Drospirenone 4 mg in a 24+4 regimen in women with contraindications to oestrogen use for contraception: bleeding patterns according to previous menstrual characteristics

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Abstract

Purpose

A new POP consisting of 4 mg drospirenone (DRSP) for 24 days with a 4-day hormone-free interval was developed to improve bleeding predictability during POP use. The aim of this study was to evaluate the effect on bleeding patterns during use of this oral contraceptive (OC) in comparison with previous menstrual cycles before the start of OC use.

Methods

This is a pilot, prospective trial. A diary was used to collect information about daily bleeding and pelvic pain before and during treatment. During OC use, women were categorized as having 1) unscheduled bleeding or spotting days (UB), 2) scheduled bleeding or spotting days (SB) and 3) absence of bleeding/spotting (AB). SF-36 and FSFI questionnaires were used to quantify health-related quality of life and the quality of sexual life in sexually active participants.

Results

Eighteen out of 25 (72%) women completed the entire follow-up. Women with UB (44.4%) were older at inclusion ($p < 0.001$) and had higher BMIs ($p = 0.02$) than those with AB (22.2%) or SB (33.4%). Women recorded a significant reduction of menstrual flow intensity during OC use ($p < 0.0001$). Those with UB also experienced a significant reduction of menstrual pain intensity ($p = 0.006$). Women with SB during OC use had a longer baseline cycle than those who reported UB during OC use ($p = 0.008$). Satisfaction with this OC was very high (8.4 ± 2.2 points) with no modification in SF-36 and FSFI values.

Conclusion

A DRSP-only pill is a good OC option for women with contraindications to oestrogen use. Features of the menstrual cycle before the start of OC use may be used to predict associated changes in bleeding patterns.

1. Introduction

1.1 Background

Safe contraceptive methods should be offered to all women who need them, even those who may have contraindications to their use. Progestin-only pills (POPs) were created in response to the need for oestrogen-free contraceptives for women in whom oestrogen use was a contraindication [1]. Little to no increased risk of deep venous thrombosis (DVT), stroke or myocardial infarction has been associated

with the use of POPs, thus oestrogen-free contraceptives are also suitable for women with increased risk factors for cardiovascular diseases, such as migraine with aura, active smoking, hypertension or known thrombogenic mutations [2].

However, although POPs are effective methods of hormonal contraception, their use is relatively infrequent in these particular categories of women. The main reason for this is their unpredictable effect on menstrual bleeding [3]. Women on POPs often have abnormal bleeding patterns, characterized by an increased frequency of bleeding, lengthened cycles, breakthrough bleeding, spotting and prolonged bleeding.

A new oestrogen-free contraceptive consisting of 4 mg drospirenone (DRSP) for 24 days with a 4-day hormone-free interval has been developed to address this need, named the DRSP-only pill (DOP) [4]. DRSP is a progestin analogue of spironolactone with anti-androgenic and anti-mineralocorticoid properties [5]. Its bleeding profile was found to be better than that of other POP on the market in Italy based on desogetrel (DSG) 75 µg in a 28-day regimen [6, 7]. However, the specific bleeding patterns experienced by women using this type of POP are unclear; in particular, it is not clear what different women should expect depending on the length of their menstrual cycles before starting this new hormonal method.

1.2 Aim

In this independent pilot study based on a daily detailed menstrual diary, we evaluated exact bleeding patterns in terms of scheduled bleeding, unscheduled bleeding and absence of bleeding/spotting occurrence, in relation to features of the two previous menstrual cycles before the start of the method and the short-term acceptability and satisfaction of this POP in women with contraindications to oestrogen use for contraception.

2. Materials And Methods

2.1 Study design

This was a pilot, prospective, independent, single-group, monocentre, daily-diary-based trial. The study was conducted from January 2020 to February 2022 in the Family Planning clinic of the Azienda Ospedaliero-Universitaria of Modena, Italy. The study was designed and conducted in full accordance with the World Medical Association Declaration of Helsinki, 2002 revision. This study was approved by the local ethics committee, and all women gave their informed consent to the anonymous use of their data for research purposes.

