Multicenter, international observational study on quality of life and acceptability of a vaginal contraceptive ring containing etonogestrel/ethinylestradiol 11.00/3.474 mg over six months of use

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Abstract. – OBJECTIVE: The current post-market study aimed at analyzing women’s menstrual bleeding intensity, vaginal infections, and quality of life parameters using the contraceptive vaginal ring Ornibel®.

PATIENTS AND METHODS: In Germany and Spain, a multicenter study of healthy female adults (n=211) aged 18 to 45 used the vaginal ring Ornibel® for at least six months. Data collection was conducted using a patient questionnaire. The menstrual bleeding intensity was analyzed using visual analog scales (VAS). A Chi-square linear trend test assessed associations between quality-of-life parameters and continuation and recommendation of vaginal ring use.

RESULTS: Three out of four women experienced six menstrual bleedings during the first six months of using the vaginal ring, with a median duration of four days during the study. The use of the vaginal ring led to a significant reduction in menstrual flow intensity (from 60 VAS points to 40 VAS points, \( p<0.001 \)). In the German cohort, it was shown that dysmenorrhea and unscheduled bleeding and spotting were reduced with the use of Ornibel® as well.

Most women (93.7%) agreed or strongly agreed that the vaginal ring was easy to insert, and its use was rated as comfortable or very comfortable by 97.5%. Both parameters were significantly associated with the continuation of the ring (easy to insert \( p=0.01 \), feeling comfortable: \( p=0.002 \)) or its recommendation (easy to insert \( p=0.002 \), feeling comfortable: \( p=0.002 \)).

CONCLUSIONS: The observational data demonstrate that the contraceptive vaginal ring provides high acceptability and comfort. It is a well-accepted contraceptive method characterized by high efficacy and positive effects on cycle control.

Key Words: Vaginal contraceptive ring, Bleeding intensity, Acceptance.

Introduction

Because the vaginal epithelium can absorb steroid hormones and the capacity of elastomers to release hormones, vaginal rings have been developed since the 1960s. Since then, the development of vaginal rings has become a success story as more and more women appreciate the use of vaginal rings for contraception. Besides vaginal rings being easy to use, user-controlled, and providing effective contraception, they have several advantages compared to oral contraceptives: the release of the hormones is nearly constant, allowing for lower dosages that may reduce potential side effects. In addition, the bioavailability is enhanced due to the vaginal route, and cycle control is improved. Further, the vaginal way avoids potential adverse effects of gastrointestinal disorders and lowers possible interactions with other medications as there is no hepatic first-pass effect.

Three different types of contraceptive vaginal rings are currently on the market: a progesterone ring for breastfeeding women, a combined ring containing progesterone acetate and ethinylestradiol, and the vaginal ring combining ethinylestradiol (EE) and etonogestrel (ETO). The latter is the most used contraceptive vaginal ring. It is characterized by a high contraceptive efficacy, reason-
able cycle control, a safety profile, and increased user acceptability\(^7,8\). The ETO/EE combined ring is a transparent, ring-shaped device containing 11.7 mg ETO and 2.7 mg EE while releasing, on average, 120 mg ETO and 0.015 mg EE within 24 h when inserted into the vagina. The ring called NuvaRing\(^*\) was first marketed in 2001\(^7\), while in 2017, a second ETO/EE containing contraceptive vaginal ring, called Ornibel\(^*\), was approved. Although Ornibel\(^*\) received its approval as a generic drug and both ETO/EE rings have a similar external appearance, they differ slightly in their polymer composition and the amount of active ingredients. The nominal dose is 11.0 mg ETO and 3.47 mg EE for Ornibel\(^*\). Nevertheless, bioequivalence to NuvaRing\(^*\) has been demonstrated\(^9\).

Women's acceptability and satisfaction with a contraceptive method are critical for good compliance and essential for continuation with the contraceptive method. Therefore, it also determines the effectiveness of a contraceptive method. In a recently conducted systematic review\(^10\), the acceptability and satisfaction of contraceptive vaginal rings in clinical studies have been evaluated. A common finding was that ring handling was high, including the insertion, removal, and reinsertion. NuvaRing is the most studied vaginal ring. Data\(^11\) indicate high satisfaction with its use which is also mirrored by the continuation of its use.

For the vaginal ring, Ornibel\(^*\)’s first post-market data were obtained in a German study. Data indicated that the vaginal contraceptive ring Ornibel\(^*\) is a well-accepted method providing high efficacy, high satisfaction, and user comfort for the patients\(^12\). The current work aims at extending the existing data on Ornibel\(^*\) with a new data set obtained in a further retrospective study.

