N.M. PODZOLKOVA[1], T.F. TATARCHUK[2],
A.M. DOSHCHANOVA[3], G.Z. ESHIMBETOVA[4], L.V. SUMYATINA[1]

MENSTRUAL CYCLE NORMALIZATION WITH DYDROGESTERONE

[1]Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia, Moscow
[2]Institute of Pediatrics, Obstetrics, and Gynecology, National Academy of Medical Sciences, Kiev, Ukraine
[3]Medical University of Astana, Kazakhstan,
[4]Tashkent Institute of Postgraduate Medical Education, Uzbekistan

Objective. *To analyze data in a subgroup of female patients from Russia, who took part in post-marketing observational study on the use of dydrogesterone to normalize their menstrual cycle (MC).*
Subjects and methods. *The observational study (NCT01711216) aimed at evaluating the efficacy of dydrogesterone used in the treatment of menstrual irregularities was conducted in several countries (Russia, Ukraine, Kazakhstan, and Uzbekistan). The paper analyzes data on 389 women from the centers located in Russia.*
Results. *In the Russian population, at least one or more normal MCs could be achieved in 99.0% of the patients using dydrogesterone (in 99.1% in the core study). After treatment completion, at least 6 consecutive normal MCs were observed in 76.7% of the patients (in 79.1% in the core study). There was a significant relationship ($p = 0.0016$) and a direct correlation ($p = 0.0377$) between the number of treatment cycles and the preserved regular MCs. High satisfaction with therapy results was observed in 91.6% of the patients; the clinical response to treatment was regarded as good or excellent in 90.3% of patients, as assessed by medical investigators. 1.8% of patients had adverse events; all of the latter were mild or moderate.*
Conclusion. *Dydrogesterone therapy for menstrual irregularities demonstrated high efficacy and good tolerability, as well as excellent patient treatment satisfaction. A direct relationship was noted between the duration of dydrogesterone usage (the number of treatment cycles) and that of the preserved normal MCs after treatment completion.*

Keywords: *dydrogesterone, polymenorrhea, oligomenorrhea, metrorrhagia, menstruation, menstrual irregularities, abnormal uterine bleeding.*

Authors declare lack of the possible conflicts of interests.

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The typical menstrual cycle (MC) duration is 28 days, but can vary from 21 to 35 days [1,4]. In the general population, 11–13% of women experience AUB [1,2]; this increases to 24% in those 36–40 years of age [2]. This condition can have a substantial effect on a woman's quality of life, reducing both mental and physical aspects [3]. In Russia, it has been reported that AUB occurs in 10 –30% of women of reproductive age and in up to 50% of women undergoing perimenopause [4].

After organic causes have been excluded, the first-line treatment of AUB is conservative therapy, which generally includes hormonal drug products such as progestins [4]. Dydrogesterone, an oral progestin, is a well-known retroprogesterone (progesterone stereoisomer), which has an additional double bond between carbon six and seven [6]. This difference in the chemical structure of dydrogesterone is responsible for its selectivity for the progesterone receptor and its high bioavailability when administered orally, which makes dydrogesterone up to 20-fold more effective than oral progesterone [6].

Previously it was demonstrated that dydrogesterone therapy can improve MC regularity and reduce the duration of menstrual bleeding [3].

A large post-marketing observational study was undertaken across four countries (Russia, Ukraine, Kazakhstan, and Uzbekistan) between 2014 and 2016 to evaluate the efficacy of dydrogesterone treatment in MC regularization and the persistence of the effect after treatment discontinuation [11]. The present article describes a subgroup analysis of data from only the Russian centers in the study [11], with the need for such analysis justified by the high prevalence of AUB in Russia. The aim of the study was to evaluate the efficacy of dydrogesterone when used for MC regularizing in patients from Russian centers and to assess the persistence of the effect after the EOT.

Materials and methods

A prospective, non-randomized, post-marketing observational study (NCT01711216) was conducted in 64 study centers across Russia, Ukraine, Kazakhstan, and Uzbekistan in 2012-2014 [5]. Subjects were women 18–40 years of age with irregular MCs for at least 3 months and who, prior to their inclusion in the study, had been prescribed dydrogesterone (Duphaston®, Abbott Healthcare Products B.V., Weesp, Netherlands) in accordance with the approved instructions for medical use.

