix metalloproteinase (MMP)-2 and MMP-9 of the umbilical cord blood in preeclampsia [Текст] / Z. Galewska, L. Romanowicz, S. Jaworski //J. Clin. Chem. Lab. Med. -2008.-Vol.46.-№4.-P.517-522.

77. Garovic, V.D. Urinary podocyte excretion as a marker for preeclampsia [Текст] / V.D. Garovic, S.J. Wagner, S.T. Turner //J. Obstet. Gynecol.-2007.- №7.-P.196-220.

78. Goldman-Wohl, D. Regulation of trophoblast invasion: from normal implantación to preeclampsia [Текст] / D. Goldman-Wohl, S. Yagel // J. Mol. Cell Endocrinol.-2002.-Vol.22.-№12.-P.233-238.

79. Coronavirus (COVID-19) Infection in Pregnancy. Information for healthcare professionals Version 9: Published Wednesday 13 May 2020. RCOG

80. Google Формы – онлайн-инструмент для создания форм обратной связи. https://te-st.ru/enteries/google-forms/

81. Graham, C.H. Altered expression of gelatinase and surface-associated plasminogen activator activity by trophoblasts cells isolated from placentas of preeclamptic patients [Текст] / C.H. Graham, K.R. McCrae //J. Obstet. Gynecol.-1999,-Vol. 175.-№3.-P.555-562.

82. Gribouval O, Gonzales M, Neuhaus T, Aziza J, Bieth E, Laurent N et al. Mutations in genes in the renin-angiotensin system are associated with autosomal recessive tubular dysgenesis. Nat Genet 2005, 37: 964-968

83. Grishko V, Pastukh V, Solodushko V, Gillespie M, Azuma J, Schaffer S. Apoptotic cascade initiated by angiotensin II in neonatal cardiomyocytes: role of DNA damage. Am J Phisiol Heart Circ Phisiol. 2003;285:H2364-H2372

84. https://www.rcog.org.uk/en/guidelines-research-services/coronavirus-covid-19-pregnancy-and-womens-health/

85. Gupte Sanjay • Wagh Girija. The Journal of Obstetrics and Gynecology of India (January–February 2014) 64(1):4–13 DOI 10.1007/s13224-014-0502-y

86. Harma, M. Oxidative stress in women with preeclampsia [Текст] / M. Harma, O. Erel //J. Obstet. Gynecol.-2005.-Vol.l 92.-№2.-P.656-657.

87. Helske, S. Expression of vascular endothelial growth factor receptors 1, 2 and 3 in placentas from normal and complicated pregnancies [Текст] / S. Helske, P. Vuorela, O. Carpen//J. Mol. Hum. Reprod.-2001.-Vol.7.-№2.-P.205-210.

88. Hertig, A. Maternal serum sFlt 1 concentration is an early and reliable predictive marker of preeclampsia [Текст] / A. Hertig, N. Berkane, G. Lefevre // J. Clinical Chemistry.-2004.-Vol.50.-P. 1702-1703.

89. Huisman, M.A. Matrix-metalloproteinase activity in first trimester placental bed biopsies in further complicated and uncomplicated pregnancies [Текст] / M.A. Huisman, A. Timmer , M. Zeinstra // J. Placenta.-2004.-Vol.25.-№4.-P.253-258.

90. Hunter, A. Serum levels of vascular endothelial growth factor in preeclamptic and normotensive pregnancy [Текст] /A. Hunter, M. Aitkenhead, C. Caldwell // J. Hypertension.-2000.-Vol.36.- №6,- P.965-969.

91. Ke, Y. Involvement of matrix metalloproteinase-2,-9, and inhibitors of me- talloproteinase-1, 2 in occurrence of the accrete placenta [Текст] / Y. Ke, J.H. Lu, B.L.Yang // Zhonghua Fu Chan Ke Za Zhi.-2006.-Vol.41 ,-№5.-P.311-314.

