COMPREHENSIVE DIAGNOSTIC ALGORITHM FOR ENDOMETRIAL RECEPTIVITY DISORDERS IN WOMEN WITH SECONDARY INFERTILITY AND OBESITY BEFORE ASSISTED REPRODUCTIVE TECHNOLOGY PROGRAMS

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Abstract. *Endometrial receptivity disorders represent one of the key causes of reduced effectiveness of assisted reproductive technology programs, especially in women with secondary infertility and obesity. Obesity is associated with insulin resistance, chronic low-grade inflammation, adipokine imbalance, endothelial dysfunction and impaired uterine-endometrial perfusion, which may negatively affect implantation potential. The aim of the study was to develop and substantiate a comprehensive diagnostic algorithm for assessing endometrial receptivity disorders in women with secondary infertility and obesity before assisted reproductive technology programs. The study included 213 women of reproductive age with secondary infertility, including 159 patients with obesity and 54 women without obesity. The diagnostic approach was based on stepwise assessment of clinical-anamnestic, anthropometric, metabolic, inflammatory, echographic and hemodynamic criteria. The most informative diagnostic predictors included HOMA-IR >2.7, visceral obesity, high inflammatory index, endometrial thickness <7 mm, uterine artery pulsatility index >3.0, low-flow phenotype and combined dysreceptive phenotype.*

Keywords*: secondary infertility, obesity, endometrial receptivity, assisted reproductive technologies, diagnostic algorithm, implantation failure, HOMA-IR, low-flow phenotype.*

Introduction. Secondary infertility remains one of the most significant problems in modern reproductive medicine. Despite the rapid development of assisted reproductive technologies, the effectiveness of treatment is still limited by several factors, among which the functional state of the endometrium plays a crucial role. Successful implantation requires not only a morphologically competent embryo but also a receptive endometrium capable of supporting adhesion, invasion and early embryonic development (2,6,7).

Endometrial receptivity is a complex biological phenomenon determined by coordinated interaction between hormonal, structural, vascular, inflammatory and molecular mechanisms. Disruption of these mechanisms may lead to implantation failure, reduced pregnancy rates and repeated unsuccessful ART attempts (1,3,5).

Obesity has become an increasingly important factor affecting female reproductive health. In women with secondary infertility, obesity is not only associated with ovulatory dysfunction and metabolic abnormalities but also with impaired endometrial function. Insulin resistance, hyperinsulinemia, chronic low-grade inflammation and adipokine imbalance may alter endometrial proliferation, secretory transformation, decidualization and vascular adaptation (4,5).

Traditional diagnostic assessment before ART often focuses mainly on endometrial thickness, hormonal profile and general gynecological evaluation. However, in women with obesity, such an approach may be insufficient because metabolic, inflammatory and hemodynamic abnormalities can remain underestimated. Therefore, a comprehensive diagnostic algorithm is needed to identify hidden endometrial receptivity disorders and stratify patients according to implantation risk (8).

The methodological basis of this article is a comprehensive diagnostic approach developed for women with secondary infertility and obesity, including integrated assessment of clinical-anamnestic, hormonal-metabolic, inflammatory, echographic and hemodynamic criteria before ART programs.

Purpose of the study to develop and substantiate a comprehensive diagnostic algorithm for detecting endometrial receptivity disorders in women with secondary infertility and obesity before assisted reproductive technology programs.

Materials and methods of research. The study was based on the results of comprehensive examination of 213 women of reproductive age with secondary infertility. All patients were examined according to a unified diagnostic protocol. The main group included 159 women with secondary infertility and obesity. The comparison group included 54 women with secondary infertility without obesity.

The inclusion criterion for the main group was obesity defined as body mass index ≥30 kg/m². The groups were formed considering age, duration of infertility, reproductive history and comparability of clinical characteristics.

The diagnostic protocol included several consecutive stages.

The first stage consisted of clinical and anamnestic assessment. Menstrual function, reproductive history, duration of infertility, previous implantation failures, intrauterine interventions, gynecological diseases and concomitant somatic pathology were analyzed.

The second stage included anthropometric assessment. Body mass index, waist circumference, hip circumference, waist-to-hip ratio and indicators of visceral adiposity were evaluated.

The third stage was laboratory assessment of metabolic and inflammatory status. Fasting insulin, HOMA-IR, leptin, adiponectin, leptin/adiponectin ratio, high-sensitivity C-reactive protein, interleukin-6 and tumor necrosis factor-alpha were determined.

