Improvement of dysmenorrhea, menstrual bleeding and continuation rate in women using the new vaginal ring Ornibel®

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ABSTRACT

Objective: The current study evaluated menstrual bleeding profiles, dysmenorrhea, vaginal infections, quality of life parameters, and factors associated with continuation of the use of the contraceptive vaginal ring Ornibel®.

Methods: The authors conducted a non-interventional, retrospective, multi-center study of healthy female adults (n=103, aged between 18 and 45 years) using Ornibel® for at least six months. A questionnaire was used to collect data. Changes in menstrual bleeding profiles and dysmenorrhea were assessed using visual analog scales (VAS), and a chi-square linear trend test was used to evaluate the association between the vaginal ring and continuation of vaginal ring use.

Result(s): One hundred women (mean age of 28.64 ± 7.49 years; mean BMI of 23.18 ± 3.37 kg/m²) were eligible for analysis. Menstrual flow and dysmenorrhea reduced significantly during the treatment (from 50 VAS points to 34 VAS points and from 42.5 VAS points to 20 VAS points respectively; p<0.001 for both parameters). The percentage of women with intermenstrual bleeding decreased from 21% to 12% (p<0.022). Seven women experienced vaginal infections.

Most women strongly agreed or agreed that Ornibel® was easy to insert (91%). They rated the ring very comfortable or comfortable to use (97%). Continued usage of the ring was associated with these two parameters (easy to insert: p=0.017; feeling comfortable: p=0.001). Fifty percent of partners did not notice the ring during sexual intercourse, 38% occasionally, and only 6% of partners felt the ring frequently or always. Eight women experienced a ring loss during the six months of the study.

Conclusions: These data demonstrate that Ornibel® improves the menstrual cycle profile and that comfort and easy usage are significant parameters determining continued use of the vaginal ring. Clinical trial register: DRKS-ID: DRKS00014982.

KEYWORDS

Vaginal contraceptive ring, bleeding intensity, dysmenorrhea.

Background

Combined oral contraceptives (COCs) have become increasingly popular due to their low Pearl Index (PI) and low rate of side effects [1]. However, COCs have negative aspects, mainly linked to the oral administration route and the estrogenic side effects. COC use can lead to symptoms like nausea, breast tenderness, weight increase, or thromboembolic events [2]. Moreover, orally administered contraception is influenced by disorders of the gastrointestinal tract and subjected to first-pass liver metabolism. Therefore, interactions with other medicines become more frequent. As a consequence, the efficacy of COCs might be reduced [3,4]. Another disadvantage of COCs is the daily intake frequency, which increases the risk of missed pills [5,6].

Vaginal ring delivery systems are the answer to many of these drawbacks. The first available vaginal ring, called NuvaRing®, is a combined hormonal ring containing 11.7 mg etonogestrel and 2.7 mg ethinylestradiol (EE) and it was approved by the FDA in 2001 [7,8].

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The ring releases continuously, with a pharmacokinetic zero-order release and without first-pass effect. on average 0.120 mg of etonogestrel and 0.015 mg of EE daily over a three-week period of use to inhibit ovulation [4,9]. Its PI is under 1 (0.6) [3,7,8,10,11]. NuvaRing® consists of two polymers: Evatane® 28% in the core and Evatane® 9% in the membrane; this ring is a so-called reservoir ring system [12].

Ornibel® (developed by Laborarios LeonFarma, SA, Chemo Group, Spain) is a new combined contraceptive vaginal ring that has the same size and a similar external appearance to NuvaRing®. Nevertheless, Ornibel® is composed of a core of

polyurethane and an outer membrane of ethylene vinylacetate, containing 28% vinylacetate. This different polymer composition allows the active ingredients in Ornibel® to be present in a concentration below the saturation limit, unlike the reference product. An additional advantage is that no specific storage temperature is required. Ornibel® contains the same active pharmaceutical ingredients as NuvaRing® but at different nominal doses: 11.00 mg etonogestrel and 3.47 mg EE. Despite this difference in the nominal doss, the average hormonal release from both rings is the same [13].

The aim of this non-interventional retrospective study was to obtain clinical data on this new vaginal ring. Analyses were performed to evaluate menstrual cycle profile, tolerability, quality of life, infection rate, and adherence to the treatment even in cases with side effects from this new vaginal ring.

