Curr Obstet Gynecol Rep (2016) 5:1–12
DOI 10.1007/s13669-016-0141-7

FAMILY PLANNING (A. BURKE, SECTION EDITOR)

The Combined Contraceptive Vaginal Ring: an Update

Marie-Soleil Wagner[1] · **Amanda Black**[2]

Published online: 2 February 2016

Abstract The combined contraceptive vaginal ring releases 120 μg of etonogestrel and 15 μg of ethinylestradiol per day for at least a 3-week period. It is as effective as combined oral contraceptive pills with similar side effects but better cycle control. The ring is not associated with weight gain and may have many non-contraceptive benefits including a positive effect on sexual function, dysmenorrhea, premenstrual syndrome, and heavy menstrual bleeding. Contraindications are the same as for combined oral contraceptives, and serious complications are rare. The risk of venous thromboembolism with the ring is comparable with that of combined oral contraceptives. The rate of acceptability of the ring is high, and most women, including adolescents, can use the ring.

Keywords Contraceptive vaginal ring · Vaginal contraception · Etonogestrel · Combined hormonal contraception · Family planning · NuvaRing®

This article is part of the Topical Collection on *Family Planning*

✉ Marie-Soleil Wagner
marie-soleil.wagner.hsj@ssss.gouv.qc.ca

Amanda Black
ablack@toh.on.ca

[1] Department of Obstetrics and Gynecology, University of Montréal, CHU Ste-Justine, 3175 Chemin Côte-Ste-Catherine, Montréal, QC H3T 1C5, Canada

[2] Department of Obstetrics and Gynecology, University of Ottawa, Shirley E. Greenberg Women's Health Centre, 1967 Riverside Drive, Ottawa, ON, Canada

Introduction

The vaginal route of drug administration has many advantages, and over the years, many vaginal contraceptive rings have been in development. Vaginal administration avoids gastrointestinal absorption and hepatic first-pass metabolism, thus allowing a lower dose of hormones to be used and provides more uniform serum hormone concentrations as compared with daily oral administration [1]. However, only two contraceptive vaginal rings (CVR) have been brought to market: the progesterone-releasing vaginal ring, Progering® (Laboratorios Andromaco SA, Santiago, Chile), developed by Population Council and approved in many Latin and Central American countries [2] and the combined hormonal contraceptive vaginal ring, Nuvaring® (Merck & Co., Inc., Kenilworth, New Jersey, USA), marketed in North America and worldwide. Given the limited availability of the progesterone-releasing vaginal ring, this review will focus on the combined hormonal contraceptive vaginal ring.

The combined contraceptive vaginal ring is innovative in its mode of hormone delivery and its continuous 3-week administration regimen. The ring is easy to use, painless, discrete, reversible, and is inserted and removed by the woman herself. This update will discuss the advantages of the vaginal ring as a drug-delivery system [1] and will review data on the ring, including the non-contraceptive benefits, risks, and the effect on sexual function, and use in the adolescent population.

The Combined Contraceptive Vaginal Ring

The combined contraceptive vaginal ring is a flexible and transparent ring made of ethylene vinyl acetate copolymers and magnesium stearate [3]. The ring is non-biodegradable

and does not contain latex [3]. The outer diameter is 54 mm, and the cross-sectional diameter is 4 mm [3].

The ring contains a total of 11.7 mg of etonogestrel (ENG), which is the active metabolite of desogestrel (DSG), and 2.7 mg of ethinylestradiol (EE). It releases 120 μg of ENG and 15 μg of EE daily for at least 3 weeks [3–5], and the hormones are absorbed through the vaginal epithelium [1]. Serum hormonal concentrations increase immediately after insertion and then decrease slowly over the cycle [6]. The serum concentration of EE is lower with the vaginal ring versus other combined hormonal contraceptive methods [5, 6].

Mechanism of Action

The main mechanism of action is ovulation inhibition. One study showed that the ring completely inhibited ovulation for the recommended 3 weeks of use and for a subsequent 2 weeks [4]. This inhibition of ovulation is comparable or even superior with that observed with combined oral contraceptives (COC) [4, 7, 8]. Additional possible mechanisms of action are effects on cervical mucus and endometrial atrophy [9]. Fertility returns rapidly after the ring is removed, with a median time to ovulation of 17 to 19 days [10].

Effectiveness

The ring has a perfect use failure rate of 0.3 % and a typical use failure rate of 9 % [11]. In two international, multicenter, prospective, cohort studies involving a total of 2322 women, the combined intent-to-treat population Pearl Index (pregnancies per 100 women-years) was 1.18 and the per-protocol Pearl Index was 0.77 [12]. In comparative studies with COC, the intent-to-treat Pearl Indices were between 0.25 and 1.23 for the ring and 0.99 and 1.19 for COC, and there was no significant difference between the ring and COC [13–15]. A Cochrane review concluded that there was no difference in effectiveness between the ring and COC [16].

The efficacy of hormonal contraceptives in obese women has been questioned. Two pharmacokinetic studies compared hormone levels and ovarian suppression during a 28-day cycle and a 6-week extended regimen of the ring in normal weight and obese women. These studies found that the ENG serum concentrations were similar between the two groups, although the mean concentrations of EE from cycle days 1 to 21 were significantly lower in the obese group than in the normal weight group ($p < 0.012$) [17••, 18••]. In both groups, ovarian follicular development was suppressed, no ovulation occurred, and there was no difference in endometrial thickness. The authors of these studies concluded that the results support the ring having similar efficacy in obese women.

Use of the Method

Women who desire an effective and reversible method of contraception may consider using the ring provided they do not have any contraindications. The World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) have each developed Medical Eligibility Criteria for Contraceptive Use to help health care providers identify absolute contraindications (category 4) to initiation of combined hormonal contraception (CHC) (Table 1) [19–21]. Women with significant genital prolapse may have difficulty using the ring, but it is not a contraindication.

The ring is approved for 3 weeks of continuous use followed by one ring-free week. After 1 week without the ring, a new ring should be inserted. The product monograph states that women are protected for an additional week of ring use (28 days total) [3]. The malleability of the ring allows women to compress and easily insert and remove it themselves [1]. In studies, more than 90 % of women found the ring easy to insert and remove [12, 22–26]. The ring does not need to be fitted; it is a one size fits all, and there is no "correct" position. Imaging studies using MRI have demonstrated that the vaginal ring is generally located around the cervix just superior to the urogenital diaphragm, although it was positioned somewhat lower in nulliparous women just before ambulation [27].

The product monograph also suggests that the ring should be inserted on the first day of menstrual bleeding [3]. However, in practice, the ring can be initiated at any time during the menstrual cycle (Quick Start) provided it is reasonably certain that the woman is not pregnant. Backup contraception (i.e., condoms) or abstinence should be used for the first 7 days of ring use, although if the ring is inserted within the first 5 days of menstrual bleeding, backup contraception is not necessary [28••]. One study showed that Quick Start use of the ring was associated with fewer episodes of bleeding/spotting compared with Quick Start of COC (17 vs. 21.4 days, $p < 0.01$) [29] and that more women were very satisfied using the ring than using COC (61 vs. 34 %, $p = 0.003$) [30].

It is not recommended to remove the ring during intercourse. However, if removed, it should be reinserted within 3 h. Studies have shown no interactions between the ring and spermicides, antimycotics, tampons, oral amoxicillin, and doxycycline [31–34]. Similar to other methods of CHC, there are few interactions with other medications. Medications that are CYP-enzyme enhancers (e.g., certain anticonvulsants) may affect hormone levels of CHC and thus potentially affect efficacy, while CHCs can occasionally affect levels of other medications (e.g., lamotrigine) [20].

