Review article

Contraceptive vaginal rings: a review

Vivian Brachea,⁎, Anibal Faundesb

aPROFAMILIA, P.O. Box 1053, Santo Domingo 10401, Dominican Republic
bCentro de Pesquisas en Saúde Reprodutiva de Campinas, Cemicamp, 13084-970, Campinas, SP, Brazil

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Abstract

Development efforts on contraceptive vaginal rings were initiated over 40 years ago based on two principles: the capacity of the vaginal epithelium to absorb steroids and the capacity of elastomers to release these hormones at a nearly constant rate. Numerous models of contraceptive vaginal rings (CVRs) have been studied, but only two have reached the market: NuvaRing, a combined ring that releases etonogestrel (ENG) and ethinylestradiol (EE), and Progering, a progesterone-releasing ring for use in lactating women. The main advantages of CVRs are their effectiveness (similar to or slightly better than the pill), ease of use without the need of remembering a daily routine, user’s ability to control initiation and discontinuation, nearly constant release rate allowing for lower doses, greater bioavailability and good cycle control with the combined ring. The main disadvantages are related to the mode of delivery; CVRs may cause vaginal discharge and complaints, ring expulsion is not uncommon, the ring may be felt during coitus and vaginal insertion may be unpleasant for some women. The studies reviewed in this article provide evidence that CVRs are safe, effective and highly acceptable to women. There is no doubt that CVRs offer a new, effective contraceptive option to women, expanding their available choices of hormonal contraception.

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1. Introduction

The availability of modern contraceptive methods has played a fundamental role in empowering women by reducing the burden of excessive childbearing and boosting women’s opportunities for nondomestic activities. The increased availability of modern contraceptives has reduced maternal mortality and child mortality, and has made a very significant contribution to dramatically reducing the induced abortion rate in countries that had traditionally used abortion as a means of birth control [1].

Among the modern methods for fertility regulation, hormonal contraceptives have played a leading role. The combined oral pill was the first, and still the most, popular form of hormonal contraception. Although highly effective in controlled clinical studies, its effectiveness becomes considerably lower in real life, mostly for inadequate use, forgetting one or more pills or late initiation of a new cycle.

This limitation led to the search for “long-acting” hormonal methods of contraception that do not require daily action by women.

Alternative nonoral routes for contraceptive steroids are available in the form of injections, subdermal implants, transdermal patches, gels or creams, intrauterine devices and by means of a plastic ring-shaped device placed in the vagina. The clinical application of the release of contraceptive steroids through the vagina was first demonstrated four decades ago, when Mishell and Lumkin [2] published their clinical study with a vaginal ring releasing medroxyprogesterone acetate.

The development of contraceptive vaginal rings (CVRs) with the optimal characteristics of size, an adequate release rate of progestin and estrogen compatible with contraceptive effectiveness and minimal side effects has been a long process. Numerous clinical trials, testing various doses and different steroids, have been published.

However, only two contraceptive rings have progressed to the stage of a marketed product: the NuvaRing (NV Organon, Oss, the Netherlands), which releases etonogestrel (ENG; 3-keto-desogestrel) and ethinylestradiol (EE), and
Progering (Laboratorios Silesia, Santiago, Chile), the progesterone-releasing vaginal ring for nursing women.

2. Vaginal route of delivery

The concept of CVRs is based on a combination of two principles: the capacity of steroids to slowly diffuse at a constant rate through biocompatible silicone elastomers [3], and the capability of the vaginal epithelium to rapidly absorb steroids placed in the vagina into the circulation [4,5]. The vascular supply of the vagina consists of a complex network of arteries and veins which favors the absorption of steroids and other molecules through the vaginal epithelium into the systemic circulation, making it a very effective route of administration. The attractiveness of using the vaginal route for administration of steroids and other drugs resides in its quality of avoiding gastrointestinal absorption and hepatic first-pass metabolism, and the greater bioavailability, as compared with the administration of the same doses of steroids by other routes [6]. This makes it feasible to use lower doses and lower systemic exposure, yet achieving the same pharmacodynamic effect.

Most devices have an initial burst effect, probably due to accumulation of steroids on the surface of the ring during storage [7–10], but after this burst, a constant drug release from the steroid reservoir in the elastomer results in steady blood levels of the minimum dose required, in contrast with the daily fluctuations of steroids associated with oral contraceptives (OCs). In addition, orally inactive steroids can be administered using a vaginal ring.

