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COMPREHENSIVE RISK STRATIFICATION CRITERIA AND AN ALGORITHM FOR EARLY DIAGNOSIS OF MINIMAL FORMS OF ENDOMETRIOSIS IN WOMEN WITH INFERTILITY

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ABSTRACT

Minimal forms of endometriosis represent one of the most common yet underdiagnosed causes of female infertility, largely due to nonspecific clinical manifestations and the limited sensitivity of standard imaging methods at early stages of the disease. The aim of this study was to develop comprehensive risk stratification criteria and an algorithm for early diagnosis of minimal forms of endometriosis in women with infertility.

A total of 162 women of reproductive age (18–35 years) were examined, including 107 patients with endometriosis-associated infertility and 55 practically healthy women in the control group. The analysis was based on clinical and anamnestic data, assessment of pain phenotype using the Visual Analog Scale (VAS), reproductive function characteristics, results of targeted transvaginal ultrasound, pelvic MRI, and response to empirical therapy.

Key clinical predictors of minimal forms of endometriosis were identified, and a point-based risk stratification system was developed, distinguishing low-, moderate-, and high-risk groups. The proposed algorithm reduces diagnostic delays, optimizes diagnostic and therapeutic decision-making, and enhances personalization of management in women with endometriosis-associated infertility.

The relevance of the problem of minimal forms of endometriosis in women with infertility is обусловлена the high prevalence of endometriosis-associated infertility combined with significant diagnostic difficulties at the early stages of the disease [1–4, 8]. Minimal forms of endometriosis often have an oligosymptomatic course or present with nonspecific clinical manifestations such as dysmenorrhea, chronic pelvic pain, and dyspareunia, which leads to delayed diagnostic verification and loss of time that is critically important for preserving a woman's reproductive potential [2, 3, 11]. According

to a number of authors, the delay in diagnosing endometriosis may range from 5 to 8 years, while a significant proportion of patients are observed for a long time with a diagnosis of idiopathic infertility [11, 12].

Modern concepts of the pathogenesis of endometriosis consider the disease as a systemic immuno-inflammatory process accompanied by disturbances in local microcirculation, activation of angiogenesis, oxidative stress, and endometrial remodeling. These mechanisms negatively affect implantation capacity and fertility even in the presence of minimal morphological changes [1, 6, 9, 10]. This determines the particular importance of early detection of minimal forms of endometriosis. However, existing imaging methods, including ultrasound examination and magnetic resonance imaging, have limited sensitivity for superficial and minimal endometriotic lesions [5, 7, 14].

Despite active research into biochemical, immunological, and molecular-genetic markers of endometriosis, to date there is no unified comprehensive algorithm that allows integration of clinical, instrumental, and laboratory parameters into an objective risk stratification system for minimal forms of the disease [6, 13]. As a result, indications for invasive diagnostic verification (laparoscopy) are often formed subjectively, which either increases the frequency of unjustified surgical interventions or contributes to underestimation and late diagnosis of the disease [3, 12].

In this regard, the development of comprehensive risk stratification criteria and an algorithm for early diagnosis of minimal forms of endometriosis in women with infertility represents an актуальную clinical-scientific and socially significant task. Implementation of such an approach will improve the accuracy of early disease detection, optimize patient routing, shorten the time to diagnosis, and improve reproductive outcomes through timely and personalized treatment [2, 4, 12, 15].

Aim of the study: to develop and scientifically substantiate comprehensive risk stratification criteria and an algorithm for early diagnosis of minimal forms of endometriosis in women with infertility based on the integration of clinical-anamnestic, instrumental, and laboratory-molecular parameters, in order to improve the timeliness of disease detection and optimize patient management strategies.

Materials and Methods: The present study is based on the results of a comprehensive examination of 162 women of reproductive age (18–35 years) who were observed in specialized gynecological departments and reproductive health consultation centers.

From the total number of examined women, two main categories were included in the study:

- **Control group:** 55 practically healthy women of fertile age without menstrual or reproductive dysfunction, with no clinical or ultrasound signs of endometriosis, pelvic inflammatory diseases, endocrine disorders, or somatic pathology.
- **Main group:** 107 women with clinically and instrumentally confirmed endometriosis-associated infertility, who were observed to clarify pathogenetic mechanisms of reproductive disorders and to assess prognostic diagnostic criteria.