At the end of the cycle, the ring is disposed of in normal household trash [3]. One study demonstrated that the emission of EE from landfills is minimal, and hence the potential for groundwater contamination is low [35].

Table 1 Absolute contraindications to initiation of the combined contraceptive ring (category 4)

Postpartum, nonbreastfeeding, <21 days (CDC)
Postpartum, nonbreastfeeding, <21 days, with other risk factors for venous thromboembolism (WHO)
Postpartum, breastfeeding, <21 days (CDC)
Postpartum, breastfeeding <6 weeks postpartum (WHO)
Smoking ≥15 cigarettes/day
Multiple risk factors for arterial cardiovascular disease (or category 3)
Hypertension with systolic ≥160 mmHg or diastolic ≥100 mmHg
Hypertension with vascular disease
History of deep venous thrombosis/pulmonary embolism, not on anticoagulant therapy with higher risk of recurrence (CDC)
Deep venous thrombosis/pulmonary embolism on anticoagulant therapy for at least 3 months with higher risk of recurrence (CDC)
History of deep venous thrombosis/pulmonary embolism OR deep venous thrombosis/pulmonary embolism and established on anticoagulant (WHO)
Acute deep venous thrombosis/pulmonary embolism
Major surgery with prolonged immobilization
Known thrombogenic mutations
Current and history of ischemic heart disease
Stroke
Complicated valvular heart disease
Peripartum cardiomyopathy with normal or mildly impaired cardiac function of <6 months OR with moderately or severely impaired cardiac function (not mentionned in WHO)
Sytemic lupus erythematosus with positive or unknown antiphospholipid antibodies
Migraine with aura
Current breast cancer
Diabetes with nephropathy, retinopathy, neuropathy, other vascular disease, or >20 years duration (or category 3)
Viral hepatitis (acute or flare) (or category 3)
Severe cirrhosis
Hepatocellular adenoma or hepatoma
Complicated solid organ transplantation (not mentioned in WHO)

Different categories may apply to continuation of the method instead of initiation. Category 4: a condition that represents an unacceptable health risk if the contraceptive method is used. Category 3: a condition for which the theoretical or proven risks usually outweight the advantages of using the method. In italic are the conditions for which the recommendations of the CDC and WHO are discordant (adapted from the Centers for Disease Control and Prevention [19] and the World Health Organization [21])

Continuous and Extended Use of the Combined Hormonal Vaginal Ring

Although the ring is approved for use in the traditional 21/7 regimen with a withdrawal bleed during the 7-day hormone-free interval, some women may prefer to use an extended or continuous regimen, much like with the combined oral contraceptive pill. One study compared the bleeding patterns of three extended ring regimens (49-, 91-, or 364-day cycles) with the standard 28-day regimen [36]. The 28-day regimen was associated with less unscheduled bleeding than the extended regimens, and user satisfaction was higher for shorter cycles. Another study using an 84-day extended regimen for a 1-year period found that, after 1 year of use, unscheduled bleeding had decreased from 8.2 % in the first 90-day period to 1.6 % in the fourth 90-day period [37]. Both the ring and a COC using an 84-day extended regimen were associated with a significant reduction of unscheduled bleeding/spotting during a 1-year period, but the reduction was significantly higher for the ring [38].

If prolonged breakthrough bleeding/spotting occurs while using the ring in an extended or continuous fashion, removing the ring for a short period of time may help to resolve the unscheduled bleeding. Two studies showed that temporarily removing the ring for 4 days was effective in reducing the breakthrough bleeding/spotting associated with continuous use [39•, 40]. The ring should be in place for at least 21 days prior to removing it for a hormone-free interval; the hormone-free interval should never exceed 7 days [41].

Because therapeutic hormone levels are maintained for 3 weeks of use and for a subsequent 2 weeks [4], in practice, the ring can be left in place for 28 days, and then a new ring

can be inserted to start the next cycle with no hormone-free interval.

Adherence

Comparative and non-comparative trials have shown high adherence rates with the ring [12, 14, 15, 24, 26, 42–44]. The vast majority of women never temporarily removed the ring [12, 14, 15, 23, 24, 26, 42, 45].

In a randomized trial, adherence in women using the ring was better in the first 2 months compared with COC but not in the third month [46]. Another study of three contraceptive methods showed that 52 % of the women were non-compliant with their method but non-compliance was lower with the ring compared with the patch or COC (26.6 vs. 42.4 and 65.1 %, $p < 0.0001$) [47•].

Side Effects

The most frequent side effects associated with the ring are summarized in Table 2. In one study, the most common possibly ring-related side effects were headache (5.8 %), vaginitis (5.6 %), and leukorrhea (4.8 %) [12]. Only a small percentage of women experienced acne, emotional lability, nausea, or breast tenderness. In another study, 24.8 % of women reported potentially ring-related adverse events, but only 1.8 % of women reported vaginitis [42].

In many comparative trials with COC, the ring was well tolerated and had similar side effects with the exception of more vaginal symptoms (e.g., vaginitis, leukorrhea, and ring-related problems) [14, 15, 44, 45, 48]. A Cochrane review concluded that the ring was associated with less nausea, acne, irritability, depression, and emotional lability than COC [16]. In a randomized trial of COC users switching to the patch or the ring, the ring was associated with significantly less-frequent mastalgia, nausea, and skin rashes but significantly more vaginal discharge compared with the patch [49].

Table 2 Most common adverse events related to the ring

Adverse events	Percentage (%)
Weight gain	4.0–6.1
Headache	5.5–5.8
Vaginitis	1.8–5.6
Leucorrhea	4.8
Device-related events[a]	4.4
Nausea	2.5–3.2
Emotional lability	2.8
Breast tenderness	2.6
Acne	2.0

[a] Foreign body sensation, coital problems, and expulsion. Data from Dieben et al. [12] and Bruni et al. [42]

Withdrawal Bleeding and Breakthrough Bleeding

The bleeding profile for the ring used in a 21/7 regimen has been well characterized. In one study, withdrawal bleeding occurred in 98.5 % of cycles, had a mean duration of 4.5 to 5.2 days, and continued into the next cycle in 23.9 % of cycles [12]. The incidence of irregular bleeding, mostly spotting, was 5.5 % per cycle. Similar results were found in another prospective study [42]. In randomized trials, the ring was associated with better cycle control and significantly less irregular bleeding compared with COC [16, 43–45, 48, 50] and significantly shorter menstrual bleeding duration compared with the patch [49].

Vaginal Symptoms

In non-comparative and comparative studies of the ring, vaginitis was reported by 1.8 to 5.6 % of women [12, 14, 15, 26, 42, 45, 48]. Only one study specified that most cases of vaginitis were caused by *Candida* [15].

Women using the ring reported significantly more vaginal wetness compared with women using COC (63 vs. 43 %, $p < 0.001$) [51], and the ring was associated with an increase in *Lactobacilli* [51, 52•]. There was no difference in the other studied parameters (yeast colony counts, Nugent Gram stain score, vaginal white blood cell count, vaginal pH, and amount of vaginal discharge). Some authors suggested that the increase in leukorrhea reported might reflect the increase in lactobacilli populations rather than pathology [53]. The ring seems to have a positive effect on the number of lactobacilli, and despite yeast adhesion to the ring [54], studies have not demonstrated more vaginal infection with the ring.

Effects on Sexual Function

Studies have shown that the ring is well tolerated by women and their partners [10, 13, 23–25, 50]. One study found that 85 % of women rarely or never felt the ring and 71 % of their partners rarely or never felt the ring [10]. Ninety-four percent of partners did not object to use of the ring.