Another advantage is that, contrary to the diaphragm, the site in the vagina where the ring is placed is irrelevant to its effectiveness, as any part of the vaginal epithelium is equally capable of allowing the transference of steroids into the blood stream. Consequently, neither fitting nor special instructions for placement are required, making the CVR even less provider-dependent than the diaphragm. Thus, the vaginal ring has the advantage of being the only long-acting contraceptive that is “user controlled” giving women the opportunity to initiate or discontinue use whenever desired.

A very important feature of the CVR is that it does not require a daily initiative on the part of the user, eliminating the possibility of forgetting a daily intake. It is relevant to recall that the main reasons for contraceptive failure during pill use are attributed to noncompliance by women, mainly due to forgetfulness, resulting in the omission of some pills in the cycle with a consequent reduction in efficacy [11].

Acceptability studies conducted among users of different ring prototypes and among women from different cultures have shown high user satisfaction. Convenience of use, effectiveness and no requirements for taking medication daily were among the most liked attributes of the contraceptive ring [12–17]. Because of all these features, the vaginal rings have become very attractive candidates for long-acting and highly effective contraceptive methods.

3. History of development

A considerable number of contraceptive rings delivering both a progestin and an estrogen, for cyclic use (3 weeks in/1 week out), as well as progestin-only rings for continuous use have been studied in the last four decades.

3.1. Combined rings

Combined rings (progestin with estrogen) have several advantages: estrogen increases the contraceptive efficacy of the progestin by a synergistic effect on ovulation inhibition, but most importantly, estrogen maintains endometrial development, prevents breakthrough bleeding and thus provides good menstrual cycle control with regular withdrawal bleeding patterns.

In the late 1970s, the Population Council (New York, NY, USA) developed a combined ring releasing levonorgestrel (LNG; 250–290 mcg/day) and estradiol (150–180 mcg/day) [18–20]. This ring prototype was evaluated in a large multicenter clinical trial of 1103 ring users with a comparative group of 553 combined oral contraceptive (COC) users. One-year gross pregnancy rates among CVR users were less than 3/100, similar to COC users [21–23]. However, further development of the LNG/E2 rings was halted due to undesirable reductions in HDL-cholesterol [24–26] and to the finding of an increase in coronary artery atherosclerosis among cynomolgus macaques treated with this ring prototype [27].

Different dose combinations of norethindrone acetate (NETAc) and EE-releasing rings were also developed and tested by the Population Council; however, the NETAc/EE rings presented a high incidence of nausea and vomiting, particularly in the first cycle of use, which was presumably attributed to the accumulation of EE on the ring surface during storage, causing an initial burst effect [28–32].

Nestorone® (NES), a highly potent 19-nor progesterone, with an excellent metabolic profile, which is not orally active, but is effective when administered via nonoral routes such as vaginal rings, has also been tested in combination with EE in the Population Council-coordinated trials [33–37].

One six-month study evaluated rings releasing different NES/EE doses (NES 50/10 EE; NES 50/20 EE; NES 150/15 EE) on a bleeding signaled regimen. Six-month pregnancy rates were 3.9%, 1.4% and 1.4%, respectively. Adequate NES and EE serum levels were achieved with a high level of ovulation suppression; however, the pregnancy rate was apparently higher than in the cyclic, 3 week in/1 week out, scheme leading the authors to conclude that the menstrually signaled regimen may be more difficult to comply with, due to irregularity of frequent bleeding/spotting which led to frequent ring removals which in turn may reduce effectiveness [36,37].