92. Kim Yong-DIN, F. P. Nishanova, A. Kh.Karimov, A. S. Lubich. Placental circulation and pre-eclampsia outcomes under the influence of arginine therapy. Women's health, No. 6, 2019. Page 2-7

93. Khan KS, WojdylaD, Say L, et al. WHOanalysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066–74

94. Kolialexi A., Tsangaris G.T., Sifacis S. et al. Plasma biomarkers for the identification of women at risk for early-onset preeclampsia. Expert rev. Proteomics. 2017:14(3):269-276. DOI:10.1080/1489450.2017.1291345;

95. Krauss, T. Prospective analysis of placenta growth factor (PIGF) concentrations in the plasma of women with normal pregnancy and pregnancies complicated by preeclampsia [Текст] / T. Krauss, H.U. Pauer, H.G. Augustin // J. Hypertens Preg- nancy.-2004.-Vol.23 .-№ 1 .-P. 101-111.

96. Lam, C. Circulating angiogenic factors in the pathogenesis and prediction of preeclampsia [Текст] / C. Lam, K.H. Lim, S.A. Karumanchi //J. Hypertension.-2005.-Vol.46.-P. 1077—1085.

97. Lash, G. E. Vascular endothelial growth factor and placental growth factor release in cultured trophoblast cells under different oxygen tensions [Текст] / G. E. Lash, C. M. Taylor, A. J. Trew // J. Growth Factors.-2002.-Vol.20.-№4.-P.189-196.

98. Lee, K.J. Vascular endothelial growth factor induces endothelin-1 production via matrix metalloproteinase-2 rather than endothelin-converting enzyme-1 [Текст] / K.J. Lee, M.K. Kim, Y.H. Park // J. Hypertens pregnancy.-2007.-Vol.26,-№2.-P. 189-199.

99. Lei, T. Influences of Extracellular Matrix and of Conditioned Media on Differentiation and Invasiveness of Trophoblast [Текст] / T. Lei, H.P. Hohn, R. Behr //J. Placenta.-2007.-Vol.28.-№1.-P.14-21

100. Levine, R.J. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. [Текст] / R.J. Levine, C. Lam, C. Qian // Engl. J Med.-2006.-Vol.7.- №10.-P.992-1005.

101. Levine, R.J. Circulating angiogenic factors and the risk of preeclampsia [Текст] / R.J. Levine, S.E. Maynard, C. Qian // Engl. J Med.-2004.-Vol.350.-P.672- 683.

102. Levine, R.J. Urinary placental growth factor and risk of preeclampsia [Текст] / R.J. Levine, R. Thadhani, C. Qian //JAMA-2005.-Vol.293.-P.77-85.

103. Li H., Gu B., Zhang Y. Hypoxia-induced increase in soluble Flt-1 production correlates with enhanced oxidative stress in trophoblast cells from the human placenta [Текст] / H. Li, B. Gu, Y. Zhang // J. Placenta.-2005.-Vol.26.-№3.-P.210- 217.

104. Li, J.K. Differences between the expression of matrix metalloproteinase- 2,9 in preeclampsia and normal placental tissues [Текст] / J.K. Li, Q. Xiong, S. Zhou // Zhonghua Fu Chan Ke Za Zhi.-2007.-Vol.42.-№2.-P.73-75.

105. Lindheimer, M.D. Explaining and predicting preeclampsia [Текст] / M.D. Lindheimer, J.G Umans //N Engl. J Med.-2006.-Vol.7.-№10.-P.l 056-1058.

106. Livingston, J. C. Placenta growth factor is not an early marker for the development of severe preeclampsia [Текст] / J. C. Livingston, L. A., Gorski, P. Neb- lett // J. Obstetrics & Gynecology. -2001.-Vol.184.-№6-P. 1218-1220.

107. Lockwood, C.J. Cell-expressed Tissue Factor in Human Pregnancy and Its Involvement in Hemostasis and Preeclampsia-related Angiogenesis [Текст] / C.J Lockwood, G. Krikun, R. Caze // Ann N Y Acad. Sci.- 2008.-Vol.l 127.-P.67-72.

108. Lockwood, C.J. Matrix metalloproteinase -9 (MMP-9) expression in preeclamptic decidua and MMP-9 induction by tumor necrosis factor alpha and inter- leukin 1 beta in human first trimester decidual cells [Текст] / C J. Lockwood, C. Oner, U.A. Kayisli //J. Biol. Reprod.-2008.-Vol.78.-№6.-P. 1064-1072.