Patient visits were scheduled at (1) Screening/Baseline; (2) after 3 cycles of dydrogesterone therapy (if treat-

ment duration was >3 MCs); (3) after EOT; (4) after 3-month FU (if MC regularization was achieved at EOT); and (5) after 6-month FU (if MC regularization was maintained at 3-month FU). In order to increase data objectivity, all patients kept a diary in which they recorded the first and last days of MCs, menstrual bleeding duration, their mental state (anxiety) during menstruation (scale from 0 to 11), pain duration (days), and intensity (scale from 0 to 11). In the case of a missed visit, the data from the patient's diary for that day was disregarded.

All patients received dydrogesterone (10 mg once or twice daily from Day 11 to Day 25 of the MC) in accordance with the Russian approved label for medical use.

Adverse events (AEs) and pregnancies were monitored throughout the study until 30 days after the final dose of dydrogesterone. A regular MC was defined as 21–35 days in duration. Three patient subgroups were defined based on the type of MC disorder: patients with polymenorrhea (MC <21 days), oligomenorrhea (MC >35 days), or a MC disorder of mixed nature.

The present analysis includes only a subgroup of patients from the 20 study centers in Russia that were included within the original study by Podzolkova *et al* (2016) [5].

The analysis established the proportion of patients reporting ⩾1 regular MC over the treatment period; the proportion of patients reporting ⩾6 regular MCs during FU; the effect of treatment duration on the persistence of MC regularization during FU; the intensity of menstrual pain and associated anxiety at EOT and end of FU; and overall patient satisfaction and clinical response at EOT. In order to assess a possible relationship between duration of dydrogesterone treatment and number of subsequent normalized MCs, an analysis of subgroups of patients who received either 3 or 6 full cycles of dydrogesterone was performed.

All statistical analyses were performed using SAS® (Version 9.4). Tests were 2-sided, performed at the 5% significance level, and all confidence intervals were 2-sided 95% intervals, unless otherwise specified.

The number and percentage of patients achieving regular MCs at EOT and during FU were assessed. The number and percentage of patients in each satisfaction category and clinical response category at EOT were assessed.

Results

A total of 996 women from study centers in Russia, Ukraine, Kazakhstan, and Uzbekistan were included in the main study [5]. In FAS, a total of 99,1% 946/955) of patients achieved ⩾1 regular MC over the treatment period, and 79,1% (680/860) of FU patients maintained ⩾6 regular MCs during FU [5]. The total proportion of FU patients with ⩾6 consecutive regular MCs during FU was 78.5% (675/860) [5].

MC duration was significantly improved (p⩽0,0001 versus baseline) in all patient subgroups [5]. The median MC duration for all subgroups was 28–29 days (mean: 27,9–29,6 days) at EOT, which is within the range of regular MCs (21–35 days) [5]. The median change in MC duration was +7 days for polymenorrhea, −11 days for patients with oligomenorrhea and −2 days for undefined irregularity [5].

A subgroup of 389 women that were enrolled from Russian centers were used in the present analyses, of which 382 were included in the full analysis set (FAS), 369 were included in the FU analysis set (FUAS), and 383 were included in the safety analysis set (all patients who received ⩾1 dose of dydrogesterone). In the FAS, 41 had polymenorrhea, 319 had oligomenorrhea, and 22 patients had a MC disorder of mixed nature, respectively. The mean age of patients in the subgroup analysis was 28.7 years, with the majority being Caucasian (Table 1).

In the FAS, 99.0% (378/382) of patients achieved ⩾1 regular MC over the treatment period (Figure 1). After EOT, 89.5% (307/343) of patients had consecutive regular MCs and 76.7% (263/343) of patients maintained ⩾6 consecutive regular MCs during FU (Figure 1).