Methods

Study design

This was a non-interventional, retrospective, multi-center study conducted between October 2018 and May 2019 in 13 centers in Germany. The study was conducted in accordance with the Declaration of Helsinki as well as in compliance with local legal and regulatory requirements.

Study medication

Ornibel® (etonogestrel/ethinylestradiol 11.00/3.47 mg, Exeltis Healthcare SA, Spain) was used for over six months. According to the recommended mode of use,once the ring is inserted, it should be left in the vagina continuously for three weeks. The ring must be removed after three weeks of use on the same day of the week as it was inserted, and after a ring-free interval of one week, a new ring is to be inserted.

Study population

Adult female patients (n=103) who had been using Ornibel® as a contraceptive for a minimum of 6 months were recruited for the study. Women were eligible for the study if they were aged between ≥18 and ≤45 years, had been using Ornibel® as a contraceptive method for at least six months, and gave written, signed informed consent. Women with a BMI > 30 kg/m² were excluded from the study. Further exclusion criteria were women using intrauterine devices or intrauterine systems and breastfeeding women.

Study procedure

Women were asked to participate in the study after at least 6 months' use of Ornibel®. If the patient had been using Ornibel® for more than six months, the first six months of usage were assessed.

After written informed consent, the women filled in a questionnaire where parameters regarding quality of life, menstrual cycle profile, and vaginal infections were documented. Demographic data, medical history, concomitant medications, and any (severe) adverse events that occurred during the treatment phase with Ornibel® were recorded.

Study objectives

Primary efficacy endpoints

Menstrual bleeding profiles and tolerability in women following usage of Ornibel® over an observation period of 6 months.

Secondary efficacy endpoints

1) Quality of life after at least six months' usage of Ornibel®.
2) Rate of vaginal infections diagnosed by a health care professional.

Statistical methods

Quantitative and semi-quantitative measurements were tested for normal distribution using the Kolmogorov-Smirnov test. VAS assessment of menstrual flow and cramping pain showed significant deviations from a normal distribution. Comparisons of treatment times were consequently made using non-parametric Wilcoxon matched-pairs test.

Ordinally and nominally scaled values were expressed as absolute and percent frequencies. Two of each of these values were compared in contingency tables and tested for association using the chi-square test or in the case of ordinally scaled variables using the chi-squared linear trend test. If the expected frequencies turned out to be too small, exact tests (according to Fisher or accurate linear trend test) were used. Comparisons of treatment times were performed using the McNemar test.

All tests were two-sided with a significance level of 5%. Statistical analyses were performed using SPSS Statistics 25 (SPSS Inc., an IBM Company, Chicago, IL).

Ethical approval

For each of the investigational centers, ethical approval was obtained. The overall approval from the leading ethics committee was given on 23.07.2018 by the Ethikkommission der Ärztekammer Nordrhein, Germany, with the number 2018180. Clinical trial register: DRKS-ID: DRKS00014982. Date of registration: 06.08.2018. The date the first subject entered was 04.10.2018. End of study: 09.05.2019.

Results

Baseline data

Of 103 women who were screened for the study, 100 women were eligible for analysis. One woman was excluded from the study due to BMI, and two women did not hand in the completed patient questionnaire (Figure 1). The women had a median age of 27 years and a mean BMI of 23.18 kg/m² (Table 1). None of the women used non-steroidal antiphlogistics. Previously, the women had used oral contraceptives (37%), progesterone-only pill (2%), intrauterine device (3%), non-hormonal contraception (6%), or had not used any form of contraception (52%).

Cycle control

During the first six months of Ornibel® usage, 73 of the 100 women experienced six menstrual bleeds with a median bleed duration of 4 days. Menstrual flow and dysmenorrhea significantly reduced after the six months of ring use. The median

Figure 1 Consort diagram of the study.

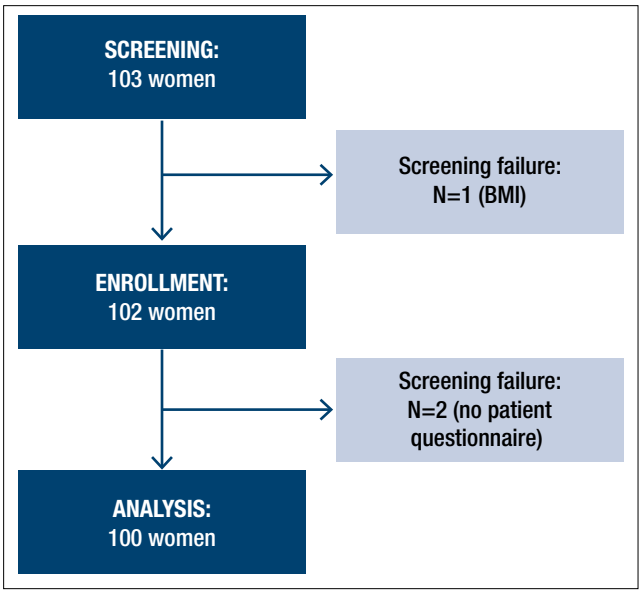

Table 1 Baseline characteristics of the women included in the study.

