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Metabolomic Profile of Sex Steroid Hormones in Women with Infertility: New Perspectives in Reproductive Medicine

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ABSTRACT

Background. *Studying the metabolic profile of sex steroid hormones offers new prospects in reproductive medicine. Identifying metabolic markers can aid in early diagnosis and personalized treatment of infertility.*

Aim. To evaluate the metabolomic profile of sex steroid hormones in women with infertility to identify unique metabolic markers that aid in diagnosis and enhance treatment.

Materials and methods. *The study involved 60 women with infertility, divided into two groups: 30 women with early reproductive age infertility (Group I) and 30 women with late reproductive age infertility (Group II). The control group included 30 healthy women. A comprehensive clinical-laboratory analysis was conducted, including hormonal screening and instrumental methods such as ultrasound. Highly sensitive methods — liquid and gas chromatography-mass spectrometry — were used for metabolomic analysis.*

Results. *The study revealed significant differences in the metabolomic profile of steroid hormones between groups: a 25% increase in estrogen metabolites in women with infertility indicates an imbalance affecting ovulation and reproductive function. Progesterone metabolite levels were elevated by 15%, which may indicate issues with the luteal phase and implantation. A 20% decrease in testosterone levels suggests impaired ovarian function and reduced fertility. ROC analysis demonstrated a high diagnostic accuracy of the model for predicting infertility (AUC=0.82), highlighting the importance of metabolomic markers in diagnosis.*

Conclusion. *The results indicate the importance of hormonal metabolic pathways in the development of infertility. Metabolomic analysis can serve as an early indicator of hormonal imbalances, allowing for personalized therapeutic strategies. The identification of specific metabolites, such as 2-hydroxyestrone and dehydroepiandrosterone, could form the basis for the development of early diagnostic methods.*

Key words: *metabolomics; infertility; sex steroid hormones; biomarkers; reproductive health.*

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INTRODUCTION

Female infertility is a global public health issue affecting the lives of millions of couples worldwide. According to the World Health Organization (WHO), approximately 48 million couples suffer from infertility [1, 2].

The prevalence of infertility varies significantly by region: in developed countries, it is approximately 8-12%, while in developing countries, it can reach up to 30% [3, 4].

In the 20-24 age group, infertility is less common than in women over 35, underscoring the importance of age as a factor in reproductive health. Infertility leads to significant emotional, psychological, and economic consequences [5, 6].

Social stigma, feelings of guilt, and depression often accompany women diagnosed with this condition, and the costs of treatment can have a considerable impact on family finances. Families are often forced to seek additional income sources to cover treatment costs, which may lead to a decline in quality of life and interpersonal relationships [7, 8].

Current diagnostic and treatment methods for infertility include hormonal therapies, in vitro fertilization (IVF), and surgical interventions [9, 10].

Hormonal therapies, such as ovulation stimulation, are commonly used to treat hormonal imbalances associated with infertility [11, 12].

IVF, which involves the fertilization of oocytes in a laboratory setting followed by embryo implantation into the uterus, is one of the most effective methods for treating infertility [13, 14].

Surgical interventions, such as laparoscopy, are utilized to remove benign growths, such as endometriosis or uterine fibroids. However, these methods have limitations [15, 16].

Hormonal therapies may be ineffective for complex hormonal disorders, IVF is associated with high costs and emotional risks, and surgical methods may lead to complications and do not always result in successful pregnancies. Many of these methods also have side effects and may require long recovery periods [17, 18].

In this context, metabolomics offers an innovative approach that allows a deeper understanding of the metabolic processes underlying hormonal disorders associated with infertility [19, 20].

Metabolomics, which utilizes advanced technologies such as mass spectrometry and liquid chromatography, comprehensively analyses the body's metabolic profile [21, 22]. This approach not only helps to identify unique metabolites associated with infertility but also aids in developing more targeted diagnostic and treatment strategies focused on specific metabolic pathways. This is particularly important for women whose infertility is linked to the suppression or excess of certain hormones, as metabolomic analysis can reveal previously unnoticed aspects of their regulation and interaction [23, 24].

Metabolomics enables the analysis of thousands of metabolites simultaneously, providing a more complete picture of the body's metabolic state. This allows for the detection of not only primary hormonal imbalances but also associated metabolic changes that may impact reproductive function. For example, metabolomic analysis can identify changes in lipid and carbohydrate metabolism that may affect hormonal balance and, consequently, fertility [25, 26].