Studies have addressed the effect of the ring on sexual function. One study showed a significant improvement from baseline in sexual function experienced by women (anxiousness, sexual pleasure and interest, orgasm, satisfaction, complicity) and their partners after 3 months of using the ring or COC compared with women not using hormonal contraception ($p < 0.05$) [55]. This effect persisted up to 6 months. In addition, a significant increase in sexual fantasy was reported in the ring group compared with the two other groups

($p < 0.001$). Another study showed that users of the ring reported an increase in sexual desire and satisfaction compared with COC users [45]. Women using the ring in an extended regimen also experienced a significant improvement in their sexual function and quality of life [56•]. A recent cohort study showed that the subdermal implant, the ring, and a COC containing 20 μg EE all had a positive impact on sexual function indicators [57•].

Other studies have not demonstrated a positive effect on sexual function [58, 59•]. One study found that ring users had significantly more sexual dysfunction (feeling the ring during intercourse, negative partner reaction) compared with patch users (37.9 vs. 28.7 %, $p = 0.03$) [58], although the authors concluded that this was not likely to be clinically significant. Another study assessed the sexual function in users of the ring and users of COC containing 30 μg EE and 3 mg of drospirenone (DRSP) [59•]. Both groups experienced a significant decrease in their sexual function score ($p = 0.001$); in addition, the COC group experienced a significant reduction in frequency of orgasm ($p = 0.02$) and intercourse ($p = 0.04$) that was not seen in ring users.

Weight

Many non-comparative studies have found that the ring is not associated with significant clinical changes in weight [12, 22, 23, 26]. Similar results have been found in studies comparing the ring with COC [44, 50, 60].

Risks Associated with Ring Use

Cardiovascular

All combined hormonal contraceptives are associated with an increased risk of venous thromboembolism (VTE). Although two retrospective database studies found an increased risk of VTE in ring users compared with COC users [61••, 62••], a large prospective cohort study [63••] and a third retrospective database study did not find an increased risk in ring users compared with COC users [64••]. One retrospective, cohort study based on a national registry found that ring users had an increased risk of VTE compared with women using COCs containing levonorgestrel (relative risk (RR), 1.9 (95 % confidence interval (95 % CI), 1.33–2.71)) [61••]. Another cohort study based on the same registry found an increased risk of thrombotic stroke in ring users compared with non-users (31.4 per 10,000 women-years (WY) vs. 24.2/10,000 WY; RR, 2.49 (95 % CI, 1.41–4.41)) but no significant increase in the risk of myocardial infarction (7.8/100,000 vs. 13.2/100,000 WY; RR, 2.08 (95 % CI, 0.67–6.48)) [62••]. The absolute risk for both thrombotic stroke and myocardial infarction remains very low. Conversely, another retrospective database study found that new users of the ring did not have an increased risk of VTE or arterial thromboembolism (ATE) compared with older generations of COC [64••]. A large international, prospective, cohort active surveillance study of 33,295 new users of the ring or COC was conducted to compare the cardiovascular risks of the two methods [63••]. Loss to follow-up was only 2.9 %. In this study, there was no significant difference in the incidence of VTE between ring users and COC users (8.3/10,000 vs. 9.2/10,000 WY; adjusted hazard ratio (HR_{adj}), 0.8 (95 % CI, 0.5–1.5)), and no difference in the incidence of ATE (HR_{adj}, 0.7 (95 % CI, 0.2–2.3)). The quality of studies, level of evidence, and potential confounders and biases should be considered when discussing the cardiovascular risk of combined hormonal contraceptives, including the vaginal ring. Based on the best available evidence from large prospective cohort studies, there does not appear to be a significant difference in the incidence of VTE or ATE in ring users compared with COC users.

Although one small study of ring users undergoing 24-h blood pressure monitoring found a slight statistically significant increase in mean and 24-h diastolic blood pressure [65•], the majority of studies have shown that the ring is not associated with significant changes in blood pressure [12, 14, 15, 22, 23, 26, 44, 66, 67].

Metabolic Effects

The ring seems to have minimal effect on adrenal or thyroid function [66]. There are minimal changes in carbohydrate metabolism [66, 68•, 69–71], and the ring seems to have less impact than COC [70, 71]. Some studies have shown minimal effects of the ring on lipid metabolism [71, 72], while others have shown increases in triglyceride levels similar to those seen with COC [70, 73, 74•].

The ring appears to have minimal effects on hemostatic parameters [75]. While some studies have found that the ring is associated with a greater increase in sex hormone-binding globulin (SHBG; a biomarker of thrombosis) than COC [71, 72, 76], while other studies have not [5, 77]. The clinical relevance of this is uncertain, and caution should be used when interpreting these results due to the limitations of using surrogate markers to assess risk [78].

Cervical Effects

The ring has not been associated with major changes in cervical cytology [12, 26]. In one study, a minority of women presented with changes in their cytology results: 1.3 % of women changed their cytology from normal to low-grade squamous intraepithelial lesion (LGSIL) and 0.4 % from normal to high-grade squamous intraepithelial lesion [12]. However, in the same study, 11 women started the study with LGSIL and 8 of them had normal cytology results at the end of

the study. The authors noted that these shifts are common and might be detected because of more frequent screening. In another non-comparative study of the ring for 13 cycles, 80 % of women had normal colposcopic assessment at the beginning and at the end of the study [79]. A similar percentage of women showed colposcopic changes from normal to abnormal (11 %) and from abnormal to normal (11 %). There were no major changes in cytology results.

Bone Effects

There is limited evidence regarding the effect of the ring on bone mineral density (BMD) or fracture. One study in premenopausal women using the ring found that there was no change in BMD after 26 cycles of ring use compared with baseline [80]. The control group had a slight increase in BMD from baseline at the lumbar spine and femoral neck. There was a statistically significant difference in the BMD of the control group vs. the ring after 26 cycles of treatment ($p < 0.0001$); however, the authors did not consider this to be clinically significant. In a randomized, controlled study of the ring and the patch, no difference was seen in BMD between the groups or in comparison with the baseline values after 1 year of treatment [81].

Non-contraceptive Benefits of the Ring

The combined oral contraceptive pill has a number of non-contraceptive benefits, including decreased menstrual bleeding, decreased acne and hirsutism, decreased premenstrual dysphoric disorder symptoms, and decreased ovarian and endometrial cancer [82, 83]. The ring likely has many of the same non-contraceptive benefits, but only a few studies have been performed to specifically evaluate the non-contraceptive benefits of the ring.

Dysmenorrhea

In one randomized study, the prevalence of moderate or severe dysmenorrhea was lower after 1 year of ring use compared with baseline (5.9 vs. 17.4 %) [50]. Four observational studies of varying durations of ring use (2 to 7 months) have reported an improvement in dysmenorrhea [22–24, 84]. A reduction in dysmenorrhea was also reported after an extended 84-day regimen of the ring for 1 year (56 to 20 %, $p < 0.001$) [67].

Heavy Menstrual Bleeding

In a randomized trial, both the ring and noresthisterone were effective for treatment of idiopathic heavy menstrual bleeding; the average reduction of blood loss after 3 cycles of ring use was 68.6 % [85•]. More women were satisfied or very satisfied with the ring compared with noresthisterone (70.8 vs. 42.5 %, $p = 0.003$).

Premenstrual Syndrome

One randomized study found a decrease in premenstrual syndrome (PMS) after 1 year of ring use compared with baseline (4.5 vs. 12.6 %) [50]. Two observational studies also reported an improvement in PMS with ring use [24, 84].

Migraine

In an observational study, 6.6 % of women using the ring reported an improvement in moderate to severe menstrual headache compared with baseline ($p < 0.025$) [84]. Another small study evaluated the effect of an extended ring regimen on migraine with aura and on menstrual-related migraines and found a significantly reduced frequency of migraine with aura. Menstrual-related migraines disappeared in the majority of women [86].

