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Safety, efficacy and quality of life of the novel vaginal contraceptive ring containing etonogestrel/ethinylestradiol 11.0/3.474 mg after 3 years of "real life" experience

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Abstract. – Combined contraceptive vaginal rings (CVR) are increasingly appreciated due to several beneficial properties like avoidance of the hepatic first-pass effect, a comparatively low dosage of hormones and comfortable use. A further development of the widely used CVR releasing 0.12 mg etonogestrel (ETO) and 0.015 mg ethinylestradiol (EE) per 24 hours has been marketed since 2017. The 11.00/3.474 mg ETO/EE CVR Ornibel® is bioequivalent to the former product but differs in its polymer composition leading to improved stability.

Here, results from recent studies on the novel CVR Ornibel® are reviewed including clinical trials on bleeding profile, acceptability, sexual function and other quality of life (QoL) parameters as well as *in vitro* studies on microbial adhesion to the CVR and the influence of ring rupture on hormone release. Findings are complemented with new data on contraceptive efficacy and safety of the new CVR that were assessed during 3 years of real-life experience.

Key Words:
Vaginal contraceptive ring, Elution, Safety, Efficacy.

Introduction

The vaginal route of drug administration offers several advantages compared to oral dosage forms. It is not impaired by gastrointestinal disturbances or interferences with additional oral medication. Furthermore, the hepatic first pass effect is avoided, which allows for lower drug dosing and may generally result in fewer side effects[1]. Hence, the development of vaginal rings (VR) in women's health has started in the 1960s, offering a drug-delivery platform for continuous release of therapeutics that can easily be applied by the woman herself. VR of different polymer composition and therapeutic purposes have been developed, including estrogen-releasing VRs for management of menopausal symptoms[2,3] or VRs for the treatment of deep pelvic endometriosis[4] or long-term delivery of a HIV microbiocide[5]. They have gained immense importance in the field of hormonal contraception, as they offer several advantages compared to their oral, intrauterine or transdermal counterparts. They do not require daily application like oral contraceptives (OC), are nonetheless patient-controlled and their constant hormonal release rate results in lower systemic hormone exposure compared to OC or transdermal patches[6]. Consequently, vaginal contraceptive rings have become increasingly important in both higher and lower income countries and are generally well accepted by the women, when adequate counselling is provided[7,8]. Different variants of progestin-only rings have been developed for contraception but were associated with unfavorable bleeding patterns and did not suppress ovulation[9]. Consequently, development progressed towards combined contraceptive vaginal rings and different combinations of estradiol or ethinylestradiol and progestin were studied[10-14]. Nowadays the CVR combining ethinylestradiol (EE) and etonogestrel (ETO) has prevailed due to its excellent contraceptive efficacy, favorable safety profile, advantageous cycle control and high user acceptability[11,15]. NuvaRing®, marketed since 2001, is a transparent, ring-shaped device measuring 54 nm in diameter and 4 mm in cross-section and consists of a core made from magnesium stearate plus 28% ethylene vinylacetate (EVA) and is covered by an external membrane containing 9% EVA. Loaded with 11.7 mg

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ETO and 2.7 mg EE, it releases on average 0.120 mg ETO and 0.015 mg EE within 24 h when inserted into the vagina[15]. The ring is usually placed into the vagina at day 1 of the cycle and is removed after 3 weeks of use. During the following ring-free interval of 1 week, withdrawal bleeding occurs and finally, a new ring is inserted. Following this regimen, ovulation is suppressed and contraceptive efficacy comparable to that of oral contraceptives (OC) is maintained from the first day of use and throughout the ring-free interval[15-17]. In contrast to OC however, the hormones are provided more uniformly and in lower concentrations, which may reduce EE-induced side effects[18].