2.2 Subjects

The inclusion criteria were

- Women requiring effective, modern contraception

- Contraindications to combined contraceptive use according to the World Health Organization (WHO) medical eligibility criteria published in 2015 (class 3 or 4) [1]
- Regular menstrual cycles (cycle length between 21 and 35 days) [8]
- 18–50 years of age

2.3 Definition of bleeding pattern during treatment

The first cycle of use of the DOP was not considered (first blister pack).

From the second blister pack of the DOP onward, bleeding patterns were described as follows:

- **Unscheduled bleeding or spotting days** were defined as any day with bleeding/spotting that occurred during active hormone administration (days 2–23) in cycles 2 and 3 (group 1).
- **Scheduled bleeding or spotting days** were defined as any bleeding or spotting that occurred only during hormone-free intervals (defined as days 25–28 ± 1) in cycles 2 and 3. Up to 8 consecutive bleeding/spotting days were considered as regular bleeding days (group 2). If some days of other bleeding days occurred, we considered the woman in the group above (group 1, unscheduled bleeding).
- **Absence of bleeding/spotting** was defined as the absence of bleeding during the reference period (cycles 2 and 3) (group 3).

Bleeding patterns were recorded as in previously published studies on the same preparation [6, 7] and in accordance to recent proposed published recommendations [9].

2.4 Study evaluations

At Visit 1 (enrolment), we verified the inclusion criteria, and the participant signed the informed consent. Basal characteristics were collected, and the daily diary of bleeding and pain (1–60 days) was assigned. Questionnaires about health-related quality of life (Short Form 36) and sexual life (Female Sexual Function Index FSFI) were completed.

After 2 months without treatment, during Visit 2, the completed daily diary (1–60 days) was collected, and the daily diary of bleeding and pain (other 64 days) was assigned. At this visit, three blister packs of Slinda® (Exeltis®, Peschiera Borromeo, Milan, Italy) were delivered to the patients.

At Visit 3 (around three cycles after Visit 2), questionnaires on health-related quality of life (SF36) and sexual life (FSFI) were repeated, and the bleeding dairy for the treatment period was collected.

The included women were required to complete a diary card on a daily basis to determine their effective intake of the study medication. The diary included information about daily bleeding (none, mild, moderate or intense) and pelvic pain (none, mild, moderate or intense). The mean intensities of bleeding and pain were obtained by summing the bleeding and pain values of each day of menstrual flow and then dividing the total obtained by the duration of menstruation in days (points per day of flow). A validated Italian

version of the SF-36 and FSFI questionnaire were used to quantify health-related quality of life and the quality of sexual life in sexually active participants.

2.4 Outcomes of the study

The primary outcome of the study was the change in bleeding days, in particular, in the occurrence of irregular bleeding/spotting days in users of DRSP 24 + 4. Pain and bleeding profiles, health-related quality of life and the quality of sexual life were considered as secondary outcomes of the trial. Other outcomes included the types and frequencies of adverse events in patients included and treated.

2.5 Statistical analysis

2.5.1 Data analysis

Data were analyzed by one of the authors (G. G.). Statistical analysis was performed using the statistical package StatView (version 5.01.98, SAS Institute Inc., Cary, NC). Within-group comparisons were performed with the t-test for paired data and the Wilcoxon signed-rank test for normal and non-normal data distributions, respectively. For all analyses, the null hypothesis was rejected at a two-tailed p value of 0.05. Results are expressed as the mean ± standard deviation (SD).

2.5.2 Potency of the study

To determine the sample size, we chose the primary outcome of the study: the possible increase in the irregular bleeding/spotting rate during DRSP 24 + 4 use. Based on previous data, we assumed a possible increase of 30% (from 0–30%) during DOP after 3 months of irregular bleeding [10].

When the the type I error was set at 0.05 and the type II error at 0.20, 21 subjects were sufficient to document a significant effect in treated patients. Assuming a patient withdrawal rate of about 20%, we set our sample size to 25 subjects.

3. Results

A total of 25 women were eligible according to the inclusion/exclusion criteria of the study and were invited to participate. Of these, 21/25 (84.0%) subjects accepted to participate in the study, signed the informed consent and were then included in this pilot study. Out of these 21, 1 woman (4.8%) did not want to attent the scheduled controls and was lost to follow-up, leaving 20 women for the analysis. The baseline features of the 20 included women are reported in Table 1. The specific contraindications to estrogen use are reported in Table 1 and were mainly controlled hypertension, migraine with aura, smokers older than 35 years and known hypercoagulability.

