Faculty of Sexual & Reproductive Healthcare
New Product Review

Combined Vaginal Ring
(NuvaRing®)

Clinical Effectiveness Unit
March 2009

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Faculty of Sexual and Reproductive Healthcare
Clinical Effectiveness Unit

A unit funded by the FSRH and supported by NHS Greater Glasgow & Clyde to provide guidance on evidence-based practice

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Combined Vaginal Ring (NuvaRing®)

PRODUCT SUMMARY

Description
- Vaginal ring licensed for contraceptive use
- Combined hormonal method, releasing 15 \( \mu \)g/day ethinylestradiol and 120 \( \mu \)g/day of etonogestrel
- Flexible, transparent ring, 4 mm thick and 54 mm in diameter
- Latex-free, consisting of ethylene vinylacetate, magnesium stearate, 2.7 mg ethinylestradiol and 11.7 mg etonogestrel

Administration and Use
- One ring inserted vaginally for 3 weeks of use per cycle
- New ring inserted after 7-day ring-free break
- May be used during sexual intercourse and tampon use

Pharmacology
- Vaginal administration avoids first-pass metabolism and gastrointestinal interference with drug absorption
- Systemic ethinylestradiol exposure is 50% of that of a 30 \( \mu \)g combined oral contraceptive pill (COC)

Efficacy
- Studies suggest efficacy comparable with that of the COC
- Pearl index for per protocol (perfect) use 0.64 (95% CI 0.35–1.07)\(^1\)

Compliance
- >85% of cycles compliant in clinical trials

Tolerability and Acceptability
- Low incidence of breakthrough bleeding
- Comparative studies suggest cycle control superior to that of COC
- >90% of trial subjects found ring easy to insert or remove

Safety
- Low incidence of adverse events, of which <5% are directly related to the ring
- Metabolic and coagulation effects mostly consistent with other combined hormonal methods
- Available data suggest minimal disturbance of cervical and vaginal epithelium or flora

Storage
- Rings must be stored in a refrigerator at 2–8°C prior to dispensing to patient
- After dispensing, rings should be be stored at room temperature and used within 4 months

Cost
- Net price: 3 rings £27.00 (£9.00 per month)

Background

The combined vaginal ring (CVR), NuvaRing®, was launched in the UK in January 2009. It has been available in the USA since 2002 and is used by women in several other countries worldwide.

Although new to the UK market, a relatively large quantity of clinical trial data exists. Much of the published research has been supported by the pharmaceutical industry, and there has been a tendency to recruit a high proportion of ‘switchers’ (i.e. women already using a combined hormonal method). In addition, all the randomised trials have been open-label because of the impracticalities of blinding subjects to drugs administered by different routes. These potential sources of bias should be taken into account when assessing the available evidence and how it may translate into clinical practice in the UK.
What is the CVR?
NuvaRing is a combined hormonal method of contraception that is administered vaginally. It is a flexible, transparent ring measuring 4 mm in cross-section and 54 mm in diameter (Figure 1). It is latex-free and consists of ethylene vinylacetate copolymers, magnesium stearate, 2.7 mg ethinylestradiol and 11.7 mg etonogestrel.

How does the CVR work?
When placed in the vagina, ethinylestradiol and etonogestrel are delivered by controlled release at rates of 15 µg/day and 120 µg/day, respectively. As with other combined contraceptives, the main mechanism of action is inhibition of ovulation by suppression of gonadotrophins. The CVR’s secondary actions include alteration of the cervical mucus and endometrium, inhibiting sperm penetration and implantation.

How should the CVR be used?
One ring is inserted and left in the vagina continuously for 3 weeks. The ring is then removed on the same day of the week as it was inserted. A withdrawal bleed will usually occur during the ring-free week. Women should be advised how to insert and remove the ring. To insert the CVR, the ring should be compressed and inserted into the vagina until it feels comfortable. The exact position is not critical for the ring to provide effective contraception. Women should be advised to regularly check the presence of the ring. The CVR can be removed either by hooking the index finger under the ring or grasping it between the index and middle finger. The ring should be replaced in its sachet and disposed of with normal household waste.