Fertility Treatment

The use of the ring for pre-treatment in one in vitro fertilization (IVF) cycle has been compared with use of a COC [87]. The side effect profile of the two groups was similar with the exception of more breast tenderness in the COC group. Clinical pregnancy rates were not significantly different between the two groups (19 % per cycle for the ring vs. 25.9 % per cycle for COC, $p = 0.56$), but there were fewer embryos of ≥5 cells on day 3 in the ring group ($p = 0.02$) and more cycles in the ring group were canceled due to poor response to stimulation ($p = 0.05$). The authors concluded that oocyte and embryo quality may not be as good with the ring compared with COC; however, the small sample size and multiple IVF protocols utilized made it difficult to determine if the effects of the ring were more marked in some protocols than others, and further studies are required.

Endometriosis

A study comparing the effect of the ring with COC for the treatment of rectovaginal endometriosis infiltrating the rectum found that COC users were more satisfied after 12 months of treatment (61.7 vs. 36.1 %, $p = 0.004$) and had significantly less pain and gastrointestinal symptoms [88•]. Both treatments were associated with a significant reduction in nodule volume, and this reduction was not different between the two groups. Rates of dissatisfaction were the same (approximately 22 % for each group, $p = 0.998$).

Polycystic Ovary Syndrome

The effects of the ring and a COC containing DRSP on metabolic parameters in women with polycystic ovary syndrome were compared. Hirsutism and serum parameters of hyperandrogenemia improved with both treatments [89].

Continuation and Satisfaction

Non-comparative studies have reported discontinuation rates of up to 35.4 % in ring users over the course of 13 cycles [12, 26]. Reasons for discontinuation included non-medical or non-device-related reasons (18.5 %) and adverse events (15.1 %) [12]. The most common side effects associated with discontinuation were device-related events (foreign body sensation, coital problems, and device expulsion; 2.5 %), headache (1.3–2.1 %), emotional lability (1.2 %), weight gain (1 %), vaginal discomfort (1 %), and nausea (1 %) [12]. In comparison with the pill, a 2013 Cochrane review found a significant difference in continuation rates in only 2 of the 11 included studies. In these two studies, ring users were less likely to discontinue the ring than COC users [16]. In a randomized trial of the ring compared with COC, 6-month continuation rates for both groups were low (26 % for the ring and 29 % for COC, $p = 0.61$) [46]. In a recent analysis of the prospective CHOICE study, 3-year continuation rates for the ring, the COC, and long-acting reversible contraceptive (LARC) methods were 30, 31.5, and 67.2 %, respectively [90••]. Reasons for ring discontinuation included side effects (26.7 %) and logistical reasons (time, hard to get, remember; 23.7 %).

Acceptability of the ring is high [22–25]. In one acceptability study, 96 % of women were satisfied or very satisfied and 97 % would recommend the ring [25]. Two studies found that satisfaction with the ring was high and similar to COC [14, 46]. In one study, using Quick Start, more women were very satisfied using the ring as compared with COC (61 vs. 34 %, $p = 0.003$) [30]. When compared with the patch, 71 % of women using the ring planned to continue using their method after the study compared with 26.5 % using the patch ($p < 0.001$) [49].

Various factors are associated with the use of or willingness to use the ring [91•, 92–95]. Attitudes toward ring use are affected by convenience, frequency of use, acceptability of self-insertion, feeling the ring during intercourse, lower probability of inadvertent omission, concern over potential hormonal side effects, willingness to use the contraceptive patch, being employed at least 20 h/week, and tampon use.

Use by Adolescents

Because it is discrete and less user dependent, the ring may be an appealing choice for adolescents. Although COCs have been well studied in the adolescent population, fewer studies of the ring have targeted the adolescent population. Compared with other contraceptive methods, the contraceptive ring is not often used by adolescent women. A survey of 14- to 18-year-old girls in Finland showed that oral contraceptives (OC) were used by 20 % of the participants compared with 0.9 % for the ring and 0.1 % for the patch [96]. In another survey, only 1.5 % of adolescents between 14 and 18 years of age had ever used the ring [97]. An analysis of 1404 adolescents between 14 and 19 years of age who participated in the prospective cohort CHOICE study found that 4.9 % of adolescents chose the ring compared with 2.0 % for the patch, 9 % for depot medroxyprogesterone acetate, 12.5 % for OC, 34.5 % for the etonogestrel implant, and 37 % for intrauterine devices (IUD) [98••]. A study of 3207 adolescent mothers 15–19 years old showed that the ring was used by only 3.1 % of adolescents postpartum compared with 30 % for pills and 10.8 % for the IUD [99].

Acceptability of the ring in adolescents has been studied. Although one study in women aged 15 to 21 found higher acceptability of the ring compared with the COC, compliance with the two methods was the same [100]. Two studies have shown that between 34 and 52 % of adolescents have never heard of the ring [97, 101]. However, in one study, after receiving information, 57.9 % liked the idea of the ring, and 45.7 % said that they would consider using the ring. The significant factor associated with considering ring use was comfort with ≥1 vaginal products (e.g., vaginal spermicide, vaginal lubricant, vaginal douche, and topical vaginal yeast medication) [101]. In the other study, willingness to try the ring was associated with previous use of the patch, indices of comfort with one's genitals, comfort with insertion and removal and with possible insertion options such as with an applicator or a rubber glove, and knowledge of positive method characteristics [97].

As with many other contraceptive methods, continuation rates can be problematic in adolescent ring users. In a prospective cohort study of women 15 to 24 years old, composed of 67 % adolescents, there was no difference in continuation rates between the ring and OC (29.4 per 100 vs. 32.7 per 100 WY, $p = 0.06$) [102]. The main reason for discontinuation of the OC or the ring was side effects. In the prospective CHOICE study, adolescent ring users aged 14 to 19 years had the lowest 12-month continuation rate (31 %) and the highest rates of not being satisfied [103]. A recent study of 145 adolescents aged 13 to 20 found that only 17 % who had started the ring or the patch were still using it after 6 months, compared with 43 % for the OC [104]. Common reasons for discontinuation were side effects and difficulty getting refills.

Interviews with 32 women 15 to 24 years old demonstrated that adolescents undergo a multi-stage process when adopting the ring and the investigators subsequently proposed a model for the stages of adolescent

adoption and discontinuation of the ring. These stages include (1) hearing about the ring, (2) initial reactions, (3) first experiences with insertion and removal, (4) first sexual experiences, (5) assessment and adjustment period, and (6) sharing experiences with friends [105]. This model may be helpful when counseling adolescents about the ring. Focus groups that have evaluated perceptions about the ring and the patch in women aged 15 to 26 revealed themes unique to the ring, such as "concerns regarding vaginal insertion" and "sexual partner perceptions" [106]. The authors concluded that women expressed more positive attitudes toward the patch as compared with the ring and that providers should be aware of women's apprehensions and misperceptions in order to reduce barriers to use in adolescents.

Future Directions

At this time, other contraceptive vaginal rings are under development and study. Population Council has developed a combined contraceptive vaginal ring. This ring is made of silicone with a two-channel core containing the hormones: one channel with nestorone (NES) and the other with NES and EE [107]. NES is a 19-norprogesterone derivative that binds exclusively to the progesterone receptor, has an excellent metabolic profile, and is not orally active but is effective by the vaginal route [107–109]. The ring releases 150 μg of NES and 15 μg of EE/day [107]. It is designed to provide contraception for 1 year of use and to be used in a 21-day/1-week-free regimen [107]. As opposed to the combined ENG/EE ring, one of the advantages of the NS/EE ring is that refrigeration is not required [110]. A large phase III trial involving more than 2000 women in 27 sites is now complete, but data on safety and efficacy has not been published yet. Safety substudies were also conducted to evaluate the effects of the ring on different parameters [107]. One of the substudies showed that the ring was not associated with an increased rate of vaginal infections or with significant changes in the vaginal flora [111]. The other substudy demonstrated that the ring was associated with an increase, within the normal range, in three hepatic proteins and an increase above the normal range for SHBG [110].

