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PROFILE OF STEROID HORMONES IN PREGNANT WOMEN WITH HYPERANDROGENEMIA, COMPARATIVE ASSESSMENT

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Abstract*. Problems of miscarriage occupy an important place in modern reproductive medicine. According to the World Health Organization, the rate of miscarriage of wanted pregnancies is 20%, of which 15% are spontaneous miscarriages and 5% are premature births. An unfavorable outcome of a previous pregnancy negatively affects a woman's reproductive health and her ability to subsequently conceive and bear a child (A.V. Zaichenko, "Modern approaches to the treatment of miscarriage," Medical News No. 5 2015).*

Keywords*: hyperandrogenism, miscarriage, steroid hormones, mixed saliva, immunoluminescence*

Recurrent miscarriage (RP) is a polyetiological complication of pregnancy, which is based on dysfunction of the reproductive system. The structure of habitual pregnancy losses includes genetic (5%), anatomical (10-14%), endocrine (10-17%), infectious (5%), immunological (up to 30%) factors and others, such as thrombophilia (13%) ["High-risk pregnancy - opinion of the world's leading experts", Obstetrics. Gynecology. Reproduction. 2017. Volume 11. No. 3]. Different stages of pregnancy are characterized by different etiological factors of recurrent miscarriage. Termination of pregnancy at 7–9 weeks is often associated with hormonal disorders: luteal phase insufficiency (LPF) of any origin, hyperandrogenism (adrenal, ovarian, mixed), sensitization to hormones (antibodies to HCG, progesterone) (Mikhalevich S.I., Habitual miscarriage: a social problem, medical solutions, No. 2 2012). In 50% of cases, the causes of miscarriage remain unclear, but each subsequent loss worsens the prognosis by 5–10% [O.A. Pustotina, A.E. Akhmedova, "Preconception preparation for women with a history of miscarriage," Medical Council No. 04, 2016]. Among hormonal disorders, hyperandrogenism is one of the leading pathogenetic causes of reproductive dysfunction. Elevated androgen levels lead to luteal phase deficiency, which in turn causes miscarriage in the first trimester.

At the moment, there are no generally accepted methods for diagnosing NB. A study of serum progesterone levels is not very informative for diagnosing NB and prognosis of pregnancy due to pulsed secretion and significant variations in its concentration in the blood. There is also no sufficient correlation between the level of progesterone in the systemic circulation and the endometrium. Low serum progesterone levels may be a marker of threatened miscarriage or a consequence of fetal pathology, including anembryonics [Howard JA. Carp. Recurrent pregnancy loss: causes, controversies and treatment. Second edition. New York: CRC Press; 2015: 1-16., Wetendorf M, DeMayo FJ. The progesterone receptor regulates implantation, decidualization, and glandular development via a complex paracrine signaling network. Mol Cell Endocrinol, 2012, 357: 108-18]. A universal recommendation for NB is to identify and correct all unfavorable factors and compensate for the lack of progesterone in the second phase of the menstrual cycle.

In the blood, steroid hormones for the most part (95-99%) are bound to specific sex steroid binding globulin (SHBG), and only 1% is in a free state. Hormones not associated with GSPC penetrate the cell membrane, turning into intracellular metabolites with high biological activity. Changes in the content of steroid hormones in blood plasma are often associated with a violation of the binding capacity of SHB (Grodnitskaya E.E. et al., 2012). The influence of fluctuations in SHB levels can be avoided by studying steroid hormones in saliva, which does not contain significant amounts of proteins and is therefore an optimal biological material (Marek B. et al., 2013).

Purpose of the study

The purpose of this study was to conduct a comparative study of the level of steroid hormones in blood serum and mixed saliva in women with hyperandrogenism and a history of miscarriage.

Materials and methods

The study involved 56 pregnant women in the first trimester of pregnancy. The main group consisted of 36 women with a threat of miscarriage due to elevated levels of androgens in the blood and a history of two or more cases of pregnancy loss due to hyperandrogenism. The control group consisted of 20 apparently healthy pregnant women. Clinical manifestations of hyperandrogenism included hirsutism, seborrhea, acne, stretch marks, and acanthosis nigricans.

The criteria for selecting women into the main group for hormonal screening of hyperandrogenism were menstrual irregularities, a history of infertility and miscarriage, the presence of clinical manifestations of virilization and the threat of miscarriage.