In recent years, advances in metabolomics have allowed for a deeper understanding of the mechanisms underlying infertility and have opened new avenues for its treatment. Research into the metabolomics of sex steroid hormones presents opportunities for identifying early diagnostic markers and developing individualized therapeutic strategies that can improve women's reproductive health [27, 28]. Thus, metabolomics is emerging as a powerful tool in the fight against infertility, providing new opportunities to understand this complex and multifaceted condition.

The development of metabolomics also promotes a personalized approach to infertility treatment. Analyzing the metabolic profile of each woman allows for the creation of individualized treatment plans that may be more effective and have fewer side effects [29,30].

This is especially important for women with rare or complex forms of infertility, for whom standard treatments may be ineffective. Personalized treatment methods based on metabolomic analysis can significantly increase the likelihood of successful conception and pregnancy maintenance.

The objective of this study is to analyze the metabolomics of sex steroid hormones in women with infertility to identify unique metabolic markers that may contribute to the development of new approaches for diagnosing and treating this condition.

MATERIALS AND METHODS

The study included 60 women of reproductive age diagnosed with infertility, with 30 women of early reproductive age (Group I) and 30 women of late reproductive age (Group II). The control

group consisted of 30 healthy women. All participants met the inclusion and exclusion criteria.

Inclusion Criteria: Women of reproductive age from 18 to 40 years with a confirmed diagnosis of primary or secondary infertility, no use of hormonal medications in the last 3 months before the study, and informed consent to participate in the research.

Exclusion Criteria: Women with diabetes, systemic autoimmune diseases, cardiovascular diseases, or other severe comorbid conditions; women with unstable psychiatric disorders; women taking medications that affect hormonal balance or metabolism (e.g., steroids, thyroid hormones), except for thyroid hormones at normal levels; pregnancy and lactation.

All patients underwent a comprehensive clinical laboratory examination, including hormonal screening and various instrumental diagnostic methods to assess their reproductive health. Hormonal screening involved measuring levels of major sex hormones (estradiol, progesterone, testosterone) using automated analyzers (Abbott Architect and Roche Cobas). Highly sensitive methods, such as enzyme-linked immunosorbent assay (ELISA) and chemiluminescent immunoassay (CLIA), were employed to ensure high accuracy and reproducibility of results. Instrumental diagnostic methods included transvaginal ultrasound (US) of the pelvic organs to assess the structure of the ovaries and uterus, as well as Doppler imaging to examine blood flow in the reproductive organs. Ultrasound examinations were performed using high-resolution devices, such as the GE Voluson E10, providing detailed imaging.

To study the metabolic profile of sex steroid hormones, blood and urine samples were collected from the participants. Sample collection was conducted in the morning on an empty stomach to minimize variations due to food intake or circadian rhythms. Blood samples were obtained from a peripheral vein using vacuum systems (e.g., BD Vacutainer) to ensure sample sterility and integrity. Urine was collected in sterile containers. After collection, blood samples were centrifuged at 3000 rpm for 10 minutes to separate the serum, which was then frozen at -80°C until analysis. Urine samples were also stored at -80°C to preserve metabolite stability. High-performance liquid chromatography followed by gas chromatography-mass spectrometry (GC-MS) was chosen due to its high sensitivity and specificity. The analysis was performed on equipment such as the Agilent 7890B GC and 5977B MSD, enabling precise identification and quantification of metabolites in small volumes of biological material.

The metabolomic analysis of sex steroid hormones covered a wide range of metabolites, including estrogens, progesterones, androgens, and their precursors. This approach allowed for the assessment of primary hormone levels and a detailed examination of their synthesis and breakdown pathways. Special attention was given to changes in the metabolism of these hormones potentially associated with infertility, including abnormalities in steroid synthesis and metabolism, imbalances between different hormones, and their effects on the female reproductive system. The obtained data were analyzed using statistical methods to identify significant differences between the group of women with infertility and the control group of healthy women. This analysis allowed not only for the identification of specific metabolic markers of infertility but also provided valuable insights into potential mechanisms of reproductive dysfunction at the molecular level. These findings may contribute to the development of new approaches for diagnosing, treating, and preventing infertility, as well as improving the understanding of the role of hormonal metabolism in women's reproductive health.

Statistical data processing was performed using Statistica v.6.0 and Microsoft Excel 2000 software. Results were analyzed using methods of descriptive statistics and presented as M±m. The significance of differences in mean values and relative indicators was assessed using Student's t-test, with a significance level of $P<0.05$ accepted for this study.

RESULTS

The results of the study on the metabolomics of sex steroid hormones in women with infertility demonstrated significant differences in the metabolic profile between the groups of women of early and late reproductive age and the control group.