An ETO/EE CVR of Novel Polymer Composition: Hormone Release, Pharmacokinetics, and Stability

In 2017, a novel ETO/EE CCVR with the same size and external appearance as NuvaRing® was approved for market. Ornibel® (developed by Laboratories LeonFarma, SA, Chemo Group, León, Spain) contains the same active compounds as the reference product NuvaRing® and its bioequivalence was demonstrated[19]. Albeit approved as a generic drug, it differs in its polymer composition with its core consisting of polyurethane and an outer membrane containing 28% EVA. This alteration allows the hormones to be dissolved below the saturation limit as opposed to the reference product. Slightly different amounts of active compounds are loaded (11.0 mg ETO and 3.474 mg EE), but the average daily release and resulting plasma concentrations were proven bioequivalent[19]. In this randomized crossover comparative bioavailability study, the ETO- and EE plasma concentrations of women using Ornibel® were compared to those of NuvaRing® users, during an application period of 28 days. Bioequivalence was demonstrated as the primary parameters lay within the requested 80-125% acceptance range for both ETO and EE (Figure 1)[19]. However, a difference in drug delivery during the first day of use was observed with NuvaRing® showing a significant peak release of the active compounds ("burst effect", Figure 1). The phenomenon is especially noticeable for EE and leads to peak concentrations that are higher than the mean level for the next few days and were also significantly higher than those observed for the novel CVR. The burst effect is a known phenomenon for NuvaRing®[20] and has been associated with nausea and vomiting in a further CVR containing norethindrone and ethinyl estradiol[21]. The more gradual hormone release from the novel ETO/EE CVR is attributed to the different polymer composition, which allows dissolution of the hormones below their saturation limit resulting in higher stability of the system. This also leads to the benefit that no cold chain is needed when handling the device[22] thus manifesting an advantage for pharmacists and users. This comparative study also showed the high acceptability of Ornibel® among the users, equal local tolerability and an advantageous

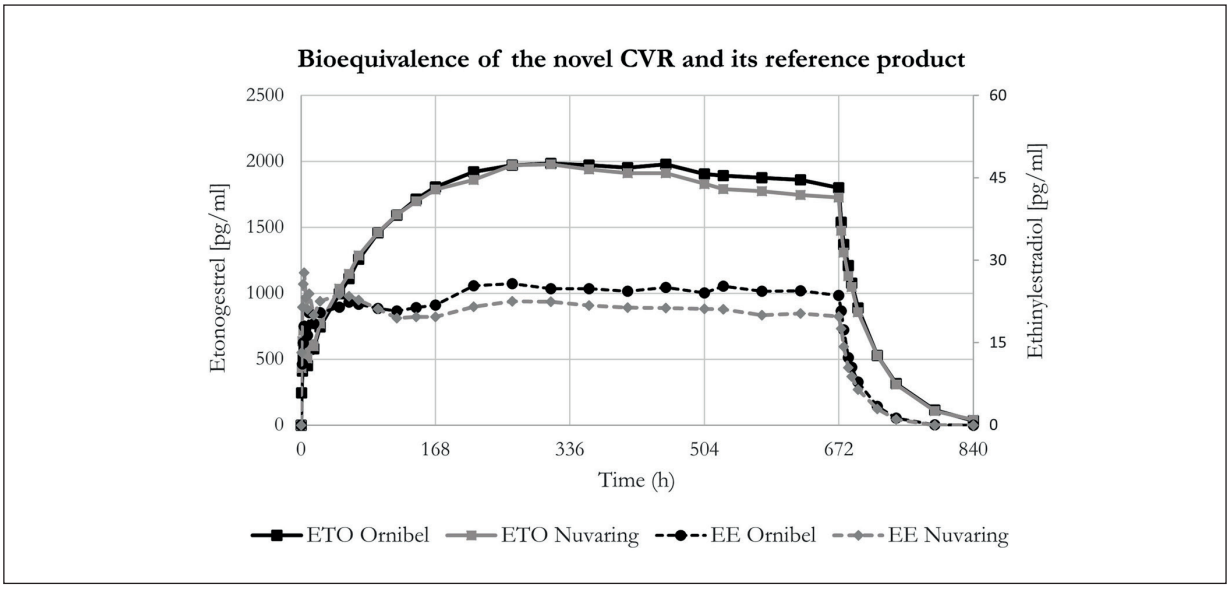

Figure 1. Mean plasma concentration-time curves of etonogestrel (*squares*) and ethinylestradiol (*circles*) by treatment with the novel CVR (*black*) or its reference product (*gray*) during four weeks of use and 1 week after removal.

risk profile as determined from adverse events[19].