Item	Mean ± SD
Age [years]	28.64 ± 7.49
Height [cm]	167.70 ± 6.89
Weight [kg]	65.31 ± 11.44
BMI [kg/m²]	23.18 ± 3.37
Heart rate	73.53 ± 6.40
Blood pressure [mmHg]	
Systolic	118.84 ± 10.84
Diastolic	74.83 ± 8.69

VAS score for the menstrual flow was 50 before the treatment and 34 after treatment ($p < 0.001$) (see Figure 2a). Regarding the development of dysmenorrhea, statistically significant improvements were also observed. The median VAS score was 42.5 before and 20 after the six months ($p<0.001$) (see Figure 2b). Both parameters improved, especially during the first three months of usage. The percentage of the sample without spotting or unscheduled bleeding increased from 79% to 88% after the six months use of Ornibel®. In contrast, the percentage who did present spotting and/or unscheduled bleeding fell from 21% to 12% ($p<0.022$) (Table 2). Seven women experienced mild or moderate vaginal infection.

Quality of life

A high rate of women strongly agreed or agreed that Ornibel® was easy to insert (91%). They rated the ring as very comfortable or comfortable (97%). Continuation of the usage of the ring and willingness to recommend the ring were significantly associated with these two parameters even for those women belonging to the group that did not agree on the easiness of ring insertion or comfortability of its use (continuation rate: easy to insert: p=0.017; feeling comfortable: p=0.001; recommendation: easy to insert: p=0.004; feeling comfortable: p=0.005).

Daily activities were never affected by the ring in 85% of women. Only 15% of women mentioned that their daily activities were occasionally affected, and none of the women rated the interference of the daily activities with frequently or always. There was a significant association between "ring never or occasionally affected my daily activities" and "continuation of usage" (p=0.027) as well as "recommendation of the ring" (p=0.023).

Fifty percent of the partners did not notice the ring during sexual intercourse, 38% occasionally, and only 6% of the partners felt the ring frequently or always. Eight women experienced a ring loss, a number that could be expected according to the summary of product characteristics. No association was found for the parameters "ring was noticed by my partner during sexual intercourse" (continuation of usage: p=0.074, recommendation of the ring: p=0.108) and "ring lost during usage" (continuation of usage: p=0.077, recommendation of the ring: p=0.611).

Most women learned about the ring from their physician (81%), will continue to use the ring (91%), and will recommend the ring (95%) to other women.

Figure 2 A: Median VAS score values for menstrual bleeding before (blue) and after (grey) the 6-month treatment with Ornibel. 75th, 50th, and 25th percentile. Median reduction of 16 points ($p < 0.001$). B: Median VAS score values for dysmenorrhea before (blue) and after (grey) the 6-month treatment with Ornibel. 75th, 50th, and 25th percentile. Median reduction of 22.5 points ($p < 0.001$).

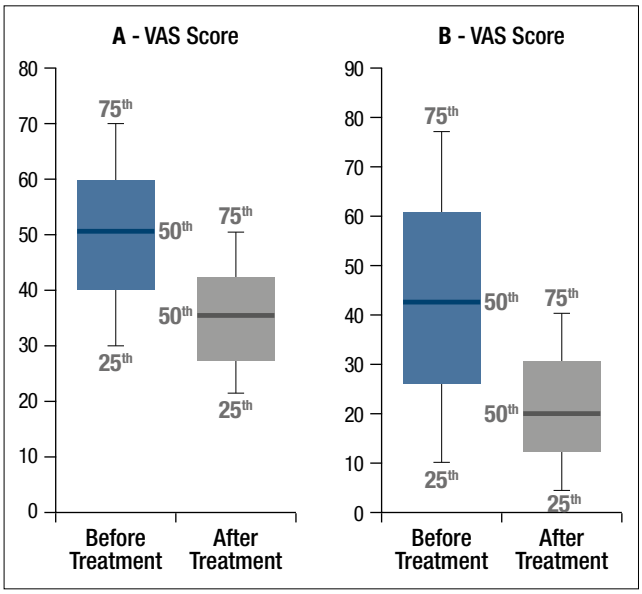

Table 2 Unscheduled bleeds or spotting before and during the 6-month treatment with Ornibel ($p < 0.022$).

