

10-month retrospective study on compliance and tolerability of the drospirenone-only pill

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Abstract. – OBJECTIVE: The current study evaluated menstrual bleeding profiles, compliance and tolerability in women using a drospirenone (DRSP) only pill.

PATIENTS AND METHODS: This is a non-interventional, retrospective, multi-center study on healthy female adults [n=276, aged between 18 and 53 years and premenopausal using a DRSP-only pill for at least six months with a mean duration of 10.4 months (+/-SD 4.0) months]. 75.6% used other contraceptives than POP before starting with the DRSP-only pill. A questionnaire was used to evaluate the bleeding profile. 56.5% of the women had associated cardiovascular risk factors.

RESULTS: Two hundred and sixty-two (262) women (mean age of 32.5 ± 9.1 years; mean BMI of 23.1 ± 3.8 kg/m²) were eligible for analysis. 42.6% of the users had a scheduled bleeding, 33.3% unscheduled bleeding and 48% no bleeding during the last evaluable cycle. 75.4% evaluated the bleeding profile in the last cycle as very good or good, 13.8% said there was no change since starting the medication, 8.4% declared the profile was bad and 2.3% as very bad. 87.8% of the users evaluated the general satisfaction of the contraception as very good or good, whereas only 8.8% and 3.4% said there was no change or that it was bad. No women evaluated the general satisfaction as very bad.

CONCLUSIONS: These data demonstrate that the DRSP-only pill is associated with a very high satisfaction as a contraceptive in general and in the individual bleeding profile. These aspects reaffirm the acceptability not only in women with cardiovascular risk factors.

Key Words:

Drospirenone-only pill, Compliance, Tolerability.

Introduction

Progestogen-only contraceptives containing levonorgestrel, norethisterone acetate, or desogestrel have

traditionally been associated with strict schedule intake rules and a suboptimal bleeding pattern¹. The intake at a fixed time, particularly for the formulation containing levonorgestrel, with an allowed time variation of 3 hours, and the strict consumption of delayed or forgotten pills requires a high level of discipline by the users. This situation can lead to poor adherence to treatment and, therefore, contraceptive failure¹. Menstrual irregularities, often associated with the treatment, are a frequent reason for discontinuation of the therapy². They involve irregular bleeding, short or long cycles, spotting, prolonged bleeding, or amenorrhea. In general, progestogen-only contraceptives are associated with more bleeding and spotting days than combined oral contraceptives (COC), but this also depends on the amount and type of estrogen used in the respective COC. Above that, also COC is associated with irregular uterine bleeding, especially during the first three months of consumption³.

Desogestrel 0.075 mg as an estrogen-free pill is a safe and effective alternative⁴⁻⁶ with a narrower margin of effectiveness after 12 hours of forgotten intake vs. 24 hours that is found with certain COC and the drospirenone-only pill with 4 mg. Nevertheless, it shows a higher rate of discontinuation due to cycle irregularities compared to COC^{1,7,8}.

Why hormonal contraceptives can cause irregular or unscheduled bleeding is still unexplained. Some data suggest that due to the hormonal exogenous influence superficial endometrial blood vessels can be damaged or that there is a change in the steroidal receptor mechanism leading to bleeding disorders. Other hypotheses associate the bleeding irregularities to the fact of changing angiogenetic factors and hence the local endometrial perfusion^{9,10}.

These bleeding disorders relative to the contraceptive use are one of the most common quoted reasons for discontinuation in up to 25% of users^{11,12}.

In previous studies¹³⁻¹⁵, the efficacy, the bleeding pattern, the drop-out rates of a drospirenone (DRSP) only pill was described. The present study aimed to further assess the improvement in the bleeding profile of a drospirenone-only pill containing 4 mg over 9 Cycles in comparison with desogestrel 0.075 mg.