In another Population Council-sponsored multicenter trial involving 150 women, three dose combinations of NES/EE...
were compared in a 1-year duration prototype ring (NES 150/EE 15 mcg/day; NES 150/EE 20 mcg/day; NES 200/EE 15 mcg/day) [35]. The silicone elastomer rings were 58 mm in overall diameter and 8.4 mm in cross-sectional diameter. This ring was used on a 3-week in/1-week out regimen over 13 cycles of use. All three doses tested were effective (Table 1). Bleeding control was excellent as reflected in the very low 1 year discontinuation rate for this reason (<2.5%). Device-related terminations accounted for 4.0–9.7% of the discontinuations (expulsions or lost rings). Colposcopy examinations documented the absence of major vaginal or cervical problems during ring use [38]. User satisfaction was high based on a 1-year continuation rate of 68–76% (Table 1) [35]. Of the three tested doses, the ring releasing 150 mcg/day NES and 15 mcg/day EE was selected for a large Phase III multicenter trial launched by the Population Council in 2006. The primary objective of this trial was to evaluate 1-year data on the contraceptive efficacy and safety of the 150/15 mcg NES/EE contraceptive vaginal ring as the basis for FDA regulatory approvals of this CVR as a new delivery system for contraception. Cycle control, bleeding patterns, adverse events, return to fertility and acceptability were also evaluated. A total of 27 sites (20 in the USA, three in Latin America, three in Europe and one in Australia) participated in this trial that enrolled over 2000 women. This study was jointly funded by NICHD, USAID and WHO, and results will be available in 2010 (Population Council, personal communication).

The feasibility of using this same prototype CVR as an emergency contraceptive was also tested in 48 women. Interference with the ovulatory process was observed in 87.5% of the cycles, suggesting that this ring may be used as an emergency contraception method, with the potential advantage of serving as a bridging method for the continuous regular use of the CVR for 12 additional cycles [39].

In the early 1990s, several clinical dose-finding studies with a combination ring delivering 3-keto-desogestrel and EE, developed by NV Organon, were published [40–44]. The prototype selected from these studies is the NuvaRing (NV Organon), a flexible, soft, multicompartment, transparent vaginal ring made of ethinyl vinyl acetate, with an outer diameter of 54 mm and a cross-sectional diameter of 4 mm. The ring releases 120 mcg/day of ENG (the biologically active metabolite of desogestrel) and 15 mcg/day EE. It is intended for only one cycle of use (3 weeks in/1 week out), to be replaced monthly. Extensive literature has been published regarding NuvaRing and will be reviewed below. The NuvaRing was initially approved by the FDA in October 2001 and is currently marketed in the US, Europe and many other countries.

### 3.2. Progestin-only rings

Three progestin-only rings have also been evaluated: the progesterone, the LNG and the NES rings. Only the progesterone ring, which is effective solely during breastfeeding, is currently commercially available in Chile, Peru, Bolivia and Ecuador (Progering).

The Special Programme of Research, Development and Research Training in Human Reproduction of the World Health Organization (WHO) initiated the development of a LNG vaginal ring in the mid-1970s. The ring had an in vitro release rate of approximately 20 mcg/day of steroid, and an effective life of three continuous months. This ring prototype was tested in a WHO multicenter clinical trial involving 1005 women accumulating 8176.4 women-years of exposure and reported a cumulative 1-year pregnancy rate of 4.5% (confidence interval 2.9–6.0), which dropped to 3.7% when pregnancies that occurred during incorrect use of the ring were disregarded [45–48]. However, as expected with progestin-only contraception, menstrual disturbances were the main reason for discontinuation, with a 12-month termination rate of 17.2% [45]. Furthermore, vaginal erythematous reactions located in the posterior fornix of the vagina or on the cervix were observed among 48 of 139 women participating in a clinical trial evaluating the LNG contraceptive ring [49]. The etiology of these lesions was unknown, although it was hypothesized that they could be due to a combined effect of pressure from the ring and thinning of the vaginal epithelium due to local exposure to LNG.

The Population Council conducted a dose-finding study with three prototypes of NES-only rings, releasing 50, 75 or 100 mcg/day of NES [7,50]. Among a total of 178 women who participated in a 6-month Phase II dose-finding clinical trial with the NES ring, no pregnancies occurred with the low-dose ring, while one pregnancy each occurred in the intermediate- and high-dose ring groups, resulting in a 6-month cumulative pregnancy rate of 0.0%, 1.9% and 2.1%, respectively [7]. However, menstrual disturbances were also associated with this ring, more so in the lower doses, while the higher dose had reduced bleeding.

