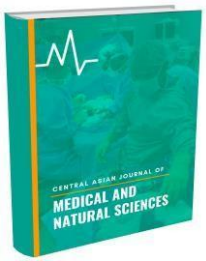

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Article

Prognostic Significance of Hormonal Markers of Recurrent Pregnancy Loss in Women With Hyperprolactinemia

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Abstract: This study is aimed at assessing the levels of fertility indicators (inhibin A, activin and chorionic gonadotropin - HCG) and their dynamic changes during pregnancy in women with hyperprolactinemia, as well as determining their prognostic significance in the development of habitual miscarriage in the first trimester. The study was conducted by a prospective comparative method, in which 93 pregnant women participated: 73 with hyperprolactinemia and habitual miscarriage, and 20 - healthy pregnant women. During the study, the levels of activin, inhibin A, HCG, and prolactin were studied throughout the trimester, and the results were statistically processed using the $\chi 2$ test, ANOVA, and ROC analysis methods. The results showed that in women with hyperprolactinemia, the hormonal profile is significantly disrupted in the early stages of pregnancy: the level of activin increases, inhibin A decreases, and the HCG level is significantly lower than in the control group. According to the results of ROC analysis, HCG has the highest prognostic value (AUC = 0.873; sensitivity - 93.2%), inhibin A is moderate, and activin has low diagnostic value.

Keywords: Hyperprolactinemia, habitual miscarriage, inhibin A, activin, HCG, hormonal markers, pregnancy prognosis.

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Introduction

Habitual miscarriage remains one of the most complex and clinically significant medical and social problems in modern obstetrics, gynecology, and endocrinology. According to various authors, 10-15% of clinically confirmed pregnancies and up to 30% of all pregnancies end in spontaneous abortion, making it the most common complication of gestation . About 5% of women have two or more miscarriages in a row, and in 0.4-1% there are three or more spontaneous abortions, that is, habitual miscarriage is formed. At the same time, the risk of repeated pregnancy loss progressively increases with the increase in previous miscarriages and the woman's age[1].

According to WHO definition, PNB refers to the presence of three or more spontaneous miscarriages in a history up to 22 weeks of gestation. PNB is considered a multifactorial, often genetically determined condition, in the development of which anatomical malformations of uterine development, chromosomal abnormalities, infectious and immune disorders, thrombophilia, as well as endocrine pathology are involved . The

proportion of endocrine factors in the structure of habitual miscarriage averages 17-20%, however, according to individual studies, it can reach 60%, which is due to differences in the design and criteria for patient selection. The most significant endocrine causes of PON are ovarian hypofunction, hyperandrogenism, thyroid diseases, and hyperprolactinemia[2].

Among endocrine disorders, hyperprolactinemia holds a special place - one of the key manifestations of hypothalamic-pituitary-gonadal axis dysregulation. Hyperprolactinemia is detected in less than 1% of the general population, but it occurs in 5-14% of patients with secondary amenorrhea, 40-70% of women seeking infertility, and 12-36% of patients with miscarriage . The prevalence of hyperprolactinemia is estimated at approximately 10 per 100,000 men and 30 per 100,000 women of reproductive age, and it is the second most frequent endocrine cause of female infertility[3].

The pathogenetic mechanisms of hyperprolactinemia's impact on the reproductive system are multi-component. Excessive prolactin secretion leads to impaired pulsatory secretion of LH and FSH, the formation of hypogonadotropic hypogonadism, anovulation, and luteal phase deficiency. At the endometrial level, hyperprolactinemia contributes to insufficient secretory transformation and decidualization, disruption of local cytokine and hormonal balance, leading to incomplete implantation and increased risk of early pregnancy loss. It has been shown that in pregnant women with initial hyperprolactinemia in the first trimester, the threat of termination, underdeveloped pregnancy, as well as pronounced changes in progesterone-dependent endometrial restructuring are registered significantly more often[4].

Pregnancy against a background of hyperprolactinemia is characterized by a high risk of obstetric and perinatal complications at all stages of gestation. In the first trimester, a significant increase in the frequency of threatened abortion and spontaneous abortions is noted; in the second and third trimesters, the frequency of threatened abortion, placental insufficiency, premature birth, edema, uteroplacental and fetal blood flow disorders, and signs of chronic fetal hypoxia increases. In childbirth, premature rupture of membranes, weakness of labor activity, and acute fetal hypoxia are more often observed, which is accompanied by an increase in the proportion of surgical delivery and a high frequency of newborn asphyxia. Together, these data allow us to consider hyperprolactinemia as an important risk factor for unfavorable pregnancy and perinatal outcomes[5].