Other contraceptive vaginal rings in development are combined NES and EE rings intended to be used for three continuous cycles [112] and also a 3-month vaginal ring containing ulipristal acetate [113, 114]. Research and development with vaginal rings is focusing not only on contraceptive rings but also on vaginal rings that can deliver microbicides, as well as on multipurpose vaginal rings that could be used continuously for contraception and prevention of human immunodeficiency virus (HIV) infection [115, 116].

Conclusions

The ring is a contraceptive method with many advantages. It is as effective as COC with a similar safety profile but has demonstrated better cycle control. For most women, the ring is well accepted and easy to use. It also has many non-contraceptive benefits, such as the improvement or amelioration of dysmenorrhea, premenstrual syndrome and heavy menstrual bleeding. Despite its many advantages, the continuation rate is low and similar to that for COC. The ring is underutilized in the adolescent population. Educating women about all of their contraceptive options, including the vaginal ring, may help to increase awareness of the vaginal ring as well as uptake of this method of contraception. Despite the advantages of the vaginal route of administration, there are very few vaginal rings available and only one ring in the North American market. Hopefully, research and development will continue so that women of reproductive age can have access to a wide range of contraceptive options that best suit their needs.

Compliance with Ethical Standards

Conflict of Interest Marie-Soleil Wagner declares personal fees from Bayer for serving on the Advisory Board, as a Speaker, for Participation in the INTRAduction Workshop supported by Bayer, and for being a Member of the Canadian Network for Intrauterine Contraception supported by Bayer. She also declares personal fees from Actavis for Advisory board work; personal fees from Pfizer for Participation in a Continuing Medical Education program. Amanda Black declares personal fees from Bayer for serving as a Speaker and on the Advisory Board in the last 2 years, personal fees from Merck for serving on the advisory board, and personal fees from Pfizer and Actavis for serving as a speaker and on the advisory boards.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Alexander NJ, Baker E, Kaptein M, Karck U, Miller L, Zampaglione E. Why consider vaginal drug administration? Fertil Steril. 2004;82(1):1–12.
2. RamaRao S, Clark H, Merkatz R, Sussman H, Sitruk-Ware R. Progesterone vaginal ring: introducing a contraceptive to meet the needs of breastfeeding women. Contraception. 2013;88(5):591–8.
3. Merck. NuvaRing® Prescribing Information. November 2014. Available at: http://www.nuvaring.com/consumer/prescribing_information/. Accessed 16 September 2015

4. Mulders TM, Dieben TO. Use of the novel combined contraceptive vaginal ring NuvaRing for ovulation inhibition. Fertil Steril. 2001;75(5):865–70.
5. Timmer CJ, Mulders TM. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. Clin Pharmacokinet. 2000;39(3):233–42.
6. van den Heuvel MW, van Bragt AJ, Alnabawy AK, Kaptein MC. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. Contraception. 2005;72(3): 168–74.
7. Petrie KA, Torgal AH, Westhoff CL. Matched-pairs analysis of ovarian suppression during oral vs. vaginal hormonal contraceptive use. Contraception. 2011;84(5):e1–4.
8. Duijkers I, Klipping C, Verhoeven CH, Dieben TO. Ovarian function with the contraceptive vaginal ring or an oral contraceptive: a randomized study. Hum Reprod. 2004;19(11):2668–73.
9. Killick S. Complete and robust ovulation inhibition with NuvaRing. Eur J Contracept Reprod Health Care. 2002;7 Suppl 2:13–8.
10. Mulders TM, Dieben TO, Bennink HJ. Ovarian function with a novel combined contraceptive vaginal ring. Hum Reprod. 2002;17(10):2594–9.
11. Trussell J. Contraceptive failure in the United States. Contraception. 2011;83(5):397.
12. Dieben TO, Roumen FJ, Apter D. Efficacy, cycle control, and user acceptability of a novel combined contraceptive vaginal ring. Obstet Gynecol. 2002;100(3):585–93.
13. Mansour D, Inki P, Gemzell-Danielsson K. Efficacy of contraceptive methods: a review of the literature. Eur J Contracept Reprod Health Care. 2010;15:4–16.
14. Ahrendt HJ, Nisand I, Bastianelli C, Gómez MA, Gemzell-Danielsson K, Urdl W, et al. Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 30 μg of ethinyl estradiol and 3 mg of drospirenone. Contraception. 2006;74(6):451–7.
15. Odsson K, Leifels-Fischer B, de Melo NR, Wiel-Masson D, Benedetto C, Verhoeven CHJ, et al. Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial. Contraception. 2005;71(3):176–82.
16. Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz JKF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database Syst Rev. 2013;4, CD003552.
17.•• Dragoman M, Petrie K, Torgal A, Thomas T, Cremers S, Westhoff CL. Contraceptive vaginal ring effectiveness is maintained during 6 weeks of use: a prospective study of normal BMI and obese women. Contraception. 2013;87(4):432–6. **This study demonstrated that the ring had similar ovarian suppression in normal weight and obese women using an extended 6-week regimen**.
18.•• Westhoff CL, Torgal AH, Mayeda ER, Petrie K, Thomas T, Dragoman M, et al. Pharmacokinetics and ovarian suppression during use of a contraceptive vaginal ring in normal-weight and obese women. Am J Obstet Gynecol. 2012;207(1):39.1–6. **This study demonstrated that the ring had similar ovarian suppression in normal weight and obese women**.
19. Centers for Disease Control and Prevention. Update to CDC's U.S. Medical eligibility criteria for contraceptive use, 2010: revised recommendations for the use of contraceptive methods during the postpartum period. MMWR. 2011;60(26):878–83.
20. Centers for Disease Control and Prevention. U.S. medical eligibility criteria for contraceptive use, 2010. Adapted from the World Health Organization medical eligibility criteria for contraceptive use, 4th edition. MMWR. 2010;59(RR04):1–85.
21. World Health Organization. Medical eligibility criteria for contraceptive use. Fifthth ed. Switzerland: World Health Organization; 2015.
22. Brucker C, Karck U, Merkle E. Cycle control, tolerability, efficacy and acceptability of the vaginal contraceptive ring, NuvaRing: results of clinical experience in Germany. Eur J Contracept Reprod Health Care. 2008;13(1):31–8.
23. Merki-Feld GS, Hund M. Clinical experience with NuvaRing in daily practice in Switzerland: cycle control and acceptability among women of all reproductive ages. Eur J Contracept Reprod Health Care. 2007;12(3):40–7.
24. Roumen FJ, op ten Berg MM, Hoomans EH. The combined contraceptive vaginal ring (NuvaRing): first experience in daily clinical practice in The Netherlands. Eur J Contracept Reprod Health Care. 2006;11(1):14–22.
25. Novák A, de la Loge C, Abetz L, van der Meulen EA. The combined contraceptive vaginal ring, NuvaRing: an international study of user acceptability. Contraception. 2003;67(3):187–94.
26. Roumen FJ, Apter D, Mulders TM, Dieben TO. Efficacity, tolerability and acceptability of a novel contraceptive vaginal ring releasing etonogestrel and ethinyl oestradiol. Hum Reprod. 2001;16(3):469–75.
27. Barnhart KT, Timbers K, Pretorius ES, Lin K, Shaunik A. In vivo assessment of NuvaRing® placement. Contraception. 2005;72(3): 196–99.
28.•• Centers for Disease Control and Prevention. U.S. Selected practice recommendations for contraceptive use, 2013 adapted from the world health organization selected practice recommendations for contraceptive use, 2nd edition. MMWR. 2013;62(5):1–60. **This document contains all the recommendations for use of contraceptive methods including information on timing of initiation, examinations needed before initiation of the method, and follow-up**.
29. Westhoff C, Osborne LM, Schafer JE, Morroni C. Bleeding patterns after immediate initiation of an oral compared with a vaginal hormonal contraceptive. Obstet Gynecol. 2005;106(1):89–96.
30. Schafer JE, Osborne LM, Davis AR, Westhoff C. Acceptability and satisfaction using Quick Start with the contraceptive vaginal ring versus an oral contraceptive. Contraception. 2006;73(5):488–92.
31. Dogterom P, van den Heuvel MW, Thomsen T. Absence of pharmacokinetic interactions of the combined contraceptive vaginal ring NuvaRing® with oral amoxicillin or doxycycline in two randomised trials. Clin Pharmacokinet. 2005;44(4):429–38.
32. Verhoeven CH, Dieben TO. The combined contraceptive vaginal ring, NuvaRing®, and tampon co-usage. Contraception. 2004;69(3):197–9.
33. Verhoeven CH, van den Heuvel MW, Mulders TM, Dieben TO. The contraceptive vaginal ring, NuvaRing®, and antimycotic co-medication. Contraception. 2004;69(2):129–32.
34. Haring T, Mulders TM. The combined contraceptive ring NuvaRing® and spermicide co-medication. Contraception. 2003;67(4):271–2.
35. Geurts MG, de Boer W, de Graaf JS, van Ginkel CG. Environmental exposure assessment of ethinyl estradiol (EE) from a combined hormonal vaginal contraceptive ring after disposal; leaching from landfills. Sci Total Environ. 2007;377(2–3): 366–70.
36. Miller L, Verhoeven CH, Hout J. Extended regimens of the contraceptive vaginal ring: a randomized trial. Obstet Gynecol. 2005;106(3):473–82.
37. Barreiros FA, Guazelli CA, de Araújo FF, Barbosa R. Bleeding patterns of women using extended regimens of the contraceptive vaginal ring. Contraception. 2007;75(3):204–8.
38. Guazelli CA, Barreiros FA, Barbosa R, de Araújo FF, Moron AF. Extended regimens of the vaginal contraceptive ring: cycle control. Contraception. 2009;80(5):430–5.