A statistically significant association (p=0.0016; Mantel-Haenszel chi-square test with a Monte Carlo estimation) and a slightly positive, significant correlation (p=0.0377; Spearman's rank correlation) was established between the number of dydrogesterone treatment cycles and the number of regular MCs for the Russian patient subgroup (Figure 2). The analysis was performed on a subset of patients who received either ⩽3 or >3 to ⩽6 dydrogesterone treatment cycles (141 and 202 patients, respectively). It should be noted that the original publication did not reveal this correlation.

The duration of MCs was normalized during treatment in both polymenorrhea and oligomenorrhea subgroups (p⩽0.0001 *vs* Baseline). Mean MC duration at Baseline and EOT, respectively, was 20.1 and 27.6 days for polymenorrhea, 41.6 and 28.3 days for oligomenorrhea, and 27.4 and 35.6 days for a MC disorder of mixed nature. The mean change in MC duration at EOT was +7.8 ± 4.4 days in patients with polymenorrhea, −13.5 ± 22.1 days in patients with oligomenorrhea, and +0.5 ± 2.9 days in patients with a MC disorder of mixed nature.

Both pain intensity and anxiety level during menstruation were significantly decreased at EOT and end of FU (p⩽0.0001 *vs* Baseline and EOT).

At EOT, 91.6% (350/382) of patients were either satisfied or very satisfied with their treatment outcomes. Clinical response to treatment was considered good or excellent in 90.3% (345/382) of patients, as rated by physicians.

Overall, 10 AEs in 1.8% (7/383) of patients were reported in the safety analysis set, all of which were graded as either mild or moderate. Eight of the ten were categorized as 'reproductive system and breast disorders'; of these, metrorrhagia (3 events) and dysmenorrhea (3 events) were the most frequent events. No serious AEs were reported.

Of the 100 patients (25.7% of 389 enrolled patients) who prematurely terminated the study, 1 discontinued treatment due to a non-serious AE, 25 patients were removed due to pregnancy, 4 patients withdrew their consent, 24 patients were lost to FU, and 46 patients were removed due to other reasons.

Discussion

Dydrogesterone has been used in clinical practice for over 55 years and is available in more than 100 countries globally. It is a therapeutic option for the treatment

of gynecological conditions associated with progesterone deficiency, such as AUB [3-6,12], endometriosis [3,4,13,14], premenstrual syndrome [4], infertility associated with luteal-phase defect [4,16], threatened miscarriage [4,16], recurrent pregnancy loss, and luteal-phase support when using assisted reproductive technologies [4,7,8,15,16]. According to post-marketing safety data, the cumulative exposure to dydrogesterone from 1960 to 2017 was estimated to be more than 113 million patients, of which more than 20 million pregnancies were exposed to dydrogesterone *in utero* [7].

The results of this analysis showed that dydrogesterone was effective in regularizing MCs in patients from Russian centers, the majority of which maintained ⩾6 regular MCs after the end of treatment. Overall, the efficacy of dydrogesterone in the present study supports the results of other prospective studies, where MC regularization was achieved in 82–96.7% of patients treated with dydrogesterone [3,5].

It was found that the duration of dydrogesterone treatment is associated with the number of subsequent regular MCs. Further analysis confirmed a positive, significant correlation, suggesting that dydrogesterone treatment was more effective when administered for 6 months.

Further to the normalization of patients' MCs, dydrogesterone treatment was effective in significantly reducing the intensity of menstrual pain and associated anxiety during treatment, and for up to 6 months after the EOT. Given the impact that AUB can have on a woman's quality of life [11], these findings are of high importance.

According to the Russian Society of Obstetricians and Gynaecologists, progestins are the drugs of choice in the prevention of AUB recurrence, as they are able to normalize MCs, decrease duration and intensity of menstrual bleeding, and neutralize menstrual pain [4]. A pharmacological treatment that allows women to preserve reproductive functions is considered a first-line therapy in patients with AUB who have no organic disorders. Dydrogesterone has particular advantages over other hormonal drug products, such as combined oral contraceptives (COCs), for women whose reproductive plans are either partially or completely unfulfilled and who are planning to become pregnant in the future. COCs contain progestins, which possess antigonadotropic effects, i.e. they can suppress follicle-stimulating hormone and luteinizing hormone peaks, thus blocking an ovulation [4,9]. Available data indicates that dydrogesterone does not inhibit ovulation at therapeutic doses [6,8,14]. The most compelling clinical evidence that dydrogesterone does not inhibit ovulation comes from its use in the treatment of endometriosis-associated infertility, where a substantial proportion of the patients treated with dydrogesterone became pregnant while on treatment [13,14]. It has been shown in patients with irregular MCs that treatment with dydrogesterone from Day 11 to Day 25 of the MC is able to physiologically support a preovulatory progesterone peak [6]. It is also able to promote proper secretory transformation of the endometrium without ovulation suppression [8].