Concerning hormone release, the elution of ETO and EE from broken Ornibel® vaginal rings in comparison to intact ones was investigated *in vitro*[23]. CVRs occasionally break during use[17,22], which frequently raises the question, whether the clinical efficacy is maintained in these cases. For that purpose, a fully validated *in vitro* elution method (IVE) was applied which has also been used for the regulatory procedures during market authorization of the novel vaginal ring. Contraceptive rings from the same batch were either cut or left intact and were incubated in a defined elution buffer for 21 days. Daily hormone elution was determined by HPLC. For both ETO and EE the hormone release was similar for intact and broken rings and were within the acceptance limits specified for the device. Resulting elution profiles for ETO and EE are shown in Figure 2 and demonstrate the equivalence of hormone release between broken and intact Ornibel® VR. The IVE test system allows some extrapolations to the situation *in vivo*, since it is based on an *in vivo*/*in vitro* correlation model of category A as defined by the FDA[24] and can potentially be used for bioequivalence studies[25]. Therefore, it may be concluded that a rupture of the ring will not influence the pharmacokinetic behavior of released ETO and EE and will not impair the overall efficacy and safety of CVR[16,11].

Bleeding Pattern, Acceptance, Sexual Function, And Quality Of Life with the Novel CCR

Many different parameters influence women's decision for and adherence to a contraceptive method. For example, ease of use in daily life, probability of omission, adequate cycle control, a favorable side effect profile and further non-contraceptive benefits[26]. For Ornibel®, a retrospective multi-center observational study with 103 women, wo used the novel CVR for at least 6 months was performed to assess its impact on bleeding profile, dysmenorrhea, general acceptance and the continuation rate[27]. After 6 months of application, unscheduled bleeding or spotting was reduced from 21% to 12% and furthermore, a significant reduction of menstrual flow and dysmenorrhea was observed as determined by a VAS scoring system. As displayed in Figure 3, median reduction was 16 points ($p<0.002$) for menstrual flow and 22.5 points ($p<0.001$) for dysmenorrhea. Hence, as described for NuvaRing®[28], the novel CVR shows beneficial effects on cycle stability and bleeding parameters. Evaluation of additional aspects associated with quality of life (Qol) revealed that the vast majority (97%) of users rated the ring as very comfortable or comfortable and agreed that it was easy to insert (91%). These perceptions were significantly associated with the willingness to continue usage of the contraceptive

