Review of the vaginal contraceptive ring (NuvaRing®)

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Overview

The forthcoming introduction of the vaginal contraceptive ring into the British market provides another contraceptive choice for women. In this review of the ring we highlight the current scientific literature and describe our experience in the USA over the past 7 years.

The vaginal contraceptive ring (NuvaRing®, Organon, Oss, The Netherlands) is a flexible, latex-free ring made of the plastic, ethylene vinyl acetate, which releases 120 µg etonogestrel (the biologically active metabolite of desogestrel) and 15 µg ethinylestradiol (EE) daily. The ring is 54 mm in diameter and 4 mm thick. The ring is placed vaginally once every 3 weeks by the woman and hormone is continuously absorbed through the vaginal mucosa. The ring is removed after 3 weeks, and following a 1-week ring-free interval a new ring is inserted. In common with the contraceptive patch and oral contraceptive pills (OCPs) the ring's effects are systemic.

Vaginal administration has the potential benefits of avoiding oral administration and hence issues related to broad-spectrum antibiotic interactions and potential lack of efficacy from gastrointestinal upsets. By avoiding first-pass hepatic metabolism, lower doses of hormones can be used to provide effective contraception.

Search strategy

We conducted a MEDLINE search from 1950 to May 2008 using the keywords 'vaginal ring' and 'NuvaRing'. This search identified 292 publications, which were then evaluated for relevance. Additional references from the authors' files were reviewed also.

Efficacy

The ring's effectiveness is similar to other combined hormonal contraceptive methods, with pregnancy rates less than 1% in large efficacy trials. Increased effectiveness may result from ease of use and the minimal user intervention required.

Four efficacy trials supported by Organon, the developer and manufacturer of the ring, all showed pregnancy rates similar to combined oral contraceptive (COC) pills.

Two open-label, non-comparative efficacy studies were performed and analysed together. One study was performed in 52 European centres, with the second carried out in 48 centres in Canada and the USA.^{1,2} A total of 2322 women aged 18–40 years in need of contraception were recruited. The studies assessed efficacy over 13 cycles. Compliance with ring use was defined as use for 3 weeks ± 48 hours, and the ring-free period did not deviate by more

than 24 hours from the scheduled 1-week period. The intention-to-treat (ITT) population consisted of 23 298 cycles, equivalent to 1786 woman-years. There was 85.6% compliance to the regimen in the ITT population. In total, 21 pregnancies were reported in the ITT population resulting in a Pearl index of 1.18 (95% CI 0.73–1.80). Eleven of the pregnancies occurred in women who did not comply with the ring regimen, resulting in a per-protocol (PP) Pearl index of 0.77 (95% CI 0.37–1.40).

There were more pregnancies in the North American study (15 pregnancies) than in the European study (six pregnancies.) However, levels of compliance in the North American study were lower than in the European study (i.e. 80% of cycles in North America vs 91% in Europe).

A third study compared the efficacy of NuvaRing with a levonorgestrel COC pill containing 30 µg EE and 150 µg levonorgestrel (LNG). This Phase III, open-label, randomised, multicentre study was conducted in 11 countries across Europe and South America. A total of 1030 subjects received treatment with NuvaRing ($n = 512$) or the COC ($n = 518$) for 13 cycles. There were an equal number of user and method failure pregnancies ($n = 5$) in each group, with a Pearl index of 1.23 (95% CI 0.40–2.86) for ring users compared with 1.19 (95% CI 0.39–2.79) for COC users.³

A fourth study compared the efficacy of NuvaRing with a drospirenone-containing COC pill (30 µg EE, 3 mg drospirenone) over 13 cycles. This randomised, open-label, multicentre trial recruited subjects from 10 European countries. A total of 983 subjects were randomised to receive NuvaRing ($n = 499$) or COC ($n = 484$). The Pearl indices in the ITT population were comparable. In the NuvaRing arm the Pearl index was 0.245 (95% CI 0.006–1.363) compared to the Pearl index in the COC arm of 0.988 (95% CI 0.269–2.530).⁴

Once the ring was on the market, three studies examined effectiveness in everyday practice. One study recruited 5823 women from gynaecology clinics in Germany.⁵ A total of nine on-treatment pregnancies occurred, of which six could be attributed to non-compliance or pregnancy occurring prior to starting treatment. A Dutch study found that in a cohort of 854 women seen by family practitioners, of which 82.6% completed the three cycles, one pregnancy occurred during the 3-month trial.⁶ A Swiss study found that three pregnancies occurred among 2642 women using the ring for a total of 15 900 cycles.⁷ These three studies thus reaffirmed the efficacy demonstrated in the randomised controlled trials (RCTs).