Inclusion criteria: reproductive age (18–35 years); regular menstrual cycle; pregnancy planning; absence of acute or chronic somatic pathology preventing pregnancy; informed consent to participate in the study.

Exclusion criteria: pronounced inflammatory diseases of the pelvic organs; congenital anomalies of the uterus and adnexa; endocrine infertility; severe extragenital pathology (heart, kidney, liver diseases); malignant neoplasms and systemic autoimmune diseases.

To assess the severity of endometriosis and the extent of the adhesive process, the revised classification of the American Fertility Society (r-AFS, 1985) was used.

As a result, patients in the main group were divided into two subgroups:

- **Subgroup 1:** 80 women with minimal forms of endometriosis (stages I–II), characterized by superficial lesions and minimal adhesions;
- **Subgroup 2:** 27 women with advanced forms of endometriosis (stages III–IV), accompanied by pronounced adhesions, deformation of pelvic anatomical structures, and signs of functional impairment of the reproductive system.

All patients in the main group underwent comprehensive clinical and gynecological examination, including visual assessment of the external genitalia, examination of the cervix using speculums, as well as bimanual vaginal and rectovaginal examination to identify anatomical changes and possible signs of pelvic organ involvement. Pain severity was assessed using the Visual Analog Scale (VAS).

Ultrasound examination of the pelvic organs was performed using a Mindray DSN 3 device (China) with convex abdominal transducers (3.5 MHz) and transvaginal transducers (5–7.5 MHz).

MRI of the pelvis was performed using 1.5–3.0 T scanners with a phased-array pelvic coil. The protocol included thin-slice T2-weighted images (3–4 mm) in sagittal/true axial/coronal planes; T1 and T1FS axial/sagittal sequences; DWI (b = 0–800/1000) with ADC calculation; contrast-enhanced T1FS when indicated (suspected solid component). MRI was performed in 15 patients during the early proliferative phase (days 5–12 of the menstrual cycle).

Statistical analysis was performed using Microsoft Office 2017 software and built-in Excel functions, with calculation of mean values and standard deviation. Differences were considered statistically significant at $p < 0.05$.

Results:

The age distribution of the examined women showed (Table 1) that the majority of patients in both groups were in the most active reproductive age range of 25–34 years (63.6% in the control group and 69.1% in the main group, $p > 0.05$).

Table 1.

Age distribution of the examined women (n = 162)

Age, year	Control group (n=55)		Main group (n=107)		I–II stages (n=80)		III–IV stages (n=27)		χ^2	p
	n	%	n	%	n	%	n	%		
18–24	14	25,5	19	17,8	16	20,0	3	11,1	1,82	>0,05
25–29	17	30,9	33	30,8	25	31,3	8	29,6	0,01	>0,05
30–34	18	32,7	41	38,3	32	40,0	9	33,3	0,48	>0,05

≥35	6	10,9	14	13,1	7	8,7	7	25,9	3,91	<0,05
Average age, year (M±SD)	28,9 ± 3,8		29,6 ± 4,2		29,4 ± 3,9		30,3 ± 4,6		-	>0,05

At the same time, it should be noted that women with severe forms of endometriosis (stages III–IV) were significantly more likely to be aged 35 years and older (25.9% versus 8.7% in stages I–II, $p < 0.05$), which reflects a tendency toward progression of endometriosis with increasing age and disease duration.

Among women in the main group, primary infertility (Figure 1) was observed significantly more frequently than secondary infertility (61.7 ± 2.8% versus 38.3 ± 2.8%, $p < 0.05$).

