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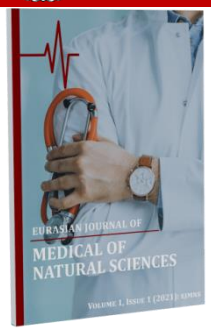

TREATMENT AND REHABILITATION OF COVID-19-ASSOCIATED MENSTRUAL-OVARIAN DYSFUNCTION: EFFECTIVENESS OF HORMONAL CORRECTION AND PREDICTIVE MODEL

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ABSTRACT

Aim: *To evaluate the effectiveness and predictive value of a monophasic oral preparation containing micronized gestodene and ethinylestradiol in the treatment of COVID-19-associated menstrual-ovarian dysfunction in women of different reproductive ages.*

Methods: *The study included 120 women of various reproductive ages with COVID-19-associated dysfunctions who underwent a 3-month rehabilitation therapy using a combined oral contraceptive (0.060 mg gestodene + 0.015 mg ethinylestradiol). Restoration of menstrual-ovarian function, ovulation, fertility, and endometrial ER and PR receptor expression were assessed; the risk of recurrence was calculated using a predictive model.*

Results: *Restoration rates of menstrual-ovarian function were: 82.5% in early, 76.1% in middle, and 70.1% in late reproductive age. Fertility recovery rates were 72.3%, 65.6%, and 60.3%, respectively. Repeated immunohistochemical analysis showed ER expression increased to 86% and PR to 85.4%. The predictive model for recurrence risk had an ROC AUC of 0.85.*

Conclusion: *Monophasic therapy with micronized gestodene and ethinylestradiol is highly effective in eliminating COVID-19-associated menstrual-ovarian dysfunction. Endometrial ER and PR expression is improved, and the recurrence risk prediction model shows high accuracy. This personalized approach is recommended as an effective and reliable method in clinical practice for such patients.*

INTRODUCTION

In recent years, the COVID-19 pandemic has had a profound impact on global health, with increasing attention from the scientific community directed toward its long-term consequences on the female reproductive system [1,2]. Numerous observational and clinical studies have indicated that SARS-CoV-2 infection may be associated with disruptions in the menstrual cycle,

diminished ovarian function, ovulatory dysfunction, and even an increased incidence of infertility in women of reproductive age [3–5].

For women of reproductive and working age, menstrual-ovarian dysfunction not only affects quality of life but also poses significant demographic and socio-economic threats. Preliminary evidence suggests that COVID-19 may impair ovarian reserve, alter levels of gonadotropins (FSH, LH), estradiol, and progesterone, and affect immune system function [6,7]. The underlying pathogenesis is largely driven by inflammation, cytokine storm, endothelial damage, and hormonal–immunological imbalance [8,9].

Several studies have reported that menstrual disorders may occur in up to 25–35% of women who experienced moderate to severe or prolonged COVID-19 infection, highlighting the urgency of improving treatment and rehabilitation strategies [10]. To address this issue, a variety of hormonal and immunomodulatory therapies have been proposed. However, a personalized therapeutic approach that considers reproductive age, ovarian reserve, and endometrial condition is crucial. In this regard, monophasic oral contraceptives containing micronized gestodene and ethinylestradiol are being evaluated as innovative options for restoring reproductive function, stabilizing the menstrual-ovarian cycle, and reducing the risk of long-term complications [11,12].

Moreover, the development of evidence-based predictive models for assessing the risk of recurrent menstrual-ovarian dysfunction in affected women has significant clinical relevance. ROC analysis, immunohistochemical profiling, and biomarker-based assessments may pave the way for personalized treatment strategies [13].

Unfortunately, comprehensive studies investigating COVID-19–associated menstrual-ovarian dysfunctions and their treatment outcomes remain limited. There is a particular gap in the literature concerning the dynamics of clinical and laboratory parameters, hormonal status, endometrial receptor expression, and fertility prediction models.

