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Modern and differentiated approaches to the management of pregnant with a dead fetus

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Based on data of a follow-up of 104 patients with non-developing pregnancy (a study group), 39 females with physiological pregnancy (a control group), and 43 with the clinical picture of spontaneous abortion (a comparison group), the authors analyze the present views of the dead fetus syndrome in obstetric and gynecological care. Particular emphasis is laid on the currently available methods of the diagnosis, prevention, and treatment of this complication in relation to the terms of pregnancy and the length of stay of a dead fetus in the uterine cavity.

Keywords: *abortion, nondeveloping pregnancy, missed abortion, mifepristone.*

The problem of developing pregnancy is extremely actual both a clinical and a social aspect, as the proportion of this disease among the causes of reproductive loss is quite high at 10-20% [2, 6, 7, 11, 13]. According to the literature, this pathology is known as a no developing pregnancy (NP), missed abortion (attempted abortion), missed labour (missed labor), depending on whether intrauterine death occurred before 28 weeks or at a later date. The International Classification of Diseases, 10th revision (1995) is allocated to the state under the heading O02.1 - frustrated miscarriage. The delay of the dead fetus (fetus) in the uterus affects the subsequent reproductive function of women, threatening not only her health, but also due to the possible life-physiologically hemostatic complications. Found that intrauterine dead fetus (fetus) affects the mother's body, causing a pathological condition - dead fetus syndrome, the main manifestations of which are the inhibition of uterine activity (UA) and hemostasiological dysfunction [3, 7, 8, 10]. Currently, there are new approaches to the treatment of this pathology of pregnancy. There are many special studies of issues of etiology, pathogenesis, diagnosis and prevention of preclinical developing pregnancy complications [1, 5, 7].

Objective: study the hormonal homeostasis in DP in the formation of pathological inertia of the uterus in women with intrauterine fetal death and its relationship with steroid hormones. In addition, an analysis of the hemostatic system and the immune status at the DP (nondeveloping pregnancy).

Subjects and methods

We observed 104 women with non-developing pregnancy (study group) for pregnancies between 16 and 30 weeks, at the age of 16 to 38 years. Given the length of stay of the dead fetus in the uterus in the main group of women surveyed identified two subgroups: the 1st subgroup consisted of 63 (60.6%) pregnant women with a delay of the dead fetus in the uterus up to 3 weeks, 2nd subgroup - with a delay of the dead fetus more than 3 weeks - 41 (39.4%) pregnant. The

control group consisted of 39 women with physiological pregnancy and the comparison group - 43 women with a clinical picture of spontaneous abortion. Clinical examination of pregnant women was carried out on a specially designed the map and included, above all, a thorough medical history data and the results of objective research. The level of prolactin (PR), estradiol (E), dehydroepiandrosterone sulfate (DHEAS) in the serum of pregnant women were measured by enzyme-linked immunosorbent assay using commercially available kits. For the determination of progesterone in the blood (P), cortisol (C) used as commercial kits. Determination of cytokine was carried out immunoenzyme method using a commercial reagent kit. Study of hemostasis was performed by standard methods.

Results.

The results of hormonal studies in study groups of women showed that in the second half of the physiological pregnancy is a progressive increase in serum concentration of PR was significantly correlated with gestational age ($r = 0,585$; $p < 0,02$). When an electron-microscopic study of the placenta in a similar gestational age immunohistochemically identified APUD cells responsible for the synthesis and secretion of PR ($4,04 \pm 0,15$). If you missed abortion (study group) decreased the level of PR ($74,28 \pm 8,34$ ng / ml) within a specified time, compared with the control group. This difference in the patients 1st subgroups and unreliable control group ($p > 0,05$), patients 2nd subgroup \neg reliable ($p < 0,05$), but only the period from 21 to 30 weeks. Saving and even a marked enhancement function of PG-apudocytes in decidua tissue the first 3 weeks of retained placenta in the uterus ($4,77 \pm 0,25$ \neg cell current of 1 p / sp.; $P < 0,05$) was driven by apparently, stored in the active period sufficient intervillous hematogenous perfusion. Continued synthesizing function argyrophilic PR-placental cells is likely to maintain a sufficiently high concentration of PR in the blood serum of women in this group. The total space filling intervillous fibrin at long intrauterine dead fetus in the uterus causing a secondary PR-apudopati ($2,36 \pm 0,56$; $p < 0,02$) and in connection with the sharp decrease serum levels of PR. An even more pronounced reduction (compared to the control group), plasma concentrations of the PR ($48,62 \pm 10,64$ ng / ml) was observed in patients with clinical manifestations missed abortion on the eve of abortion, and in patients with spontaneous abortion. In physiological pregnancy (control group), we found a positive correlation between the content of prolactin and progesterone in the maternal blood ($r = 0,696$; $p < 0,01$). In intrauterine fetal death (study group) were able to trace a positive correlation between the content of the PR and P ($r = 0,451$; $p < 0,01$). Identify the nature of the relationship changes in the concentration of PR and content of other steroid hormones in the main group of surveyed women was not possible, since the accuracy of the measurement is not different from zero at any level of significance. This, in turn, constitutes a violation of the unity of the system mother-placenta-fetus for missed abortion. He noted the correlation PR and P at a given gestational complications suggests that PR plays a regulatory role in the biosynthesis of P and,