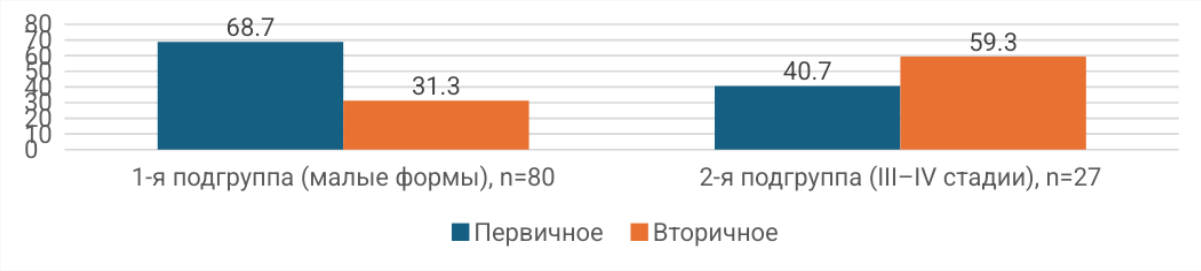

Figure 1. Frequency of primary and secondary infertility

As can be seen from the presented data, primary infertility is predominantly characteristic of patients with minimal/mild forms of endometriosis; the likelihood of its presence in this group is several times higher than in advanced stages of the disease (stages III–IV).

In addition, a statistically significant predominance of women with delayed establishment of the menstrual cycle was identified in the main group ($\chi^2 = 6.88$ (0.88–51.39); $p = 0.03$; OR = 6.88), particularly in subgroup 2 ($\chi^2 = 7.21$ (0.91–53.5); $p = 0.03$). We also found that short menstrual cycles occur more frequently in endometriosis and are specifically associated with an increased risk of the disease ($\chi^2 = 6.38$ (0.81–54.4); $p = 0.02$).

Analysis of the prevalence of extragenital pathology among women with endometriosis demonstrated that in minimal forms of the disease, gastrointestinal tract (GIT) disorders and allergic reactions were significantly more frequent ($p < 0.01$) compared both with the control group and with subgroup 2 ($p < 0.05$).

ROC analysis incorporating clinical and anamnestic data allowed us to identify risk factors for the development of minimal forms of endometriosis: delayed onset of menstruation (RR 1.34, 95% CI 1.17–1.53); history of allergic reactions (RR 1.35, 95% CI 1.20–1.50); pelvic inflammatory disease (RR 1.33, 95% CI 1.19–1.49); previous abdominal surgical interventions (RR 1.31, 95% CI 1.16–1.48); and the presence of bacterial or viral infections (RR 1.31, 95% CI 1.17–1.47).

Patients with stage III–IV endometriosis develop a more severe pain phenotype: the probability of chronic pelvic and acyclic pain is significantly higher ($p < 0.001$), whereas the odds of these complaints at early stages are 5–6 times lower (OR = 0.19–0.20). Regular dyspareunia is also more frequent in stage III–IV endometriosis (OR = 0.35; $p = 0.026$).

Dysmenorrhea demonstrated borderline statistical significance (p = 0.057) with the same direction of effect. Taken together, these findings reflect intensification of pain and its progressive dissociation from the menstrual cycle as the disease advances.

From a clinical perspective, the VAS pain profile confirms that with disease progression, pain becomes more intense and less closely related to the menstrual cycle. The highest pain intensity scores were recorded in subgroup 2 (stages III–IV), reflecting a more severe clinical course: dysmenorrhea reached 7.8 ± 1.4 points, chronic non-menstrual pelvic pain 6.7 ± 1.8 points, and dyspareunia 6.3 ± 1.7 points. In subgroup 1 (stages I–II), pain scores were significantly lower but still markedly exceeded control values (p < 0.001).

At stages III–IV of endometriosis, cyclic intestinal (dyschezia/tenesmus) and urogenital (dysuria/pollakiuria) symptoms were observed significantly more often (p = 0.001 and p = 0.012, respectively), which is consistent with involvement of adjacent organs and/or a pronounced adhesive process (Table 2). In the control group, cyclic organ-related symptoms were rare. Heavy and/or prolonged menstrual bleeding was also more common in advanced forms of the disease (p = 0.033).

Table 2.

Cyclic organ-related symptoms and menstrual characteristics in women of the examined groups: a comparative analysis

Symptoms	I–II stages (n=80)	III–IV stages (n=27)	Control (n=55)	p (Фишер) I–II и III–IV	OR (I–II и III–IV)	95% ДИ OR
Cyclic dyschesia/tenesmus	16 (20,0%)	15 (55,6%)	3 (5,5%)	0,0010	0,20	0,08–0,51
Cyclic dysuria/pollakiuria	8 (10,0%)	9 (33,3%)	2 (3,6%)	0,0116	0,22	0,08–0,66
Heavy/prolonged menstruation	22 (27,5%)	14 (51,9%)	8 (14,5%)	0,0328	0,35	0,14–0,87
Premenstrual spotting	18 (22,5%)	11 (40,7%)	7 (12,7%)	0,081	0,42	0,17–1,07

Premenstrual spotting in subgroup 1 tended to occur more frequently compared with the control group (22.5% versus 12.7%, respectively; p > 0.05). Thus, women in subgroup 1 develop a characteristic “organ-related” symptom complex that is typically associated with later stages of the disease.