A safety profile of dydrogesterone has been shown in a number of clinical studies, including randomized controlled trials [3,5-8,14]. The AEs observed in this subgroup analysis comply with the known safety profile of dydrogesterone [3,5,7,16]. Due to its favorable safety profile, dydrogesterone can be a drug of choice to normalize MCs in women of reproductive age, particularly in patients considering pregnancy [4,6,16]. The results of a recently published study in Japan, which

Table. Patient demographic and other Baseline characteristics

Menstrual cycle disorder	Full analysis set (N=382)	Follow-up analysis set (N=369)	Safety analysis set (N=383)
Age, years			
Mean (SD)	28.7 (5.5)	28.7 (5.5)	28.7 (5.5)
Median	28.0	28.0	28.0
Q1, Q3	24.0, 33.0	24.0, 33.0	24.0, 33.0
Min, Max	18, 40	18, 40	17, 40
Age group, n (%)			
18–20 years	23 (6.0)	23 (6.2)	23 (6.0)
21–25 years	102 (26.7)	99 (26.8)	102 (26.6)
26–30 years	114 (29.8)	108 (29.3)	114 (29.8)
31–35 years	83 (21.7)	81 (22.0)	83 (21.7)
36–40 years	60 (15.7)	58 (15.7)	60 (15.7)
Race, n (%)			
White	378 (99.0)	365 (98.9)	379 (99.0)
Black	1 (0.3)	1 (0.3)	1 (0.3)
Asian	3 (0.8)	3 (0.8)	3 (0.8)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Body mass index, kg/m²			
Mean (SD)	23.19 (3.92)	23.18 (3.94)	23.17 (3.93)
Median	22.42	22.41	22.41
Q1, Q3	20.28, 25.53	20.28, 25.40	20.24, 25.53
Min, Max	16.7, 38.8	16.7, 38.8	16.5, 38.8
Menstrual cycle disorder, n (%)			
Polymenorrhea (cycle <21 days)	41 (10.7)	40 (10.8)	41 (10.7)
Oligomenorrhea (cycle >35 days)	319 (83.5)	309 (83.7)	320 (83.6)
Undefined menstrual cycle disorder	22 (5.8)	20 (5.4)	22 (5.7)

Max, maximum; Min, minimum; SD, standard deviation

described the superiority of dydrogesterone over COCs in the treatment of menstrual disorders in women of late reproductive age, demonstrated that the administration of COCs for 3 months in these patients resulted in increased blood oxidative stress parameters; this effect was not seen in patients treated with dydrogesterone [10]. Moreover, when COCs were replaced by dydrogesterone, the increased oxidative stress parameters were reduced [10].

Our study revealed high patient and clinician satisfaction associated with dydrogesterone treatment; these data are in accordance with the previous study results [3,5]. This factor should be taken into account when choosing the therapy for MC disorders. According to another recent study, women receiving COCs were not completely satisfied with their treatment, with 69% of the patients reporting at least one side effect. Of those patients who experienced a side effect, 65% reported that the side effect was the reason for stopping COC use [11]. Patients suffering from COC side effects and those with contraindications (overweight, smokers over 35 years of age, high risk of thrombosis, etc.) could benefit from progestins therapy for their MC disorders [4].