Since NES is not orally active, it is an excellent progestin for use during lactation. Accordingly, the low-dose NES ring (50 mcg/day) was also tested in a pilot study as a contraceptive for breastfeeding women [51]. Fifty breastfeeding women were enrolled on Postpartum Day 58±2. The ring prototype was designed for 1-year continuous use and had the advantage that women could continue use even after weaning. No pregnancies were observed in 555 women-months of use and the 1-year continuation rate was high (80.4%). The ring prolonged postpartum amenorrhea, while

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**Table 1**

Dose-finding study of the 1-year CVR releasing Nestorone® and ethinylestradiol; Population Council ICCR multicenter study

<table>
<thead>
<tr>
<th>Dose (mcg/day)</th>
<th>Pregnancy rate at 1 year (%)</th>
<th>Continuation rate at 1 year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 NES/15 EE</td>
<td>0.0</td>
<td>68.0</td>
</tr>
<tr>
<td>150 NES/20 EE</td>
<td>0.0</td>
<td>74.0</td>
</tr>
<tr>
<td>200 NES/15 EE</td>
<td>4.7</td>
<td>76.2</td>
</tr>
</tbody>
</table>

Adapted from Sivin et al. [35].
breastfeeding performance and infant growth were not different from those observed in a previous comparative group of 132 TCu IUD users.

4. Effect of the vaginal route of delivery on hemostasis variables and liver proteins

It has been postulated that the administration of estrogens through the vaginal route would permit avoiding the approximately 60% first pass of the steroid through the liver that occurs after oral administration [52]. The hypothesis was that the same dose of estrogen administered vaginally would have the desired effect on the central nervous system without affecting hepatic metabolism as occurs after oral administration. Unfortunately, studies comparing the hepatic effect of the same estrogen administered orally and vaginally in equivalent dosages have failed to show any difference in their effect over indicators of hepatic function, such as sex hormone-binding globulin (SHBG) and lipoprotein concentration [53,54]. A recent study comparing daily vaginal and oral administration of 15 mcg of EE for 21 days found there were similar alterations in hemostasis variables and estrogen-sensitive liver proteins, providing evidence that the effects of combined hormonal contraceptives on clotting factors and markers of coagulation and fibrinolysis are largely due to the EE component and independent of the route of administration. Similarly, expected EE effects on lipids (HDL-C and TG) and increase in angiotensinogen and, to a lesser extent, HDL-C and triglyceride increase and protein C resistance more than COC. Similarly, significant differences were found for all estrogen- and androgen-sensitive proteins, including SHBG between the Population Council’s NES/EE CVR and a 150 LNG/30 EE COC. The CVR changed most hemostasis variables similar to the COC, but raised factor VII, and extrinsic activated protein C resistance more than COC, while also reducing protein S and factor VIIt, and extrinsic activated protein C resistance more than COC, while also reducing protein S and extrinsic activated protein C. Similar changes in biomarkers of thrombosis measured at the fourth cycle of use; however, it must be noted that 68.4% of participants were prior users of third-generation progestin pills [59].

5. Currently marketed rings

5.1. Progesterone ring for nursing women

Progesterone has potential advantages for contraception during lactation because it is the natural hormone and is nearly inactive when given by the oral route, thus is unlikely to affect the infant even when present in breast milk. This ring has a homogenous design with 22.5% w/w progesterone dispersed in silicone. The external diameter and its cross-sectional diameter are 58 and 8.4 mm, respectively. The in vitro release is approximately 10 mg/day of progesterone for an effective life span of 3 months.

The progesterone ring was first tested among 128 healthy nursing women in Chile [60]. Rings releasing either 5 or 10 mg progesterone/day were inserted at Day 60 postpartum and replaced every 3 months, while women were still breastfeeding, for a maximum of 2 years’ follow-up. One pregnancy was observed in 739 women-months of progesterone ring use in contrast with 19 pregnancies among 677 women-months of untreated nursing women. No deleterious effects were detected in lactation, infant growth and maternal/infant health.

Due to its homogenous design, the progesterone vaginal ring (PVR) has declining serum levels throughout its 3-month duration of use. The highest progesterone concentrations were attained at Week 1 of ring use (33.7 nmol/L), decreasing to 50% and 30% of this level at 9 and 16 weeks of use [61].

In another Chilean study, 187 lactating women initiated ring use at Day 57±3 postpartum and were followed up for 1 year or until weaning. No pregnancies were observed in 1339 women-months of exposure. The duration of lactational amenorrhea was significantly longer than in a copper T 380A comparative group [62].