**Patients and Methods**

**Study Design**

This is a pooled analysis of two post-authorization, observational, retrospective, multi-center studies conducted in Germany between October 2018 and May 2019 in 13 centers and Spain in 18 centers between October 2019 and January 2020.

For the study, 211 women who had been using the contraceptive vaginal ring Ornibel\(^*\) for a minimum of 6 months were recruited. The eligibility criteria for inclusion were: age ≥ 18 and ≤ 45 years, use of Ornibel\(^*\) for at least six months as a contraceptive method and signed informed consent. The main exclusion criteria were: BMI > 30 kg/m\(^2\), migraine, history of cardiovascular events or advanced hypertension or diabetes, undiagnosed vaginal bleeding, or chronic or acute diseases like pancreatitis or hepatitis (Figure 1).

Participants gave their written informed consent. Afterward, women were asked to complete a questionnaire to document parameters regarding their quality of life, menstrual cycle profile, and vaginal infections. The assessment period was defined as the first six months of Ornibel\(^*\) use. If women had been using the vaginal ring for more than six months, they were also asked to document their experience during the first six months of use. Additionally, demographic data, medical history, concomitant medications, and any (severe) adverse events that occurred during the use of the vaginal ring were documented. Some data were only reported by the German study cohort, including data on the use of non-steroidal anti-inflammatory drugs and data on unscheduled bleedings and spotting, and dysmenorrhea.

The pooled analysis of this study aimed at elucidating the menstrual bleeding profiles, the quality of life, safety, and tolerability of women using the vaginal ring over an observation period of six months.

**Study Medication**

The vaginal ring Ornibel\(^*\) (Exeltis Healthcare SA, Spain) is a combined contraceptive containing etonogestrel (11.00 mg) and ethinylestradiol (3.47 mg). It is recommended that Ornibel\(^*\) should be left in the vagina continuously for three weeks once the ring is inserted. After three weeks, the ring must be removed. After a ring-free interval of 7 days, a new vaginal ring is inserted.

**Statistical Analysis**

As described previously\(^12\), statistical analysis was performed as follows. In brief, a test for normal distribution was achieved for all quantitative and semi-quantitative data using the Kolmogorov-Smirnov test. The visual analog scale (VAS) assessment (menstrual flow and cramping pain) did not show a normal distribution. Consequently, the Wilcoxon matched-pairs test was applied.

Ordinarily and nominally scaled values were expressed as frequencies (absolute and percent) and compared in contingency tables. Association tests depended on the scaling of the data performed using the Chi-square test or the Chi-squared linear trend test. In case of the expected frequencies turned out to be too small, exact tests like Fisher or accurate linear trend tests were used. The McNemar test was used to compare treatment times.
All tests were two-sided with a significance level of 5%. Statistical analyses were performed using SPSS Statistics 25 (SPSS Inc., IBM Corp., Armonk, NY, USA). $p < 0.05$ was defined as significant.

**Ethical Approval**

Both studies were conducted following the Declaration of Helsinki and in compliance with local and regulatory requirements. For the German study, the overall ethical approval was given on 23.07.2018 by the Ethikkommission der Ärztekammer Nordrhein, Germany, number 2018180 (Clinical trial register: DRKS-ID: DRKS00014982. Date of registration: 06.08.2018). In addition, the ethical approval of each local study center was obtained. The Spanish study received its ethical approval on 25.09.2019 and registered at the EC CElm Hospital Clinico San Carlos. The current works represent a pooled analysis of both data sets.

**Results**

**Baseline Data**

211 women were screened for the study. Four were excluded due to BMI, age + migraine, migraine, or vaginal bleeding. Two women did not fill out the patient questionnaire. 205 women were eligible for analysis. They had a mean age of 29.41 ± 7.33 years and a mean BMI of 22.84 ± 2.99 kg/m², women’s heart rate and blood pressure were within the normal range. Table I shows the baseline data of the women included in the study. In the German study cohort (n=100), none of the women used non-steroidal antiphlogistics. Previously, most women had used oral contraceptives (37%), followed by non-hormonal contraception (17%). Few women had used a progesterone-only pill (2%) or an intrauterine device (2%) before.

**Cycle Control**

Three of four women experienced six menstrual bleedings during the first six months of using the vaginal ring. The median bleeding duration was four days. About 60% of women experienced a bleeding duration of 4 days (35%) or 5 days (25%).

