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A COMPREHENSIVE APPROACH TO THE DIAGNOSIS OF MISCARRIAGE IN THE FIRST TRIMESTER

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ABSTRACT

Miscarriage is a pressing issue in modern medicine. Clinical, morphological and immunohistochemical features of the endometrium structure may be the basis of this pathology, which is why it is very important to study its features and structure in healthy women and women with reproductive losses of reproductive age. And only on the basis of these parameters can we prove a change from the norm and understand the cause of miscarriage from a clinical and pathomorphological point of view.

Key words: endometrium, immunohistochemistry, hormonal receptors, antibodies to hCG.

INTRODUCTION

Relevance: Recurrent pregnancy loss (RP) remains one of the most important issues in modern obstetrics. Habitual spontaneous abortion is defined by the American Society for Reproductive Medicine as the occurrence of two or more natural pregnancy losses before 20 weeks in the same partner, with an estimated incidence of 1% of all pregnancies. In 2022, the European Society of Human Reproduction and Embryology defined it as the loss of two or more pregnancies, affecting approximately 1-2% of couples. However, multiple miscarriages pose a serious risk, they can lead to fertility problems, since each miscarriage can damage the uterine lining and its health, thereby reducing the chances of conception. In the structure of miscarriage, one of the leading positions is occupied by non-viable pregnancy, its incidence rate increases annually, ranging from 2.8% to 15% in different countries [1,3]. A history of non-viable pregnancy in a woman negatively characterizes her reproductive function. In the absence of rehabilitation and pre-

pregnancy preparation, in every second case there is a repeated loss of pregnancy, and in 27.4% of observations, three or more episodes of miscarriage are noted [2,4]. Sporadic pregnancy loss occurs randomly throughout the reproductive period of a woman's life. Habitual pregnancy loss is considered a separate disease, affecting 1-3% of women.

In married couples, infertility is detected in more than 15% of cases, early reproductive losses occur in 15-20% of pregnancies and their frequency does not decrease, despite the numerous diagnostic, preventive and treatment methods developed in recent years. Almost every 5th pregnancy is spontaneously lost, and therefore this problem has a special social significance, given the current unfavorable demographic situation [5].

The aim of the study. To study the hormonal and immunological characteristics of the blood, the immunohistochemical characteristics of the decidual membrane of the endometrium, to identify the mechanisms of the causes of miscarriage in the early stagespregnancy termsin women,living in the Aral Sea regionfor the development of diagnostic methods.

Materials and methods of research. The immunohistochemistry study was conducted in the pathomorphological laboratory of FBC NGS MEDICAL LLC. Scrapings from the uterus were collected at the Perinatal Center of the Khorezm Region in the gynecology department from women with habitual miscarriage after miscarriage in the period 2021-2023.

To achieve this goal, a retrospective analysis of 382 case histories of patients observed in the gynecological departments of the Regional Perinatal Center of the Khorezm Region and the City Maternity Hospital of the city of Urgench in the period from 2019 to 2022 was carried out. The diagnosis was made according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). The study was conducted in women with miscarriage up to 13 weeks. The age of the patients ranged from 20 to 40 years, the average age was 23 years, all women were married, the average age at marriage was 21.9 ± 0.28. Retrospectively, the medical history was carefully studied and the following data was found: history of somatic, gynecological and obstetric pathologies.

A prospective observational comparative controlled study was performed in 258 women with habitual miscarriage. The first group included 198 women with habitual miscarriage. The control group consisted of 60 healthy fertile women with no history of miscarriage, with a history of full-term birth through the birth canal, without deviation from the physiological course of pregnancy and the act of birth, as a result of which healthy children were born. For the second stage of the study,

the main group was divided into two subgroups: Group 1(n = 100):Group I was formed from patients who subsequently received a personalized, comprehensive examination and pre-pregnancy preparation; Group II (n = 98) was formed from patients who subsequently received the generally accepted scope of diagnostics and treatment.

The material for the morphological study was scrapings from the uterine cavity (n=40), including decidual tissue of the endometrium. The comparison group consisted of a biological substrate obtained from women who decided to terminate an uncomplicated pregnancy at 4 to 12 weeks bymartificial (medical) abortion (n=20). The main group included scrapings obtained from patients with habitual early pregnancy loss of various etiologies (main group, n=40).

Pregravid preparation for women was recommended for three to six months. Pregravid preparation included: correction of hormonal changes, hepatoprotective therapy, antibacterial therapy taking into account bacteriological culture with determination of sensitivity to antibiotics, intrauterine plasma lifting once a week for 3 months. Corticosteroid therapy was performed when immune factors leading to miscarriage were detected, during the month before planning pregnancy and during pregnancy in the first trimester.

Research results: Analysis of hereditary diseases of parents and close relatives showed: arterial hypertension occurred in 20.16%; varicose veins in 21.2%; hereditary and acquired thrombophilia in 2.9%; stroke/heart attacks in 3.9%; obesity in 21.7%; diabetes in 4.9%; infertility in 6.3%; thyroid pathology in 21.7%; systemic diseases in 5.5%. The most common pathology was cardiovascular disease such as arterial hypertension and varicose veins, and endocrine pathology in the form of diffuse goiter.