39.• Weisberg E, Merki-Feld GS, McGeechan K, Fraser IS. Randomized comparison of bleeding patterns in women using a combined contraceptive vaginal ring or a low-dose combined oral contraceptive on a menstrually signaled regimen. Contraception. 2015;91(2):121–6. **This study demonstrated that when using a continuous ring regimen, temporarily removing the ring is associated with less breakthrough bleeding/spotting**.

40. Sulak P, Smith V, Coffee A, Witt I, Kuehl AL, Kuehl TJ. Frequency and management of breakthrough bleeding with continuous use of the transvaginal contraceptive ring: a randomized controlled trial. Obstet Gynecol. 2008;112(3):563–71.

41. Guilbert E, Boroditsky R, Black A, Leboeuf M, Mirosh M, Senikas V, et al. Canadian consensus guideline on continuous and extended hormonal contraception, 2007. J Obstet Gynaecol Can. 2007;29(7 Suppl 2):S1–32.

42. Bruni V, Pontello V, Luisi S, Petraglia F. An open-label, multicentre trial to evaluate the vaginal bleeding pattern of the combined contraceptive vaginal ring NuvaRing. Eur J Obstet Gynecol Reprod Biol. 2008;139(1):65–71.

43. Odsson K, Leifels-Fischer B, Wiel-Masson D, de Melo NR, Benedetto C, Verhoeven CH, et al. Superior cycle control with a contraceptive vaginal ring compared with an oral contraceptive containing 30 μg ethinylestradiol and 150 μg levonorgestrel: a randomized trial. Hum Reprod. 2005;20(2):557–62.

44. Bjarnadottir RI, Tuppurainen M, Killick SR. Comparison of cycle control with a combined contraceptive vaginal ring and oral levonorgestrel/ethinyl estradiol. Am J Obstet Gynecol. 2002;186(3):389–95.

45. Sabatini R, Cagiano R. Comparison profiles of cycle control, side effects and sexual satisfaction of three hormonal contraceptives. Contraception. 2006;74(3):220–3.

46. Gilliam ML, Neustadt A, Kozloski M, Mistretta S, Tilmon S, Godfrey E. Adherence and acceptability of the contraceptive ring compared with the pill among students: a randomized controlled trial. Obstet Gynecol. 2010;115(3):503–10.

47.• de Zarate Martínez-Astorquiza-Ortiz T, Díaz-Martín T, Martínez-Astorquiza-Corral T, MIA Study Investigators. Evaluation of factors associated with noncompliance in users of combined hormonal contraceptive methods: a cross-sectional study: results from the MIA study. BMC Womens Health. 2013;13:38. **This study showed that less women were noncompliant with the ring as compared to the patch or COC**.

48. Mohamed AM, El-Sherbiny WS, Mostafa WA. Combined contraceptive ring versus combined oral contraceptive (30-μg ethinylestradiol and 3-mg drospirenone). Int J Gynaecol Obstet. 2011;114(2):145–8.

49. Creinin MD, Meyn LA, Borgatta L, Barnhart K, Jensen J, Burke AE, et al. Multicenter comparison of the contraceptive ring and patch: a randomized controlled trial. Obstet Gynecol. 2008;111(2 Pt1):267–77.

50. Milsom I, Lete I, Bjertnaes A, Rokstad K, Lindh I, Gruber CJ, et al. Effects on cycle control and bodyweight of the combined contraceptive ring, NuvaRing, versus an oral contraceptive containing 30 μg ethinylestradiol and 3 mg drospirerone. Hum Reprod. 2006;21(9):2304–11.

51. Veres S, Miller L, Burington B. A comparison between the vaginal ring and oral contraceptives. Obstet Gynecol. 2004;104(3):555–63.

52.• De Seta F, Restaino S, De Santo D, Stabile G, Banco R, Busetti M, et al. Effects of hormonal contraception on vaginal flora. Contraception. 2012;86(5):526–9. **This study demonstrated that the ring was associated with an increase in Lactobacilli compared to COC**.

53. Nappi RE, Group INS. Counseling on vaginal delivery of contraceptive hormones: implications for women's body knowledge and sexual health. Gynecol Endocrinol. 2013;29(12):1015–21.

54. Camacho DP, Consolaro ME, Patussi EV, Donatti L, Gasparetto A, Svidzinski TI. Vaginal yeast adherence to the combined contraceptive vaginal ring (CCVR). Contraception. 2007;76(6):439–43.

55. Guida M, Di Spiezio SA, Bramante S, Sparice S, Acunzo G, Tommaselli GA, et al. Effects of two types of hormonal contraception-oral versus intravaginal-on the sexual life of women and their partners. Hum Reprod. 2005;20(4):1100–6.

56.• Caruso S, Cianci S, Malandrino C, Cicero C, Presti LL, Cianci A. Quality of sexual life of women using the contraceptive vaginal ring in extended cycles: preliminary report. Eur J Contracept Reprod Health Care. 2014;19:307–14. **This study demonstrated that an extended regimen of the ring was associated with improvement in sexual function and quality of life**.

57.• Guida M, Cibarelli F, Troisi J, Gallo A, Palumbo AR, Di Spiezio Sardo S. Sexual life impact evaluation of different hormonal contraceptives on the basis of their methods of administration. Arch Gynecol Obstet. 2014;290(6):1239–47. **This study demonstrated that three types of hormonal contraceptives, including the ring, were associated with an improvement in sexual function**.