In recent years, significant attention has been paid to the search for early biochemical markers that allow predicting the outcome of pregnancy in high-risk women, including patients with PNB against the background of endocrine pathology. One of the most promising is the peptide group of the transforming growth factor β (TGF-β) superfamily - inhibitors and activins[6]. These glycoprotein dimers are synthesized in the ovaries, placenta, and other tissues, participating in the regulation of folliculogenesis, the function of the corpus luteum, placental steroidogenesis, and the secretion of gonadotropins. It has been shown that inhibin A is a sensitive marker of placental function and can be used to predict miscarriage, preeclampsia, and other pregnancy complications, while changes in the "inhibin-activin" balance reflect disorders in the "fetoplacental complex - endometrium" system[7].

Despite the accumulated data on the prevalence of hyperprolactinemia, its role in the genesis of infertility and miscarriage, many aspects of the problem remain insufficiently studied. In particular, the prognostic significance of fertility predictors (inhibin A, activin, HCG) in women with habitual first-trimester miscarriage against the background of hyperprolactinemia, especially in real clinical practice, has not been fully determined. Information is also insufficient on how the dynamics of these markers under the influence of pathogenetic therapy correlate with the course of pregnancy and its outcomes for the mother and fetus[8].

Considering the high prevalence of PNB, the significant proportion of endocrine factors in its structure, as well as the important role of hyperprolactinemia in reproductive dysfunction, a comprehensive study of the levels of fertility predictors in this category of patients is relevant. This will clarify the pathogenetic mechanisms of miscarriage, identify groups with increased risk of non-developing pregnancy, and justify individualized approaches to managing women with PNB against a background of hyperprolactinemia[9].

Research Objective

to assess the levels and dynamic changes in fertility predictors (inhibin A, activin, and chorionic gonadotropin) during pregnancy in women with hyperprolactinemia, as well as to determine their prognostic significance in the development of habitual miscarriage in the first trimester.

Materials and Methods

The study was conducted as a prospective comparative observation and conducted at the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after A.K. To'raqulov, the 6th City Maternity Hospital, and the Diyor Medical private clinic from October 2023 to September 2025.

The study included women aged 20-37 years in the first trimester of pregnancy with a diagnosis of hyperprolactinemia and a history of habitual miscarriage in the first trimester.

Inclusion criteria:

1. 20-37 years old;

2. habitual miscarriage of the first trimester of pregnancy in hyperprolactinemia;

3. the presence of a non-developing pregnancy in the anamnesis, excluding other reasons;

Exclusion criteria

1. age over 37 years;

2. any concomitant endocrine or gynecological pathology capable of independently causing pregnancy termination (hyperthyroidism, diabetes mellitus, CNS, PPI, etc.);

3. presence of pituitary adenomas.

The formation of groups was carried out taking into account anamnestic data and endocrine status: the main group included patients with PNB in the first trimester against a background of hyperprolactinemia, and the control group included somatically healthy pregnant women of the same age and reproductive profile.

The methodological complex of the study included clinical, laboratory, and instrumental examination. The clinical part involved collecting complaints, obstetric-gynecological and endocrinological history, and assessing anthropometric indicators. The laboratory part included determining the levels of inhibitor A, activin, chorionic gonadotropin, and prolactin. Blood sampling was performed on an empty stomach during each trimester of pregnancy to assess the dynamics of the studied hormones. Instrumental methods included ultrasound examination of the pelvic organs and uterus with appendages, and, if necessary, magnetic resonance imaging of the pituitary gland.

For statistical processing, descriptive and inferential statistics methods were used. The differences between the groups were assessed using the $\chi 2$ test and one-factor analysis of variance (ANOVA). Multiple regression was used to determine significant predictors. The diagnostic value of hormonal markers was assessed by ROC analysis method with

calculation of AUC, sensitivity, and specificity. Data analysis was performed in the Statistica and IBM SPSS programs, significance level - $p < 0.05$.

Research Results

The dynamics of the main hormonal indicators in the two groups are presented in Tables 1 and 2, which allows us to trace their changes at different stages of pregnancy[10].

Table 1. Hormone levels dynamics in two groups at different stages of pregnancy ($P < 0.001$)[11].