To determine the hormonal status, blood was taken from the ulnar vein in the morning on an empty stomach, while saliva was collected. Hormone levels were determined by immunoluminescence (ICL) using standard IMUNOTECH kits (Czech Republic). Data from the immunofluorescent laboratory were used as standard indicators. The levels of steroid hormones (free testosterone, estradiol, progesterone) and sex hormone binding globulin (SHBG) in peripheral blood and mixed saliva were determined for all patients.

Results and its discussion

Data analysis showed that among women in the first group, the number of multipregnant women was more than three times higher than the number of first-time pregnant women, while in the control group this ratio was 5.7 times. Among the multipregnant women of the first group, 67.5% of women gave birth, in the control group - 94.1%.

When analyzing gynecological pathology in women of the first group, the presence of primary (26.7%) and secondary (20%) infertility was noted. In the first group, cases of spontaneous abortion were observed 13 times more often, recurrent miscarriage - in 10% of women, and artificial abortion - in 16.7%. Non-developing pregnancy and premature birth in women of the first group occurred 1.5 and 2 times more often, respectively. The incidence of ectopic pregnancy was approximately the same in both groups (6.67% and 5%). Average hormone values were also examined and analyzed.

In the main group of pregnant women in the first trimester (5-12 weeks), a slight decrease in the content of estradiol (E2) in saliva was observed against the background of increased levels of testosterone (T). The level of dehydroepiandrosterone sulfate (DEAS) in pregnant women of the main group was significantly higher than control values, almost twice (11.29±1.12 μg/ml versus 6.8±0.16 μg/ml, $P<0.001$).

Average values of hormones in blood serum and saliva in pregnant women of both groups in the first trimester (M±m)

Studied parameters	Main, n=30		Control, n=20	
	In the blood	In the saliva	In the blood	In the saliva
T, nmol/l	7,3±0,2 (1,9↑)	6,9±1,32 (4,7↑)	3,87±0,09	1,45±0,03
DEAS, μmol/l	11,29±1,12 (1,7↑)	5,2±1,05 (2,3↑)	6,8±0,16***	2,3±1,1
E2, nmol/l	13,4±1,25 (1,1↓)	1,45±1,1 (1,2↓)	11,96±1,42***	1,7±0,1
P, ng/mg	1,31±0,08 (2,3↓)	0,5±0,01 (1,3↓)	3,07±0,07***	0,65±0,11

The level of progesterone (P) in the main group was significantly lower, almost twofold (1.81±0.08 nmol/l versus 1.07±0.07 nmol/l, P<0.001). The E2/P ratio in saliva was 2.96±0.14, which is significantly higher than the normative values (P<0.001).

Pregnant women with hyperandrogenism and elevated T and DEAS levels in the first trimester received hormonal therapy, including dexamethasone (0.125–0.5 mg per day) until the T and DEAS levels decreased to normal levels. Further use of dexamethasone was regulated by the levels of T, DEAS, E2 and P in saliva. Pregnant women with low P levels in the first trimester took progesterone drugs: Duphaston (10 mg, 1 tablet 3 times a day, then 2 times a day) or Utrozhestan (100-200 mg 2 times a day, depending on the clinical manifestations of the threat of miscarriage) up to 16 weeks. When prescribing these drugs, the E2/P ratio was taken into account, since relative hyperestrogenism (E2/P>1.5) is an indication for the use of progesterone drugs.

During treatment, hormonal parameters were assessed. During dexamethasone therapy, there was a significant decrease in T concentration from 6.9±1.32 nmol/l to 4.1±1.03 nmol/l (P<0.001), and DEAS level from 11.29±1.12 μg/ml to 6.8±1.11 μg/ml (P<0.001) and E2 from 1.45±1.1 pmol/l to 1.87±0.03 pmol/l (P<0.001). As a result of treatment, P level increased from 1.31±0.08 nmol/l to 2.3±0.1 nmol/l (P<0.001).

Conclusion. Analysis of average values of steroid hormone levels based on a single analysis in blood serum in the first trimester in women with hyperandrogenism is not very informative. This is due to the fact that sex steroids in the blood serum are predominantly in a bound state with specific globulin (GSPC), and only about 1% of steroid hormones are in a free, biologically active state and are excreted in saliva. Determination of hormones in saliva may be a more informative method for diagnosing hyperandrogenism than in blood serum.

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