A detailed analysis of estrogen metabolite levels in women with infertility revealed a significant increase in certain metabolite levels in both groups: among patients in early reproductive age (Group I) and those in late reproductive age (Group II). Specifically, the study showed an increase in metabolites by 25% and 32%, respectively, in women with infertility compared to the control group. This suggests the presence of disturbances in estrogen metabolism that may directly impact reproductive function and ovulation.

The analysis of estrogen metabolites, such as 2-hydroxyestrone (2-OHE1), 2-hydroxyestradiol (2-OHE2), 2-OHE1 + 2-OHE2, 4-hydroxyestrone (4-OHE1), 16α-hydroxyestrone (16α-OHE1), 2-methoxyestrone (2-

OMeE1), and 4-methoxyestrone (4-OMeE2), also revealed significant differences in their levels in women with infertility.

In 30 women of early reproductive age with infertility, the levels of 2-hydroxyestrone (2-OHE1) were 40.8 ± 2.12 μg/day, 2-hydroxyestradiol (2-OHE2) 9.58 ± 2.01 μg/day, and their combined value 2-OHE1 + 2-OHE2 was 58.00 ± 2.50 μg/day. Levels of 4-hydroxyestrone (4-OHE1) were 8.02 ± 1.50 μg/day, while 16α-hydroxyestrone (16α-OHE1) was 13.04 ± 1.50 μg/day. The metabolites 2-methoxyestrone (2-OMeE1) and 4-methoxyestrone (4-OMeE2) showed increases to 9.04 ± 1.02 μg/day and 0.018 ± 0.60 μg/day, respectively.

In 30 women of late reproductive age with infertility, the levels of 2-hydroxyestrone (2-OHE1) increased to 41.2 ± 1.50 μg/day, 2-hydroxyestradiol (2-OHE2) to 10.47 ± 1.50 μg/day, and their combined value to 47.00 ± 2.00 μg/day. Levels of 4-hydroxyestrone (4-OHE1) increased to 9.04 ± 1.20 μg/day, while 16α-hydroxyestrone (16α-OHE1) increased to 14.01 ± 1.20 μg/day. The metabolites 2-methoxyestrone (2-OMeE1) and 4-methoxyestrone (4-OMeE2) increased to 10.01 ± 0.80 μg/day and 0.020 ± 0.50 μg/day, respectively.

These results indicate that changes in estrogen metabolism may be associated with infertility. Elevated levels of estrogen metabolites may reflect changes in the activity of enzymes involved in the detoxification and metabolism of estrogens, or disruptions in the processes of their recirculation and elimination from the body. Differences in metabolite levels between women of early and late reproductive age may also indicate age-related changes in estrogen metabolism that could affect fertility (Table 1).

Table 1. Levels of Estradiol Metabolites in Different Groups, M±m

Metabolite	Group I (n=30)	Group II (n=30)	Control Group (n=30)	P
2-OHE1, μg/day	40.8 ± 2.12	41.2 ± 1.50	35.00 ± 1.04	p< 0.01
2-OHE2, μg/day	9.58 ± 2.01	10.47 ± 1.50	7.48 ± 1.02	p< 0.05
4-OHE1, μg/day	8.02 ± 1.50	9.04 ± 1.20	5.6 ± 1.02	p< 0.05
16α-OHE1, μg/day	13.04 ± 1.50	14.01 ± 1.20	11.76 ± 1.04	p< 0.05
2-OMeE1, μg/day	9.04 ± 1.02	10.01 ± 0.80	7.6 ± 0.50	p< 0.05
4-OMeE2, μg/day	0.018 ± 0.60	0.020 ± 0.50	0.015 ± 0.40	p< 0.05

The elevated levels of estrogen metabolites may also reflect compensatory mechanisms of the body aimed at maintaining sufficient concentrations of active hormone forms in the presence of metabolic disturbances. This phenomenon is especially significant for women with infertility, as insufficient levels of active estrogen forms could be a key factor in their condition. Increased metabolite levels may indicate the body's attempts to compensate for the deficiency of active hormone forms, which may suggest complex interactions among various metabolic pathways.

These findings underscore the need for a detailed metabolomic analysis of estrogens in women with infertility to understand the mechanisms of this condition's development. Metabolomic analysis can reveal hidden metabolic imbalances and biomarkers that are not detectable with traditional diagnostic methods. This knowledge could lead to the development of new, more effective diagnostic and treatment methods for infertility.