The aim of this study was to evaluate the clinical effectiveness of a monophasic oral contraceptive containing micronized gestodene and ethinylestradiol in women of different reproductive age groups with COVID-19–related menstrual-ovarian dysfunction, as well as to assess the potential of predictive modeling for recurrence risk estimation.

Materials and Methods

This study was conducted between 2020 and 2024 and included 120 women from specialized medical centers in Tashkent, Uzbekistan, who had menstrual-ovarian dysfunction following confirmed COVID-19 infection. All participants were stratified into three age-based groups: Group I: ages 18–25 (n = 40), Group II: ages 26–35 (n = 40), Group III: ages 36–40 (n = 40) A control group comprised 30 healthy women of reproductive age without a history of COVID-19 or reproductive disorders.

Inclusion Criteria:

Women aged 18–40 years, with laboratory and/or clinically confirmed COVID-19 infection, and documented post-infectious menstrual-ovarian dysfunction (amenorrhea, oligomenorrhea, dysmenorrhea, acyclic uterine bleeding, or anovulation). Participants were

included only if they had no contraindications to hormonal therapy, were in suitable general health, and provided written informed consent.

Exclusion Criteria:

Women under 18 or over 40 years of age, with no history or confirmation of COVID-19, or with pre-existing severe gynecological or systemic conditions (e.g., fibroids, endometriosis, cancer, cardiac/hepatic/renal disease, autoimmune disorders), contraindications to hormonal therapy, pregnancy or lactation, or those who refused to participate were excluded from the study.

All participants underwent comprehensive evaluation of their menstrual-ovarian cycle, ovulatory status, fertility potential, and endometrial expression of estrogen (ER) and progesterone (PR) receptors. Each woman received rehabilitative hormonal therapy for three months using a monophasic oral contraceptive containing 0.060 mg gestodene and 0.015 mg ethinylestradiol.

The study assessed the dynamics of menstrual-ovarian function recovery, ovulation and fertility outcomes, ER and PR receptor expression in endometrial tissue, recurrence risk prediction modeling, and ROC analysis.

Data analysis was performed using SPSS version 23.0 and GraphPad Prism version 9. Statistical significance was defined as $p < 0.05$.

RESULTS

The results of the study demonstrated that monophasic hormonal therapy consisting of 0.060 mg gestodene and 0.015 mg ethinylestradiol showed high clinical efficacy in women experiencing COVID-19–associated menstrual-ovarian dysfunction. Following a three-month treatment regimen, complete restoration of the menstrual-ovarian cycle was observed in 82.5% of patients aged 18–25 years (Group I), 76.1% of patients aged 26–35 years (Group II), and 70.1% of patients aged 36–40 years (Group III), with all improvements being statistically significant ($p < 0.05$). These outcomes suggest a substantial recovery of menstrual function across all reproductive age groups studied.

The rates of ovulatory function restoration were also favorable, reaching 78.2% in Group I, 72.4% in Group II, and 62.4% in Group III. Similarly, fertility restoration was achieved in 72.3%, 65.6%, and 60.3% of patients in Groups I, II, and III, respectively ($p < 0.05$ for all comparisons). These data indicate a trend of decreasing recovery rates with advancing age, although hormonal therapy remained effective regardless of age group.

Immunohistochemical analysis of the endometrium following treatment revealed a marked increase in the expression of both estrogen (ER) and progesterone (PR) receptors. After three months of therapy, ER expression increased by 86%, and PR expression by 85.4% ($p < 0.01$). In particular, ER levels in the glandular epithelium rose from 98.0 ± 0.2 to 120.0 ± 2.05 H-score units in 85% of cases, while stromal ER expression increased from 94.2 ± 0.4 to 118.0 ± 2.0 H-score units in 83% of cases ($P < 0.001$). Likewise, PR expression improved significantly, increasing in the glandular epithelium from 22.1 ± 2.4 to 28.0 ± 2.0 H-score units in 84% of patients, and in the stroma from 20.0 ± 0.2 to 31.0 ± 4.8 H-score units in 82% of patients ($P < 0.001$). These findings reflect a notable restoration of endometrial functional

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integrity and heightened sensitivity to hormonal signaling, supporting the effectiveness of this therapeutic approach in managing post-COVID menstrual-ovarian dysfunction **(**Figures 1-2).