The Population Council conducted a large multicenter trial among lactating women comparing the 10 mg/day progesterone ring with the copper T 380A [63]. A total of 802 ring users and 734 IUD users were enrolled between Days 29 and 63 postpartum. The progesterone ring released an average dose of 10 mg/day for a 3-month period. The 1-year pregnancy rate for the PVR was 1.5 per 100 and did not differ significantly from the IUD. More than half of the ring subjects were continuing use at 6 months postadmission. Ring users had more complaints of vaginal problems than IUD users (25.8% and 16.8%, respectively). Only 5.8% of users had discontinued ring use due to menstrual problems at
12 months, while 46 per 100 continuing ring users remained in amenorrhea at 12 months postpartum. Lactation performance and the health and weight gain of the infants were similar among users of either the ring or the IUD.

A pre-registration study evaluating 285 volunteers was undertaken in Chile with locally manufactured rings; no pregnancies occurred among 2320 women-months of exposure. A significant proportion of ring users (26.8%) discontinued due to use-related problems: lack of compliance with the instructions, expulsions or uncomfortable use of the ring. The duration of lactational amenorrhea was 361 ±9 days for the PVR in comparison with 198±8 days in the T-Cu group. Infant weight increase was similar in both groups. No serious adverse events were detected. These results led to the registration of the PVR by the Chilean Public Health Institute in February 1998, being the first vaginal ring approved for contraceptive use [61].

Regrettably, this progestergone contraceptive ring for nursing women is only currently marketed in Chile, Peru, Bolivia and Ecuador. The Population Council is coordinating a large study in India with the purpose of extending the information on safety and efficacy of this ring for contraceptive use during breastfeeding in different populations (Population Council, personal communication).

5.2. NuvaRing

The NuvaRing is made of the copolymer evatane, in which 2.7 mg of EE and 11.7 mg of ENG are equally dispersed. ENG is 3-keto-desogestrel, which is the active metabolite of desogestrel. The ring steadily releases 15 mcg EE and 120 mcg ENG daily. Inhibition of ovulation is the contraceptive mechanism of action [65,66]. Each ring is intended for use in only one cycle with a 3 week in/1 week out schedule. After the insertion of NuvaRing, serum concentrations of 1578 ng/L of etonorgestrel and 19.1 ng/L of EE were achieved in approximately 1 week, with a slow, gradual linear decrease with time, down to an average of 1374 and 17.6 ng/L, respectively, at Week 3 of use [10].

Systemic exposure to ENG is similar between NuvaRing and an OC containing 150 mcg desogestrel and 30 mcg EE, whereas systemic exposure to EE with NuvaRing is about 50% of that for COC [10]. Exposure to EE was 3.4 times lower (p<.05) with NuvaRing than with the transdermal patch releasing 20 mcg EE (Evra, Ortho-McNeil Pharmaceutical, Raritan, NY, USA) and 2.1 times lower (p<.05) than with a 30-mcg COC [67].

Two large open-label, noncomparative, multicenter registration studies were conducted in Europe, USA and Canada [68,69], while another two large open-label, randomized, Phase III studies comparing NuvaRing with COCs were also conducted in Europe and Latin America. One of these studies compared NuvaRing with an OC containing 150 mcg of LNG and 30 mcg of EE [70], while the other compared NuvaRing with a pill containing 30 mcg of EE and 3 mg drospirenone [17]. Extensive reviews of all of these studies were recently published by Roumen [71,72]. A Cochrane review comparing vaginal rings with OCs was also updated in 2009 [73].

5.2.1. Effectiveness

NuvaRing studies have consistently shown high contraceptive efficacy with no significant differences with OCs [73]. In a 1-year multicenter trial, comprising 1145 NuvaRing users in 52 centers mostly in Europe, six pregnancies occurred in 12,109 cycles of exposure, giving a Pearl Index of 0.65 (95% confidence interval 0.24–1.41) [68]. In another publication, combining the above European data set with data from 48 centers in Canada and the United States, 21 pregnancies occurred among 2322 NuvaRing users who were followed for 23,298 cycles, giving a Pearl Index of 1.18 (95% confidence interval 0.73–1.80) [69]. In the comparative trials with OCs, the Pearl Index was similar for both methods, 1.23 and 1.19 for NuvaRing and LNG/EE COC, respectively, and 0.25 and 0.99 for NuvaRing and DRSP/EE COC, respectively (Table 2) [17,70].