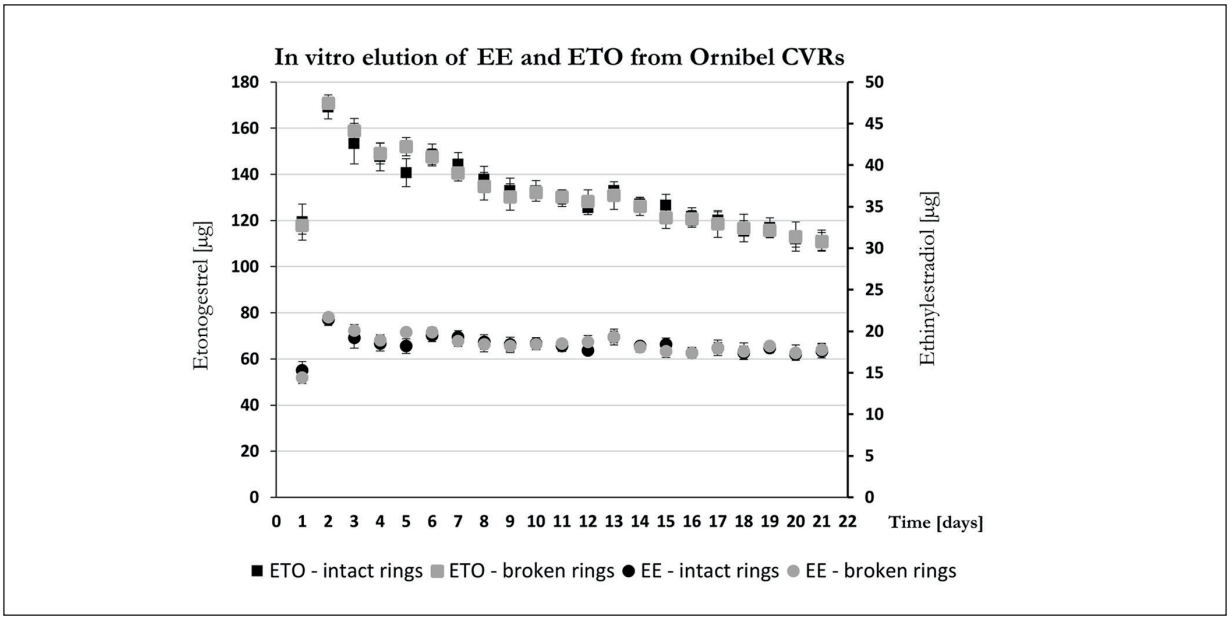

Figure 2. *In vitro* elution of ETO (*squares*) and EE (*circles*) from intact (*gray*) and broken (*black*) Ornibel® vaginal rings. Each 6 rings were broken at day 1 or left intact and were incubated in the IVE buffer system for 21 days. Mean daily release of the hormones (µg/day) is displayed (error bars: standard deviations between replicates).

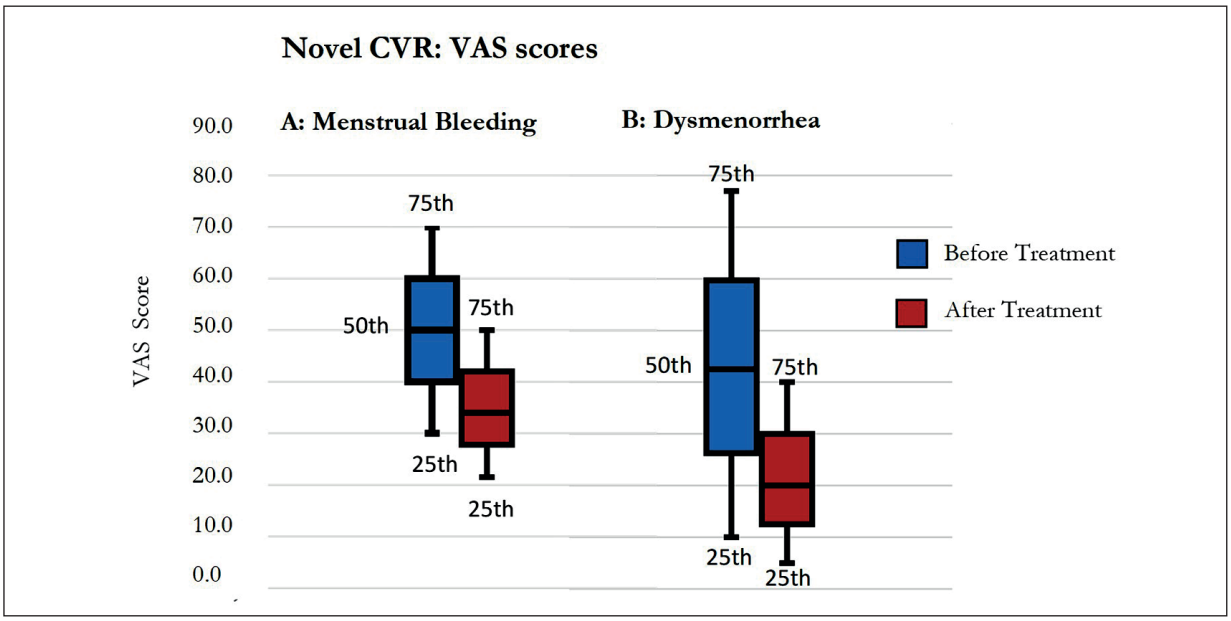

Figure 3. A, Median VAS score values for menstrual bleeding before *(blue*) and after (red) the 6-months treatment with Ornibel®. 75th, 50th and 25th percentiles are given. Median reduction of 16 points (p<0.001). **B,** Median VAS Score values for dysmenorrhea before (*blue*) and after (*red*) the 6-months treatment with Ornibel®. 75th, 50th and 25th percentile. Median reduction of 22.5 points (p<0.001). Adapted from reference 27.

method (91%) and to recommend it to other women (95%). Only 15% of the participants mentioned occasional interference with daily activities and usually (in 88% of cases) the partners did not or only occasionally notice the ring during sexual intercourse[27]. The superior cycle control of CVRs compared to COCs due to the constant low-dose release of EE has been demonstrated in several clinical studies and is characterized by low rates of irregular bleeding among VR users[28-30]. Also, the general good acceptability and high continuation rates have been shown for the ETO/EE CVR[16,28,29]. Both aspects have been observed for the novel CVR[19,27].