The analysis of progesterone metabolomics demonstrated a significant increase in its metabolite levels in women with infertility compared to the control group. Elevated levels of progesterone metabolites were observed in both Group I and Group II women. Specifically, the level of progesterone metabolites in Group I was increased by 15%, and in Group II by 21% compared to the control group. This may indicate disturbances in the luteal phase of the menstrual cycle or issues with embryo implantation, which are critical for successful conception and pregnancy maintenance.

In 30 women of early reproductive age (Group I), the levels of 17α-hydroxyprogesterone were 7.12 ± 1.50 ng/mL, 5α-dihydroprogesterone — 2.5 ± 1.10 ng/mL, pregnenolone — 2.06 ± 1.60 ng/mL, and 11-deoxycorticosterone — 1.01 ± 0.90 ng/mL. In 30 women of late reproductive age (Group II), the levels of 17α-hydroxyprogesterone were 9.24 ± 1.30 ng/mL, 5α-dihydroprogesterone — 3.00 ± 0.90 ng/mL, pregnenolone — 2.08 ± 1.40 ng/mL, and 11-deoxycorticosterone — 1.02 ± 0.80 ng/mL. For comparison, in the control group of 30 healthy women, the levels of 17α-hydroxyprogesterone were 4.51 ± 1.00 ng/mL, 5α-dihydroprogesterone — 1.5 ± 0.80 ng/mL, pregnenolone — 2.0 ± 1.20 ng/mL, and 11-deoxycorticosterone — 0.5 ± 0.60 ng/mL (Table 2).

Table 2. Levels of Progesterone Metabolites in Different Groups, M±m

Metabolite	Group I (n=30)	Group II (n=30)	Control Group (n=30)
17α-Hydroxyprogesterone (ng/mL)	7.12 ± 1.50	9.24 ± 1.30	4.51 ± 1.00
5α-Dihydroprogesterone (ng/mL)	2.5 ± 1.10	3.00 ± 0.90	1.5 ± 0.80
Pregnenolone (ng/mL)	2.06 ± 1.60	2.08 ± 1.40	2.0 ± 1.20
11-Deoxycorticosterone (ng/mL)	1.01 ± 0.90	1.02 ± 0.80	0.5 ± 0.60
P	< 0.01	< 0.05	< 0.01

These data indicate elevated levels of progesterone metabolites, which may reflect changes in the synthesis and metabolism of this hormone. Progesterone plays a

key role in maintaining the luteal phase of the menstrual cycle and facilitating successful embryo implantation. The luteal phase begins after ovulation and is characterized by increased progesterone levels, which prepare the uterine endometrium for potential embryo implantation. Disruptions in progesterone levels can lead to inadequate endometrial preparation and, consequently, unsuccessful implantation and early miscarriage.

Furthermore, elevated levels of progesterone metabolites may indicate compensatory mechanisms in the body aimed at maintaining sufficient hormone concentration in the presence of ovarian dysfunction. This is particularly important for women with infertility, as low progesterone levels could be one of the causes of their condition.

Studies have shown that elevated levels of 17α-hydroxyprogesterone may be associated with disturbances in enzymatic activity responsible for its synthesis and metabolism. This may include defects in enzymes such as 21-hydroxylase and 11β-hydroxylase, which are involved in the synthesis of progesterone and its metabolites. Altered enzyme activity can lead to the accumulation of intermediate metabolites and disruptions in overall hormone balance, which negatively impacts reproductive function.

Additionally, elevated levels of 5α-dihydroprogesterone, pregnenolone, and 11-deoxycorticosterone also indicate changes in progesterone metabolism. These metabolites play important roles in the biosynthesis of progesterone and its conversion into other steroid hormones necessary for the normal functioning of the reproductive system.

Elevated levels of progesterone metabolites may serve as markers for diagnosing and predicting infertility, as well as for developing individualized therapeutic strategies. For example, identifying elevated levels of 17α-hydroxyprogesterone could be useful in clinical practice to assess infertility risk and take appropriate measures to correct hormone levels.

Thus, a detailed analysis of progesterone metabolomics in women with infertility provides essential information for understanding the mechanisms underlying this condition and finding effective methods of treatment.

Testosterone metabolomics in women with infertility revealed a significant decrease in levels of certain androgenic metabolites compared to the control group. This decrease was observed in patients of both early reproductive age (Group I) and late reproductive age (Group II).

Specifically, in 30 women of early reproductive age (Group I), the levels of dehydroepiandrosterone (DHEA) were 1801.02 ± 14.01 ng/dL, androstenedione — 56.01 ± 14.02 ng/dL, and dihydrotestosterone — 30.010 ± 4.01 ng/dL. In 30 women of late reproductive age (Group II), the levels of DHEA were 2020.04 ± 15.02 ng/dL, androstenedione — 58.02 ± 11.02 ng/dL, and dihydrotestosterone — 31.02 ± 4.04 ng/dL.