109. Luo X, Li X.Long Non-Coding RNAs Serve as Diagnostic Biomarkers of Preeclampsia and Modulate Migration and Invasiveness of Trophoblast Cells.Med Sci Monit. 2018 Jan 5;24:84-91

110. Mackay AP, Berg C, Atrash H (2001) Pregnancy-Related Mortality From Preeclampsia and Eclampsia. Obstet Gynecol 97(4):533–538

111. Mahameed, S. The effect of serum from women with preeclampsia on JAR (trofoblast-like) cell line [Текст] / S. Mahameed, S. Goldman, D. Gabarin // J. Soc. Gynecol. Inwestig.-2005.-Vol. 12.-№6.-P.45-50.

112. Malemud, C.J. Matrix metalloproteinases in health and disease: an overview [Текст] / C.J. Malemud //J. Front Bioci.-2006.-Vol. 1 .-№ 11 .-P. 1696-1701

113. Masuyama, H. Circulating angiogenic factors in preeclampsia, gestational proteinuria, and preeclampsia superimposed on chronic glomerulonephritis [Текст] / H. Masuyama, N. Suwaki, H. Nakatsukasa \\ J. Obstet. Gynecol.- 2006.-Vol.194,- №2.-P.551-556.

114. Maymon, E. A role for the 72 kDa gelatinase (MMP-2) and its inhibitor (TIMP-2) in human parturition, premature rupture of membranes and

intraamniotic infection [Текст] / E. Maymon, R. Romero, P. Pacora //J. Perinat. Med.-2001.- Vol.29.-№4.-P.308-316.

115. Maynard, S.E. Excess placental soluble fms-like tyrosine kinase -1 (sFltl) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia [Текст] / S.E. Maynard, J.Y. Min, J. Merchan // J Clin. Invest.-2003.- Vol. 111.-P.649-658.

116. Merchant, S.J. The role of matrix metalloproteinases in vascular function: for normal pregnancy and preeclampsia [Текст] / S.J. Merchant, S.T. Davidge // B JOG.-2004-Vol. 111 ,-№9.-P.931 -939.

117. Merchant, S.J. The effects of preeclampsia and oxygen environment on endothelial release of MMP-2 [Текст] / S.J. Merchant, H. Narumiya, L.J. Guilbert // J. Hypertens Pregnancy.- 2004.- Vol.23.-№1.-P.47-60.

118. Michael, A. MMP-9 activity in urine of patients at risk premature delivery [Текст] / A. Michael, G. Xinhua, G. Warwick// J. Obstet. Gynecol.-1999.- Vol. 181.- P.387-388.

119. Mignini, L.E. Mapping the theories of preeclampsia: The need for systematic reviews of mechanisms of the disease [Текст] / L.E. Mignini, J. Villar, K.S Khan // American Journal of Obstetrics & Gynecology.-2006.-Vol.l94.-P.317-321.

120. Moore Simas, T.A. Angiogenic factors for the prediction of preeclampsia in high-risk women [Текст] / T.A Moore Simas, S.L. Crawford, M.J. Solitro //J. Obstet. Gynecol.-2007.-Vol.l97.-№3.-P.244-248.

121. Moretti, M. Increased breath markers of oxidative stress in normal pregnancy and in preeclampsia [Текст] / M. Moretti, M. Phillips, A. Abouzeid //J. Obstet. Gynecol.-2004-Vol.190.-№5.-P.1184-1190.

122. Muller, P.R. Circulating angiogenic factors and abnormal uterine artery Doppler velocimetry in the second trimester [Текст] / P.R. Muller, A.H. James, A.P. Murtha //J. Hypertens Pregnancy.- 2006.-Vol.25.-№3.-P.l 83-192.

123. Munaut, C. Hypoxia is responsible for soluble vascular endothelial growth factor receptor-1 (VEGFR-1) but not for soluble endoglin induction in

villous trophoblasts [Текст] / C. Munaut, S. Lorquet, C. Pequeux // J. Hum. Reprod.-2008.- Vol.l4.-P.48-61.

124. Murphy, G. Mechanisms for pro matrix metalloproteinase activation [Текст] / Murphy G., Stanton H., Cowell S. // APMIS.-1999.-Vol.l07.-P.38-^4.

125. Mutter, W.P. Molecular mechanisms of preeclampsia [Текст] / W.P. Mutter, S.A. Karumanchi // J. Microvasc. Res.-2008.-Vol.75.-№l.-P.l-8.

126. Myers, J.E. MMP-2 levels are elevated in the plasma of women who subsequently develop preeclampsia [Текст] / J.E. Myers, S.J. Merchant, M. Macleod //J. Hypertens Pregnancy.-2005.-Vol.24.-№2.-P. 103-115.

