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Criteria For Prediction Of Complications In Pregnant Women With Antenatal Fetal Death

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Urgency: Natural population growth in the Republic depends on the age structure of the population, which is characterized by low reproductive potential, which increases the relevance of the preservation of each desired pregnancy. In these circumstances, the main focus of the maternal health service should be the development of a system for the prevention of reproductive losses. Therefore, reproductive losses are considered as the final result of the impact of social, medical and biological factors on the health of women, the fetus and the newborn and lead not only to the loss of reproductive, labor, intellectual, defense capital of the country, but also to the loss of life potential of the population. The main task of prevention of reproductive losses is to assess the role of each factor in the formation of complications during pregnancy, and not only to highlight this factor.

The study of the etiology of antenatal fetal death, despite the large number of studies, remains relevant. This is due, firstly, to the increase in the share of antenatal fetal death in the structure of miscarriage (from 45 to 86.6%), and secondly, in 20-40% of cases, the cause of antenatal fetal death remains unknown.

According to the literature, about 7% of the causes of antenatal fetal death (AFD) are chromosomal abnormalities. Endocrine disorders are from 8 to 20 %, 12-15 % have anatomical features and functional disorders of the uterus. Chronic infectious and inflammatory diseases account for about 70 % of cases. Particular attention is paid to disorders in the hemostasis system - genetically determined, acquired and

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combined forms of thrombophilia (from 45 to 75 %). Undoubtedly, even after one antenatal fetal death, the most important task of an obstetrician-gynecologist is to conduct a thorough clinical and laboratory examination of patients using modern diagnostic methods to determine the leading etiological factors and the pathogenesis of this pathology. This is the basis for the development of a program of individual rehabilitation and training. In this regard, the creation of a model for predicting antenatal fetal death based on the analysis of laboratory and instrumental examination data, with the identification of individual risk factors is extremely relevant.

Body weight is one of the most important health indicators.Underweight or overweight is a risk factor for disorders reproductive system. Were no significant differences between the groups in IMB. More patients with antenatal fetal death were obese. The calculation of the relative risk showed that patients with IMB > 30 had a 1.5-fold higher risk of AFD than in the comparison group.

Objective: to develop a differentiated approach to the management of pregnancy in women with antenatal fetal death on the basis of the study of the immune and hormonal systems to reduce perinatal morbidity and mortality.

Materials and methods research: We studied indicators of gemostoziogramma, hormone status, saliva and blood, the excretion of blood cytokines and growth factors in patients with AFD, the complement system and NST test in pregnant healthy and AFD. Group I control - 20 pregnant healthy women, group II-40 women with AGP.

Results of research: It is known that increased IMB (>30kg/m) is associated with an increase inthe risk of thromboembolic conditions (Rocky M. G., 2007; Mochalov, A. A. 2011; Rudakova E. B. 2015). In this context, there were analyzed the indices of coagulation in the groups studied (1табл).There was a connection of

BMI increase and positive markers of thrombus formation in 100% of cases. Among patients with signs of activation of intravascular coagulation (RCMP) 11 people (55%) had excess body weight and 9 people (45%) - obesity of various degrees. Of the patients with high rates of D-dimer19 people (54.3%) had excess body weight.

Evaluation of the results of coagulation in the subgroups showed that in the group with AGP increase in RKMF was observed in 19 people (47.5%), which is significantly higher. The growth of D-dimer was observed in 21 people (52.5%), which is statistically significant.