A further randomized comparative study assessed the influence of Ornibel® on female sexual function and Qol compared to women using NuvaRing®[31]. 58 women who did not use hormonal contraception were randomly assigned to two groups and either started using Ornibel® or the reference product. After 3 and 6 months FSFI (female sexual function index), FSDS (female sexual distress scale), Qol parameters (determined by SF-36 questionnaire), occurrence of premenstrual syndrome (PMS) and dysmenorrhea (each assessed *via* VAS scoring) were compared. In both groups, FSFI, FSDS and Qol parameters improved after 6 months, but improvement was faster and more pronounced in the group utilizing the novel device. Improvement in PMS and dysmenorrhea were observed in both groups and did not differ significantly between the CVRs. Furthermore, the breakthrough bleeding rate was slightly higher in the NuvaRing® group causing discontinuation of the contraceptive method in 13.8% of the cases[31]. The authors speculated, whether the reduced burst effect with the novel CVR might be accountable for the observed differences. However, since no plasma hormone levels had been determined, no direct conclusions could be drawn. Furthermore, the number of participants in the trial had been low. Nevertheless, the study confirmed the high acceptability and beneficial effects of the novel CVR, including its positive impact on sexual function.

Microbial Adhesion to Ornibel® Compared to NuvaRing®

Although combined contraceptives rather seem to positively influence the vaginal flora[32] or even exert a positive or stabilizing effect[33] also in the case of VRs[34], higher incidences of vaginal infections and irritations with CVR users compared to women using COC[28,29] have been reported for contraceptive vaginal rings and according to the SPCs, vaginal infections are frequently reported (incidence 1/100-1/10)[17,22].

One of the major pathogens causing vaginal infections is the human commensal *Candida albicans*, which colonizes the vaginal tract and may turn into a pathogen under certain circumstances[35]. Its ability to adhere to medical devices with subsequent biofilm formation is an important virulence factor in this context[36]. A recent *in-vitro* study analyzed the adhesion of *C.albicans* to Ornibel® in comparison to NuvaRing® and was found significantly lower of for the novel device[37]. In contrast, no difference in adhesion was observed for *Lactobacillus acidophilus*. When the CVRs were co-incubated with both types of microorganism, no difference in colonization were observed for *C.albicans*, but significantly lower numbers of *L.acidophilus* CFUs (cell forming units) were counted on Ornibel® compared to NuvaRing®. Interestingly, previous scholars[38] have shown, that presence of lactobacteria enhances the adhesion capacity of *C.albicans* to a CVR *in vitro*. It may thus be speculated, whether a reduced number of lactobacilli on Ornibel® might lead to reduced virulence of *C.albicans in vivo*. However, interactions between microorganisms, vaginal epithelium and medical devices are highly complex *in vivo* and further extended studies will be necessary to understand the practical relevance of the observation.

Differences in surface roughness between the devices might be a reason for altered microbial adhesion but could not be confirmed by comparative scanning electron microscope (SEM) analyses[39]. However, these SEM studies were performed on "fresh" CVRs and surface conditions might be different after incubation of the ring in buffer systems (or the vaginal environment). Hence, the topic needs further investigation.