When can the CVR be started?
Women who have not been using a hormonal method should be advised to insert the ring on the first day of menstrual bleeding. The ring can also be started on Days 2–5 of the menstrual cycle but the Summary of Product Characteristics (SPC) advises additional barrier contraception in the first 7 days of use. There is some evidence to suggest that ovulation is suppressed when starting NuvaRing up to Day 5, but studies have been too small to prove this conclusively.

Recommendations for switching from other contraceptive methods to the CVR and for starting the CVR after pregnancy are detailed in the SPC. Alternative starting regimens such as ‘Same Day Start’ and the ‘Calendar Start’ methods have been described but their use is outside the terms of the product licence.

Can the CVR be used continuously?
A randomised study investigated the impact of consecutive 3-weekly cycling without a ring-free period. The standard 28-day regimen (21 days’ ring use and 7-day break) was compared with 49-, 91- and 364-day
cycles. The extended regimens were associated with fewer bleeding days but more spotting and lower study completion rates than the standard regimen. Adverse events were comparable, suggesting that extended use is safe and may be acceptable to women who are willing to tolerate some spotting. However, continuous use of NuvaRing is outside the terms of the product licence.

**How effective is the CVR?**

**Efficacy**

Combined data from two observational studies enrolling over 2000 European and North American women showed Pearl indices of 1.18 [95% confidence interval (CI) 0.73–1.80] in the intention to treat population and 0.77 (95% CI 0.37–1.40) for per protocol use. Randomised studies comparing NuvaRing to the combined pill reported efficacy rates for NuvaRing that were consistent with the earlier observational studies. A Cochrane systematic review of these randomised studies concluded that the CVR and COC did not differ in contraceptive effectiveness.

**Compliance**

Compliance rates are difficult to compare due to different definitions of non-compliance and different methods of monitoring. Despite its longer duration of action and once a month administration, compliance with the CVR has not been shown to be superior to compliance with the COC. Randomised studies have shown rates of compliance of 86–88% for both methods. Non-compliance in CVR users was mainly due to extension of the ring-free period or temporary removal of the ring.

**What are the advantages of the CVR?**

**Cycle control**

The main advantage of NuvaRing over other methods is its good cycle control. Clinical trials have consistently shown infrequent breakthrough bleeding and low rates of absent withdrawal bleeding. Cycle control was significantly better than that of a 30 µg ethinylestradiol/levonorgestrel COC in one randomised trial (breakthrough bleeding and spotting 2.0–6.4% in the NuvaRing group vs 3.5–12.6% in the COC group). In another comparison with a 30 µg ethinylestradiol/drospirenone COC the odds ratio for reduced breakthrough bleeding and spotting associated with NuvaRing was 0.61 (95% CI 0.46–0.80).

**Acceptability**

Overall, the acceptability of the ring appears to be high. More than 90% of users have found the ring easy to insert and remove. Apart from a higher incidence of vaginal symptoms (see section on adverse events) the side effect profile is similar to that of the COC. Non-comparative studies reported low incidences of nausea and breast pain. However, in randomised trials comparing the CVR to the COC and combined patch, significant differences were only seen in comparison with the patch (frequent mastalgia and nausea 2% and 1%, respectively, in NuvaRing users vs 25% and 8%, respectively, in patch users; p<0.001).

**Pharmacology**

Compared with oral administration, the vaginal route offers the advantage of avoidance of first-pass metabolism and gastrointestinal interference with drug absorption. Pharmacokinetic studies have shown that maximum serum concentrations of ethinylestradiol and etonogestrel are approximately 30% and 40%, respectively, of those for an orally administered 30 µg ethinylestradiol/desogestrel pill. It is estimated that systemic exposure to ethinylestradiol from NuvaRing is 50% lower than from the COC. Whether the theoretical advantages of the vaginal route confer significant clinical benefits is not known.