Mechanism of action

The ring's main mechanism of action is inhibition of ovulation. In a crossover study randomising 16 women to either one cycle of the ring or an oral contraceptive pill followed by a cycle of the other method, five markers were used to assess ovulation: follicle-stimulating hormone (FSH), luteinising hormone (LH), progesterone, 17β estradiol, and mid-cycle follicle formation as seen on ultrasound. Serum hormone levels were drawn and ultrasounds performed every other day during the initial 3 weeks of ring use and daily for 2 additional weeks. Ovulation was inhibited in all women.⁸ During the study the ring was used for up to 35 days and no ovulation was seen despite extended ring use.

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This was confirmed in another pharmacokinetic RCT comparing the ring and COCs. The 20 women using the ring had inhibition of ovulation during two consecutive cycles. Serum estradiol, progesterone, LH and FSH together with follicular sonographic measurements were used as markers for ovulation. These were performed every third day through the two cycles, except for a 4-day interval from Days 20–24.⁹

Secondary mechanisms of action similar to other COCs include cervical mucus changes and endometrial thinning. In a study where endometrial biopsies were performed after 13 and 26 cycles of continuous ring use, atrophic or inactive endometrial changes were noted in the majority of cases.¹⁰

Ovulation inhibition appears robust as demonstrated by another pharmacodynamic study involving 45 women.¹¹ Women were randomised to three arms. The first arm used the ring for two cycles of 3 weeks' continuous use and one ring-free week. No ovulations were seen. The second arm utilised the ring for one normal cycle, after which the ring was inserted for only 3 days. The median time to ovulation following ring removal was 17 days. The third arm utilised the ring for one normal cycle but the ring-free week was extended until follicles were visualised at 13 mm in size. At this point a new ring was inserted. The ring appeared to prevent ovulation despite allowing the follicles to first develop to 13 mm.

Pharmacokinetics

A study published in 2005 measured serum EE levels in 24 users of either the ring, patch or COC (eight women in each group.) Peak EE levels (C_{max}) reached 37.1 pg/ml in ring users, 105 pg/ml in patch users and 168 pg/ml in pill users. Total exposure to EE over the 21-day active hormone period (or area under the curve, AUC) was lowest in ring users (10.6 ng*h/ml), higher in pill users (21.9 ng*h/ml) and highest in patch users (35.8 ng*h/ml). Ring users had serum EE levels 3.4 times lower than patch users and 2.1 times lower than COC users.¹² In view of the vaginal method of administration, a number of other pharmacokinetic analyses were performed for the ring.

The effects of nonoxynol-9, a commonly used spermicide, were studied in a randomised crossover trial on 12 women for two ring cycles. Women underwent a cycle with the ring only, and another cycle with the ring and spermicide. Serum hormone levels were not altered by concurrent ring and spermicide administration.¹³

Tampons may be used in conjunction with the ring. In a crossover study that measured mean serum EE and etonogestrel absorbed while the ring and a vaginal tampon were both in place (4 weeks, with four tampons per day from Days 8–10 of the cycle) and then with ring only (4 weeks) there were no differences in serum hormone levels.¹⁴

A similar study assessed the effect of antifungals in association with ring use.¹⁵ Both the antifungal pessary and the cream led to increased release of hormones, with the pessary leading to greater release than the cream, presumably due to the lipophilic nature of miconazole. However, the increased release of hormones is unlikely to lead to reduced efficacy.

Two separate studies were performed assessing the impact of amoxicillin 875 mg bd and doxycycline 100 mg daily on serum hormone levels. Sixteen women were recruited in each study and used the antibiotics for the first 10 days of the cycle. No differences in serum hormones were seen with antibiotic use.¹⁶

Cycle control

Our patients have also experienced good cycle control and minimal unscheduled bleeding with the ring. This has been

attributed to sustained release of EE in contrast to fluctuating levels of hormone delivery with pills where a peak and trough of hormones occurs daily.

Many attempts have been made to minimise EE levels with the intention of reducing serious adverse events, especially thrombosis. Unfortunately, significantly lowering EE generally results in poor cycle control.¹⁷ The ring has the advantage of good cycle control with a low level of EE. Cycle control with the ring appears to be at least equivalent to COC.

In the Organon efficacy trial in which 2322 women were followed for 13 ring cycles, 98.5% reported regular cycles with the ring, with an average of 5.5% experiencing irregular bleeding or spotting. The bleeding and spotting decreased during consecutive cycles.¹ A small number (6%) of women experienced early withdrawal bleeding (bleeding starting before the ring was removed) and 24% reported late withdrawal bleeding (bleeding which continued past the ring-free week).

Two comparative studies have reported bleeding patterns in comparison with a LNG-containing pill³ and a drospirenone-containing pill.¹⁸ In both studies the bleeding profile for NuvaRing was superior to that of the COC. Again the ring led to irregular bleeding in 2–6% of cycles.