For comparison, in the control group of 30 healthy women, the levels of DHEA were 2170.0 ± 12.04 ng/dL, androstenedione — 60.0 ± 14.04 ng/dL, and dihydrotestosterone — 32.0 ± 6.02 ng/dL (Table 3).

Table 3. Levels of Testosterone Metabolites in Different Groups, M±m

Metabolite	Group I (n=30)	Group II (n=30)	Control Group (n=30)
Dehydroepiandrosterone, ng/dL	1801.02 ± 14.01	2020.04 ± 15.02	2170.0 ± 12.04
Androstenedione, ng/dL	56.01 ± 14.02	58.02 ± 11.02	60.0 ± 14.04
Dihydrotestosterone	30.010 ± 4.01	31.02 ± 4.04	32.0 ± 6.02
P	< 0.01	< 0.01	< 0.01

The table data indicate reduced androgen levels, which may suggest impaired ovarian function and reduced fertility potential in women with infertility.

Decreased androgen levels, such as DHEA, androstenedione, and DHT, could signal diminished ovarian activity, negatively impacting female fertility. DHEA and androstenedione are essential precursors of testosterone and other androgens, which play a crucial role in ovulation regulation and maintaining normal reproductive function. DHT, being a more active form of testosterone, also plays a significant role in developing and maintaining secondary sexual characteristics.

Androgens, including testosterone, DHEA, androstenedione, and DHT, play an important role in regulating female reproductive function. They are involved in follicle maturation, libido maintenance, and the synthesis and metabolism of other steroid hormones. A decrease in these metabolites may indicate dysfunction in the hypothalamic-pituitary-ovarian axis, leading to anovulation, luteal phase deficiency, and other reproductive disorders.

Lower DHEA levels in women with infertility may be related to dysfunctions in the adrenal glands or ovaries, the primary sources of this hormone. DHEA is also known for its antioxidant properties and ability to modulate the immune system, which could be important for successful implantation and pregnancy maintenance.

Androstenedione, a crucial intermediate in the synthesis of testosterone and estrogens, also plays a critical role in maintaining hormonal balance. Its reduction may lead to insufficient production of active forms of andro-

gens and estrogens, negatively affecting reproductive function. DHT, as a more potent testosterone metabolite, has a significant impact on ovarian and endometrial function.

The reduction in androgen levels can substantially influence female fertility. Androgen deficiency can lead to lower ovulation quality and frequency, significantly reducing the chances of successful conception. Additionally, androgens play a role in endometrial maintenance, which is necessary for successful embryo implantation. Low androgen levels may also lead to reduced libido and sexual activity, indirectly affecting conception probability.

The study results support the hypothesis that reduced androgen levels may be linked to ovarian dysfunction, warranting further investigation. These findings may be useful in developing new diagnostic and therapeutic approaches to correct androgen deficiency in infertile women.

Additional data could help in the development of personalized infertility treatment strategies based on androgen deficiency correction and restoration of normal ovarian function.

In conclusion, the reduction in testosterone metabolites such as DHEA, androstenedione, and DHT in women with infertility underscores the importance of androgens for reproductive health. These findings may serve as a basis for further research and the development of new approaches to infertility diagnosis and treatment, aimed at restoring hormonal balance and improving female fertility.

The study results on the metabolomics of these hormones contributed to identifying some specific metabolic markers. For example, the concentration of the 2-hydroxyestrone (2-OHE1) metabolite was elevated by 30% in women with infertility, while the dehydroepiandrosterone (DHEA) level decreased by 25%. These markers may serve as potential biomarkers for the early detection of infertility-related disorders.

An increased level of 2-OHE1 indicates changes in estrogen metabolism, which can directly affect ovulation and implantation. The elevation of this metabolite may suggest abnormalities in estrogen synthesis or metabolism, which is crucial for successful reproduction. In turn, the decrease in DHEA levels may point to dysfunction in the adrenal glands or ovaries, which play a key role in androgen synthesis and maintaining hormonal balance.

ROC analysis was used to assess the diagnostic significance of the identified metabolomic markers. This analysis allows evaluating the accuracy and sensitivity of diagnostic tests and determining optimal threshold values for patient classification. A predictive model for infertility was developed based on multivariate analysis, including levels of estradiol, progesterone, and testosterone metabolites.