5.2.2. Continuation rates, compliance and acceptability

Continuation rates in the large noncomparative and randomized trials have been good for NuvaRing, ranging from 71.1% to 74.9% of the women reaching the end of the 1-year study, similar to 71.2–74.6% of the pill users [17,68–70].

Compliance was above 85% in most of the noncomparative and randomized trials (ranging from a high of 90% in the European sites to 79.9% in North America). Compliance was similar between the NuvaRing users and COC users in the randomized trials [17,70].

In a large acceptability study among 1950 NuvaRing users participating in two clinical trials conducted in North America and Europe, 98% of the women at the end of Cycle 13 reported that the ring was easy to insert or remove, while this figure was slightly above 90% for early discontinuers. Similarly, the most popular reason for liking the ring was “not having to remember anything” (45.5%), followed by

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>n</th>
<th>Pearl Index</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roumen et al., 2001 [68]</td>
<td>NuvaRing</td>
<td>1145</td>
<td>0.65</td>
<td>0.24–1.14</td>
</tr>
<tr>
<td>Dieben et al., 2002 [69]</td>
<td>NuvaRing</td>
<td>2322*</td>
<td>1.18</td>
<td>0.73–1.80</td>
</tr>
<tr>
<td>Oddsson et al., 2005 [70]</td>
<td>NuvaRing</td>
<td>512</td>
<td>1.23</td>
<td>0.40–2.86</td>
</tr>
<tr>
<td>Ahmed et al., 2006 [17]</td>
<td>DRSP 3/30EE COC</td>
<td>484</td>
<td>0.99</td>
<td>0.27–2.53</td>
</tr>
</tbody>
</table>

* Includes women in the Roumen et al. [68] study.
“ease of use” cited by 26.6% of the women and effectiveness (12.7%) [16].

User satisfaction was also assessed in randomized clinical trials that assigned women to NuvaRing or low-dose OC. In a study evaluating the immediate start of NuvaRing or low-dose OC, 61% of ring subjects and 34% of pill users were very satisfied with their method (p=.003). After the trial, 79% of ring users chose to continue with the ring vs. 59% of the pill users [74]. In another randomized trial, 84% of NuvaRing users were satisfied/very satisfied with the ring, similar to 87% of pill users [17].

In a comparative study that enrolled previous OC pill users and randomly assigned them to either NuvaRing use (n=249) or contraceptive patch use (n=251), both on a 3 week on/1 week out schedule, 94.6% of ring users and 88.2% of patch users completed three cycles of use. Of these women, 71% and 26.5% of ring and patch users, respectively, planned to continue use of their method at the end of the study (p<.001) [75].

Fifteen percent to 18% of women reported feeling the ring during sexual intercourse, while 28–37% of their male partners also felt the ring. Most partners did not object to ring use [16,68,69].

5.2.3. Adverse events

At least one adverse event was reported among 58–66% of NuvaRing users and 54–63% of COC users in four large trials. Of these, 29–38% and 22–23% adverse events among NuvaRing and OC users were at least possibly related to contraceptive use. The most frequently reported possibly related adverse events were headache, ring-related issues, vaginitis, leucorrhea and nausea (Table 3) [17,69,70]. However, these individual complaints were reported with a low frequency (<8%). The incidence of estrogen-related adverse events such as breast tenderness, headache and nausea was similar between NuvaRing and OC users. The only difference between the NuvaRing and OC users was the higher incidences of local events such as leucorrhea, vaginitis, vaginal discomfort and ring-related events (foreign body sensation, coital problems, expulsions).

An open-label, randomized, cross-over study was designed to investigate genital symptoms, signs and laboratory findings with NuvaRing in comparison with a COC containing 100 LNG/20 EE. Seventy-two percent of the women reported that the ring never slipped out (expulsion), while in 9% the ring slipped out at least once a week or more. The concentration of Lactobacillus colony-forming units positive for hydrogen peroxide production significantly increased during ring use, possible due to the effect of EE on the vaginal flora. All other laboratory findings were not significantly different including Nugent score, pH and white blood cell count. However, 63% of NuvaRing users reported vaginal wetness in comparison with 43% of COC users [76]. Another microbiological study reported no significant change in vaginal flora or vaginal cells between pretreatment and after 21, 28, 42 and 56 days of NuvaRing, suggesting that ring use was not associated with an increase in inflammatory cells or pathogenic bacteria [77].