In a prospective study in Switzerland where 2642 women were followed for six cycles, 97% of women reported regular cycles with the ring, and irregular bleeding days decreased from 12% at baseline to 7% at final assessment.⁷

While irregular bleeding or spotting may occur with immediate start, a study that compared bleeding patterns in 201 women randomised to ring or pill 'quick start' protocol demonstrated less spotting/bleeding in ring users than pill users. During the reference period of 84 days, 17.0 days of total spotting or bleeding occurred in the ring group compared with 21.4 days in the pill group.¹⁹

Side effects

In our experience the side effect profile of the ring is similar to that of COC pills, with fewer complaints of nausea or breast tenderness. Conversely, more women report vaginal symptoms. It is difficult to assess whether this is due to a greater incidence of symptoms or a greater awareness of vaginal symptoms secondary to ring presence.

Common side effects attributed to the ring were described in the large efficacy trial where 2322 women were followed for 13 ring cycles for a total of 1786 woman-years. The most common side effects included headache (5.8%), vaginitis (5.6%), leucorrhoea (4.8%) and device-related events such as foreign body sensation, coital problems and expulsion (4.4%).¹

Given the lower level of EE absorbed from the ring, it was anticipated that lower levels of nausea and breast tenderness would occur in ring users when compared with users of a drospirenone-containing pill. Indeed, in a study that compared the ring to the pill in 13 cycles of 983 women, a smaller proportion of women using the ring experienced breast tenderness ($n = 16$, 3%) or nausea ($n = 4$, 0.8%) than those using oral contraceptive pills (OCPs) (breast tenderness, $n = 23$, 4.7%; nausea, $n = 18$, 3.7%).⁴ These findings were different from a study comparing the ring with a LNG-containing pill.³ The ring users reported nausea in 2.7% ($n = 14$) and breast pain in 3.1% ($n = 16$). This compared with the COC users who reported nausea and breast pain in 4% ($n = 21$) and 1.3% ($n = 7$), respectively.

The ring does not appear to promote weight gain. In a multicentre European trial where 1017 women were

randomised to either ring or OCP for 13 cycles, weight neutrality was achieved in both groups. However, there was insufficient power to determine non-inferiority.¹⁸ In another study where 201 women were randomised to ring or OCPs for 3 months and weight gain recorded throughout the study, a small weight gain was noted in both ring and pill groups, with no statistically significant difference between the two.²⁰

NuvaRing has been tested for interactions with metabolic parameters such as adrenal and thyroid function and carbohydrate metabolism. In studies comparing these parameters with an oral levonorgestrel containing pill, there was no clinically relevant changes with either treatment.^{21,22}

Bone mineral density (BMD) does not appear to change with ring use even though EE levels are much lower than in OCPs. In a multicentre study examining lumbar and femoral BMD at baseline and after 13 and 26 cycles of ring or OCP use no statistically significant changes were detected from baseline in ring users.²³

Several studies have examined the effect of the ring on bacterial vaginosis and cervical cytology. In a study of 59 women using the ring for cycles varying from 21–56 days no differences were detected in vaginal and endocervical bacteria after ring use. This suggests that there is no increased risk of bacterial vaginosis from ring use.²⁴ A study that examined cytological changes in 76 women after 20 ring cycles found no unfavourable cytological changes in the cervico-vaginal epithelium.²⁵

Starting the ring

The Summary of Product Characteristics (SPC) states the ring may be started by Day 5 of the cycle, even if the woman is still bleeding, with an additional 7 days of backup method of contraception if started after Day 1. The ring may also be started at any other time of the month if the woman is not pregnant, but a backup method needs to be used for 7 days.

The ring may be started any time throughout the cycle following the 'quick start' protocol. 'Quick start' allows the woman to insert the ring herself during the clinical consultation so that any placement concerns may be allayed by the clinician present. This is followed by 7 days of condom (or other backup method) use and a pregnancy test to confirm that a window pregnancy did not occur in the period immediately prior to method initiation.

Different regimens exist if switching to the ring from other methods. If switching from COCs, the ring should be inserted at the time a new pack of pills would be initiated. If switching from progestogen-only pills, the ring may be inserted when the last pill of the cycle is taken. If switching from an intrauterine contraceptive device or an implant, the ring should be inserted the day the device/implant is removed. If switching from injections, the ring should be started when the woman is due for her next injection. In all cases of switching from these methods the SPC recommends an additional barrier method be used for the first 7 days. Women may insert the ring no sooner than 4 weeks postpartum or after second-trimester abortion.