Parameter	Baseline	1st Trimester	2nd Trimester	3rd Trimester
Activin (pg/ml)				
Activin (Hyperprolactinemia group, n=73)	5.02 ± 0.37	14.4 ± 0.34	3.52 ± 0.31	2.53 ± 0.20
Activin (Control group, n=20)	3.96 ± 0.35	1.68 ± 0.15	3.75 ± 0.37	2.44 ± 0.20
p-value (P1–P2)	0.041	<0.001*	n/s (p=0.636)	n/s (p=0.751)
Inhibin A (pg/ml)				
Inhibin A (Hyperprolactinemia group, n=73)	11.5 ± 0.60	100.49 ± 4.68	318.6 ± 15.7	442.7 ± 14.6
Inhibin A (Control group, n=20)	13.075 ± 3.19	759.2 ± 54.6	267.5 ± 9.8	392.3 ± 10.1
p-value (P1–P2)	n/s (p=0.633)	<0.001*	p=0.007	p=0.006
Prolactin (μIU/ml)				
Prolactin (Hyperprolactinemia group, n=73)	645.96 ± 32.68	3980 ± 194.5	9236.6 ± 324.48	10654.1 ± 218.2
Prolactin (Control group, n=20)	209.0 ± 12.45	1002.7 ± 76.3	7497.3 ± 364.4	9616.5 ± 416.1
p-value (P1–P2)	<0.001*	<0.001*	<0.001*	p=0.035

Analysis of changes in the levels of activin, inhibin A, and prolactin revealed pronounced differences between the hyperprolactinemia group and the control group in the early stages of pregnancy. Table 1 indicates that already in the first trimester, statistically significant deviations were observed in all the main markers of the hormonal profile. Thus, the level of activin in patients with hyperprolactinemia was significantly higher than in the control group (14.4±0.34 versus 1.68±0.15 pg/ml, $p<0.001$), which reflects the increased compensatory activity of the activin-inhibitor system against the background of endocrine imbalance[12].

Conversely, the levels of inhibitor A in the first trimester were significantly lower in women of the main group (100.49 ± 4.68 pg/ml versus 759.2 ± 54.6 pg/ml, $p < 0.001$), indicating suppressed functional activity of the trophoblast and early placental insufficiency. In the second and third trimesters, against the background of treatment with dopamine receptor agonists, a persistent trend towards the restoration of the synthetic function of the placenta was noted: the level of inhibitor A in the second trimester was

practically comparable to the control, and by the third trimester, the convergence of indicators became even more pronounced[13].

Prolactin in the hyperprolactinemia group showed a significant increase as pregnancy progressed (from 3980±194.5 μM/ml in the first trimester to 10654.1±218.2 μM/ml in the third trimester), which corresponds to the physiological growth of the hormone, however, the levels were significantly higher than normal values. This emphasizes the need for control and timely correction of hyperprolactinemia to normalize the hormonal background[14].

The behavior of chorionic gonadotropin, which is a key marker of early trophoblast development, is of particular interest.

Table 2. Dynamics of changes in HCG levels during pregnancy in women in two groups[15].

Parameter (IU/L)	1–4 weeks (160–7200)	5–8 weeks (1000–15000)	9–12 weeks (46000–210000)	2nd trimester (10000–30000)	3rd trimester (5000–15000)
Hyperprolactinemia group (n=73)	512.2 ± 25.71	3635.8 ± 297.6	20581.6 ± 2737.4	19298.9 ± 642.6	10440.9 ± 353.6
Control group (n=20)	3683.9 ± 301	72218 ± 4267	150197 ± 9416	20518.3 ± 948	10065.0 ± 593.1
p-value (P1–P2)	<0.001*	<0.001*	<0.001*	n/s (p=0.294)	n/s (p=0.590)

In women with hyperprolactinemia, the HCG level in the first trimester was significantly lower compared to the control group. At 1-4 weeks, the concentration was only 512.2 ± 25.7 IU/L, while in healthy pregnant women it was 3683.9 ± 301 IU/L ($p < 0.001$). Similar differences persisted at 5-8 weeks and 9-12 weeks, when the physiological peak of HCG was observed in the women of the control group. Only from the second trimester did the differences cease to be statistically significant[16].

This dynamic indicates early disruption of the implantation-placental complex in patients with hyperprolactinemia and emphasizes the diagnostic value of early determination of HCG for identifying the risk group for non-developing pregnancy[17].

The obtained data on hormone dynamics served as the basis for subsequent assessment of their prognostic significance, which was carried out using ROC analysis.ROC analysis allowed for a quantitative assessment of the diagnostic effectiveness of the studied hormonal markers. According to the data in Table 3, the largest area under the ROC curve (AUC) was demonstrated by HCG - 0.873 ($p = 0.001$), which corresponds to a high prognostic ability. Its sensitivity was 93.2%, specificity - 65%. Such indicators make HCG the most sensitive marker of early unfavorable pregnancy prognosis in women with hyperprolactinemia[18].