The fourth stage included transvaginal ultrasound examination in the periovulatory period. Endometrial thickness, echographic structure and trilaminar pattern were assessed.

The fifth stage involved Doppler assessment of uterine-endometrial blood flow. Uterine artery pulsatility index, subendometrial vascularization and perfusion phenotype were evaluated.

The final stage consisted of integral interpretation of the obtained data with identification of phenotypic variants of endometrial receptivity disorders and risk stratification before ART.

Research results. The conducted analysis demonstrated that endometrial receptivity disorders in women with secondary infertility and obesity are formed as a result of interaction between several pathological mechanisms. Metabolic dysfunction, chronic inflammation, structural endometrial insufficiency and impaired uterine-endometrial perfusion were the most clinically significant components.

Clinical-anamnestic analysis showed that women with obesity had a more unfavorable reproductive profile. The duration of infertility was longer in the main group compared with the comparison group. Low physical activity, sedentary lifestyle, high-calorie nutrition, polycystic ovary syndrome and chronic anovulation were also more common among women with obesity.

Anthropometric assessment revealed predominance of the visceral obesity phenotype in the main group. Visceral obesity was detected in 92.5% of women with obesity compared with 20.4% in the comparison group. This finding indicates that abdominal-visceral fat accumulation plays an important role in the formation of metabolically unfavorable reproductive phenotype.

Metabolic analysis showed that insulin resistance was one of the leading predictors of impaired endometrial receptivity. HOMA-IR was significantly higher in women with obesity. Insulin resistance defined as HOMA-IR >2.7 was detected in 74.8% of patients in the main group compared with 25.9% in the comparison group. According to multivariate analysis, HOMA-IR >2.7 increased the risk of endometrial receptivity disorders by 4.82 times.

The adipokine profile was also significantly altered in women with obesity. Leptin levels were increased, while adiponectin levels were decreased. The leptin/adiponectin ratio was markedly higher in the main group, reflecting a shift toward a pro-inflammatory and insulin-resistant metabolic state.

Inflammatory markers showed a clear tendency toward systemic low-grade inflammation in patients with obesity. High-sensitivity C-reactive protein, IL-6 and TNF-α levels were significantly

higher in the main group. A high inflammatory index ≥20 was detected in 65.4% of women with obesity compared with 16.7% in the comparison group. This criterion increased the risk of impaired receptivity by 4.26 times.

Ultrasound evaluation revealed structural features associated with reduced implantation potential. Endometrial thickness <7 mm was detected in 29.6% of women with obesity compared with 11.1% of women without obesity. A complete trilaminar endometrial pattern was observed less frequently in the main group. Endometrial thickness <7 mm increased the risk of receptivity disorders by 3.71 times.

Doppler assessment demonstrated significant impairment of uterine-endometrial hemodynamics in women with obesity. Uterine artery pulsatility index was higher in the main group. PI >3.0 increased the risk of impaired receptivity by 3.43 times. Reduced subendometrial vascularization was also more common among women with obesity.

Particular attention was paid to hemodynamic phenotypes. Normal uterine-endometrial perfusion was registered in only 28.9% of women with obesity compared with 55.6% in the comparison group. Pathological hemodynamic phenotypes were detected in 71.1% of the main group and 44.4% of the comparison group.

The low-flow phenotype was one of the most significant vascular predictors. It increased the probability of endometrial receptivity disorders by 4.97 times. This phenotype reflects marked insufficiency of uterine-endometrial perfusion and may indicate a high risk of hidden implantation failure.

Phenotypic analysis of endometrial receptivity demonstrated that the normoreceptive phenotype was significantly less common in women with obesity. It was detected in 25.8% of the main group compared with 51.9% in the comparison group. Structural-dysreceptive and combined dysreceptive phenotypes were more frequent in women with obesity.

The combined dysreceptive phenotype had the highest prognostic significance. Its presence increased the risk of impaired endometrial receptivity by 5.68 times. This phenotype reflects simultaneous structural insufficiency and hemodynamic impairment of the endometrium, making it the most unfavorable variant of dysreceptive disorders.

Based on the obtained results, a comprehensive diagnostic algorithm was developed. It includes stepwise identification of clinical, metabolic, inflammatory, echographic and hemodynamic abnormalities, followed by integral risk stratification.

Comprehensive Diagnostic Algorithm.

The proposed diagnostic algorithm consists of five main stages.