127. Nagase, H. Matrix metalloproteinases [Текст] / H. Nagase, J.F. Woess- ner// J. Biol. Chem.-1999.-Vol. 274-P.1491-1494.

128. Nakano, M. Membrane-type 1 matrix metalloproteinase is induced in decidual stroma without direct invasion by trophoblasts [Текст] / M. Nakano, T. Hara, T. Hayama //J. Mol. Hum. Reprod.-2001.-Vol. 7.-P.271-277.

129. Narumiya, H. MMP-2 is elevated in the plasma of women with preec-lampsia [Текст] / H. Narumiya, Y. Zhang, C. Fernandez-Patron // J. Hypertens Pregnancy. -2001 .-Vol.20.-№2.-P. 185-194.

130. Ong, S. Angiogenesis and placental growth in normal and compromised pregnancies [Текст] / S., Ong, G. Lash, P.N. Beker // Best practice&research.-2000.- Vol. 14.-№6.-P.969-980.

131. Palei, A.C. Comparative assessment of matrix metalloproteinase (MMP)-2 and MMP-9, and their inhibitors, tissue inhibitors of metalloproteinase (TIMP)-l and TIMP-2 in preeclampsia and gestational hypertension [Текст] / A.C. Palei, V.C. Sandrim, R.C. Cavalli //J. Clin. Biochem.-2008.-Vol.41.-№10.-P.875-880.

132. Pang, Z.J. Expression profile of trofoblast invasion-associated denes in preeclamptic placenta [Текст] / Z.J. Pang, F.Q. Xing // J. Biomed. Sci.-2003.-Vol. 60.-№2.-P.97-101.

133. Papageorghiou, A.T. Uterine artery Doppler screening for adverse pregnancy outcome [Текст] / A.T. Papageorghiou., N. Roberts //J. Obstet. Gynecol.-2005.-Vol. 17.-№6.-P.584-590.

134. Park, S.Y. Increased sFlt-1 to P1GF ratio in women [Текст] / S.Y. Park, M.H. Lee, D.J. Kim //J Korean Med. Sci.-2007.-Vol.22.-№5.-P.873-877.

135. Pasha O., McClure E.M., Saleem S. et al. A prospective cause of death in low and middle-income countries: result from global Network Maternal Newborn Health Registry. BJOG. 2018; 125 (9):1137-1143. DOI: 10.1111/1471-0528.-15100

136. Petersen, T.M. Angiogenic proteins: possible markers of physiopatho- logical processes during fetal development [Текст] / T.M. Petersen, T. Larsen, H.J. Nielsen // Ugeskr. Laeger.-2003.-Vol.l65.-№32.-P.3082-3087.

137. Pilka, R. Significance of matrix metalloproteinases in pregnancy [Текст] / R. Pilka, M. Prochazka, M. Kudela //J. Ceska Gynekol. -2003.-Vol. 68.-№4.-P.259-264.

138. Porter, S. The ADAMTS metalloproteinases [Текст] / S. Porter, I.M. Clark, L. Kevorkian // J. Biochem. -2005.-Vol.15.-P.l 5-27.

139. Pridjian, G. Preeclampsia: past 1-clinical and pathophysiologyc considerations [Текст] / G. Pridjian, J.B. Puschett // J. Obstet. Gynecol.-2002.-Vol.57.- P.598-618.

140. Qiao, C. Expression of trophoblast invasion related genes mRNA and protein in human placenta in preeclampsia [Текст] / C. Qiao, S.L. Zhang, Q.D. Lin // Zhonghua Fu Ke Chan Za Zhi.-2006.-Vol.41 ,-№8.-P.509-513.

141. Qiao, C. The role of KISS-1 and MMP-9 in regulation of invasion of trophoblasts [Текст] / C. Qiao, D.L. Cheng, S.L. Zhang // Zhonghua Yi Xue Za Zhi. -2005.-Vol.85.-№12.-P.839-842.

142. Raffetto, J.D. MMPs and their inhibitors in vascular remodeling and vascular disease [Текст] / J.D. Raffetto, R.A. Khalil // J. Biochem. Pharmacol.-2008.- Vol. 75.-№2.-P.346-359.