Discontinuations due to adverse events were between 11% and 14% for NuvaRing users, slightly higher than discontinuations among OC users (8.7–9.9%) (Table 3). This difference was mostly due to ring-related discontinuations, which was the most frequent adverse event that led to discontinuation followed by headaches. Very few women discontinued due to bleeding irregularities (0.8%) [17,68–70].

Serious adverse events related to treatment were very few. Two vaginal ring users had deep venous thrombosis, although one of these women was heterozygous for factor V Leiden, which is associated with increased risk for venous thrombosis. Among the contraceptive pill users, one had cholelithiasis and another hypertension [17,70].

Blood pressure remained unchanged in the noncomparative studies and in most of the randomized studies for both NuvaRing and OC users [17,66–68]. Reported in only one study, eight COC users and four NuvaRing users (1.5 and 0.8%, respectively) experienced hypertension [70].

A slight mean body weight increase of 0.84±3.81 kg was observed in the noncomparative study [69], while in the

<table>
<thead>
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<th>Table 3</th>
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<tr>
<td>Frequency of women reporting adverse events and discontinuation due to adverse events with NuvaRing and COCs</td>
</tr>
<tr>
<td><strong>Dieben et al., 2002 [69]</strong></td>
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<tr>
<td><strong>NuvaRing</strong></td>
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<tr>
<td><strong>Possible related AE</strong></td>
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<tr>
<td><strong>Headache</strong></td>
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<tr>
<td><strong>Ring related</strong></td>
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<tr>
<td><strong>Vaginitis</strong></td>
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<tr>
<td><strong>Leucorrhea</strong></td>
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<tr>
<td><strong>Nausea</strong></td>
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<tr>
<td><strong>Discontinuations</strong></td>
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<tr>
<td><strong>Discontinuations due to AE</strong></td>
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<td><strong>Discontinuations due to device-related events</strong></td>
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<td><strong>Discontinuations due to headache</strong></td>
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randomized studies no marked changes in body weight were seen. In a smaller comparative study between NuvaRing and low-dose triphasic OC (Ortho Tricyclen Lo), the mean weight gain after 3 months of use was 2.5 and 3.1 lb for the ring and pill users, respectively [78]. The comparative trial between NuvaRing and DRSP/EE pill concluded that changes from baseline in mean body weight were small for both groups with no significant difference between methods; mean weight gain was 0.37 kg for NuvaRing and −0.03 kg for COC [79].

A study that investigated the effects of NuvaRing and LNG/EE OC on lipid profiles found that total cholesterol was unchanged with both treatments, whereas NuvaRing was not associated with significant changes in HDL (slight increase in Cycle 3) or in LDL (slight decrease in Cycle 3), while COC treatment led to a reduction in HDL and a small increase in LDL. Triglycerides and SHBG levels were increased with both treatments but slightly higher with the NuvaRing. These changes are consistent with the low androgenicity of ENG as compared with LNG, even when given in combination with a lower dose of EE [80].

No clinically relevant effect on carbohydrate metabolism, adrenal or thyroid function was seen in a comparative study of NuvaRing with LNG/EE COCs [81]. Another study concluded that there was no effect of NuvaRing on bone mineral density in premenopausal women after 13 and 26 cycles of use [82].

No adverse effects were seen on endometrial histology evaluated after 13 and 26 cycles of use. All biopsies presented normal results, with atrophic or inactive endometrium and secretory changes present in the majority of cycles [83].

5.2.4. Cycle control

One of the attractive features of NuvaRing is the predictability of its bleeding patterns. In the noncomparative large trials, 98.5% of the women had a withdrawal bleeding, while only 6.1% had an early withdrawal bleeding and in 23.9% of the women, bleeding persisted after ring insertion. The incidence of irregular bleeding was very low, 5.5% per cycle over Cycles 1–13. Sixty-three percent of the women had an intended bleeding pattern, with no early or continued withdrawal bleeding, no irregular bleeding and a withdrawal bleeding in the ring-free week [69,72].