Contraceptive Efficacy of Ornibel®

Contraceptive efficacy is a key feature for contraception. For the novel CVR, no unintended pregnancies have been reported during the clinical trials[19,27,31]. These trials had not been intended to evaluate contraceptive efficacy and included a limited number of participants. Hence, in order to obtain further data from "real life", reporting of unintended pregnancies by the established German pharmacovigilance surveillance system were evaluated. According to German pharmaceutical law and the EMA guidelines on good pharmacovigilance practice (GVP)[40], each marketing authorization holder is obliged to provide a pharmacovigilance system that ensures proper collection of reports on all adverse reactions with a possible causal relationship to the use of a medicinal product. All kinds of reporting resources must be considered (including for example healthcare providers, consumers or reports in the literature), evaluated and classified according to Eudra guidelines[41] and resulting individual case safety reports (ICSR) are provided to central regulatory authorities. Unintended pregnancies are also covered by this system and we used this data to roughly estimate the number of contraceptive failures per 100 woman-years of exposure (Pearl Index, PI). Until end of June 2020 13 pregnancies (confirmed or potential pregnancies) were reported, while 2573018 cycles have been sold to the customers ("sell-out data"). From this data, the PI was estimated as follows:

$$PI = \frac{(100^* \text{ number of pregnancies}^*13)}{(\text{number of cycles})}$$

Assuming all sold cycles have been used, this resulted in an extremely low PI of 0.007. The capacity of ETO/EE CCVR to efficiently suppressing ovarian function and inhibiting ovulation reliably even in certain scenarios of non-intended use has been described for NuvaRing®[42]. According to the specifications, PI ranges between 0.64-0.96[17,22] and is considered comparable to COCs with PIs ranging between 0.29 and 1.98 depending on dosage, composition, and further parameters[43]. For both CVR and COC the WHO describes the PI for consistent and correct use with 0.3, rising to 7 for common use[44]. In Figure 4 the estimated PI of the novel CRV is compared to that of several hormonal contraceptive methods as given by the WHO for correct use. The evaluated pharmacovigilance data for Ornibel® may be biased, since not every single sold VR may have been utilized and not every unintended pregnancy may have been reported. Nevertheless, it speaks for the high contraceptive efficacy of the novel CVR.

Safety of Ornibel®

The safety of the novel CVR® regarding adverse events was proven in several clinical studies[19,27,31] showing a general advantageous risk profile and similar incidences of adverse events as the reference product. Furthermore, the safety of the new CVR was assessed based on pharmacovigilance reporting of serious adverse events (SAE) according to Eudra Classification[41]. Until the end of July 2020, 10 SAE were reported for the novel CVR, including 4 cases of venous thromboemholism

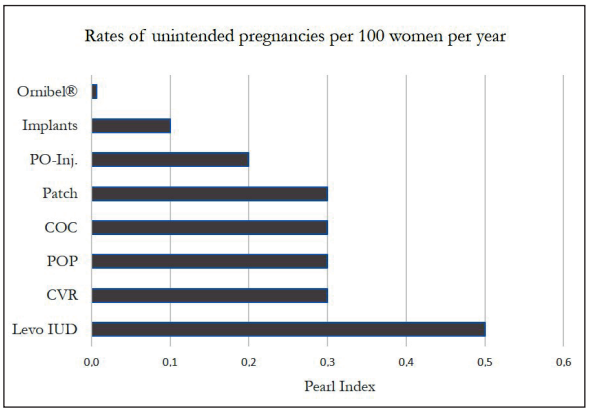

Figure 4. Contraceptive effectiveness of different hormonal contraceptive methods compared to the novel CRV. PI data for consistent and correct use of the respective contraceptive methods as given by WHO[42] are displayed and compared to Data obtained for the new ETO/EE CVR® after 3 years of marketing. PO-inj: Progestin-only injectable; Patch: combined contraceptive patch; COC: combined oral contraceptive; POP: progestin-only pill; CVR: combined vaginal ring; Levo-IUD: intrauterine device releasing levonorgestrel.

(VTE) (1 case of deep vein thrombosis, 1 case of 1 sinus vein thrombosis and one case of pulmonary embolism), Urticaria (1 case), Angioedema (1 case), Cervical eversion (1 case), a general state of fatigue associated with depression and constipation (1 case), exacerbation of Morbus Crohn (1 case) and 1 case of emotional stress due to broken ring .