Table 3. Predictive significance of hormones in the group with hyperprolactinemia.

Hormones	AUC	Standard Error	p-value	95% CI (Lower)	95% CI (Upper)
Activin	0.578	0.056	0.168	0.467	0.688
Inhibin A	0.763	0.052	0.001	0.662	0.864
hCG	0.873	0.052	0.001	0.771	0.976

Hormones	Sensitivity (%)	Specificity (%)

Activin	58.9%	55%
Inhibin A	74%	65%
hCG	93.2%	65%

Ingibin A also showed good prognostic ability (AUC = 0.763, p = 0.001) with a sensitivity of 74% and a specificity of 65%. It is especially useful as an additional marker for assessing the functional activity of the trophoblast in the first trimester. Activin ranked lower among markers (AUC = 0.578, p = 0.168), demonstrating limited diagnostic value for predicting the risk of non-developing pregnancy. Its sensitivity and specificity were 58.9% and 55%, respectively[19].

Discussion

The obtained results confirm the significant influence of hyperprolactinemia on the hormonal profile of pregnant women, especially in the early stages of gestation. The most pronounced deviations were related to the levels of activin, inhibin A, and HCG, which corresponds to literature data on trophoblastic function disorders and early placentation in endocrine disorders[20]. Significant decrease in HCG in the first trimester in patients with hyperprolactinemia indicates inadequacy of the implantation process, which can be a key risk factor for non-developing pregnancy. Simultaneously, the observed increase in activin and decrease in inhibitor A reflect the disorganization of the activin-ingibin regulatory system involved in placental implantation and development[21].

The gradual normalization of A inhibition levels in the second and third trimesters against the background of dopamine receptor agonists therapy indicates the restoration of the placenta's endocrine function and the effectiveness of the treatment. This emphasizes the importance of timely correction of hyperprolactinemia to improve pregnancy outcomes[22].

The results of ROC analysis showed that among the studied markers, HCG has the highest prognostic value, surpassing activin and inhibitor A. The high sensitivity of HCG makes it an irreplaceable marker for early detection of risk groups, while inhibitor A can be used as an additional indicator for assessing the functional state of the trophoblast. Activin, however, showed limited diagnostic value. Overall, the research results confirm the need for comprehensive hormonal monitoring in women with hyperprolactinemia, which allows for the timely detection of early embryogenesis disorders and improvement of pregnancy outcomes through early intervention[23].

Conclusion

The results of this study confirm the high diagnostic and prognostic significance of hormonal markers in pregnancies complicated by hyperprolactinemia. Analysis of data from 93 pregnant women (73 in the main group and 20 in the control group) demonstrated that women with hyperprolactinemia exhibit pronounced hormonal imbalance in the early stages of pregnancy. In particular, at 1–4 weeks of gestation, the HCG level in the main group was 512.2±25.7 IU/L, which was significantly lower compared to the control group (3683.9±301 IU/L, $p<0.001$).

In addition, an increase in activin levels (14.4±0.34 pg/ml) and a marked decrease in inhibin A levels (100.49±4.68 pg/ml) indicate impaired trophoblastic function and inadequate implantation processes. According to ROC analysis, HCG demonstrated the highest prognostic value (AUC = 0.873) with a sensitivity of 93.2%. Inhibin A showed

moderate prognostic significance (AUC = 0.763), whereas activin exhibited limited diagnostic value (AUC = 0.578).

Overall, the findings suggest that hyperprolactinemia has a negative impact on the fetoplacental system in early pregnancy. The use of markers such as HCG and inhibin A is essential for early identification of high-risk cases. Furthermore, timely pathogenetic therapy contributes to the normalization of hormonal parameters and improves pregnancy outcomes.

1. Hyperprolactinemia is accompanied by pronounced hormonal profile disorders in the early stages of pregnancy, which manifests as a decrease in the levels of HCG and inhibin A and an increase in activin, indicating the inadequacy of implantation and early placentation.

2. Against the background of dopamine receptor agonist therapy, gradual normalization of hormonal indicators, especially inhibin A, is observed, which reflects the restoration of placental functional activity and confirms the effectiveness of hyperprolactinemia correction.

3. According to ROC analysis, HCG is the most informative marker of the early risk of adverse pregnancy outcomes, while inhibin A has additional prognostic value, and activin demonstrates limited diagnostic significance.

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