143. Redman, C.W. Preeclampsia, the placenta and the maternal systemic inflammatory response [Текст] / C.W. Redman, I.L. Sargent //J. Placenta.-2003.-Vol.24.-P.21-24.

144. Reister, F. Altered proteases expression by periarterial trophoblasts cells in severe early-onset preeclampsia with IUGR [Текст] / F. Reister, J.C. Kingdom, P. Ruck//J. Placenta. -2006.-Vol.34.-№4.-P.272-279.

145. Reuvekamp, A. Selective deficit of angiogenic growth factors characterises pregnancies complicated by preeclampsia [Текст] / A. Reuvekamp, F.V. Vels- ing-Aarts, I.E. Poulina // J. Obstet Gynaecol.- 1999.-Vol.l06.-№10.-P.1019-1022.

146. Richard, J. Urinary Placental Growth Factor and Risk of Preeclampsia [Текст] / J.Richard, M.D. Levine, M.S. Cong Qian // JAMA.-2005.-Vol. 293- №1.- P.77-85.

147. Riley, S. Involvement of matrix metalloproteinases -2 and 9, tissue inhibitor of metalloproteinases and apoptosis in tissue remodelling in the sheep placenta [Текст] / S. Riley, C.J Webb, R. Leask // J. Reprod. Fertil.-2001.-Vol. 118.-P. 19-27.

148. Riley, S.C. Secretion of MMPs -2 end 9 and tissue inhibitor of metallo- proteinases into the intrauterine compartments during early pregnancy [Текст] / S.C. Riley, R. Leask, T. Chard // J. Mol. Hum. Reprod. -1999.-Vol. 5.-№4.-P.376-381.

149. Riley, S.C. Involvement of MMPs-2 and 9, tissue inhibitor of metallo- proteinases and apoptosis in tissue remodeling in sheep placenta [Текст] / S.C. Riley, C.J. Webb, R. Leask//J. Reprod. Fertil.-2000.-Vol.l 18.-№1.-P. 19-27.

150. Roberts, J.M. Pathogenesis and genetic of preeclampsia [Текст] / J.M. Roberts, D. W. Cooper// J. Lancet.-2001.-Vol.357.-P.53-56.

151. Robinson, C J. Evaluation of placenta growth factor and soluble Fms-like tyrosine kinase -1 receptor levels in mild and severe preeclampsia [Текст] / C.J. Robinson, D.D. Johnson, E.Y. Chang // J. Obstet. Gynecol.- 2006.-Vol.l95.-№1.-P.255-259.

152. Roten et al. The Norwegian preeclampsia family cohort study: a new resource for investigating genetic aspects and heritability of preeclampsia and related phenotypes/ BMC Pregnancy and Childbirth (2015) 15:319 DOI 10.1186/s12884-015-0754-2

153. Rundhaud, J.E. Matrix metalloproteinases end angiogenesis [Текст] / J.E. Rundhaud //J. Cell. Mol. Med.-2005.-Vol.9.-№2.-P.267-285.

154. Sane, D.C. Angiogenic growth factors and hypertension [Текст] / D.C. Sane, L. Anton, K.B. Brosnihan//J. Angiogenesis.-2004.-Vol.7.-№3.-P. 193-201.

155. Schmidt, M. Altered angiogenesis in preeclampsia: evaluation of a new test system for measuring placental growth factor [Текст] / M. Schmidt, C. Dogan, C. Birdir//J Clin. Chem. Lab. Med.-2007.-Vol.45.-№11.-P. 1504-1510.

156. Semczuk-Sikora, A. Maternal serum concentration of placental growth factor (PIGF) and endothelial growth factor (VEGF) in pregnancies complicated by preeclampsia [Текст] / A. Semczuk-Sikora, A. Krzyzanowski, M. Kwiatek // J. Gi- nekol.Pol.-2007.-Vol.78.-№l 1 .-P.873-876.

157. Sidorova I.S., Nikitina N.A. Science-based system of predicting preeclampsia // Obstetrics and Gynecology, 2017.-N 3.-P.55-61

158. Shaila, J.M. The role matrix metalloproteinases in vascular function: implications for normal pregnancy and preeclampsia [Текст] / J.M. Shaila, S.T. Davidge // BJOG.-2004.-Vol.l 11-P.931-939.

159. Shen, H. Analysis of placental growth factor in placentas of normal pregnant women and women with hypertensive disorders of pregnancy [Текст] / H.