On transvaginal ultrasound (TVUS), endometriotic ovarian cysts were visualized as round or oval fluid-filled formations with a capsule thickness of up to 3–4 mm and sizes ranging from 9 × 8 mm to 15 × 13 mm, containing a characteristic fine, non-shifting internal echogenic suspension. The cyst structure was homogeneous in 47.1% of cases and fine-reticular in 52.9%, reflecting the characteristics of hemorrhagic contents and the severity of the adhesive process. Endometriotic lesions in the pouch of Douglas were detected during primary ultrasound examination in 76.9% of cases; in 39% of patients, retrocervical heterotopias without complete obliteration of the space were identified, represented by irregularly shaped formations with reduced echogenicity and heterogeneous structure. Pelvic peritoneal endometriotic lesions were visualized in 13% of patients, while multiple heterotopias were detected in 27%, more often in combination

with small ovarian cysts and a moderate adhesive process. The “sliding sign” (folding sign), indicating involvement of adjacent organs, was observed in 83.1% of cases.

As a result, we proposed a consolidated comparative table of classical TVUS features of endometriosis depending on disease stage (Table 3). B-mode transvaginal ultrasound in endometriosis demonstrates a clear stage-dependent gradation of echographic findings: from minimal or normal findings at stages I–II to pronounced morphological changes in the posterior compartment and ovaries at stages III–IV.

Table 3.

Summary table of classical transvaginal ultrasound features of endometriosis depending on disease stage

Anatomical area/feature (B-mode)	I–II стадия	III–IV стадия
Ovarian endometrioma (ground-glass, thin walls)	less common; usually ≤ 3–4 cm; often unilateral	often; often bilateral; >4–5 cm
Indirect signs of ovarian adhesions (uneven contour, fixed position)	rare/minimal	frequent/expressed
Retrocervical hypoechoic plaques/nodes	usually indistinct/no	distinct, with heaviness
Infiltration of the CMS (thickening, "stringiness")	focal subtle changes/normal	clear thickenings, often bilateral
RVP nodes (hypoechoic "tongues")	as a rule, they are absent	typical, deform the posterior arch
Dugovlas space: fibrous bands, unevenness	single/none	multiple, "fused" type, indirect obliteration
Position of the uterus (retroflexion, fixation)	usually mobile/anteversion	retroflexion, tendency to fixation
Associated signs of adenomyosis (B-mode)	rare/moderate	are detected more often

Among the examined patients, MRI findings were available for 15 women: adenomyosis was diagnosed in 10 cases, and minimal forms of endometriosis in 5 cases. In 8 of 10 patients with minimal forms of endometriosis, thickening of the junctional zone was observed (JZmax > 12 mm; median 14.2 mm), while myometrial cysts were detected in 7 of 10 patients (1–3 foci, 2–6 mm). In 6 of 10 cases, a focal-dominant pattern localized to the posterior uterine wall was identified, whereas a diffuse pattern was observed in the remaining 4 of 10 patients. A JZdiff ≥ 5 mm was recorded in 7 of 10 patients, and a JZratio ≥ 40% in 6 of 10 cases.

Clinically, these MRI findings corresponded to pronounced dysmenorrhea (according to symptom questionnaires) and heavy menstrual bleeding; 60% of patients also reported pulling pain in the lumbosacral region.

Endometriomas were visualized in 3 of 10 patients (2 unilateral and 1 bilateral), with sizes ranging from 28 to 46 mm (volume 10–35 mL). These lesions demonstrated a typical MRI signal pattern: hyperintense contents on T1 and T1FS images with T2 shading, wall thickness of 2–3 mm, absence of solid or papillary components, and no pathological contrast enhancement.