When studying the somatic pathology of patients with early miscarriage, endocrine pathology was more often observed. Among endocrine diseases, thyroid pathology prevailed in the form of hypothyroidism, which amounted to 217 (56.8%), hyperthyroidism in 17 (4.5%), autoimmune thyroiditis 83 (21.7%), metabolic syndromes such as insulin resistance 89 (23.3%), obesity 78 (20.4%), prediabetes 16 (4.2%), as well as hyperandrogenism, hyperprolactinemia 12 (3.1%).

An analysis of extragenital diseases was also performed, where the presence of cardiovascular diseases was assessed, such as: arterial hypertension was observed in 33 (8.6%) women, varicose veins in 104 (27.2%) women; diseases of the urinary tract and kidneys: the most common in patients were chronic pyelonephritis in 94 (24.6%) and chronic cystitis in 27 (7.06%); respiratory organs (chronic tonsillitis) in 63 (16.5%) and diseases of the gastrointestinal tract. Also,

during the analysis of extragenital pathology, systemic diseases were detected in 53 (13.87%) cases. Taking this into account, we can say about the timely detection of pathology, taking into account regular visits to a general practitioner, timely detection and treatment of this pathology. And for women planning further pregnancy, pre-pregnancy preparation should also be carried out taking into account the anamnesis, hereditary diseases and extragenital pathology.

The average age of the examined women in the main group was 28±3.6 years, in the control group 24±5.2 years. Statistically significant differences in age were revealed $p \leq 0.05$.

When analyzing menarche, cycle duration and cycle length in the examined patients, it was not possible to identify statistically significant differences. The obstetric history of women with habitual pregnancy loss was complicated by spontaneous miscarriage, premature birth, medical abortion, non-viable pregnancy, and operative birth. In the obstetric history, significant intergroup differences were found ($p \leq 0.05$).

One of the signs that attracted us was the increase in body temperature above 37.2 degrees in women of the main group during pregnancy, which was significantly different from the control group ($p \leq 0.001$). And the most interesting thing is that when intrauterine death of the fetus occurs, the body temperature drops automatically.

In addition, from the indicators of hematological research, a tendency was revealed to increase the absolute number of leukocytes in women of group 1 during developing pregnancy, as the death of the fetus or spontaneous miscarriage occurred, leukocytes began to decrease.

It should be noted that when assessing the biochemical parameters of pregnant women in the main group, a statistically significant increase in the reference values of ALT and AST was found.

When determining antibodies to human chorionic gonadotropin in the blood, an increase in antibodies was found in the first group, which was significantly different from the control group ($p \leq 0.001$).

Changes in the above indicators indicate that the immune properties of the body during miscarriage are at a higher level.

A change in the amount of TSH was noted in 36 (33.9%) women of the 1st group, it changed in the amount of 5.2-6.4. Only in the 1st group the average value of TSH was relatively high compared to the control group ($p \leq 0.001$).

One of the main indicators was the determination of the level of androgens, the average amount of testosterone in the 1st group was 4.85 ± 0.087 nmol / l, in

the 3rd group - 1.8. ± 0.047 nmol / l. The indicators were significantly different compared to the 1st and 2nd groups ($p \leq 0.001$).

The results of the immunohistochemical study of CD34 were assessed as weakly, moderately and highly positive. The minimum number of cells with a low expression index was detected in very early stages. The maximum proportion of cells with highly expressed CD34 expression was detected at the end of the first trimester of pregnancy in the precursors of predecidual cells and the predecidual cells themselves.

Table No. 1

Expression of CD 34 in decidual tissue in the examined groups

No.	Degree of reaction	4-6 weeks		7-9 weeks		10-12 weeks	
		Control group n-10	Main group n-24	Control group n-6	Main group n-14	Control group n-4	Main group n-2
1	Negative reaction	-	10(41.7)	-	-	-	
2	<10% - low positivity	2 (20%)	14(58.3%)	-	8(57.1%)	-	
3	10-20% - average positive	8(80%)		4(66.7%)	4(28.6%)	-	2(100%)
4	>20% high positive	-		2(33.3%)	2(14.3%)	4(100%)*	

In the main group, compared to the control group, up to 6 weeks of pregnancy, medium and high expressions of vascular density were not detected. Expression of CD34 significantly ($p=0.05$) increased with increasing gestational age (Table No. 1), however, in the main group these indicators were significantly lower than in the control group ($p<0.05$) . Intragroup correlation analysis in uncomplicated pregnancy showed a reliable ($p<0.05$) highly positive correlation between the Ki67 indicator, responsible for the proliferation of the endometrial stroma, and the size of differentiating stromal cells in women in the control group (Fig. 1).