58. Gracia CR, Sammel MD, Charlesworth S, Lin H, Barnhart KT, Creinin MD. Sexual function in first-time contraceptive ring and contraceptive patch users. Fertil Steril. 2010;93(1):21–8.

59.• Battaglia C, Morotti E, Persico N, Battaglia B, Busacchi P, Casadio P, et al. Clitoral vascularization and sexual behavior in young patients treated with drospirenone-ethinyl estradiol or contraceptive vaginal ring: a prospective, randomized, pilot study. J Sex Med. 2014;11(2):471–80. **Study demonstrated that the ring was associated with vaginal wetness**.

60. O'Connell KJ, Osborne LM, Westhoff C. Measured and reported weight change for women using a vaginal contraceptive ring vs. a low-dose oral contraceptive. Contraception. 2005;72(5):323–7.

61.•• Lidegaard Ø, Nielsen LH, Skovlund CW, Løkkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001–10. BMJ. 2012;344, e2990. **This study showed that the ring was associated with an increased risk of venous thrombosis compared to COC containing LNG**.

62.•• Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. N Eng J Med. 2012;366(24):2257–66. **This study showed that current use of the ring was associated with an increased risk of thrombotic stroke**.

63.•• Dinger J, Möhner S, Heinemann K. Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring. Obstet Gynecol. 2013;122(4):800–8. **This study showed that the ring was associated with the same risk of venous and arterial thromboembolic events compared to COC**.

64.•• Sidney S, Cheetham TC, Connell FA, Ouellet-Hellstrom R, Graham DJ, Davis D, et al. Recent combined hormonal contraceptives (CHCs) and the risk of thromboembolism and other cardiovascular events in new users. Contraception. 2013;87(1):93–100. **This study showed that the ring was not associated with a higher risk of thromboembolic or thrombotic events compared to low-dose COC in new users**.

65.• Cagnacci A, Zanin R, Napolitano A, Arangino S, Volpe A. Modification of 24-h ambulatory blood pressure and heart rate during contraception with the vaginal ring: a prospective study. Contraception. 2013;88(4):539–43. **This study demonstrated that the ring was associated with a small increase in 24-h blood pressure**.

66. Duijkers I, Killick S, Bigrigg A, Dieben TO. A comparative study on the effects of a contraceptive vaginal ring NuvaRing® and an oral contraceptive on carbohydrate metabolism and adrenal and thyroid function. Eur J Contracept Reprod Health Care. 2004;9(3):131–40.

67. Barreiros FA, Guazelli CA, Barbosa R, de Assis F, de Araújo FF. Extended regimens of the contraceptive vaginal ring: evaluation of clinical aspects. Contraception. 2010;81(3):223–5.
68.• Guazelli CA, Barreiros FA, Torloni MR, Barbieri M. Effects of extended regimens of the contraceptive vaginal ring on carbohydrate metabolism. Contraception. 2012;85(3):253–6. **This study showed that an extended regimen of the ring was not associated with significant changes in carbohydrate metabolism as measured over 1 year**.
69. Grodnitskaya EE, Grigoryan OR, Klinyshkova EV, Andreeva EN, Melnichenki GA, Dedov II. Effect on carbohydrate metabolism and analysis of acceptability (menstrual cycle control) of extended regimens of the vaginally inserted hormone-releasing system 'NuvaRing' as compared with the standard 21/7 regimen in reproductive-age women with type 1 diabetes mellitus. Gynecol Endocrinol. 2010;26(9):663–8.
70. Cagnacci A, Ferrari S, Tirelli A, Zanin R, Volpe A. Route of administration of contraceptives containing desogestrel/etonorgestrel and insulin sensitivity: a prospective randomized study. Contraception. 2009;80(1):34–9.
71. Elkind-Hirsch KE, Darensbourg C, Ogden B, Ogden LF, Hindelang P. Contraceptive vaginal ring use for women has less adverse metabolic effects than an oral contraceptive. Contraception. 2007;76(5):348–56.
72. Tuppurainen M, Klimscheffskij R, Venhola M, Dieben TO. The combined contraceptive vaginal ring (NuvaRing®) and lipid metabolism: a comparative study. Contraception. 2004;69(5):389–94.
73. Barreiros FA, Guazelli CA, Barbosa R, Torloni MR, Barbieri M, Araujo FF. Extended regimens of the combined contraceptive vaginal ring containing etonogestrel and ethinyl estradiol: effects on lipid metabolism. Contraception. 2011;84(2):155–9.
74.• Guazelli CA, Barreiros FA, Barbosa R, Torloni MR, Barbieri M. Extended regimens of the contraceptive vaginal ring versus hormonal oral contraceptives: effects on lipid metabolism. Contraception. 2012;85(4):389–93. **This study showed that an extended regimen of the ring was associated with similar changes in lipid metabolism compared to COC**.
75. Magnusdóttir EM, Bjarnadóttir RI, Önundarson PT, Gudmundsdóttir BR, Geirsson RT, Magnusdóttir SD, et al. The contraceptive vaginal ring (NuvaRing®) and hemostasis: a comparative study. Contraception. 2004;69(6):461–7.
76. Fleischer K, van Vliet HA, Rosendaal FR, Rosing J, Tchaikovski S, Helmerhorst FM. Effects of the contraceptive patch, the vaginal ring and an oral contraceptive on APC resistance and SHBG: a cross-over study. Thromb Res. 2009;123(3):429–35.
77. Piltonen T, Puurunen J, Hedberg P, Ruokonen A, Mutt SJ, Herzig KH, et al. Oral, transdermal and vaginal combined contraceptives induce an increase in markers of chronic inflammation and impair insulin sensitivity in young healthy normal-weigh women: a randomized study. Hum Reprod. 2012;27(10):3046–56.
78. Jensen JT, Burke AE, Barnhart KT, Tillotson C, Messerle-Forbes M, Peters D. Effect of switching from oral to transdermal or transvaginal contraception on markers of thrombosis. Contraception. 2008;78(6):451–8.
79. Archer D, Raine T, Darney P, Alexander NJ. An open-label noncomparative study to evaluate the vagina and cervix of NuvaRing users. Fertil Steril. 2002;78 Suppl 1:S25.
80. Massai R, Mäkäräinen L, Kuukankorpi A, Klipping C, Duijkers I, Dieben T. The combined contraceptive vaginal ring and bone mineral density in healthy pre-menopausal women. Hum Reprod. 2005;20(10):2764–8.
81. Massaro M, Di Carlo C, Gargano V, Formisano C, Bifulco G, Nappi C. Effect of the contraceptive patch and the vaginal ring on bone metabolism and bone mineral density: a prospective, controlled, randomized study. Contraception. 2010;81(3):209–14.
82. Bahamondes L, Bahamondes MV, Schulman LP. Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods. Hum Reprod Update. 2015;21(5):640–51.
83. Dragoman MV. The combined oral contraceptive pill—recent developments, risks and benefits. Best Pract Res Clin Obstet Gynaecol. 2014;28(6):825–34.
84. Merki-Feld GS, Hund M. Clinical experience with the combined contraceptive vaginal ring in Switzerland, including a subgroup analysis of previous hormonal contraceptive use. Eur J Contracept Reprod Health Care. 2010;15(6):413–22.
85.• Abu Hashim H, Alsherbini W, Bazeed M. Contraceptive vaginal ring treatment of heavy menstrual bleeding: a randomized controlled trial with norethisterone. Contraception. 2012;85(3):246–52. **This study demonstrated that the ring was as effective as noresthisterone to reduce heavy menstrual bleeding**.
86. Calhoun A, Ford S, Pruitt A. The impact of extended-cycle vaginal ring contraception on migraine aura: a retrospective case series. Headache. 2012;52(8):1246–53.
87. Liu KE, Alhajri M, Greenblatt E. A randomized controlled trial of NuvaRing versus combined oral contraceptives pills for pretreatment in in vitro fertilization cycles. Fertil Steril. 2011;96(3):605–8.
88.• Leone Roberti Maggiore U, Remorgida V, Scala C, Tafi E, Venturini PL, Ferrero S. Desogestrel-only contraceptive pill versus sequential contraceptive vaginal ring in the treatment of rectovaginal endometriosis infiltrating the rectum: a prospective open-label comparative study. Acta Obstet Gynecol Scand. 2014;93(3):239–47. **This study demonstrated that the ring was effective to reduce symptoms of rectovaginal endometriosis. However, satisfaction was lower than with COC**.
89. Battaglia C, Mancini F, Fabbri R, Persico N, Busacchi P, Facchinetti F, et al. Polycystic ovary syndrome and cardiovascular risk in young patients treated with drospirenone-ethinylestradiol or contraceptive vaginal ring. A prospective, randomized, pilot study. Fertil Steril. 2010;94(4):1417–25.
90.•• Diedrich JT, Zhao Q, Madden T, Secura GM, Peipert JF. Three-year continuation of reversible contraception. Am J Obstet Gynecol. 2015;213:662.e1–8. **This study compared the three-year continuation rates of the LARC methods to those for the non-LARCS methods**.
91.• Madden T, Secura G, Nease RF, Politi MC, Peipert JF. The role of contraceptive attributes in women's contraceptive decision making. Am J Obstet Gynecol. 2015;213:46.1–6. **This study showed that the three most important method attributes when choosing a contraceptive method were effectiveness, safety and affordability**.
92. Egarter C, Tirri BF, Bitzer J, Kaminskyy V, Oddens BJ, Prilepskaya V, et al. Women's perceptions and reasons for choosing the pill, patch, or ring in the CHOICE study: a cross-sectional survey of contraceptive method selection after counseling. BMC Womens Health. 2013;13:9.
93. Tepe M, Mestad R, Secura G, Allsworth JE, Madden T, Peipert JF. Association between tampon use and choosing the contraceptive vaginal ring. Obstet Gynecol. 2010;115(4):735–9.
94. Gilliam M, Holmquist S, Berlin A. Factors associated with willingness to use the contraceptive vaginal ring. Contraception. 2007;76(1):30–4.
95. Lete I, Doval JL, Pérez-Campos E, Sànchez-Borrego R, Correa M, de la Viuda E, et al. Factors affecting women's selection of a combined hormonal contraceptive method: the TEAM-06 Spanish cross-sectional study. Contraception. 2007;76(2):77–83.
96. Falah-Hassani K, Kosunen E, Shiri R, Rimpela A. The use of the vaginal ring and transdermal patch among adolescent girls in Finland. Eur J Contracept Reprod Health Care. 2010;15(1):31–4.