While 71.43% of women’s use of the vaginal ring decreased menstrual flow, about 20.69% of patients reported no change and 7.88% a worsening in the flow intensity. Overall, the use of the vaginal ring significantly reduced menstrual flow intensity. At baseline, a median VAS score of 60 was documented, while after the use of the ring, the median VAS score was reduced to 40 ($p<0.001$) (Figure 2). The change in flow intensity
occurred in over 90% of the cases within the first three months of ring use.

The German cohort only assessed data on spotting and unscheduled bleedings and dysmenorrhea. As reported previously\cite{12}, dysmenorrhea improved significantly with using the vaginal ring (median VAS score at baseline: 42.5; median VAS score after six months: 20), particularly within the first three months of use. In addition, there was a significant reduction in the number of women who experience unscheduled bleeding and spotting from 21% to 12%.

**Vaginal Infections**

Ten reports of vaginal infections occurred during the first six months of use. Seven were rated as light, while three were moderate.

**Quality of Life**

The 89% of the women indicated that they planned to continue the ring. The primary reason for discontinuing the use of the vaginal ring was gestational desire. Nearly all women (97.5%) plan to recommend its further use.

Most women strongly agreed (49.3%) or agreed (44.4%) that the ring was easy to insert, while about 98% of the women rated the use of the vaginal ring as comfortable (38.5%) or very comfortable (59%). Both parameters were significantly associated with the continuation of the vaginal ring (easy to insert $p=0.01$, feeling comfortable: $p=0.002$) or its recommendation (easy to insert $p=0.002$, feeling comfortable: $p=0.002$). Table II shows the rating of quality-of-life parameters.

Nine out of 10 women indicated that ring use never affected daily activities, while ring use occasionally affected daily activity in 10% of the women. None of the women rated interference with daily activities as “frequently” or “always”. For the parameter “ring use never or occasionally affected my daily activities”, there was a significant association between the continuation of the ring ($p=0.003$) and its recommendation ($p=0.005$) (Table II).

While more than half of the partners never noticed the ring during sexual intercourse (51.7%), about 36.6%, 4.9%, and 6.8% noticed the ring occasionally, frequently, or permanently. While there is a significantly higher likelihood that the use of the vaginal ring will be continued by women whose partner never or sometimes noticed the ring during sexual intercourse compared to users that stated the vaginal ring was frequently or constantly noticed by the partner ($p=0.035$), there was no association found between the parameter “my partner noticed ring during sexual intercourse” and the recommendation of the ring ($p=0.10$) (Table II).

Figure 2.

![Box-whisker-plots displaying the visual analogue scale (VAS) score for menstrual flow intensity before ring use (left boxplot) and after 6 months of ring use (right boxplot). Median reduction of 20 ($p<0.001$).](Image)

Table I. Baseline data of the women included in the study.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Mean ± SD</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>205</td>
<td>29.41 ± 7.326</td>
<td>18</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>204</td>
<td>166.21 ± 6.442</td>
<td>147</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>204</td>
<td>63.179 ± 9.914</td>
<td>48</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>204</td>
<td>22.841 ± 2.999</td>
<td>17.99</td>
</tr>
<tr>
<td>Heart rate</td>
<td>135</td>
<td>75.33 ± 8.057</td>
<td>50</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>152</td>
<td>117.25 ± 11.374</td>
<td>90</td>
</tr>
<tr>
<td>Systolic</td>
<td>152</td>
<td>73.67 ± 8.945</td>
<td>50</td>
</tr>
<tr>
<td>Diastolic</td>
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</tbody>
</table>
Most women learned about the contraceptive vaginal ring from their physician (84.4%), followed by friends (12.7%), media (2%), family (0.5%), and others (0.5%) (Table II).

**Discussion**

**Findings and Interpretation**

Globally, there is still an unmet need for contraceptive methods among women of reproductive age. Of about 1.1 billion women needing family planning, only about 842 million are using contraceptive methods, while 270 million cannot use modern methods. It is estimated that about 44% of worldwide pregnancies between 2010 and 2014 were unintended. The development and availability of new contraceptive methods are critical to targeting these unmet needs. An increased choice of contraceptive options has improved sexual and reproductive health outcomes.

With the development of contraceptive vaginal rings, women have the choice of a self-controlled method with a low pearl index (0.65) and improved compliance when compared to oral contraceptives, as missed pill intake is avoided. Mode of use and ease of management contribute to the effectiveness of a contraceptive method. Noteworthy, about 94% and almost 98% of women agreed or strongly agreed that Ornibel® was easy to insert or rated the ring as comfortable or very comfortable to use. These high numbers match close with data from the recent literature. Studies investigating NuvaRing generally reported a high satisfaction of 80 and 90%.