Table 1
Baseline features of the subjects included in the study.
Values are expressed in mean ± standard deviation (SD).

	Subjects (n = 20)
Age (years)	36.0 ± 10.6 (20–50)
BMI (Kg/m^2)	25.2 ± 5.9 (17.6–38.2)
Nulliparous (%)	9/20 (45%)
Previous C-section	2/20 (10%)
Contraindications to estrogens	7/20 (35%)
Controlled hypertension	5/20 (25%)
Trombophilic mutation	3/20 (15%)
Migraine with aura	2/20 (10%)
Smokers older than 35 years old	3/20 (15%)
Others	

The pill was given at no cost to all participants for the first three cycles. Two out of 20 (10%) women did not follow the requested regimen and abandoned the study before 3 months of use. The final analysis was thus performed on the n = 18 women who completed the entire follow-up period (2 cycles without treatment and three cycles of treatment).

A slight, nonsignificant reduction in BMI was registered during the first 3 months of treatment with DRSP 24 + 4 (n = 18 from 26.0 ± 6.0 to 25.6 ± 5.5 kg/m^2, p = 0.19).

3.1 Bleeding profile

The women's regular bleeding patterns (100% of regular bleeding occurrence) were significantly altered during the inclusion period by the use of DRSP 24 + 4. According to the groups described above, 4/18 (22.2%) women were in amenorrhea **(women with absence of bleeding/spotting)** in the second and third cycles, while 8/18 women (44.4%) presented with irregular bleeding (p = 0001) **(women with unscheduled bleeding or spotting days)**. Six of 18 women (33.4%) still had regular menstrual cycles with bleeding or spotting occurring during hormone-free intervals (defined as days 25–28 ± 1) in cycles 2 and 3 **(women with scheduled bleeding or spotting days)**.

Women with unscheduled bleeding were older at inclusion (mean age 44.0 ± 3.3 vs. 31.6 ± 7.4 years old, p < 0.001) and had a higher BMI (mean BMI 31.1 ± 6.4 vs. 25.0 ± 3.4 kg/m^2, p = 0.02) than women with absence of bleeding or scheduled bleeding.

The change in the bleeding profile and pelvic pain on bleeding days obtained from the diaries is reported in Table 2 for all women, women with absence of bleeding and women with scheduled and unscheduled bleeding. We recorded a significant reduction in menstrual flow intensity (points per day of flow) ($p < 0.0001$) in the total group. Women with unscheduled bleeding experienced a significant reduction of menstrual pain intensity ($p = 0.006$). Women with scheduled bleeding during treatment had a longer baseline cycle length than those who reported unscheduled bleeding during treatment ($p = 0.008$).

Table 2
Baseline and after treatment characteristics of bleeding and pain during menstruation, according to specific bleeding patterns.

	Mean of baseline cycles (n = 18)	Mean of 3 cycles of treatment (n = 18)	p
Total group (n = 18)			
Cycle length (days)	28.9 ± 3.0	22.6 ± 7.1	NS
Menstrual flow length (days)	5.6 ± 0.7	4.3 ± 1.5	NS
Menstrual flow intensity (points per day of flow)	2.0 ± 0.3	1.0 ± 0.3	< 0.0001
Menstrual pain intensity (points per day of flow)	1.0 ± 0.5	0.5 ± 0.3	NS
Women with absence of bleeding/spotting (n = 4)			
Cycle length (days)	28.5 ± 0.3	0 ± 0	
Menstrual flow length (days)	5.0 ± 0.6	0 ± 0	
Menstrual flow intensity (points per day of flow)	2.0 ± 0.5	0 ± 0	
Menstrual pain intensity (points per day of flow)	0.7 ± 0.4	0 ± 0	
Women with scheduled bleedings (n = 6)			
Cycle length (days)	33.8 ± 2.6	30.2 ± 1.6	0.02
Menstrual flow length (days)	5.8 ± 0.6	5.0 ± 0.8	NS
Menstrual flow intensity (points per day of flow)	1.9 ± 0.3	1.3 ± 0.3	0.006
Menstrual pain intensity (points per day of flow)	0.2 ± 0.2	0.6 ± 0.3	NS
Women with unscheduled bleedings (n = 8)			
Cycle length (days)	25.4 ± 3.0	28.3 ± 5.0	NS
Menstrual flow length (days)	5.7 ± 0.9	5.9 ± 1.3	NS
Menstrual flow intensity (points per day of flow)	2.2 ± 0.4	1.3 ± 0.2	0.01
Menstrual pain intensity (points per day of flow)	1.8 ± 0.4	0.5 ± 0.2	0.006