			Bleed between periods during treatment		
			no	yes	total
Bleeds between periods before treatment	no	Count	77	2	79
		% of Total	77.0%	2.0%	79.0%
	yes	Count	11	10	21
		% of Total	11.0%	10.0%	21.0%
Total		Count	88	12	100
		% of Total	88.0%	12.0%	100.0%

Table 3 Discontinuation rates (% of study group): comparison between NuvaRing® and Ornibel®.

	Dieben et al. 2002 NuvaRing®	Oddison et al. 2005 NuvaRing®	Ahrend et al. 2006 NuvaRing®	Evol Study Ornibel®
Discontinuation due to adverse events	14.1	11.3	12.3	9
Discontinuation due to device-related events	2.5	2.1	3	1
Discontinuation due to headache	1.3	0.8	1	0
Ring-related vaginitis	4.4	4.7	6.8	1
Nausea	3.2	2.7	0.8	0
Headache	5.8	7.2	6.8	0

Discussion

The basis of effective contraception involves factors like ease of access to the given method, its adverse event profile, mode of use, and ease of use [4, 14]. Careful patient counseling is, therefore, a vital component in improving compliance. On the one hand, vaginal rings avoid the problem of reduced efficacy due to missed pill intake [5, 6]. On the other hand, the vaginal route still impedes full acceptance [4]. The existing vaginal ring, NuvaRing, is associated with continuation rates of between 85.9% and 88.7% after one year of use. The new ring showed a similar or even better continuation rate, i.e. 91%, after six months of use. These data are identical or even superior to the rates obtained for oral contraceptive systems [2, 7, 8, 11, 15] (Table 3).

The rate of breakthrough bleeding is lower that what is observed with different oral combined formulations. A prospective study has shown that 97% of 2642 women reported regular cycles with the ring. Irregular bleeding was only rarely observed: 12% at baseline level and 7% at the final examination [16, 17]. Also, the planned withdrawal bleeds were observed in up to 98.5% of the users and irregular bleeding/spotting rates did not exceed 5.5% of the investigated cycles [7]. In a 1-year survey of 2322 woman with 23,298 cycles, 85% of the users reported being satisfied with the ring [7]. In another investigation of 1950 women, 85% of these women and 71% of the sexual partners never or rarely felt the ring during vaginal sexual intercourse, and 94% of the partners never or rarely minded that the woman was using a vaginal ring [8]. In the case of Ornibel, only 6% of the sexual partners noticed the ring frequently during sexual intercourse. At the same time, 98% of the women documented that the ring was easy to insert, and this was also the case in 90% of early discontinuers. With Ornibel, similar data were achieved [7, 8].

Data have also shown that ring users do not have an increased risk of vaginal infections due to the use of such a device [18, 19]. The users of the new ring had, in accordance with the older data, an even lower infection rate. These data support, therefore, the *in vitro* data on microbiological adherence to the new ring. The *in vitro* low adhesion of candida was reflected in this *in vivo* study [20].

When analyzing the discontinuation rates, a clear difference toward Ornibel® can be found. Only 9% of the women using Ornibel® discontinued, as compared with up to 14% with NuvaRing®. This could be due to the new polymers used in Ornibel® (Table 3).

Conclusion

The new generation of vaginal contraceptive rings shows not only high efficacy but also high satisfaction and user comfort for the patients. Even adverse events, occurring in a small number of cases, were not a reason for discontinuation of the use of this contraceptive method.

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Consent for publication: *All authors have consented for publication.*

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Competing interests: *Pedro-Antonio Regidor, Manuela Sailer, Enrique Calvo, and Enrico Colli are employees of Exeltis Healthcare. Santiago Palacios and Thomas Römer declare no conflict of interest.*

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Authors' contributions: *Pedro-Antonio Regidor and Manuela Sailer were responsible for the practical realization of the study. Enrique Calvo and Enrico Colli were responsible for the study design. Santiago Palacios was accountable for the coordination of the centers and scientific support.Thomas Römer was responsible as principal investigator of the study.*

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