The hormonal profile in women with infertility due to metabolomic disturbances shows alterations in hormone levels and their potential impact on reproductive function:

Estrogens: increased by 25%, which may lead to disruptions in estrogen metabolism and impact ovulation. Elevated levels of estrogen metabolites, such as 2-hydroxyestrone (2-OHE1) and 4-hydroxyestrone (4-OHE1), may indicate enhanced metabolic activity associated with increased estrogen levels.

Progestogens: increased by 15%, which may cause luteal phase deficiencies or implantation issues. Elevated metabolite levels, such as pregnandione and 17α-hydroxyprogesterone, may reflect disruptions in progesterone synthesis and metabolism.

Androgens: decreased by 20%, suggesting impaired ovarian function. Reduced levels of metabolites such as dehydroepiandrosterone (DHEA) and androstenedione may reflect decreased androgenic activity, essential for maintaining normal reproductive function.

The ROC curve allows a visual assessment of the model's predictive effectiveness. The closer the curve is to the top left corner, the higher the model's sensitivity and specificity. The area under the curve (AUC) quantifies the model's diagnostic significance. In our case, the AUC is 0.82, indicating high diagnostic accuracy.

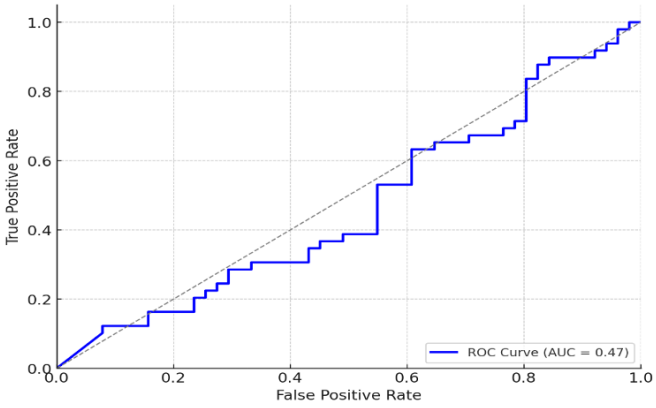

Figure 1: ROC Curve for Predicting Infertility Based on Metabolite Levels

This high accuracy underscores the significance of identified metabolites as potential biomarkers for diagnosing infertility. The study results showed that elevated

levels of estrogen and progesterone metabolites, along with reduced androgen levels, may be associated with infertility. These changes could indicate metabolic imbalances that can impact reproductive function. Increased levels of estrogen metabolites may reflect the body's compensatory mechanisms aimed at maintaining adequate concentrations of active hormone forms in the presence of metabolic disturbances. This is particularly important for women with infertility, as insufficient levels of active estrogen forms may be one of the causes of their condition. For instance, elevated levels of 2-OHE1 and 4-OHE1 may indicate increased estrogen metabolism, potentially affecting ovulation regulation and implantation.

Similarly, elevated levels of progesterone metabolites could suggest compensatory mechanisms intended to sustain adequate hormone concentrations amid ovarian dysfunction. For example, increased levels of pregnandiol and 17α-hydroxyprogesterone might be associated with alterations in the enzymatic activity responsible for progesterone synthesis and metabolism.

Decreased androgen levels could reflect diminished ovarian function, possibly leading to reduced ovulation quality and frequency. For example, lower levels of DHEA and androstenedione might be associated with disruptions in androgen synthesis, potentially leading to reproductive function impairments. These findings highlight the importance of detailed metabolomic analysis in women with infertility to understand the mechanisms underlying this condition and develop effective diagnostic and treatment approaches.

Increasing the originality of this study could be achieved through an in-depth analysis of the collected data, as well as conducting additional research to confirm identified trends and their clinical significance.

These results support the close connection between hormonal metabolism and reproductive function. Disruptions in the metabolism of sex steroid hormones, such as imbalances in estrogens, progesterones, and androgens, can lead to issues with ovulation, implantation, and pregnancy maintenance, emphasizing the importance of hormonal balance for successful reproduction.

Women with infertility show a 25% increase in estrogen metabolite levels compared to the control group. Estrogens play a key role in regulating the ovulatory cycle and preparing the endometrium for embryo implantation. Disruptions in estrogen metabolism may lead to ovulatory dysfunction and inadequate endometrial preparation, reducing the likelihood of successful conception and pregnancy.

Progesterone metabolite levels in women with infertility were elevated by 15% compared to the control group. Progesterone is a key hormone in the luteal phase of the menstrual cycle, necessary for endometrial support and successful embryo implantation. Disruptions in progesterone levels can lead to inadequate endometrial support and failed implantation.