3.2 Treatment satisfaction

In the 18 women who finished the first 3 months of follow-up during DRSP 24 + 4, satisfaction with treatment was very high, with a mean of 8.4 ± 2.2 points (median: 8.0, range 2–10). This value was not related to age or BMI at inclusion (p = 0.87 and 0.30, respectively).

3.3 Changes in health-related quality of life

Although there was a slight improvement, no significant changes were observed in health-related quality of life (mean SF-36 questionnaire from 69.9 ± 4.1 to 75.2 ± 5.2, p = 0.46) and its domains (Fig. 1a).

3.4 Changes in sexual life

No change in sexual life were observed in sexually active women of the study group (n = 16) before and after the first three cycles of DRSP 24 + 4 treatment (mean FSFI questionnaire from 29.2 ± 5.3 to 31.2 ± 2.2, p = 0.29). This was true for the different domanis of the FSFI (desire, arousal, lubrication, orgasm, satisfaction and pain) (Fig. 1b).

3.5 Further continuation of the DRSP-only pill

Of the 18 women participating after the first three cycles of use, another 5 (27.8%) women decided to discontinue use of the pill in the next follow-up period. Three out of 4 women (75%) with absence of bleeding discontinued treatment for ‘menstrual cycle desire’, one women stopped because of irregular menstrual bleeding after 9 months of treatment and another one for a severe adverse effect (breast cancer occurrence) after 11 months of treatment.

The 13 remaining subjects were observed for a mean of 5.3 ± 4.1 further cycles of follow-up. Ongoing women are still satisfied (n = 13) with the treatment with a mean rate of 7.5 ± 2.7 VAS points (median: 8.0, range 2–10). However, in this real-life study, we observed a high rate of DRSP 24 + 4 treatment discontinuation (7/20, 35%) in a mean of 9 months of follow-up.

4. Discussion

4.1 Principal findings of the study

In this pilot study, we evaluated the characteristics of uterine bleeding in users of the DRSP 24 + 4 only pill who presented contraindications to oestrogen use during the first months of treatment, in relation to the previous characteristics of their natural menstrual cycle. We have not found any previous published study comparing bleeding patterns in women using any hormonal contraceptive, in particular a POP, with those of the last natural menstrual cycles in the same subjects before the start of treatment.

In general, the results of our study demonstrated a significant reduction of menstrual flow intensity during treatment. Women with scheduled bleeding during DRSP treatment had a longer baseline cycle length

than those who reported unscheduled bleeding, and women with unscgeduled bleeding were older and had a higher BMI at inclusion than women experiencing absence of bleeding or scheduled bleeding during DRSP use.

We did not record any impairment in health-related quality of life or sexual life in these women during short-term hormonal contraceptive treatment. Despite these results and very high satisfaction with the treatment among women who completed the requested follow-ups, in this real-life study, we observed a high rate of treatment discontinuation (7/20, 35%) of DOP in a mean of 9 months of follow-up.