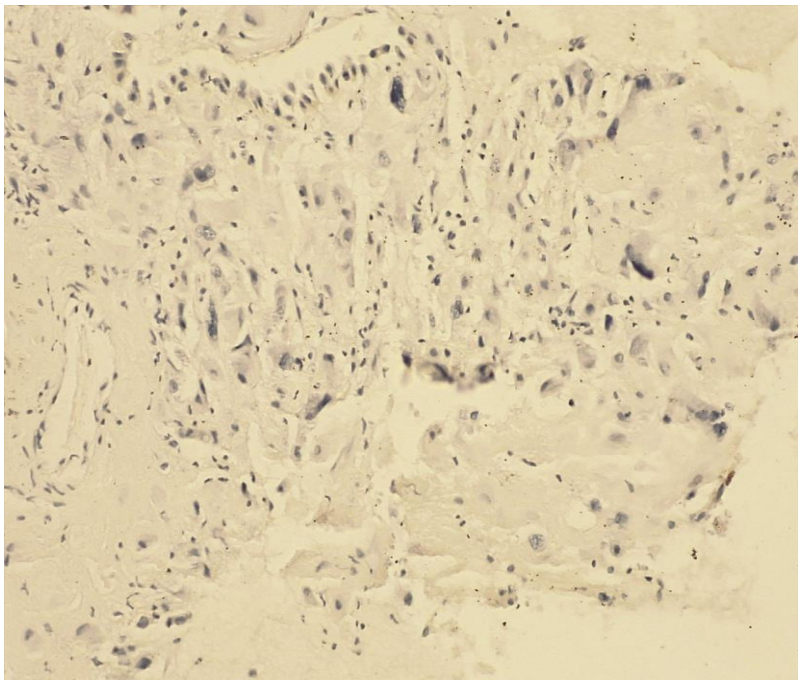

Figure 1. Ki 67 positive reaction. IHC – Dab chromagen. Ob10. Ok40

Immunohistochemical examination with antibodies that bind to progesterone receptors showed pronounced and moderately pronounced staining of the cytoplasm and cell nuclei (Table No. 2).

Table No. 2

Expression of hormonal receptors in decidual tissue in the examined groups

No.	Degree of reaction	Estrogen receptors		Progesterone receptors		hCG receptors	
		n-20	n-40	n-20	n-40	n-20	n-40
1	Negative reaction	-	14(70%)	-	-	-	-
2	<10% - low positivity	1(5%)	8(20%)	2(10%)	10(25%)	6(30%)	20(50%)
3	10-20% - average positive	4(20%)	4(10%)	4(20%)	20(50%)	10(50%)*	20(50%)
4	>20% high positive	15 (75%)*	-	14(70%)*	10(25%)	4(20%)	-

Immunohistochemical study of antibodies associated with steroid receptors of endometrial cells during uncomplicated pregnancy revealed a significant predominance of progesterone receptors in glandular epithelial cells compared to fibroblast-like stromal cells.

Hormone XGCH -It is a hormone that is produced in the membrane of the embryo during pregnancy. All 40 patients were tested for the presence of hCG receptors using the immunohistochemical method, with a positive reaction in 100%. Positive staining was observed in 50% of mild and 50% of moderate expression. Negative reactions and high expression were not detected.

Progesterone -Progesterone is usually the only progestin. Immunohistochemistry showed a positive reaction (100%), with 10 patients having a highly positive reaction, 50% of patients having a moderately positive reaction, and 25% having a mildly positive reaction.

Estrogen -Of the 40 patients, 8 (20%) had a low positive reaction, 4 of them (10%) had a moderate positive reaction, and 70% of 14 patients showed a negative reaction.

The decidual index of the main group of estrogen receptors in the membrane during expression is reduced by 2.1 times.

The membrane level of progesterone in cells 3 and 11, respectively, compared with uncomplicated pregnancies, in decidual receptors of immune expression is reduced by 3 times.

Thus, the study of the expression of estrogens and progesterone in the endometrial structures of the study groups revealed significant differences in the form of a reliable decrease in indicators in women suffering from habitual miscarriage, in contrast to patients with uncomplicated pregnancy.

In chronic endometritis, a more than 2-fold decrease in the expression of receptors to estrogens and progesterone in the nuclei of decidual epithelial cells was noted compared to normal endometrium. In quantitative terms, the expression of progesterone receptors was detected on average in a larger number of cells than the expression of estrogen receptors. The ratio of steroid receptors ER/PR in the epithelium in miscarriage was 0.97, which differs significantly from the values in normal endometrium - 1.42. The presence of changes in the ratio of steroid receptors in the endometrium indicates primarily dysfunctional disorders of tissue reception against the background of chronic inflammation.

CONCLUSION

Thus, a successful pregnancy requires the correct interaction between individual hormones and their respective receptors. In addition, adhesion molecules are responsible for the necessary physical interaction between the endometrium and the blastocyst, and finally, immune cells and cytokine signaling pathways act as mediators for the so-called embryo-mother dialogue.

Dysregulation or inadequate expression in one of these three compartments can lead to implantation failure or pregnancy loss.

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