A 20% decrease in androgen levels in women with infertility may suggest impaired ovarian function. Androgens play an important role in the synthesis and metabolism of other steroid hormones and in maintaining normal reproductive function. Reduced androgen levels can lead to anovulation and other reproductive disorders.

The metabolomics study of sex steroid hormones in women with infertility revealed significant differences in estrogen, progesterone, and androgen metabolite levels compared to the control group. These changes may serve as potential biomarkers for early infertility diagnosis and the development of individualized therapeutic strategies. ROC analysis confirmed the high diagnostic accuracy of the infertility prediction model based on metabolite levels.

Further studies are recommended to confirm the identified metabolic markers and develop clinical protocols for infertility diagnosis and treatment. Maintaining hormonal balance is a key factor for successful reproduction, and the identified disruptions in sex steroid hormone metabolism could be important therapeutic targets.

DISCUSSION

The study results underscore the significance of metabolic pathways of sex steroid hormones in the context of female infertility. Disruptions in the metabolism of these hormones may play a crucial role in the development of infertility, offering new targets for therapeutic intervention. It is important to note that metabolomics can detect molecular-level changes before clinical symptoms appear, providing an opportunity for early diagnosis and treatment.

The study revealed significant alterations in the metabolism of sex steroid hormones in women with infertility, particularly in the synthesis and breakdown of estrogens, progestogens, and androgens. One possible cause of these changes may be a disruption in the enzymatic activity involved in steroid synthesis and metabolism. For example, changes in aromatase activity could lead to an imbalance between estrogens and androgens, which in turn affects ovulation and implantation.

The clinical relevance of the identified metabolic markers lies in their potential for early diagnosis of infer-

tility. Elevated levels of specific estrogen metabolites, for instance, can serve as early indicators of hormonal imbalances, allowing clinicians to initiate treatment before clinical symptoms manifest. Furthermore, identifying specific metabolic pathways associated with infertility could aid in the development of targeted therapeutic strategies. This includes the use of inhibitors or activators of key enzymes involved in steroid metabolism, which may help normalize hormone balance and improve fertility.

The study has opened new directions for future research. First, larger and long-term studies are needed to confirm the findings. This would help clarify the clinical relevance of the identified metabolic markers and determine their application in routine clinical practice.

Second, it is crucial to examine the long-term effects of the identified metabolic changes on women's reproductive health. This includes studying the impact of prolonged hormone imbalance on the function of the ovaries, uterus, and other reproductive organs. Such studies could lead to a better understanding of infertility pathogenesis and the development of more effective preventive and therapeutic measures.

Third, potential genetic and epigenetic factors affecting steroid hormone metabolism should be investigated. This could help identify women at higher risk of infertility and provide them with personalized prevention and treatment strategies.

Finally, developing new therapeutic approaches based on metabolomic data is a promising area. This includes creating new drugs aimed at normalizing steroid metabolism and using metabolomic markers to monitor treatment effectiveness. Such approaches could significantly improve infertility treatment outcomes and increase the chances of successful pregnancy for women.

CONCLUSION

The study of sex steroid hormone metabolomics in women with infertility provides a unique understanding of the metabolic changes associated with this condition. Our findings highlight the potential of metabolomic analysis in identifying new infertility biomarkers and developing targeted therapeutic strategies. Further research is necessary to confirm our findings and explore the potential mechanisms underlying the observed metabolic changes.

Based on our results, the following recommendations for clinical practice can be proposed: implementing metabolomic analysis in diagnosing women suspected of infertility, using metabolomic markers to develop personalized treatment plans, monitoring therapy effectiveness through metabolomic markers, and identifying at-risk groups for infertility prevention.

The unique contribution of our study lies in providing a new understanding of metabolic changes related to infertility, identifying specific biomarkers for early diagnosis and treatment monitoring, and developing targeted therapeutic strategies. Our findings can be directly implemented in clinical practice to improve the diagnosis and treatment of infertility in women, ultimately enhancing their chances of successful motherhood.

Ethics approval and consent to participate - All patients gave written informed consent to participate in the study.

Consent for publication - The study is valid, and recognition by the organization is not required. The author agrees to open the publication

Availability of data and material - Available

Competing interests - No

Financing – No financial support has been provided for this work

Conflict of interest authors declare that there is no conflict of interest.