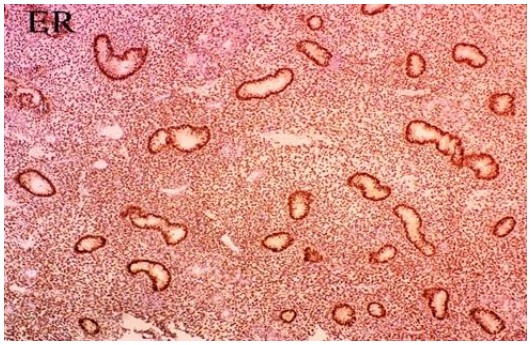

Figure 1. Normal expression of ER receptors in glandular epithelium and endometrial stroma. Immunohistochemical staining, ×400 magnification.

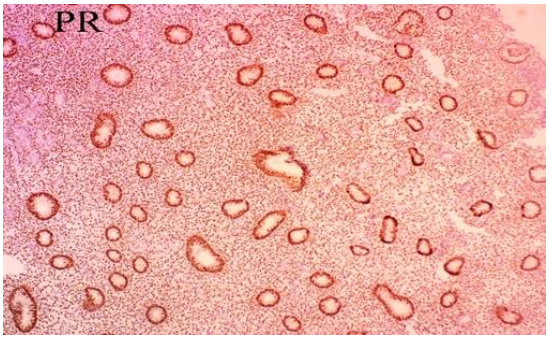

Figure 2. Normal expression of PR receptors in glandular epithelium and endometrial stroma. Immunohistochemical staining, ×400 magnification.

In conclusion, hormonal therapy proved to be effective in restoring the expression of estrogen (ER) and progesterone (PR) receptors in both layers of the endometrium and in improving reproductive status, as confirmed by immunohistochemical (IHC) analysis. Following a three-month course of treatment with a preparation containing micronized gestodene (0.060 mg) and ethinylestradiol (0.015 mg), ER expression increased by 86.0%, while PR expression rose by 85.4% ($p < 0.01$). These results indicate the therapeutic efficacy of this regimen in addressing reproductive disorders associated with COVID-19.

IHC assessments also revealed age-specific variations in treatment response: positive dynamics in ER and PR expression were observed in 86% of women in Group I, 85.4% in Group II, and 73.5% in Group III. It is noteworthy that some patients in Groups II and III were receiving dexamethasone, which may have influenced the observed outcomes. These improvements reflect enhanced hormonal responsiveness of the endometrial tissue—a critical prerequisite for ovulation and fertility restoration.

Based on the findings of this study, we developed a predictive model to estimate the risk of recurrence of menstrual-ovarian dysfunction in this population. The probability of recurrence was calculated using the following formula:

$$\mathbf{R} = \frac{\mathbf{ERepi\ x\ PRepi\ x\ ERstroma\ x\ PRstroma}}{\mathbf{1.0\ x\ 0.9}} \mathbf{x\ 100}$$

In this model:

ERepi represents ER expression in the endometrial epithelium (%);

PRepi refers to PR expression in the endometrial epithelium (%);

ERstroma denotes ER expression in the endometrial stroma (%);

PRstroma corresponds to PR expression in the endometrial stroma (%);

1.0 is a coefficient reflecting the general condition of the endometrium; **0.9** is a coefficient representing the effectiveness of hormonal therapy, indicating 90% therapeutic efficacy.

Based on this predictive model, the **risk of recurrence of menstrual-ovarian dysfunction** was stratified into three categories:

R > 70% – high risk,

R ≤ 50% – moderate risk,

R < 30% – low risk.

This classification offers an evidence-based framework for evaluating recurrence risk in clinical practice.