Increasing satisfaction with contraception is essential to help women feel comfortable with the method and continue its use. The most common reason for stopping a contraceptive method completely due to dissatisfaction is the bleeding profile. Hooper¹⁶ described that the side-effect profile of a contraceptive is another crucial determinant governing selection, as this may negatively influence compliance and persistence with the prescribed regimen¹⁷⁻²⁰.

Our approach to investigating the discontinuation rates due to bleeding is also following the findings by Hooper¹⁶, who could show that women (especially those in the older age groups) are willing to compromise between effects on the menstrual cycle and other contraceptive attributes when selecting the method that is right for them. More than 40% of the survey participants mentioned above indicated that they would consider using a highly effective contraceptive even if it might cause bleeding irregularities. Over 50% documented their wish to accept irregular bleeding if they could have fewer or no periods over time. Nevertheless, the reasons for asking for a switch from one hormonal contraceptive to another indicate that bleeding/spotting issues and other contraceptive-related side effects remain a potential barrier to the continuance of such methods¹⁶.

Hence, the aim of the following study was to record the bleeding profile of women using the drospirenone-only pill in the clinical routine as this represents a step forward in evaluating contraceptive acceptability.

Patients and Methods

Study Design

This is a non-interventional, retrospective, multicenter study conducted between May 2021 and February 2022 in 99 centers in Spain. The study was conducted in accordance with the Declaration of Helsinki, as well as in compliance with local legal and regulatory requirements.

Study Medication

A drospirenone 4 mg 24/4 only pill (Exeltis Healthcare SA, Madrid, Spain) was used for

a minimum of six months. The recommended posology dosage states that 24 active tablets should be taken every day followed by 4 placebos.

Study Population

Adult female patients (n=276) were randomized for the study. After excluding 14 that did not fulfil the including criteria, 262 women that used a DRSP-only pill as a contraceptive, for a minimum of 6 months, were recruited for the study. Women eligible for the trial were aged between ≥ 18 years and premenopausal use DRSP as a contraceptive method for at least six months and gave written signed informed consent. Women with a BMI > 30 kg/m² were not excluded from the study.

Further exclusion criteria were the following:

1. Hypersensitivity or intolerance to the components of DRSP. Lactose intolerance.
2. Previous history of undiagnosed vaginal bleeding.
3. Patients with serious acute or chronic illness (e.g., pancreatitis, liver disease, genital tumors, etc.) that in the medical opinion may interfere with the evaluation.
5. Gynecological pathologies such as endometriosis, myxomatous uterus or polycystic ovarian syndrome.
6. Coagulopathies or hematological diseases.
7. Thromboembolic history.

Study Procedure

Women were asked to participate in the study when using a DRSP-only pill for at least 6 months. If the patient was using the pill for more than six months, all the months of usage were assessed. After written informed consent, women filled in a questionnaire where the parameters regarding the satisfaction, menstrual cycle profile; side effects were documented. Demographic data, medical history, concomitant medications, and possible (severe) adverse events (S)AE, which occurred during the treatment phase were recorded.

Study Objectives

Primary efficacy endpoint

To assess the effect of DRSP on users' acceptability after six months of treatment.

Secondary efficacy endpoint

- 1) Bleeding profile after usage of a DRSP-only pill for at least six months.
- 2) Safety and tolerability.

Ethical Approval

For each of the investigational centers, ethical approval was obtained. The overall approval for the leading ethical committee was given on 12th May 2021 by the: Comité de ética de investigación con medicamentos. Hospital Universitario de La Princesa, Madrid, Spain, the 6 of May of 2021. Number: CEim 09/21. Clinical trial register: DRKS-ID: Date of registration: May 2021. The date the first subject entered was the 14th of July 2021, while the last patient was admitted on the 9th of February 2022.