on the contrary, continues to work after the death of the fetal placenta on the feedback principle, appears to support the synthesis of PR by the pituitary gland of the mother. Thus, elevated levels of PR in maternal blood during pregnancy and physiological missed abortion (mainly delayed dead fetus in the uterus to 3 weeks) has apparently a role in the formation of myometrial refractivity and decreasing its concentration in spontaneous abortion pregnancy is one of the starting points of activation of uterine activity. The analysis of the immune status of patients with non-developing pregnancy showed decrease in the concentration of interleukin-4 (IL-4), interleukin-8 (IL-8) at a disadvantage during pregnancy [9]. Thus, in physiological pregnancy of IL-4 was $14,6 \pm 0,5$ pg / ml, at a delay of the dead fetus to 3 weeks (one sub-group) - $5,1 \pm 0,3$ pg / ml and intrauterine more than 3 weeks (2 sub-group) - $3,1 \pm 0,2$ pg / ml and at spontaneous abortion (control group) - $8,6 \pm 0,4$ pg / ml. However, the reduction in IL-4 can not be considered a specific marker missed abortion, since the difference in performance in this group and the comparison group does not significant ($p > 0,05$). In comparing IL-8 concentration in the control group ($16,7 \pm 0,8$ pg / ml) and control group ($15,1 \pm 0,9$ pg / ml) there were no significant differences ($p > 0,05$). At the same time, the basic group (compared with control) decreased levels of IL-8 to $8,3 \pm 0,7$ pg / ml in patients 1st subgroups ($p < 0,05$) and to $7,9 \pm 0,8$ pg / ml in the 2nd subgroup ($p < 0,05$). The results confirm the available given literatures that the physiological course of pregnancy is associated with a predominance in the decidua tissue IL-4 and IL-8, and the decline of these indicators showed unfavorable pregnancy [4]. It is well known that IFN- γ belongs to a class of Th1 cytokines that activate cellular immunity and contributing to pregnancy loss STI. In the analysis of the results was an increase in this indicator for complications of gestation ($p < 0,05$): in the 1st sub-group concentration of IFN- γ was $16,1 \pm 1,8$ pg / ml in the 2nd sub - $10,3 \pm 1,2$ pg / ml in the control group - $14,7 \pm 1,6$ pg / ml in the control group con - $8,1 \pm 1,9$ pg / ml. It should be noted TNF part, along with IL-1, IFN- γ , in the activation of blood coagulation which is supplied with the developing embryo that can lead to death. In addition, the main group in the background of on level rise of TNF, IFN- γ was observed decrease content of IFN- α , related to the Th2 class cytokines in physiological pregnancy concentration of IFN- α was $36,1 \pm 2,4$ pg / ml, at a delay of the dead fetus to 3 weeks - $21,7 \pm 1,4$ pg / ml and intrauterine more than 3 weeks - $19,6 \pm 2,0$ pg / ml with spontaneous abortion - $24,4 \pm 1,6$ pg / ml. Summing the resulting the data, it can be stated that in all cases of miscarriage observed dissociation between the level of Th1-and Th2 cytokines. In the course of the work it was also found that the delay of non-developing gestational sac or dead fetus in the womb affects the mother's body through the resorption of products of autolysis of tissues of the ovum, which, acting in the mother's bloodstream due to enhanced permeability of membranes, violate conditions of intravascular hemostasis [7, 8]. As you increase the residence time of the dead ovum in the uterus hemocoagulation significantly reduced the activity of tissue and vascular factors placenta, which is caused by degenerative changes in the placental tissue. Report platelet diseases and the conditions plasma coagulation hemostasis in patients with PR typically proceeds as disseminated intravascular coagulation