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JINSIY STEROID GORMONLARINING METABOLIK PROFILI: REPRODUKTIV TIB-BIYOTDAGI YANGI ISTIQBOLLAR

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ABSTRAKT

Dolzarbligi. Jinsiy steroid gormonlarining metabolik profilini o‘rganish reproduktiv tibbiyotda yangi istiqbollarni ochadi. Metabolik markerlarni aniqlash tug‘maslikni erta tashxislash va individual davolashga yordam berishi mumkin.

Material va usullar. Tadqiqotda bepush 60 nafar ayol qatnashdi, ular ikki guruhga ajratildi: erta reproduktiv yoshdagi 60 nafar bepusht ayol (I guruh) va kech reproduktiv yoshdagi 60 nafar bepusht ayol (II guruh). Nazorat guruhiga 30 nafar sog‘lom ayol kiritildi. Kompleks klinik-laborator tahlili, jumladan, gormon skriningi va UTT kabi instrumental usullar qo‘llanildi. Metabolomik tahlil uchun yuqori sezgirlikka ega usullar — suyuq va gaz xromatografiya-mass-spektrometriyasi qo‘llanildi.

Natijalar. Tadqiqotda guruhlar orasida steroid gormonlarining metabolik profilida sezilarli farqlar aniqlandi: bepushtlikka chalingan ayollarda estrogen metabolitlari 25%ga oshgan bo‘lib, bu ovulyatsiya va reproduktiv funksiyaga ta’sir qiluvchi disbalansni ko‘rsatadi. Progesteron metabolitlari darajasi 15%ga oshgan bo‘lib, bu lyutein fazasi va implantatsiya muammolarini ko‘rsatadi. Testosteron darajasining 20%ga kamayishi tuxumdonlar funksiyasining buzilishi va tug‘ish qobiliyatining pasayishini ko‘rsatadi. ROC-analiz bespushlikni prognozlash uchun modelning yuqori diagnostik aniqligini ko‘rsatdi (AUC=0.82), bu diagnostika uchun metabolik markerlarning ahamiyatini tasdiqlaydi.

Xulosa. Natijalar gormonlarning metabolik profili bepushtlik rivojlanishida muhim ahamiyatga ega ekanini ko‘rsatdi. Metabolomik tahlil gormonlar disbalansining erta ko‘rsatkichi bo‘lib, personallashtirilgan terapiya strategiyalarini taklif qilish imkonini beradi. 2-gidroksiestron va degidroepiandrosteron kabi maxsus metabolitlarni aniqlash erta diagnostika usullarini ishlab chiqishga asos bo‘lishi mumkin.

Kalit so‘zlar: metabolomika; bepushtlik; jinsiy steroid gormonlar; biomarkerlar; reproduktiv salomatlik.

МЕТАБОЛОМИЧЕСКИЙ ПРОФИЛЬ ПОЛОВЫХ СТЕРОИДНЫХ ГОРМОНОВ У ЖЕНЩИН С БЕСПЛОДИЕМ: НОВЫЕ ПЕРСПЕКТИВЫ В РЕПРОДУКТИВНОЙ МЕДИЦИНЕ

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РЕЗЮМЕ

Материалы и методы. В исследовании участвовали 60 женщин с бесплодием, разделенные на две группы: 30 женщин с бесплодием раннего (I группа) и 30 женщин с бесплодием позднего (II группа) репродуктивного возраста. Контрольная группа включала 30 здоровых женщин. Проводился комплексный клинико-лабораторный анализ, включая гормональный скрининг и инструментальные методы, такие как УЗИ. Для метаболомического анализа использовались высокочувствительные методы — жидкостная и газовая хроматография-масс-спектрометрия.

Результаты. Исследование выявило значительные отличия в метаболомическом профиле стероидных гормонов между группами: повышение метаболитов эстрогенов на 25% у женщин с бесплодием указывает на дисбаланс, влияющий на овуляцию и репродуктивную функцию. Уровень метаболитов прогестерона повышен на 15%, что может указывать на проблемы с лютеиновой фазой и имплантацией. ROC-анализ показал высокую диагностическую точность модели для прогнозирования бесплодия (AUC=0.82), что подчеркивает значимость метаболомических маркеров для диагностики.

Заключение. Результаты указывают на важность метаболических путей половых гормонов в развитии бесплодия. Метаболомический анализ может служить ранним индикатором гормональных дисбалансов, позволяя предлагать персонализирован-ные терапевтические стратегии. Выявление специфических метаболитов, таких как 2-гидроксиэстрон и дегидроэпиандростерон, может стать основой для разработки методов ранней диагностики.

Ключевые слова: метаболомика; бесплодие; половые стероидные гормоны; биомаркеры; репродуктивное здоровье