The ring may be inserted within 5 days of a surgical abortion or 7 days of mifepristone administration during a medical abortion. In a cohort study where the ring was initiated in this regimen no infections or serious adverse events were noted. The incidence of hormonal side effects was similar to interval start, or not related to pregnancy.²⁶

The ring's manufacturer has labelled its use for three consecutive weeks followed by a hormone-free week that

allows for withdrawal bleeding. After the 1-week ring-free interval a new ring is inserted even if bleeding continues. Hormone levels do not decrease with a single episode of ring removal of less than 3 hours. Product labelling therefore states that the ring may be removed from the vagina for an episode up to 3 hours. No published data exist on the number of removal episodes required to decrease hormone levels. Removal of the ring is not generally recommended as it is easy to forget to reinsert the ring and contraceptive effectiveness may be compromised. If the ring remains outside the vagina for longer than 3 hours the ring may be reinserted and a backup method should be used for 7 days. Expulsion of the ring may occur with valsalva manoeuvres and so women are encouraged to check for presence of the ring after intercourse and bowel movements.

Extended use

Package labelling states that no backup method is needed if the ring is used for 4 weeks, therefore women choosing to extend their cycles may use the ring continuously for up to 4 weeks. Women may attach ring insertion to calendar months by placing the ring on the first day of the month and removing the ring during the last few days of the month, thus allowing for a short withdrawal bleed. With both conventional and extended regimens it is highly recommended that women mark a calendar with the planned date of ring removal.

As mentioned earlier, a pharmacokinetic study concluded that not only was ovulation completely inhibited for the labelled 3 weeks, but was inhibited for an additional 2 weeks if the ring was left in place. This suggests that the ring may be used for five consecutive weeks in an extended regimen, however more data are needed.⁸

The impact of extended ring use on bleeding has been studied in a 1-year RCT where 429 women underwent a run-in cycle with the ring followed by randomisation to cycles of either 28, 49, 91 or 364 days (using a new ring every 21 days). The frequency of scheduled bleeding decreased in the longer cycles as expected but the total days of unscheduled bleeding increased. The median number of unscheduled bleeding or spotting days in the 28- and 49-day cycles ranged from 1.5 to 5 days per 91 days. In the 91- and 364-day groups, median bleeding or spotting days increased to a range of 4 to 15 days per 91 days. A greater proportion of women randomised to longer cycles reported that bleeding or spotting was a problem (6%, 17%, 39% and 39% in the 28-, 49-, 91- and 364-day cycles, respectively). It was therefore not surprising to see a greater discontinuation rate among women randomised to longer cycles. This was highly statistically significant.²⁷

Acceptability

Some providers may be concerned that women using few vaginal products and therefore presumably not comfortable with genital touching, as well as women who never masturbate, may be uncomfortable with the vaginal ring. This is contradicted in the literature. In the study mentioned earlier where 201 women were randomised to 3 months of ring or pill use, baseline genital experience such as tampon use, prior use of vaginal contraceptives, current masturbation or genital shaving/waxing were not associated with ring satisfaction. The majority (87%) of participants completed follow-up interviews at 3 months. Surprisingly, even baseline discomfort with genital touching was associated with high ring satisfaction. In the pill group none of the above factors correlated with pill satisfaction. In that study, women randomised to the ring

were three times more likely to report being very satisfied than women randomised to pills. Among women choosing a method at the end of the study ($n = 162$), ring users were eight times more likely to choose the ring than pill users were to choose the pill.²⁸

Several studies have shown good acceptance of the ring. A large multicentre trial of current COC users desiring a non-daily method randomised 500 women to either ring or patch for four cycles and 94.6% of ring users and 88.2% of patch users completed the study. Of these women, 71.0% of ring users and 26.5% of patch users planned to continue the method after study completion.²⁹

Acceptability is linked with sexual satisfaction in an Italian study of ring users compared with OCP users. In this study, women were randomised to 1 year of either the ring, a COC with 20 µg EE/100 µg LNG or a COC of 15 µg EE/60 µg gestodene. Discontinuation rates were lowest among ring users (11.7%) when compared with COC-20 µg EE users (22.3%) and COC-15 µg EE users (30.4%). Loss of sexual desire and vaginal dryness were mentioned as reasons for discontinuation in the COC groups but not the ring group. Also notable was sexual satisfaction, which was increased or unchanged in all three groups at a rate of 67.9% (COC-20 µg EE), 58.6% (COC-15 µg EE) and 91.4% (ring) at 1 year.³⁰

Summary

NuvaRing represents another useful contraceptive option for women. The vaginal administration confers benefits and women do not appear to dislike this route of hormone delivery. Efficacy and cycle control are at least comparable to conventional COCs and adverse events are minimal, though vaginal side effects are reported more commonly. Women may find that trying to insert the ring in the clinic will allay any concerns they have with regard to insertion and removal.

Statements on funding and competing interests

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Competing interests Carolyn Westhoff sits on advisory committees for Organon.

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