Table 1

Indicators of hemostasiogramms (M± *m)*

Indicators	Physiological pregnancy n=20	Pregnant women with AFD
Aptv (C)	28,8±0,14	36,9±2,15
PTV (s)	11,0±0,05	14,6±0,65
Fibrinogen (g/l)	3,0±0,03	5,89±0,43
TV (s)	16,4±0,05	20,2±0,06
RCMP (mg/l)	1,7±0,05	2,87±0,15
D-dimer (ng/ml)	398,9±16,48	736,1±12,57
Antithrombin III (mg/l)	109,1 ± 2,69	75,6 ± 2,53
Protein activity C (%)	101,0 ± 9,90	81,9 ± 6,76

Serum concentration of D-dimer not exceeding 398.9±16.48 ng / ml in pregnant women in the N - W trimester of gestation indicates a favorable course and outcome of pregnancy. An increase in the D-dimer content of more than 736.1±12.57 ng/ml indicates a high probability of antenatal fetal death.

Hormonal interactions play a significant role in the development of

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spontaneous premature labor. It is known that progesterone is necessary to maintain the uterus in normal tone by suppressing the formation of slit contacts, the synthesis of prostaglandins and oxytocin receptors. The concentration of estriol in the maternal bloodstream is a direct marker of the activity of the fetal hypothalamic-pituitary-adrenal axis, which, presumably, is activated before the development of labor. At the next stage, we analyzed the features of hormonal background in women with AFD, test results are presented in the table .

Attention was drawn to a significant increase in concentrations progesterone and a-fetoprotein in the study groups of pregnant women with AFD. Progesterone is a powerful factor contributing to the emergence and preservation of pregnancy. It promotes the transition of the uterine mucosa from the proliferation phase to the secretory phase, and after fertilization creates the necessary conditions for the implantation and development of the fertilized cell. Progesterone also has a relaxing effect on the smooth muscles of the uterus. Convincing results have been obtained indicating that the protective effect of progesterone in pregnant women with angp MAY be associated with its immunomodulatory activity,including the normalization of cytokine balance during pregnancy.

Immunomodulatory activity of a-fetoprotein is shown, including its ability to enhance the activation of apoptosis of lymphoid cells, thereby limiting the processes of immune damage and inflammations.

The concentration of steroid hormones in saliva reflect not conjugated, and thus, the biologically active fraction of the hormones. In addition, the collection of samples is a simple and non-invasive test, which causes a great interest of researchers to this problem. However, clinical studies of the prognostic significance of hormones in saliva are inconsistent (Lachelin et al., 2009). The objective of this fragment of research was a comparative study of the content of

hormones of steroid nature-progesterone and estriol, in saliva in women with physiological and ANGP pregnancy, as well as an assessment of their significance in the early diagnosis and prediction of antenatal losses.

As can be seen from the results of the studies, the level of progesterone in saliva of the examined patients with physiological pregnancy was 49.04± 3.54 PG/ml.in the group of patients with ANGP, the concentration of progesterone in saliva was equal to 298.53±8.76 PG/ml (p>0.05). The concentration of estradiol in the saliva of pregnant women with physiological course of gestation amounted to 224,45± of 11.41 PG/ml.

Indicators of hormonal status of saliva and blood

Indicators	Physiological pregnancy n=20	Pregnant with AFD n=50
Progesterone PG / ml. saliva	49,04±3,54	298,53±8,76
Estradiol/ml of saliva	224,45± 11,4	134,78±9,89
HCG, blood, Mme / ml	332,91± 12,07	6561,18±10,3
Progesterone nmol / l in	70,15±5,61	171,93±13,2
a-fetoprotein in blood, IU/ml	62,15±6,9	48,18±12,2

In patients with AFD ,estradiol averaged 134.78±9.89 PG/ml.thus, the study of progesterone in saliva is one of the prognostic markers of complications in prolonged AFD in pregnant women.

In accordance with the tasks we conducted determination of daily urinary excretion of cytokines and growth factor inpregnant women with physiological course of pregnancy and AFD

Cytokines are protein-peptide factors produced by cells that carry out short-term regulation of intercellular and intersystem interactions, determining cell

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survival, stimulation or inhibition of cell growth, functional activity and cell apoptosis.