4.2 Interpretation

Previous experimental results showed that DRSP 24 + 4 users presented a more favourable bleeding pattern than users of DSG-based traditional POPs [6, 7]. In particular, in the second treatment cycle, we found a similar rate of unscheduled bleeding to that in previous studies (44.4% vs. 51.4%) [6]. We also found a similar rate of 'silent menstruation' (absence of bleeding) (22.2% vs. 30.3%) [6] and of scheduled withdrawal bleedings (33.4% vs. 40%) [6, 10]. In previous studies and in ours, the DRSP-only pill showed higher rates of scheduled bleeding, much lower rates of irregular unscheduled bleeding/spotting and a higher rate of absence of bleeding in comparison to traditional POP containing DSG. The improved predictability of bleeding during DRSP-only pill use is an important advantage of this POP in comparison to the traditional one, even if the bleeding patterns are different those observed with estro-progestin combinations containing natural oestradiol (E2) or oestetrol (E4), which are contraindicated in this group of women [4]. In particular, our results suggest that we could try to predict the specific bleeding patterns during the first months of use of this pill: longer baseline menstrual cycles could predict the occurrence of scheduled bleeding, and unscheduled bleedings may occur more often in older women and those with higher BMIs. These findings, if confirmed, would be relevant to counselling during the prescription of this specific preparation because the predictability of the bleeding patterns experienced during the first months of use of a hormonal contraceptive are highly predictive of compliance. This result is in particular contrast to a study that demonstrated a similar mean number of irregular bleeding days between women with BMI > 25 kg/m^2 or older than 35 years [11] and those BMI ≤ 25 kg/m^2 or older than 35 years; however, the outcome of our study was slightly different in that we assessed the rate of unscheduledbleeding episodes and not the number of bleeding days.

Our study showed no changes in the sexual lives of the treated women. Most studies have shown an impairment of sexual life in hormonal contraceptive users and a change in sexual functioning with regard to general sexual response, desire, lubrication, orgasm and relationship satisfaction [12], especially in users of combined hormonal contraceptives, due to a decrease in androgens caused by an increase in sex hormone binding globulin (SHBG) levels [13]. The follow-up of our study was very short for evaluation of sexual life (only 3 months), but the neutral impact of DOP in these women who did not demonstrate a basal impairment of sexual function (normal values of FSFI) is reassuring for subsequent evaluations with longer follow-ups.

We found a higher rate of discontinuation (35%) at 9 months after inclusion in comparison to those reported previously for the same preparation (9.6%) [14] in different populations (Italy vs. Austria, Czech Republic, Germany, Hungary, Poland, Romania, Slovakia, and Spain), although patient satisfaction among study participants was generally very high: these discordant results may be correlated with different cultural aspects of menstrual bleeding in the Italian population in comparison with other populations [15, 16]. In fact, 75% of women experiencing absence of bleeding in our study have stopped treatment with a DRSP-only pill after three cycles for 'menstrual cycle desire'. Our results are more comparable to those obtained from studies conducted in US with a one-year discontinuation rate of 65% [17].

4.3 Strengths and Limitations

The major limitation of this study was the small sample size (only 25 women) and the short follow-up (only 3 months): thus, it should be considered as a pilot study. Furthermore, it was conducted in a single centre, and we did not include a control group. The strengths of the study are the direct comparison with the characteristics of the previous natural menstrual cycle using a detailed menstrual diary and the complete independence of the researchers involved from the manufacturers of the preparation (Exeltis®, Argentina): the majority of existing literature on this product is in fact produced and published by company employees. These results should be considered preliminary, although the subject warrants exploration in larger investigations.

5. Conclusions

Original results from our pilot study have shown that a DRSP-only pill can a good OC option for women with contraindications to oestrogen use. The specific features of the menstrual cycle before the start of OC use may be used to predict associated changes in bleeding patterns during its use.

Declarations

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Declaration of interest statement:

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Authors contributions

Giovanni Grandi: concept and design, data analysis, interpretation, manuscript draft, final approval.

Maria Chiara Del Savio: manuscript revision, final approval.

Chiara Melotti: study execution, final approval.

Fabio Facchinetti: interpretation, data analysis, manuscript revision, final approval.

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Figures

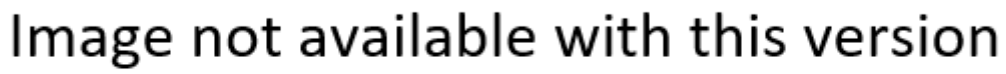

Figure 1

a, b. Change between baseline and post-treatment in a) SF-36 values and its domains (Physical Function, Physical Problems, Social Activities, Mental Health, Emotional Problems, Energy and Fatigue, General Health, Change in Health) (n=18), b) FSFI values and its domains (Desire Arousal, Lubrication, Orgasm, Satisfaction, Pain) in sexually active women included (n=16).