**Reassuring safety data**

There were no clinically relevant effects of Nuvaring in studies investigating endometrial histology and bone mineral density over 2 years of use; and carbohydrate metabolism, adrenal and thyroid functions, blood pressure and body weight over six cycles. One study found a small rise in triglyceride levels in both NuvaRing and COC users but overall the effect on lipid metabolism was minimal. A study of the effect of NuvaRing use on vaginal flora showed no increase in numbers of inflammatory cells or pathogenic bacteria. Although other types of vaginal ring have been associated with ulceration of the vaginal mucosa, this has not been shown to be a problem with NuvaRing.
What are the disadvantages of the CVR?

Adverse events

In the largest observational study the discontinuation rate was 35% after 1 year, of which 15% were due to adverse events. Similar discontinuation rates have been observed with COC use. Although ring-related problems such as foreign body sensation, coital problems and expulsion were uncommon (4.4% of adverse events), they were more likely to lead to discontinuation than other adverse events. The most common treatment-related adverse events were headache (5.8%), vaginitis (5.6%), vaginal discharge (4.8%) and weight gain (4.0%). Awareness of the ring during intercourse was reported by 18% of women and 32% of partners, but most partners did not object to women using the ring.

The incidence of serious adverse events has been very low in all studies. Although cases of deep vein thrombosis (DVT) have been reported in NuvaRing users, there is insufficient epidemiological data available to ascertain the relative risks of venous thromboembolism (VTE) associated with CVR use compared with other combined methods. In a study comparing haemostatic variables in NuvaRing and COC users, the activity of antithrombin, protein C and factor VII was higher in NuvaRing users. The clinical significance of these coagulatory changes is unknown.

Refrigeration

NuvaRing must be stored in a pharmaceutical refrigerator at a temperature of 2–8°C until the point of dispensing to the patient. The ring has a total shelf life of 40 months: 36 months under refrigeration and 4 months after dispensing. Therefore, it is recommended that women are supplied with up to three rings at a time and that they are advised to insert each ring within 4 months of the date of dispensing. The storage requirements for NuvaRing may be a disadvantage for contraceptive providers.

What are the contraindications to CVR use?

The risks associated with CVR use are assumed to be similar to those of the COC, as there is currently a lack of direct data on hormones delivered by the vaginal route. The contraindications listed in the SPC include those for COC use, and also hypersensitivity to the active substances and excipients of NuvaRing. The only SPC precautions that relate specifically to use of the CVR are conditions which may prevent a woman inserting the ring correctly or cause her to lose the ring (i.e. prolapse of the uterine cervix, cystocele and/or rectocele, and severe or chronic constipation).

Guidance on CVR use in women with specific medical conditions or circumstances (e.g. breastfeeding) is provided in the UK Medical Eligibility Criteria for Contraceptive Use (UKMEC). The restrictions applying to CVR use are identical to those applying to the COC and combined patch.

Does the CVR interact with other drugs?

Liver enzyme-inducing drugs

Ethinylestradiol and etonogestrel are metabolised in the liver, therefore drugs that induce liver enzymes may reduce the efficacy of the CVR.

Antibiotics

In clinical trials, concomitant use of NuvaRing with amoxicillin and doxycycline did not significantly affect the pharmacokinetics of ethinylestradiol and etonogestrel. Evidence is lacking for other antibiotics, therefore the SPC advises use of additional barrier contraception when using non-liver enzyme-inducing antibiotics (with the exception of amoxicillin and doxycycline) and for 7 days after their discontinuation.