Involvement of the posterior compartment and ligamentous apparatus was identified in 3 of 10 patients, characterized by signs of deep infiltrating endometriosis (DIE) according to the MR-Enzian classification (B1–B2): sacrouterine ligament involvement with nodules measuring 8–18 mm, represented by T2-hypointense plaques containing small T1-hyperintense hemorrhagic inclusions. In 3 of 10 cases, indirect signs of Douglas pouch obliteration were noted (loss of fat planes, adhesions between structures), while fixed uterine retroflexion was observed in 2 of 10 patients. Clinically, these cases were associated with cyclic dyschezia, dyspareunia, and intermenstrual pain.

Based on the obtained data, we developed risk stratification criteria using a point-based scoring system (Table 4).

Table 4.

Risk stratification criteria (composite clinical score)

Phenotype	Признаки	Баллы
Menarche and cycle	Early menarche (≤12 лет)	1
	Short cycle (Average period ≤27 days) or marked irregularity	1
Inflammatory and hereditary background	History of confirmed PID/STI episodes	1
	Allergic/gastrointestinal comorbidity (recurrent)	1
	Family history of endometriosis in first-degree relatives	1
Response to empirical therapy	Poor/temporary response to NSAIDs/hormonal suppression (COCs/progestin) ≥8–12 weeks	1
Reproductive history	Infertility for ≥12 months with regular sexual activity (male factor excluded/compensated)	2
	Primary nfertility	1
	Reproductive loss (≥1 spontaneous miscarriage/non-viable pregnancy)	1
Menstrual and pain phenotype	Dysmenorrhea, moderate/severe, onset ≤18 years or progression in severity over the past year	2
	Chronic pelvic pain ≥6 months (intermenstrually >1–2/10 according to VAS ≥ half of the days)	1
	Regular dyspareunia (in ≥50% of contacts, affects activity/VAS ≥3)	1

	Cyclic dyschezia/dysuria	1
Physical and ultrasound indirect signs (no obvious cysts/HIE)	TVUS: indirect signs of posterior adhesions (limited mobility of the uterus/ovary, “angular” contour) without endometriomas/HIE nodules	1
	Cervical displacement tenderness/retrocervical tenderness	1
Total point	Low: 0–2 points Moderate: 3–5 points High: ≥6 points	

The scale is intended for use during both primary and follow-up visits. Clinical signs reported over the preceding 12–24 months are recorded (unless otherwise specified); scores are summed.

Low risk: absence of complaints, normal menstrual cycle, negative ultrasound findings — continuation of the standard infertility management protocol is recommended, with a reminder that a *negative B-mode ultrasound does not exclude minimal forms of endometriosis*; repeat assessment is advised if symptoms develop.

Moderate risk: presence of clinical symptoms combined with indirect ultrasound signs — trial hormonal suppression therapy for 8–12 weeks is recommended; in cases of partial or absent response and an ongoing reproductive request, diagnostic laparoscopy (DL) should be considered.

High risk: multiple criteria combined with persistent pain syndrome — early diagnostic laparoscopy with a therapeutic stage is indicated, followed by a personalized reproductive strategy.

Thus, the proposed comprehensive risk criteria and early diagnostic algorithm enable systematic identification of women with a high probability of minimal forms of endometriosis among patients with infertility, minimize diagnostic delays, and facilitate timely selection of personalized management strategies — ranging from empirical hormonal suppression to diagnostic-therapeutic laparoscopy and early planning of assisted reproductive technologies. This approach integrates clinical presentation, targeted ultrasound assessment, and response to therapy, thereby increasing the likelihood of successful pain control and reproductive outcomes.

Conclusions

1. The developed comprehensive risk stratification criteria and early diagnostic algorithm allow for systematic identification of women with a high likelihood of minimal forms of endometriosis among infertile patients, significantly reducing diagnostic delays and ensuring a justified, personalized approach to clinical management and planning of assisted reproductive technologies.
2. Integration of clinical and anamnestic data, pain and organ-specific phenotypes, targeted transvaginal ultrasound and MRI findings, as well as assessment of response to empirical therapy, improves diagnostic accuracy at early stages of endometriosis, optimizes patient routing, and creates prerequisites for improved pain relief and reproductive outcomes in women of reproductive age.

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