A randomized trial showed that cycle control was superior with the combined contraceptive ring containing EE/ETO vs. an oral ethinylestradiol and levonorgestrel combination. Similar findings were also reported for women with heavy menstrual bleeding. Combined hormonal vaginal rings displayed better cycle control, and women had improved compliance compared to oral contraceptives. Duration of bleeding was reduced for the combined ring in 70% of women, consistent with the data on bleeding intensity reported here.
Both Ornibel® and NuvaRing® reduced the incidence of intermenstrual bleeding12,20.

The current study reported the ring’s expulsion by 15% of the women. This number of ring losses is slightly higher than the number that could be expected according to the summary of product characteristics. However, expulsions of vaginal rings are more frequently reported in observational studies than in randomized control trials21 and might also explain the current findings.

Vaginal rings do not increase the risk for vaginal infections22,23 and are supported by the current data. The users of Ornibel® showed even a lower infection rate12. Vaginal symptoms are commonly less reported in observational or pharmacokinetic studies than in randomized control trials; however, the findings of lower infection rates with Ornibel® also support in vitro data on microbial adherence to the ring24.

Strengths and Limitations of the Study

The strength of this clinical evaluation is that a multicenter international recording of clinical features when using the vaginal ring Ornibel® was described. The advantage of the polymer development did not result in any significant clinical disadvantage. Moreover, the overall clinical improvement in the bleeding and quality of life can be considered a step forward for patients’ satisfaction and adherence to the product with consecutive improvements in contraceptive efficacy.

The study’s weakness is that this was, due to regulatory considerations, a retrospective study with a possible bias in patient selection.

The study supports the findings of the first clinical reports.

The data presented here support Müller et al25 study, which described Ornibel® like having very low incidences of SAE, including VTEs and unintended pregnancies, during three years of “real-life experience”. This constitutes a valuable advancement in the field of hormonal contraception.

Open Questions and Future Research

Its beneficial safety aspects may also be important concerning recent challenges imposed by SARS-CoV-2 pandemic. Soon, this vaginal ring technology applying different polymers with aliphatic polyurethane in the core and 28% ethylene vinyl acetate in the membrane will also be used to deliver other hormones or drugs. In this segment, levonorgestrel or progesterone will add new contraceptive perspectives or may be used for contraception or the luteal phase support.

In the future, it can be thought that vaginal contraceptive rings may play a role in preserving fertility in patients when being under oncological treatment, for example. The review published by Zaami et al26 describes, under other options, the use of combined hormonal contraceptives that allow the management of artificial reproductive techniques without compromising the health of these women as vaginal rings have a lower systemic hormonal impact and no first-pass effect they can be considered as a helpful tool in this situation.

Finally, vaginal rings can also be used as therapeutics in benign endocrine disorders like endometriosis. Vercellini et al27 could demonstrate that the use of the ring was more effective in pain reduction compared to patches, especially in women with rectovaginal endometriosis and that the users very often well accepted long cycles.

Conclusions

The contraceptive vaginal ring demonstrates high user acceptability and comfort. It is a well-accepted contraceptive method characterized by high efficacy and positive effects on cycle control.

Conflict of Interests

Jaime de Algorta, Enrico Colli, Pedro-Antonio Regidor, and Manuela Mayr are employees of Insud Pharma. Thomas Römer: Speaker for Gedeon Richter, Aristo and Exeltis. Santiago Palacios: Grants from PFIZER, grants from AMGEN, grants from GEDEON RICHTER, grants from EXELTIS, grants from BAYER SCHERING, grants from NOVO NORDISK, grants from SERVIER, grants from MSD, grants from PROCARE HEALTH, grants from SHIONOGI, grants from TEVA, outside the submitted work.

Ethics Approval

For the German part of the study, the overall ethical approval was given on 23.07.2018 by the Ethikkommission der Ärztekammer Nordrhein, Germany, number 2018180. For the Spanish part of the study, its ethical approval was received on 25.09.2019 and registered at the EC CEIm Hospital Clínico San Carlos.

Informed Consent

Participants gave their written informed consent. Afterward, women were asked to complete a questionnaire to document parameters regarding their quality of life, menstrual cycle profile, and vaginal infections.
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Authors’ Contributions

[Authors’ contributions description].

Availability of Data and Material

All data generated or analyzed during this study are available from the corresponding author on reasonable request.

References