Generally, the use of COCs containing EE is associated with an in increased risk of VTE compared to non-users, although the absolute risk remains low and is significantly raised among pregnant women and post-partum[45]. While for non-users the absolute risk for VTE is estimated to be about 2 per 10000 women per year for non-pregnant women, it increases 2-4-fold for COCs depending on the estrogen dose and kind of progestin used[46]. It is also highly dependent on additional risk factors, such as overweight and a family history of thrombosis and differs between studies[45,47]. At present oral combinations with levonorgestrel, norethisterone or norgestimate (2nd generation) are considered to impose the lowest risk with an estimated incidence of 5-6 VTE per 10000 women and year and are considered first choice in current guidelines[48,49].

For non-oral combined contraception, an elevated VTE risk compared to non-users is also assumed[50,51]. Concerning the CVR, it is considered comparable to that of EE/LNG COCs[51-54] and in one cohort study[55] a modest increase was shown. The risk for thrombotic stroke or myocardial infection was reported to be comparable to that of EE/LNG COCs[56].

For Ornibel®, no aortic thromboembolism (ATE) and 4 cases of VTE were reported since its launch in 2017, including the clinical trials. Obviously, only a rough estimation for VTE incidence can be made, since our data is not based on a clinical trial but on pharmacovigilance data. Hence, there is no information available on the user population. We can also not rule out that VTE may have been missed. Based on 2335955 cycles sold to the customers and assuming 13 cycles per woman, such a rough estimation would result in 0.2 VTE per 10000 woman-years, which is far below the values cited above:

$$\text{Incidence of VTE} = \frac{(10000^* \text{ number of VTE}^*13)}{(\text{number of cycles})}$$

In Figure 5 the estimated VTE incidence for use of the novel CRV is compared to the estimations given for the above-mentioned methods of hormonal contraception visualizing the comparatively low rate of venous thromboembolic events.

The superiority of non-oral delivery of Estrogen concerning hemostatic safety has been discussed and was shown for 17beta-estradiol[57]. However, the potency of vaginal EE to stimulate alterations in hemostatic variables and estrogen-sensitive liver proteins was shown to be comparable to the effects of oral administration despite avoidance of the hepatic first pass effect[58]. Our observations nevertheless indicate a high thromboembolic safety of the novel CVR. Whether the described reduction of the burst effect might have an influence on these parameters is worth further investigation.

Implications for Current Challenges Regarding COVID-19-Disease

In SARS COVID-19 pandemic times the safety aspects of these vaginal rings will get more and more important. SARS-CoV-2 appears to preferentially target respiratory epithelium, where it enters host cells through the angiotensin-converting enzyme 2 (ACE2) receptor, like SARS-CoV[59,60]. However, all infectious complications in critically ill patients are known to activate multiple systemic coagulation and inflammatory responses that are vital for host defense and can lead to a disseminated intravasal coagulopathy (=DIC)[61,62]. Microorganisms and their components induce