Spermicides and antifungals

Vaginally administered spermicide (nonoxynol-9) has no effect on the efficacy or safety of the CVR. The antifungal drug, miconazole, causes increased release of ethinylestradiol and etonogestrel from the CVR, resulting in higher serum levels. Antifungal drugs do not appear to affect contraceptive efficacy but the SPC warns that antifungal ovules may increase the chance of ring breakage.

What advice should be given if the CVR is used incorrectly?

The SPC for NuvaRing contains detailed information on the management of incorrect use in specific circumstances. A brief outline is given below. If contraceptive efficacy has been reduced and unprotected
intercourse has occurred, the need for pregnancy testing and emergency contraception should be considered.

Extended ring use
NuvaRing continues to suppress ovulation if retained continually in the vagina for up to 4 weeks. Therefore, if the ring has been left in for up to 7 days after the end of Week 3, the ring should be removed for 7 days and a new ring inserted after the ring-free interval. If the ring has been left in for more than 4 weeks, the ring should be removed and a new ring inserted immediately, omitting the 7-day ring-free break. Barrier contraception should be used until the new ring has been in place for 7 continuous days.

Extended ring-free interval
If a woman forgets to insert a new ring after the 7-day ring-free break she should insert a new ring as soon as she remembers and additional barrier contraception should be used for 7 days. There may be a risk of pregnancy if intercourse took place during the ring-free interval.

Ring expulsion or removal
The CVR can be expelled from the vagina either spontaneously or during intercourse. If the ring is expelled it should be rinsed with tepid water and reinserted within 3 hours. Deliberate removal of the ring is not recommended as efficacy may be reduced if the ring is removed for more than 3 hours, or more than once per cycle.

Is the CVR cost effective?
Presently there are insufficient data to allow evaluation of the cost effectiveness of the CVR compared to other methods of contraception. Prices from the British National Formulary (BNF) are included in information in Table 1. NuvaRing is more expensive than other combined methods and, based on 1 year of use, it is also more expensive than the long-acting methods. The Clinical Effectiveness Unit does not consider the CVR to be a long-acting reversible method of contraception (LARC), which is defined by the National Institute for Health and Clinical Excellence (NICE) as a method administered less than once per month or cycle.

What does the CVR add to current contraceptive choice for women?
Availability of the CVR will enhance contraceptive choice for women in the UK by offering a new route of administration and an alternative combined method with better cycle control than the COC and fewer hormonal side effects than the combined patch. Whilst providing similar efficacy to the COC, the CVR offers the advantage of convenient monthly administration, lower systemic exposure to estrogen, and avoidance of daily fluctuations in hormone levels and interference from gastrointestinal disturbance. Although the CVR offers wider choice and some advantages over existing methods, these benefits will need to be weighed against the higher cost to health care providers.

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*Based on 3 months’ supply or 1 year’s use of an intrauterine method or subdermal implant. Cost of equipment used for insertion not included. COC, combined oral contraceptive pill; CVR, combined vaginal ring; IUD, intrauterine device; IUS, intrauterine system; POP, progestogen-only pill.
References


The FSRH Clinical Effectiveness Unit (CEU) has prepared the information given in this New Product Review. It is based on a structured search and review of published evidence available at the date of preparation. This New Product Review has been prepared as a service to FSRH Members but it is not a formal Faculty Guidance document. It is not intended to be construed or to serve as a standard of medical care. Such standards are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances. Members are welcome to reproduce this document by photocopying or other means, in order to share the information with colleagues.

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The Faculty
The Faculty of Family Planning and Reproductive Health Care (of the Royal College of Obstetricians and Gynaecologists) was established on 26 March 1993. In 2007 the organisation changed its name to the Faculty of Sexual and Reproductive Healthcare as this was more relevant to the current functions of the specialty. The Faculty grants diplomas, certificates, fellowships and equivalent recognition of specialist knowledge and skills in sexual and reproductive health care. As a body it promotes conferences and lectures, provides a clinical advisory service and publishes the Journal of Family Planning and Reproductive Health Care.

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