In one of the randomized comparative trials, the incidence of breakthrough bleeding over Cycles 2–13 was lower with NuvaRing (2.0–6.4%) than with LNG/EE OCs (3.5–12.6%), while the incidence of intended bleeding patterns was significantly higher with NuvaRing (58.8–72.8%) than with LNG/EE COC (43.2–57.9%) [84]. In a 6-month study comparing 121 ring users with 126 users of an OC containing 150 mcg LNG plus 30 mcg EE, the incidence of irregular bleeding (bleeding with the ring in situ) was very low (1.1–5.0% per cycle) among ring users as compared to 5.4–38.8% observed with OC. Similarly, the incidence of intended bleeding patterns was higher with NuvaRing (65–68%) than with OC (28–47%). Early withdrawal bleeding before ring removal occurred in 1.3–13% of ring users, similar to pill users, whereas the incidence of late withdrawal bleeding (initiation of next cycle while still bleeding) was lower among NuvaRing users [85]. Likewise, intended bleeding patterns were higher among NuvaRing users (55.2–68.5%) than with DRSP/EE COCs (35.6–56.6%), with a lower incidence of breakthrough bleeding with NuvaRing [79].

One study evaluating the QuickStart approach (contraceptive method is initiated immediately at the clinic visit, regardless of menstrual cycle day) found that NuvaRing users experience significantly less bleeding–spotting days during an 84-day reference period than users of a triphasic COC [86].

Several articles have been published regarding extended-use regimens of NuvaRing. The different schemes tested besides the recommended 28-day cycle use are a 49-day cycle (42 days of continued use/7 days out), a 91-day cycle (84 days in/7 days out), and 6 and 12 months of continuous use [87–90]. In all studies, a reduction of scheduled bleeding days was observed but with an increase in breakthrough spotting days. The number of bleeding/spotting days decreases during continuous use. These studies show that extended use provides an acceptable bleeding pattern and is an option for women willing to tolerate some irregular spotting but with reduction in flow and fewer withdrawal bleeding episodes. One of the studies evaluating continuous NuvaRing use for 6 months instructed a subgroup of users to remove NuvaRing for 4 days if a breakthrough bleeding/spotting episode of more than 5 days occurred. Women in this group had a statistically greater percentage of days without breakthrough bleeding or spotting (95%) vs. 89% in the continuous-use group. They conclude that the 4-day hormone-free interval was more effective in resolving breakthrough bleeding/spotting than continuous use [89].

6. Conclusions

Contraceptive vaginal rings have shown comparable efficacy and clinical performance as low-dose OCs, with the advantage of not requiring daily dosing. Among the advantages of CVRs are their high effectiveness, good cycle control and the fact that they are user-controlled long-acting methods which provide a constant release of low doses of contraceptive steroids. Numerous studies have shown high acceptability among women, who report ease of use and the lack of a daily action as desirable attributes.

It is surprising, however, that with the vast global effort in developing this new contraceptive option, basically only one CVR model is widely available worldwide, while the PVR is only available in two countries. The ever-increasing cost of contraceptive development, the cost and fear of litigations and the increasing complexity of the tests required by regulatory agencies make it difficult to bring a new ring to
market. However, the Population Council NES/EE ring Phase III study is near completion and, hopefully, approval by the FDA will be obtained in the near future. This ring has the advantage over NuvaRing in that its duration of use is for 1 year instead of 4 weeks. This simplifies the logistics of supplies in reproductive health clinics in the developing world. Disposable one-cycle rings may be more acceptable in developed countries where the cost is not a barrier to acceptance, but long-duration models that can be used for several months would make the ring more accessible in countries with greater economic restrictions and logistic limitations. The cost of the marketed rings will also be an important factor in determining the prevalence of use.

Some of the disadvantages are the increase in vaginal discharge associated with its use and the possibility of expulsions. Touching of the genitals and introducing an object in the vagina may be an obstacle to use for women in some cultures, but, overall, good acceptability of the CVR has been shown in a large variety of countries and cultures.

There is no doubt that contraceptive rings offer a new, effective contraceptive option to women, expanding their available choices of hormonal contraception.

References