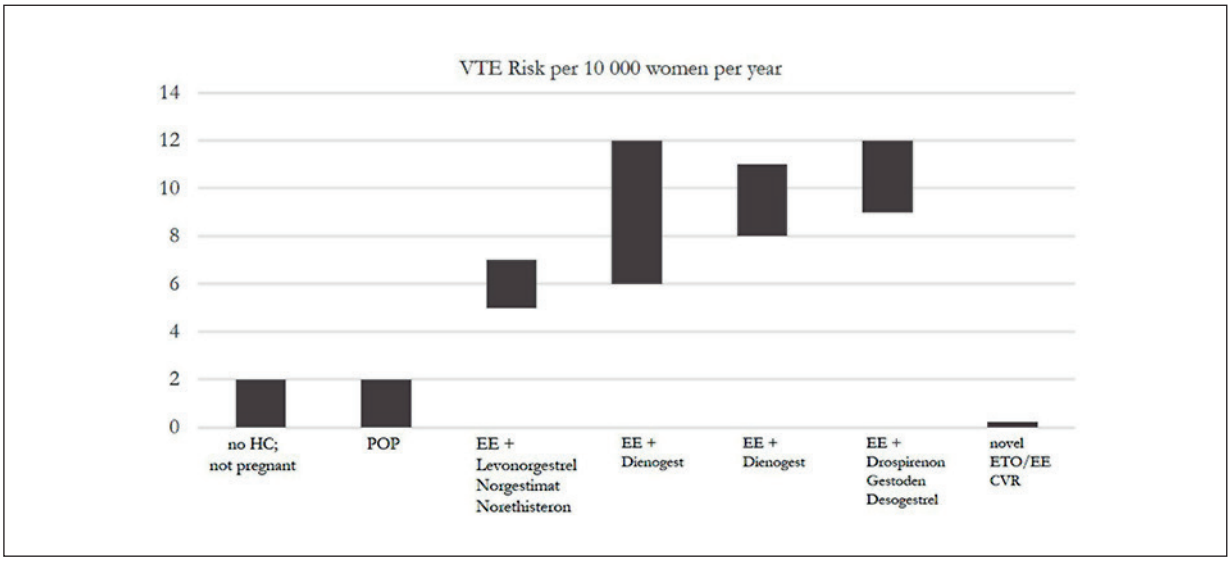

Figure 5. Estimated VTE risk of the novel ETO/EE CVR in comparison to VTE risks of different hormonal contraceptives (HC) compared to non-pregnant non-users of hormonal contraception[47-49]. HC: hormonal contraceptive; POP: progestin-only pill; EE: Ethinylestradiol; Levo: Levonorgestrel; Norg: Norgestimat; Norelg: Norelgestromin; DNG: Dienogest.

the expression of numerous products, including tissue factor by binding to pattern-recognizing receptors on immune cells[63-65]. The triggering of host inflammatory reactions also results in increased production of proinflammatory cytokines that have pleiotropic effects, including activation of coagulation which, if not checked, can lead to consumptive coagulopathy.

Coagulation is activated by the inflammatory response through several procoagulant pathways. Polyphosphates, derived from microorganisms, activate platelets, mast cells, and factor XII (FXII) in the contact pathway of coagulation, and exhibit further downstream roles in amplifying the procoagulant response of the intrinsic coagulation pathway[66]. Complement pathways also contribute to the activation of coagulation factors[67]. Although neutrophil extracellular traps are present in thrombi, the individual neutrophil extracellular trap components of cell-free DNA and histones activate the contact pathway and enhance further prothrombotic pathways resulting in thrombin generation[8,18]. Pathogen-associated molecular mechanisms are important aspects of the complex interactions between the immune response and coagulation as well as in sepsis[63,68]. The inflammatory effects of cytokines also result in activated vascular endothelial cells and endothelial injury with resultant prothrombotic properties[63,69].

The inflammation processes associated with COVID-19 and the subsequent activation of coagulation is the probable cause for the elevated levels of D-dimers. Such an increase can result from many conditions other than thromboembolism, with infection being an important cause[70]. To minimize additional cardiovascular risk factors is therefore essential in COVID-19 times. Hence, all contraceptive systems free of oestrogens like POP with desogestrel or drospirenone can be considered as safe as they do not activate the coagulatory axis in the liver. Concerning combined contraceptives, the estrogen dose should be kept as low as possible, which is ensured by vaginal delivery systems like Ornibel®.

Conclusions

Vaginal contraceptive rings with their high contraceptive efficacy, ease of use, and beneficial safety profile represent an essential option in the field of hormonal contraception[7]. The combined 0.120/0.015 mg ETO/EE 24 h vaginal hormone delivery system has been established since 2001, but required a cold chain[17] and showed a significant hormone peak release during the first day of use[19,20]. These drawbacks were overcome by the development of the novel CVR with improved thermodynamic stability due to a different polymer composition[19,22]. The bioequivalence of the device and its high tolerability, safety, and efficacy were proven in clinical studies[19,27,31], and the

hormone release was found unaltered in ruptured rings[23], adding a further aspect of safety. With very low incidences of SAE, including VTEs and unintended pregnancies during three years of "real-life experience" the new VCR constitutes a valuable advancement in the field of hormonal contraception. Its beneficial safety aspects may also be important concerning recent challenges imposed by SARS COVID-19 pandemia.

Soon, this vaginal ring technology applying new polymers with aliphatic polyurethane in the core and 28% ethylene vinylacetate in the membrane will be used to also deliver further hormones or drugs. In this segment the use of levonorgestrel or progesterone will add new contraceptive perspectives or may be used for support of the luteal phase.

Conflict of Interest

A. Müller, M. Sailer, E. Colli and P.-A. Regidor are employees of Exeltis.

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