Statistical Analysis

Statistical analysis of the results was performed with SAS[®] v9.4. Descriptive analyses of all variables were performed. Depending on the character of the variable: categorical variables were summarized by frequencies and percentages. The continuous variables were summarized by the measures of central tendency and dispersion: mean, standard deviation, median, the 25% and 75% percentiles (Q1 and Q3) and extreme values (minimum and maximum). Considering the estimation of the maximum indeterminacy value (50%), with a bilateral confidence interval of

95% and with an accuracy $\pm 6\%$ a sample of 267 patients are required for the trial. For continuous variables, the description of the mean, median, and standard deviation are presented to an additional decimal place, and the minimum and maximum values are presented with the same level of accuracy as the raw data. The number of patients is presented as a natural number. *p*-values are presented to 4 decimal places (or <0.0001 when appropriate). For categorical variables, percentages are presented to decimal places. Statistical tests are performed with significance level $\alpha=0.05$

Results

Baseline Data

Of 276 women that were screened for the study, 262 women were eligible for analysis. Fourteen women were excluded after screening due to different reasons (Figure 1). Women had a median age of 32.5 ± 9.1 years and a mean BMI of 23.1 ± 3.8 kg/m² (Table I). None of the women used non-steroidal antiphlogistic. Previously, women used combined oral contraceptives (34%), vaginal rings (5.7%), transdermal patch (0.8%), progesterone-only pill (5.3%), implants (0.8%), intrauterine device (5%), non-hormonal contraception including condoms (30.1%), or did not use any form of contraception (21.8%).

Table I. Demographical data of the trial patients.

| | | Total women (n = 262) |
|--------------------------|-----------------|--------------------------|
| Age (years) | n | 260 |
| | Mean (SD) | 32.5 (9.1) |
| | Median (Q1, Q3) | 31.0 (25.0, 40.0) |
| | Min, Max | 18, 53 |
| | Missing | 2 |
| Weight (kg) | n | 262 |
| | Mean (SD) | 62.5 (10.8) |
| | Median (Q1, Q3) | 61.0 (56.0, 67.0) |
| | Min, Max | 42, 115 |
| | Missing | 0 |
| Height (cm) | N | 262 |
| | Mean (SD) | 164.6 (6.0) |
| | Median (Q1, Q3) | 164.0 (160.0, 169.0) |
| | Min, Max | 153, 183 |
| | Missing | 0 |
| BMI (Kg/m ²) | n | 262 |
| | Mean (SD) | 23.1 (3.8) |
| | Median (Q1, Q3) | 22.4 (20.7, 24.7) |
| | Min, Max | 17, 44 |
| | Missing | 0 |

N-acetylcysteine (NAC), *Klebsiella pneumoniae* (Kp), *CR Acinetobacter baumannii* (CR-Ab), sub-minimum inhibitory concentrations (sub-MICs).

Bleeding Parameters

During the median time of 10.4 months of DRSP-only pill usage, only 102 patients (38.9%) consulted the health care provider due to the occurrence of unscheduled bleeding episodes whereas the remaining 160 patients (61.1%) did not ask the prescriber due to any unscheduled bleeding. Regarding amenorrhea only 48% (48 patients) asked the prescriber whereas the remaining 81.5% (212 patients) did not require any medical advice and did not consult the health care provider.

Regarding all possible bleeding issues only 38.9% of the 262 patients asked during the 10,4 months the prescribers.

In a subgroup of 167 patients an evaluation of the bleeding profile during the last evaluable cycle was performed. 24% (40 patients) of the users of this subgroup described to have a scheduled bleeding, 14.4% (24 patients) an unscheduled bleeding, 18.6% (31 patients) both bleeding sorts and 43.1% (72 patients) described to have a no bleeding during the last evaluable cycle.