(DIC) blood. On average, 89% of patients develop a chronic form, and 11% - a subacute form of DIC syndrome [7, 8]. Prolonged exposure to products of autolysis on the uterus decreases contractility of the myometrium [7, 8, 11, 12], which creates certain difficulties in the elimination of the ovum. A common tactic for missed abortion is the earliest possible termination of the victim of the ovum [1, 5, 7]. In order to prevent koagulopatic bleeding in chronic DIC we use Clexane dose of 0.2 units every 12 hours for 3-5 days, 12 hours before the surgery preparation of changes and re-assigned 12 hours after emptying the of the uterus . Changes koagulogicheskikh indicators of the extrinsic pathway of blood coagulation, were less pronounced. Prothrombin index (PI) immediately after the first ALP decreased on average from 1.66 to 107.41 98,32 3,34% (p <0,05), remained significantly reduced relative to the initial, up on the day after it until 101,12 3,21% (p > 0,05). Structural hypercoagulability, which depends on the quantity and quality of fibrinogen, preserved (p > 0,2). Plasma concentrations of soluble fibrin monomer of complexes and degradation products of fibrin and fibrinogen did not change much. In the immune status of the patients in this group were as follows: reduction in the relative content of T-suppressors from 24.17 to 1.48 20,18 1,72% (p <0,05) and elevated levels of T-helper cells with 27.11 1 , 96 to 34,43 2,82% (p <0,02). Furthermore, an increase in the ratio T-helper/T-supressory 1.06 0.15 1,63 0,23 (p <0,05). Artificial termination of pregnancy is not developing at the sizes of the uterus, the corresponding 16-week period (or less), according to our byzitsii need to be pursued under the control of hemostasis. The fertilized egg is removed by medication antiprogestins and prostaglandins or in the presence of careful anesthesia with simultaneous instrumental emptying the of the uterine cavity, followed by intravenous drip of oxytocin for 1-1.5 hours. Interruption of developing pregnancy by increasing the size of the uterus, the corresponding 17-week gestational age (and more), feasibility differently carried out in 2 stages:

- 1) Artificial formation of readiness of pregnant women in the exclusion and expulsion of the dead fetus (predinduksion training);
- 2) Stimulation of uterine activity.

At the 1st stage, for the relief of one of the causes of abnormal uterine inertia - estrogen deficiency characteristic of gestational complications in connection with the termination of the fetal development of the steroid derivative estrogen - dehydroepiandrosterone sulfate, you can use the standard way of predinduksionnoy training: the use of anti-progestins, mifepristone 200mg Per os. Concurrently can recover energy potential cancer by administration of vitamins, calcium chloride in combination with spasmolytic agents [7]. Our findings on the relationship prolactin and steroid hormones in physiological and miscarriage served as the theoretical precondition for the application of its antagonists in preparation for labor induction in women with intrauterine fetal death [10]. The last 5 years on the basis of our clinic as a training predinduksion used prostaglandin - Cytotec to 25 mcg vaginally, for 3 days. An important characteristic of the method are the technical simplicity of execution, its non-invasive, gentle effect on a woman's body. The use of Cytotec eliminates the need for additional use of large amounts of

drugs and is very cost-effective way to prepare for induced abortion. In order to relieve the immune tolerance of pregnant women to non-developing fetal egg, preventing exclusion and expulsion of the latter, be sure to assign an immune stimulant levamisole (150 mg on an empty stomach for 3 days). Local stimulation of the "ripening" of the cervix recommend spending by intracervical application of one dose of dinoprostone (Glandin E2). The direct induction of uterine activity (Stage 2) is, first, in the inhibition of β -adrenergic actions of it is prolonged trophoblast synthesized biologically active substances - namely, progesterone, placental lactogen, prolactin, and others, and secondly, in replacement medication for the missing initiation of labor fruit of oxytocin. To date, based on our maternity hospital to interrupt developing pregnancy in the later stages sparing technique is used pharmacological drugs mifepristone 200 mg on the first day, 25 mg of misoprostol vaginally, 36-42 hours after misoprostol under the scheme, and there is dipole miscarriage that does not require scraping instrumental. Thus, the proposed system is a differentiated approach to the management of women with non-developing pregnancy will shorten the hospital stay by an average of 8 days, to reduce the incidence of bleeding after uterine evacuation of 2.5 times; abdominal surgery and mortality in this disease are reduced to zero .

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