In chronic diseases of the kidneys and female genital organs, antigens of microbial bodies, interacting with T - helpers, markofagams, neutrophils, oth.in the system of microcirculation of the kidneys, as well as with the cells of the muscle layer and mucosa contribute to the synthesis and release of them into the renal blood flow of cytokines, which are divided into Pro-inflammatory and anti-inflammatory interleukins.

Proinflammatory cytokines (IL-6,IL-8, TNF, etc.) increase the permeability of cell membranes, activate vascular-platelet hemostasis, increase tissue swelling, are currently markers of the severity of any inflammatory process, including the kidneys. Levels of IL-1 and IL-6 in the blood reflect the activity of the inflammatory process in the kidneys and female genital organs , and IL-8 its degree.

When comparing the results of cytokine excretion and growth factors of the examined pregnant women were found to be significant differences and trends in the release of interleukins.We have proved significant differences in daily excretion blood interleukin-1 in pregnant women with normal gestation and complicated ANGP. When ANGP in pregnant women there is a decrease in blood excretion IL-1. Thus, in pregnant women with physiological pregnancy, the level of daily blood excretion IL-1 amounted to 33.09 ± 1.17 PG/ml, while in pregnant women with AFD it was11,23±0.92 PG / ml. We established differences ($p<0.001$) in daily blood excretionIL-6 in pregnant women with physiological pregnancy and physiological gestational period. In pregnant women with ANGP there is an increase in IL-6 production, which is proved by the results of daily excretion of blood interleukin in this contingent of pregnant women (13.78 ± 0.87 PG/ml),

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whereas in the physiological course of pregnancy it was equal to (6.93 ± 0.48 PG/ml).

Thus, in pregnant women with AFD, there is an increase in the production of exrection in the volume of blood-6 on average in times.We have proved the differences ($p<0.05$) in the excretion of IL-8in pregnant women with ANGP, when compared with its physiological course, it was Found that in pregnant women with physiological course the level of blood excretion IL-8 was lower (10.23±0.81 PG/ml) than in pregnant women with AFD - 21.32±1.28 PG/ml). Thus, we have proved that the complication of pregnancy AFD is accompanied by an increase in daily blood excretion IL-8.We also established significant statistical differences ($p<0.05$)in blood excretion IL-10 in pregnant women with AFD. Proven, that when a complication of pregnancy AFD Otechestvennie the production and excretion of blood IL-10. Thus, in pregnant women with physiological pregnancy, the level of daily blood excretion-10 was 8.27±0.47 PG/ml, while in pregnant women with AFD it was 22.04±1.52 PG/ml, in ANGP there is an increase in blood excretion IL-10.

We have proved significant differences ($p<0.001$) in excretion blood tumor necrosis factor-a (TNF-a) in AGP. As the progression of the term AFD there is an increase in the daily excretion of blood TNF-a. So, beremennyh with physiological course of gestation the level of excretion of blood TNF-a made up 10.13±0,81 ng/ml, while pregnant with AFD he was 17,67±0,69 ng/ml For moreprogressives AFD pregnant indicators excretion of blood TNF-a were significantly increased and ranged from 26.98 ± 1,43 ng/ml. Thus, we have proven to increase excretion krapivno, especially with the progression of time AFD.

Thus, as a result of the study we have proved the multidirectional character of cytokine excretion and growth factors in pregnant women with AFD. In General,

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on the basis of the above, it should be noted that the prognostic significance is to determine the level of IL-8 cytokine in the blood sample, which is the most objective indicator of the degree of activity of exacerbation of chronic obstructive pyelonephritis.