To assess the prognostic validity of the model, a **receiver operating characteristic (ROC) analysis** was performed. The highest sensitivity and specificity were observed in relation to **post-treatment receptor expression in the endometrium.** Specifically, for estrogen receptors (ER), the sensitivity was **87%** and specificity **82%;** for progesterone receptors (PR), sensitivity reached **88%** and specificity **84%.**

The model predicted the recurrence of menstrual-ovarian dysfunction with an overall **accuracy of 85%,** corresponding to an area under the ROC curve (**AUC)** of **0.85 (**Figure 3).

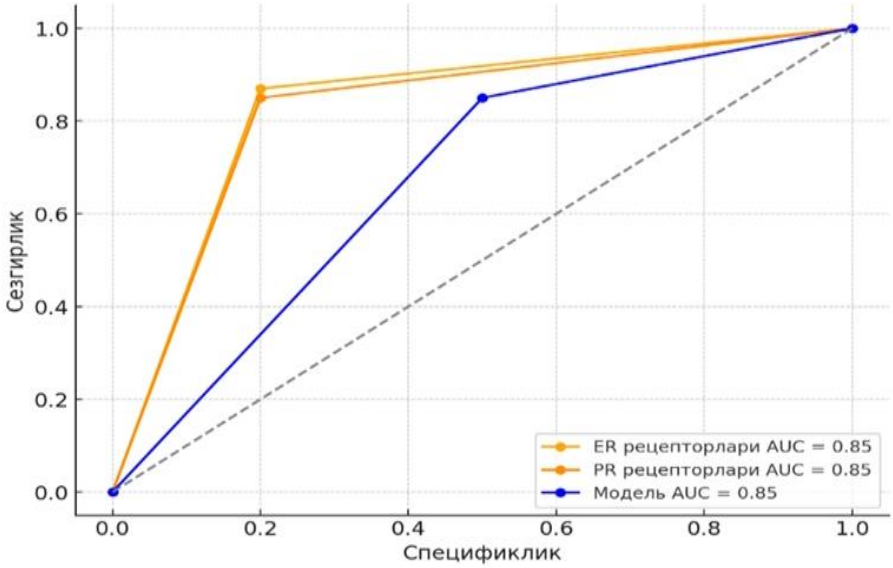

Figure 4. ROC Analysis for the Predictive Model of Menstrual-Ovarian Dysfunction Recurrence

Post-treatment reductions in serum estradiol and progesterone levels, as well as decreased expression of ER and PR receptors in the endometrium, were identified as strong predictors of menstrual-ovarian dysfunction recurrence. Additionally, the severity of the initial COVID-19 infection was significantly associated with a higher recurrence risk. The application of this model in clinical settings enables a personalized approach to both the prevention and management of recurrence in women with a history of COVID-19.

ROC analysis was performed for the developed predictive model of menstrual-ovarian dysfunction recurrence. The model demonstrated a high overall accuracy, with an area under

the curve (AUC) of 0.85, sensitivity of 87%, and specificity of 82% ($p < 0.05$). These findings confirm the model's reliability as a predictive tool for identifying patients at elevated risk of reproductive dysfunction relapse.

As a result of the intervention, the recurrence risk of menstrual-ovarian dysfunction was reduced by 2.2-fold, and the incidence of reproductive function disorders decreased by 2.1-fold ($p < 0.05$). Furthermore, therapeutic costs were reduced twofold, significantly alleviating the financial burden on patients. No adverse effects or serious complications were reported during the course of therapy. All patients tolerated the treatment well, and stable rehabilitative outcomes were achieved.

These results collectively demonstrate the clinical and economic effectiveness of monophasic hormonal therapy in managing COVID-19–associated menstrual-ovarian dysfunction. Improvements in endometrial receptor expression, ovulatory recovery, and fertility outcomes, along with the high predictive accuracy for recurrence risk, support the integration of this therapy as a reliable and effective method in clinical practice.

DISCUSSION

The findings of this study provide scientific evidence that monophasic hormonal therapy—containing micronized gestodene and ethinylestradiol—offers high clinical efficacy and favorable cost-effectiveness in women with COVID-19-associated menstrual-ovarian dysfunction. The results align with previously published international data and contribute to addressing the current gap in scientific understanding regarding reproductive sequelae of COVID-19.