Stage 1. Clinical-anamnestic screening.

At this stage, risk factors are identified, including duration of infertility, previous implantation failures, menstrual dysfunction, chronic anovulation, polycystic ovary syndrome, sedentary lifestyle, low physical activity, high-calorie nutrition and family history of obesity.

Stage 2. Anthropometric and metabolic assessment.

This stage includes determination of BMI, waist circumference, visceral obesity phenotype, fasting insulin, HOMA-IR, leptin, adiponectin and leptin/adiponectin ratio. HOMA-IR >2.7 and visceral obesity are considered significant predictors of impaired receptivity.

Stage 3. Inflammatory status assessment.

High-sensitivity C-reactive protein, IL-6 and TNF-α are evaluated. A high inflammatory index ≥20 indicates increased risk of endometrial dysfunction and requires further assessment of endometrial structure and blood flow.

Stage 4. Echographic assessment of the endometrium.

Transvaginal ultrasound is performed to determine endometrial thickness and structure. Endometrial thickness <7 mm and absence of a complete trilaminar pattern are considered unfavorable diagnostic signs.

Stage 5. Doppler assessment and phenotype identification.

Uterine artery PI, subendometrial vascularization and perfusion pattern are evaluated. PI >3.0, reduced subendometrial blood flow and low-flow phenotype indicate significant hemodynamic impairment. At this stage, patients are classified into normoreceptive, hypoperfusion, structural-dysreceptive or combined dysreceptive phenotypes.

Table 1.

Risk Stratification Scale

Criterion	Diagnostic basis	Score
HOMA-IR >2.7	OR=4.82	2
Visceral obesity	OR=3.94	2
High inflammatory index	OR=4.26	2
Endometrial thickness <7 mm	OR=3.71	2
Uterine artery PI >3.0	OR=3.43	2
Low-flow phenotype	OR=4.97	3
Combined dysreceptive phenotype	OR=5.68	3

The total score allows classification of patients into three risk groups:

Total score	Risk level	Recommended clinical approach
0–3	Low risk	Standard preparation for ART
4–7	Moderate risk	Extended diagnostic assessment
≥8	High risk	Personalized correction before ART

The main advantage of this scale is that it integrates different pathogenetic levels of endometrial dysfunction. It does not evaluate endometrial receptivity as a single ultrasound parameter but interprets it as the final result of systemic metabolic, inflammatory, structural and vascular interactions.

The results of the study confirm that endometrial receptivity disorders in women with secondary infertility and obesity should be considered a multifactorial condition. The combination of insulin resistance, visceral obesity, chronic inflammation and impaired uterine-endometrial perfusion creates an unfavorable background for implantation.

The diagnostic significance of HOMA-IR >2.7 demonstrates that metabolic dysfunction directly contributes to reproductive failure. Insulin resistance may affect ovarian function, steroid hormone metabolism, endometrial proliferation and local vascular regulation. Therefore, metabolic assessment should be included in the diagnostic pathway before ART, especially in women with obesity.

The role of chronic inflammation is also essential. Increased inflammatory markers may disrupt endometrial differentiation, decidualization and immune tolerance during the implantation window. A high inflammatory index can therefore be considered an important marker of systemic pathological burden.

Hemodynamic assessment is particularly valuable because endometrial receptivity depends not only on structural maturity but also on adequate blood supply. The low-flow phenotype and combined dysreceptive phenotype were the strongest predictors of impaired receptivity, indicating that Doppler evaluation should be considered an essential component of pre-ART assessment in women with obesity.

The proposed algorithm provides a practical framework for clinical decision-making. It allows physicians to identify patients who may undergo standard preparation, patients who require deeper diagnostic evaluation and patients who need personalized correction before entering an ART program.

Conclusion. Endometrial receptivity disorders in women with secondary infertility and obesity are formed through complex interaction of metabolic, inflammatory, structural and hemodynamic mechanisms. The proposed comprehensive diagnostic algorithm allows systematic identification of these disorders before ART programs.

The most informative predictors include HOMA-IR >2.7, visceral obesity, high inflammatory index, endometrial thickness <7 mm, uterine artery PI >3.0, low-flow phenotype and combined dysreceptive phenotype. The integration of these criteria into a risk stratification scale makes it possible to identify patients with low, moderate and high risk of implantation insufficiency.

The use of this algorithm may improve diagnostic accuracy, optimize patient selection before ART and provide a basis for personalized reproductive management.

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