Indicators of blood excretion of cytokines and growth factors of patients with AFD

Indicators cytokines and tumor necrosis factor	Physiological pregnancy n=20	Pregnant with ANGP n=50
IL-1 pg / ml	33,09 ± 1,17	11,23±0,92
IL-6 pg / ml	6,93 ± 0,48	13,78 ± 0,87
IL-8 pg / ml	10,23 ±0,81	21,32 ± 1,28 *
IL-10pg / ml	8,27 ± 0,47	22,04 ± 1,52*
FNO-apg / ml	10,13 ± 0,81	17,67±0,69*

Analysis of blood cytokine excretion (IL-1, IL - 6, IL-8,IL-10) and growth factors (TNF-a) indicate a predominance ofproduction and excretion of Pro-inflammatory cytokines and growth factors over anti-inflammatory.Thus, against the background of ANGP in pregnant women, tubulo-interstitial kidney damage was noted, which is characterized by an increase in the excretion of hemipro inflammatory cytokines: IL -1, IL-6, IL-8, about inflammatory TNF-a, and a simultaneous post-stage decrease in blood excretion of anti-inflammatory IL-10.

The complement system is a powerful tool for both protecting the body against pathogens and removing cells subjected to apoptosis, is one of the main parts of

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the innate immune system, and its activation serves to link the innate and adaptive immune response. In cytotoxic immunity, complement-mediated, antibodies attach to cell surface antigens. Then, a complement (C) is attached to the Fc fragment of antibodies, which is activated along the classical pathway with the formation of anaphylatoxins (C3A C5A) and membranes of the attacking complex (MAC) consisting of C5-9 components. Complement dependent cytolysis occurs. Complement as a protective system of the body has a certain advantage over cytotoxic cells, since its components are soluble molecules that are synthesized and secreted by many types of cells, such as macrophages, fibroblasts, endothelial cells, etc.it Should be noted that nonspecific activation of the complement can be carried out by proteases (trypsin, plasmin, kallikrein, lysosomal proteases, thrombin and bacterial enzymes) at each stage of C1 dos5. Nonspecific activation is one of the components of acute inflammation. In the literature it is indicated that during pregnancy there is an activation of the complement system both in the classical and in the alternative way on the first day after the birth period. The concentration of C1 inhibitor corresponded to normal values before delivery and was activated on the first day after delivery. In our studies, issleduemykh pregnant women revealed no activation of the system, i.e. enabledecompression the complement system. Suppression of the complement system indicate maladjustment of the mechanisms maintaining immune homeostasis in AFd. An increase in nst+ leukocytes in a spontaneous pregnancy test is most likely due to an increase in the level of biologically active substances. When AFD in pregnant women revealed a decrease in the reserve of functional activity of leukocytes.

According to the literature, the number of HCT positive (HCT+) neutrophilic leukocytes in healthy people is 3-10 %. In determining the spontaneous activity of leukocytes in healthy pregnant women, we revealed an increase in nst positive cells

(23.21±1.14). Indicators of complement system and nst-test in pregnant women with healthy and AFDIndicator Of Physiological pregnancy n=20 Pregnant women with ANGPn=40 Complement S3 mg/ DL 225,43+ 11,73 209,31+ 10,94Nst spontaneous in % 23,21+ 1,14 20,81+ 1,48 Nst stimulated in % 57,93+ 4,56 28,67+ 1,79.

When stimulated, the number of active neutrophils increased to 57.93±4.56. In pregnant women with ANGP there was a significant decrease in nst + leukocytes in the spontaneous test (20.81±1.48), the number of active cells in the stimulated test did not change significantly.Meanwhile, ANGP showed a decrease in the reserves of functional activity of neutrophils (the number of HST+cells in the stimulated test was only 28.67±1.79).

Conclusion.

1. As a result of the study, we have proved the multidirectional character of cytokine excretion and growth factors in pregnant women with ANGP. In General, on the basis of the above, it should be noted that the prognostic significance is to determine the level of cytokine IL - 8, IL-6 which is the most objective indicator of the degree of activity of exacerbation of chronic inflammatory diseases, especially obstructive pyelonephritis.

2.The revealed results regarding the content of complement components and the state of neutrophil leukocytes and their reserve capabilities can be used to predict the course of complications during pregnancy , childbirth and the postpartum period in women with AFD.

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