160. Shen, H. Liu, H. Chen 11 J. Huazhong Univ. Sci. Technolog Med. Sci.-2006.-Vol.26.- №1.-P.l 16-119.

161. Shibata, E. Soluble fms-like tyrosine kinase -1 is increased in preeclampsia but not in normotensive pregnancies with small-for-gestational-age neonates: relationship to circulating placental growth factor [Текст] / E. Shibata, A. Rajaku- mar, R.W. Powers // J. Clin. Endocrinol. Metab. -2005.-Vol.90.-№8.-P.4895-4903.

162. Sibai, B. Preeclampia [Текст] / B. Sibai, G. Dekker, M. Kupferations // J. Lancet.-2005.-Vol.365.-P.785-799.

163. Sikkema, J.M. Placental superoxide is increased in preeclampsia [Текст] / J.M. Sikkema, A. Franx//J. Placenta.-2001- Vol.22.-№4.-P.3 04-308.

164. Skvortsova, V. I. Syndrome of posterior reversible encephalopathy / V. I. Skvortsova, L. V. Gubsky, E. A. Melnikova / / Journal of Neurology and Psychiatry. Korsakov. - 2010. - No. 5. - p. 104-109

165. Smith, S.K. Angiogenic growth factor expression in placenta [Текст] / S.K. Smith, Y. He, D.E. Clark //J. Semin. Perinatal.-2000.-Vol.L-P.82- 86.

166. Solomon, C.G. Preeclampsia - searching for the cause [Текст] / C.G. Solomon, E.W. Seely //N. Engl. J Med.-2004.-Vol. 350.-№7.-P.641-642.

167. Staun-Ram, E. Human trophoblast function during the implantation process [Текст] / E. Staun-Ram, E. Shalev //J. Reprod. Biol. Endocrinol.-2005.-Vol.20.-№3.-P.56.

168. Stepan, H. Elevated sFltl level and preeclampsia with parvovirus-induced hydrops [Текст] / H. Stepan, R. Faber // N. Engl. J Med.-2006.-Vol.354.-P.1857—1858.

169. Stepan, H. Soluble fms-like tyrosine kinase -1 [Текст] / H. Stepan, A. Geide, R. Faber//N. Engl. J Med.- 2004.- Vol.351.- №21.- P. 2241-2242.

170. Sternlicht, M.D. How matrix metalloproteinases regulate cell behavior [Текст] /M.D. Sternlicht, Z. Werb //J. Cell Dev. Biol.-2001.-Vol.-17.-P.463-516.

171. Strevens, H. Glomerular endotheliosis in normal pregnancy and preeclampsia [Текст] / H. Strevens, D. Wide-Swensson, A. Hansen // BJOG.-2003.-Vol.110.-P.831-836.

172. Su, Y.N. Decreased maternal serum placenta growth factor in early second trimester and preeclampsia [Текст] / Y.N. Su, C.N. Lee, W.F. Cheng // J. Obstet. Gynecol.- 2001.-Vol.97 .-№6.-P.898-904.

173. Tamargo J., Caballero R., Delpon E. Pharmacotherapy for hypertension in pregnant patients: special considerations. Expert open Pharmacother. 2019; 20(8): 963-982.DOI: 10/1080/14656566.2019.1594773;

174. Tjoa, M.L. Markers for presymptomatic prediction of preeclampsia and intrauterine growth restriction [Текст] / M.L. Tjoa, C.B. Oudejans, J.M. Vugt // J. Hypertens Pregnancy.-2004.-Vol.23,-№2.-P. 171-189.

175. Torry, D.S. Determinants of placental vascularity [Текст] / D.S.Torry, M. Hinrichs, R.J.Torry// J Reprod. Immunol.- 2004.-Vol.51.-№4.-P.257-268.

176. Torry, D.S. Expression and function of placenta growth factor: implications for abnormal placentation [Текст] / D.S. Torry, D. Mukherjea, J. Arroyo //J. Soc. Gynecol. Investig.-2003.-Vol.l0.-№4.-P.178-88.

177. Torry, D.S. Preeclampsia is associated with reduced serum levels of placenta growth factor [Текст] / D.S. Torry, H.S. Wang, .H.T. Wang //J. Obstet. Gynecol. -1998.-Vol.l79.-№6.-P. 1539-1544.