97. Terrell LR, Tanner AE, Hensel DJ, Blythe MJ, Fortenberry JD. Acceptability of the vaginal contraceptive ring among adolescent women. J Pediatr Adolesc Gynecol. 2011;24(4):204–10.

98.•• Secura GM, Madden T, McNicholas C, Mullersman J, Buckel CM, Zhao Q, et al. Provision of no-cost, long-acting contraception and teenage pregnancy. N Eng J Med. 2014;371:1316–23. **This study compared the rates of pregnancy, birth and abortion in adolescents enrolled in the CHOICE study in the United States to the national rates**.

99. Wilson EK, Fowler CI, Koo HP. Postpartum contraceptive use among adolescent mothers in seven states. J Adolesc Health. 2013;52(3):278–83.

100. Stewart FH, Brown BA, Raine TR, Weitz TA, Harper CC. Adolescent and young women's experience with the vaginal ring and oral contraceptive pills. J Pediatr Adolesc Gynecol. 2007;20(6):345–51.

101. Carey AS, Chiappetta L, Tremont K, Murray PJ, Gold MA. The contraceptive vaginal ring: female adolescents' knowledge, attitudes and plans for use. Contraception. 2007;76(6):444–50.

102. Raine TR, Foster-Rosales A, Upadhyay UD, Boyer CB, Brown BA, Sokoloff A, et al. One-year contraceptive continuation and pregnancy in adolescent girls and women initiating hormonal contraceptives. Obstet Gynecol. 2011;117:363–71.

103. Rosenstock JR, Peipert JF, Madden T, Zhao Q, Secura GM. Continuation of reversible contraception in teenagers and young women. Obstet Gynecol. 2012;120:1298–305.

104. Maslyanskaya S, Coupey SM, Chhabra R, Khan UI. Predictors of early discontinuation of effective contraception by teens at high risk of pregnancy. J Pediatr Adolesc Gynecol. 2015. doi:10.1016/j.jpag.2015.10.014.

105. Epstein LB, Sokal-Gutierrez K, Ivey SL, Raine T, Auerswald C. Adolescent experiences with the vaginal ring. J Adolesc Health. 2008;43(1):64–70.

106. Raine TR, Epstein LB, Harper CC, Brown BA, Boyer CB. Attitudes toward the vaginal ring and transdermal patch among adolescents and young women. J Adolesc Health. 2009;45(3):262–7.

107. Bahamondes L, Bahamondes MV. New and emerging contraceptives: a state-of-the-art review. Int J Womens Health. 2014;6:221–34.

108. Brache V, Payán LJ, Faundes A. Current status of contraceptive vaginal rings. Contraception. 2013;87(3):264–72.

109. Sivin I, Mishell Jr DR, Alvarez F, Brache V, Elomaa K, Lähteenmäki P, et al. Contraceptive vaginal rings releasing Nestorone and ethinylestradiol: a 1-year dose-finding trial. Contraception. 2005;71(2):122–9.

110. Archer DF, Thomas MA, Conard J, Merkatz RB, Creasy GW, Roberts K, et al. Impact on hepatic estrogen-sentitive proteins by a 1-year contraceptive vaginal ring delivering Nestorone® and ethinyl estradiol. Contraception. 2015. doi:10.1016/j.contraception.2015.09.008.

111. Huang Y, Merkatz RB, Hillier SL, Roberts K, Blithe DL, Sitruk-Ware R, et al. Effects of a one year reusable contraceptive vaginal ring on vaginal microflora and the risk of vaginal infection: an open-label prospective evaluation. PLoS One. 2015;10(8), e0134460.

112. A dose-finding study to evaluate the effect of a contraceptive vaginal ring, releasing nestorone and estradiol, on cycle control, ovulation inhibition, and pharmacokinetics in normal cycling women. NCT01586000. Available from: https://www.clinicaltrials.gov/ct2/show/NCT01586000. Accessed 28 November 2015.

113. A study to evaluate the effect of contraceptive vaginal ring delivering ulipristal acetate combined with a single or repeated levonorgestrel on inhibition of ovulation, endometrial changes and bleeding patterns in normal cycling women. NCT02451826. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02451826. Accessed 28 November 2015.

114. Nelson AL. Investigational hormone receptor agonists as ongoing female contraception: a focus on selective progesterone receptor modulators in early clinical development. Expert Opin Investig Drugs. 2015;24(10):1321–30.

115. Katz DF, Yuan A, Gao Y. Vaginal drug distribution modeling. Adv Drug Deliv Rev. 2015;92:2–13.

116. Schurmans C, De Baetselier I, Kestelyn E, Jespers V, Delvaux T, Agaba SK, et al. RING PLUS study group. BMC Public Health. 2015;15:348.