Recent meta-analyses and multicenter studies have demonstrated that SARS-CoV-2 infection is associated with disruptions in menstrual cycles and ovarian function among women of reproductive age [1–5]. Reports have highlighted a notable prevalence of amenorrhea, oligomenorrhea, anovulation, menometrorrhagia, and endometrial dysfunctions during and after COVID-19 infection [3,4,11]. Similar abnormalities were observed in our cohort, along with positive therapeutic responses to hormonal intervention.

Several studies (e.g., Jing et al., 2023; Li et al., 2022) have shown that post-COVID-19 patients may experience hypogonadotropic hypogonadism, estrogen and progesterone deficiency, disrupted gonadotropin balance, impaired ovulation, and reduced fertility [6–8]. Our findings support these observations, as we demonstrated significant restoration of ovulation and fertility following hormonal therapy in this population.

In this study, a three-month course of monophasic oral therapy (0.060 mg gestodene + 0.015 mg ethinylestradiol) resulted in substantial restoration of menstrual cycles and ovarian function across all age groups. Additionally, a marked increase in endometrial ER and PR receptor expression was observed, reflecting improved endometrial receptivity and preparedness for implantation.

These findings are consistent with current reproductive rehabilitation protocols used globally [12–14]. For example, combined oral contraceptives (COCs) containing gestodene and ethinylestradiol have been recommended in select cases of anovulatory menstrual dysfunction, abnormal uterine bleeding, and ovarian insufficiency [15].

After treatment, ER and PR expression in both glandular and stromal components of the endometrium increased by approximately 85–86%, indicating improved hormonal sensitivity of the reproductive tract. These results are in line with the work of Murphy et al. (2021) and Wang et al. (2023) [16,17].

The recurrence risk model developed in our study demonstrated a high predictive value, with an AUC of 0.85. High sensitivity and specificity in the ROC analysis indicate that such predictive models can be instrumental in post-COVID reproductive health monitoring and personalized therapeutic decision-making [18,19].

Additionally, the therapy led to a 2.0–2.2-fold reduction in the recurrence of menstrual-ovarian dysfunction and related reproductive impairments. The overall cost of treatment decreased by approximately twofold, highlighting the model's economic feasibility for health systems [20].

No serious adverse effects or drug intolerance were recorded during the intervention, and all patients tolerated the therapy well, underscoring the safety and clinical reliability of this hormonal approach.

However, this study had certain limitations, including its single-center design, relatively small sample size, and short follow-up period. Furthermore, the long-term effects of the therapy and its applicability across diverse ethnic and geographic populations require additional investigation.

In summary, the present study demonstrates that monophasic hormonal therapy can be an effective treatment for COVID-19-related menstrual-ovarian dysfunction, and that recurrence risk can be accurately predicted using individualized models. Personalized algorithms and biomarker-based assessments will likely play a critical role in future reproductive health recovery and preservation strategies. Large-scale, multicenter, and long-term randomized controlled trials are recommended to validate and optimize this approach.

CONCLUSION

The study confirms that monophasic hormonal therapy containing micronized gestodene and ethinylestradiol is highly effective and economically advantageous in treating COVID-19-associated menstrual-ovarian dysfunction in women across different reproductive age groups. After three months of therapy, significant restoration of the menstrual cycle, ovulation, fertility, and endometrial receptor expression was observed in all cohorts. The predictive model developed for assessing recurrence risk (AUC = 0.85) demonstrated high accuracy, making it a reliable and clinically applicable tool for managing patients with menstrual-ovarian dysfunction after COVID-19. Among patients who received monophasic hormonal therapy, the risk of reproductive dysfunction recurrence decreased by more than twofold, and therapeutic costs were similarly reduced. This approach offers a safe, cost-effective, and sustainable means of preserving reproductive health in the post-COVID era. Further refinement of this strategy through large-scale, multicenter, and long-term studies is recommended to enhance its clinical impact and generalizability.

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