Fig. 1. The relationship between the number of dydrogesterone treatment cycles received and the persistence of MC regularization during FU FU, follow-up; MC, menstrual cycle

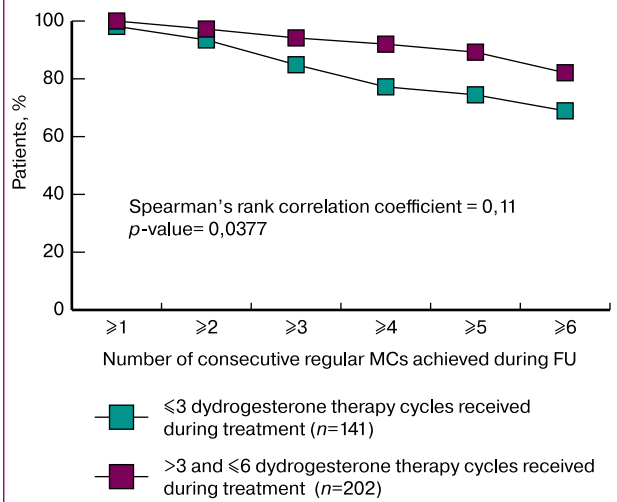
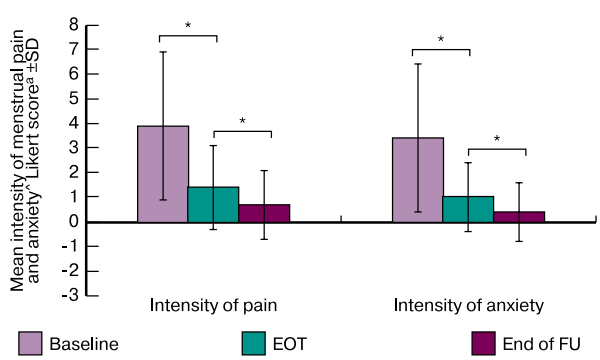


Fig. 2. Changes in menstrual pain intensity and anxiety with dydrogesterone treatment (mean)



*p<0.0001; 2-sided Wilcoxon signed rank test
aIntensity of pain and anxiety during menstruation was graded using an 11-point Likert scale from 0 (no pain, no anxiety) to 10 (severe pain, severe anxiety)
EOT, end of treatment; FU, follow-up; SD, standard deviation

Conclusion

Dydrogesterone is a drug of choice for the treatment of MC disorders in women, including those from Russia, due to its favorable safety profile and proven effectiveness in the normalization of MCs. MC normalization was seen in an absolute majority of patients treated with dydrogesterone. Dydrogesterone significantly reduced menstrual pain, associated anxiety, and demonstrated high clinical response and patient satisfaction.

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About the authors:
Podzolkova Nataliya Mikhaylovna, Doctor of Medicine, Professor, Department of Obstetrics and Gynecology, Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia. 125993, Russia, Moscow, Barrikadnaya str. 2/1. Tel.: +74997481530. E-mail: podzolkova@gmail.com
Tatarchuk Tatyana Feofanovna, MD, professor, Corresponding Member of NAMS of Ukraine, Honored Worker of Science and Technology of Ukraine, Deputy Director for Research, Institute of Pediatrics, Obstetrics and Gynecology, National Academy of Medical Sciences of Ukraine. 04050, Ukraine, Kiev, Platon Mayboroda str. 8. Tel.: +38 (044) 483-80-87. E-mail: ipag.gyn@femina-health.org
Doshchanova Aygerim Mstrovovna, MD, professor, chief freelance gynecologist-endocrinologist of the Ministry of Health of the Republic of Kazakhstan, Astana. Tel.: +77172408372. E-mail: talmas_medicus@mail.ru
Eshimbetova Gulsara Zakirovna, MD, Professor of the Department of Obstetrics, Gynecology and Perinatal Medicine, Tashkent Institute of Postgraduate Medical Education, Tashkent, Uzbekistan. Tel.: +998712681744. E-mail: kaf_ginekologiya-perinatal@tipme.uz
Sumyatina Liliana Vyacheslavovna, Ph.D., Associate Professor of the Department of Obstetrics and Gynecology, Russian Medical Academy of Continuing Professional Education, Ministry of Health of Russia. 125993, Russia, Moscow, Barrikadnaya str. 2/1. Tel.: +74997481530. E-mail: sumyatin@yandex.ru