178. Tsatsaris, V. Circulating angiogenic factors and preeclampsia [Текст] / V. Tsatsaris, F. Goffin, J.M Foidart //N. Engl. J Med.-2004.-Vol.350.-P.2003-2004.

179. Unal, E. Second-trimester angiogenic factors as biomarkers for futureonset preeclampsia [Текст] / E. Unal, C. Robinson, D. Johnson // J. Obstet. Gynecol.- 2007.-Vol.l97.-№2.-P.211-214.

180. VanWijk, M.J. Vascular function in preeclampsia [Текст] / M.J. Van- Wijk, K. Kublickiene, K. Boer //J. Cardiovasc. Res.-2000.-Vol.47-P.38-48.

181. Vatten, L.J. Changes in circulating level of angiogenic factors from the first to second trimester as predictors of preeclampsia [Текст] / L.J. Vatten, A. Eskild, T.I. Nilsen// J. Obstet. Gynecol.- 2007.-Vol.l96.-№3.-P.239-246.

182. Vegh, G.L. Matrix metalloproteinases and their inhibitors in gestational trophoblastic diseases and normal placenta [Текст] / G.L. Vegh, T.Z. Selcuk, V. Fu- lop // J. Gynecol. Oncol.-1999.-Vol.75.-P.248-253.

183. Villar, J. World health organization systematic review of screening tests for preeclampsia [Текст] / J. Villar, A. Conde-Agudelo, M. Lindheimer // J. Obstet. Gynecol.-2005.-Vol.l05.-P.l 152.

184. Wang, Y.Q. Differential expression of extracellular matrix metalloproteinase inducer in normal placenta and preeclampsia placenta [Текст] / Y.Q. Wang, S. F. Mi, J. Li // Zhonghua Fu Chan Ke Za Zhi. -2006.-Vol.41 .-№7.-P.436-439.

185. Wathen, K.A. Maternal serum-soluble vascular endothelial growth factor receptor-1 in early pregnancy ending in preeclampsia or intrauterine growth retardation [Текст] / K.A. Wathen, E.Tuutti, .U.H. Stenman // J. Clin. Endocrinol. Metab.-2006.-Vol. 91 .-№1 .-P. 100-184.

186. Widmer, M. Mapping the theories of preeclampsia and the role of angiogenicfactors [Текст] / M. Widmer, J. Villar, A. Benigni // J. Obstet. Gynecol.-2007.-Vol.l09.-№l.-P.168-180.

187. Wikstrom, A.K. Placental growth factor and soluble FMS-like tyrosine kinase-1 in early-onset and late-onset preeclampsia [Текст] / A.K. Wikstrom, A. Larsson, U.J. Eriksson // J. Obstet. Gynecol.- 2007.-Vol.l09.-№6.-P.1368- 1374.

188. Wikstrom, A.K. Early postpartum changes in circulating pro- and anti- angiogenic factors in early-onset and late-onset preeclampsia [Текст] / A.K. Wikstrom , A. Larsson, U.J. Eriksson // J. Obstet. Gynecol. Scand.- 2008.-Vol.87.-№2.-P. 146-153.

189. Woessner, J.F. Matrix metalloproteinases and TIMPs [Текст]: J.F. Woessner, H. Nagase.-New York. Oxford University Press.-2000-P.124.

190. Wojtowicz-Praga, S. M. Matrix metalloproteinase inhibitors [Текст] / S. M. Wojtowicz-Praga, R. B. Dicson, M.J. Hawkins //J. Invest. New Drugs.-1997.- Vol.l5.-№l .-P.61-75.

191. Zenebe W, Hailemariam S, Mirkuzie W. Hypertensive disorders of pregnancy in Jimma University specialized hospital. Ethiop J Health Sci. 2011;21(3):147–54

192. Zhang, H .Expression of trophoblast invasion related genes mRNA and protein in human placenta in preeclampsia [Текст] / H. Zhang, Q.D. Lin, C.Qiao // Zhonghua Fu Chan Ke Za Zhi.-2006.-Vol.41.-№.8.-P.345-363.

193. Zhou, Y. Vascular endothelial growth factor ligands and receptors that regulate human cytotrophoblast survival are dysregulated in severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome [Текст] / Y. Zhou// J. Pathol. -2002.-Vol.l60.-P.1405-1423.

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