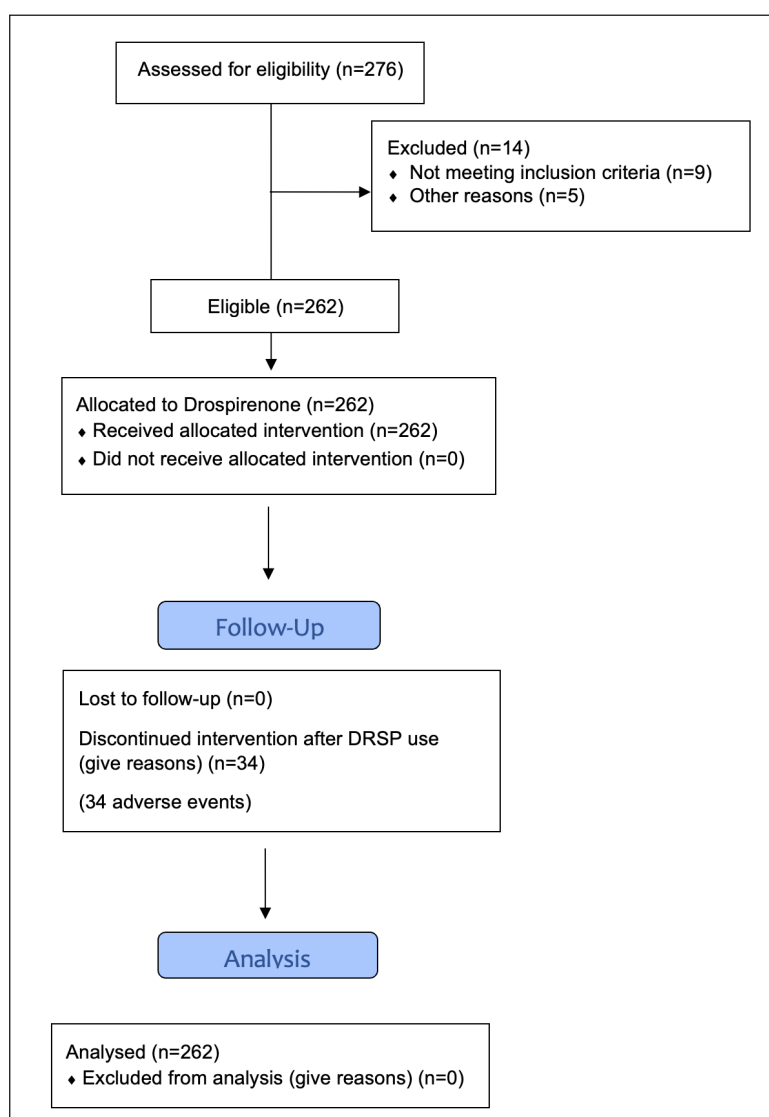


Figure 1. Consort diagram.

Acceptability

The acceptability of the bleeding profile was evaluated during the whole study between the first and the last evaluable cycle. From the user's point of view 75.4% evaluated the bleeding profile in the last cycle as very good or good, 13.8% said there was no change since starting the medication, 8.4% declared the profile was bad and only 2.3% as very bad. The total positive bleeding satisfaction rate hence was 89.2 % of the 262 patients.

General Contraceptive Satisfaction

87.8% of the users evaluated the general satisfaction of the contraception with the DRSP-only pill as very good or good, whereas only 8.8% and

3.4% told there was no change or that it was bad. No women evaluated the general satisfaction as very bad.

Adverse Events

No serious adverse event was recorded. A total of 164 women experienced non serious adverse events including bleeding disorders. The most common adverse events were amenorrhea and unscheduled bleeding/spotting. Table II depicts the dropout rates due to adverse events. In total only 13.8% of the women discontinued after the use of the investigated drug. In total the main reason were bleeding disorders. This was in 24 of the 35 cases making a total of 9.4% of all the patients.

Table II. Adverse events and dropout rates of the trial patients.

| | N women (%) | N cases | Dropout after study (cases) |
|-------------------------------|-------------|---------|-----------------------------|
| Total (n=262) | 164 (62.6%) | 254 | 35 (13.3%) |
| Amenorrhea | 91 (34.7%) | 94 | 3 (1.1%) |
| Unscheduled bleeding/spotting | 82 (31.3%) | 115 | 21 (8%) |
| Weight gain | 17 (6.5%) | 17 | 4 (1.5%) |
| Headache | 10 (3.8%) | 10 | 3 (1.15%) |
| Weight loss | 4 (1.5%) | 4 | |
| Mood changes | 3 (1.1%) | 3 | 1 (0.4%) |
| Libido loss | 3 (1.1%) | 3 | 2 (0.8%) |
| Acne | 2 (0.8%) | 2 | |
| Weight change | 1 (0.4%) | 1 | |
| Varicose | 1 (0.4%) | 1 | |
| Mastalgia | 1 (0.4%) | 1 | |
| Nausea | 1 (0.4%) | 1 | |
| Vaginal dryness | 1 (0.4%) | 1 | 1 (0.4%) |
| Mastodynia | 1 (0.4%) | 1 | |

Missing data: 8

Discussion

The basis of effective contraception involves factors like the possibility of getting access to these methods, the adverse event profile, the mode of use, and the ease in this use^{21,22}. Careful patient counselling is, therefore, vital components in improving compliance.

Increasing satisfaction with contraception is essential to help women feel comfortable with the method and continue its use. The most common reason for stopping a contraceptive method completely due to dissatisfaction is the bleeding profile. As described by Hooper¹⁶, the side-effect profile of a contraceptive is another important determinant governing selection, as this may negatively influence compliance and persistence with the prescribed regimen¹⁸⁻²².

Hence in this study it could be shown that a very high number of women were highly satisfied with their bleeding profile and the contraception in general under the use of a drospirenone-only pill.

These data reaffirm previous published data on the bleeding profile of drospirenone in comparison to the other established pop desogestrel¹³.

Also noteworthy is the fact that no serious adverse event was observed, even if the collective of patients had a mean age of 32.5 years, 16% were overweight, and 5.3% obese showing the high safety of POP under risk patients. Again, the previous data showing no single venous thromboembolic (=VTE) case in clinical trials²³ with DRSP were reinforced in this study.

When analyzing the discontinuation rates, a clear positive trend towards the DRSP-only pill can be found. Only 9.4% of the women discontinued due to

bleeding disorders showing the high acceptability in real life after the use of more than 10 months. The limitations of this clinical trial can be seen in the possible bias occurred by the selection of patients.

Another limitation is that the bleeding profile if the last cycle was not recorded in all the study population.

Conclusions

These data demonstrate that the DRSP-only pill is associated with a very high satisfaction as a contraceptive in general and in the individual bleeding profile. These aspects reaffirm the acceptability not only in women with cardiovascular risk factors.

Conflict of Interest

Maria Victoria de Diego, E. Colli and PA Regidor are employees of Exeltis Healthcare. Santiago Palacios declares no conflict of interest.

Funding

Insud Pharma funded the study. Trial code: SLI-01-21.

Ethics Approval

We performed the study in accordance with Good Clinical Practice (GCP), local requirements and the Declaration of Helsinki. For each of the investigational centers, ethical approval was obtained. The overall approval for the leading Ethical Committee was given on 12th May 2021 by the Comité de ética de investigación con medicamentos, and by the Hospital Universitario de La Princesa, Madrid, Spain, on the 6th of May of 2021. Number: CEim 09/21.

Clinical Trial Register

Clinical trial register: DRKS-ID: DRKS00014982. Date of registration: May 2021. The date the first subject entered was the 14th of July 2021. Last patient: 9th February 2022.

Informed Consent

A written informed consent was obtained from all participants that were enrolled in the clinical trial.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Authors' Contributions

Santiago Palacios: Responsible for the clinical data. Enrico Colli: Responsible for the scientific design. Maria Victoria de Diego: Responsible for data collection and data evaluation. Pedro Antonio Regidor: Responsible for the study design and writing.

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