Vaginal Ring
VAGINAL CONTRACEPTIVE RING
In Jordan, the combined vaginal ring contraceptive is likely used by less than half a percent of all women of reproductive age and was not even quantified in the 2009 Jordan Demographic Health Survey. In Jordan it is marketed under the commercial name NuvaRing®. Most women can use the vaginal ring, but health professionals should be aware of the World Health Organization Medical Eligibility Criteria for Contraceptive Use.

Effectiveness
The vaginal ring is highly effective. Among women who use the method correctly and consistently, less than 1 percent will experience a method failure in the first year of use. In terms of typical use though, no reliable estimates are available. Duration of use is not associated with any decrease in efficacy or safety suggesting that there is no need for a rest period.

Mode of Action
The primary mode of action of the vaginal ring is ovulation suppression. Other possible mechanisms include effects on cervical viscosity and endometrial thinning.

Advantages of the Vaginal Ring
In addition to being highly effective, other advantages to using the vaginal ring are:

- that it acts like a combined oral contraceptive and thus the absolute number of ectopic pregnancies are reduced
- it is rapidly reversible
- it is an option throughout reproductive years
- it decreases menstrual blood loss/regulates menses

Cycle control with the use of a vaginal ring is comparable to a combined oral contraceptive; that is, it is good and there is also a decreased menstrual blood loss.

Disadvantages of the Vaginal Ring
- Requires Weekly Administration

Differences in pregnancy rates of those taking their pill daily versus those who are not consistent compliers.
- Increased risk of vaginitis
Special Topics

• Cardiovascular Risks\textsuperscript{11}

The use of the combined contraceptive vaginal ring (NuvaRing\textsuperscript{®}) appears to have a similar risk of thromboembolism as women using standard combined low dose oral contraceptive pills. However, current data are insufficient to detect a significant increase in such a rare event.

• Breastfeeding\textsuperscript{2}

Data are not available to assess the effect of the combined contraceptive vaginal ring as used by breastfeeding women. However, based on indirect evidence drawn from studies addressing combined oral contraceptive pills and their use by breastfeeding women, the WHO does not recommend the ring for use during the first six months postpartum.

• Cancer

There is not sufficient data to assess any association of the vaginal ring and any cancer of the reproductive system or breast cancer. Because it acts similarly to the combined oral contraceptive, it may provide similar protective effects though this is speculative.
REFERENCES

Vaginal Contraceptive Rings

List of Critically Appraised Topics

1-Efficacy
2-Acceptability
3-Return to Fertility
4-Ectopic Pregnancy
5-Menstrual Blood Loss
6-Venous Thromboembolism
7-Blood Pressure
8-Headache
9-Migraine
10-Vaginitis
11-Antimycotics
12-Tampons
13-Weight Gain
14-Bone Mass Density
15-Breastfeeding

*Note that the level evidence accompanying each publication in each of the CATs refers to the study design.*
The combined contraceptive vaginal ring (NuvaRing®) is an effective contraceptive method for women preferring to use short-acting hormonal contraception.

Conclusion
The efficacy of contraceptive methods in descending order are: (1) long-acting hormonal contraceptives (LNG-IUS and single rod etonogestrel implant); (2) Cu-IUDs with at least 300 mm² surface area; (3) Cu-IUDs with less than 300 mm² surface area; (4) short-acting hormonal contraceptives (injectables, oral contraceptives, the patch and the combined contraceptive vaginal ring), and (5) barrier and natural methods.

Clinical Question
What is the efficacy of combined contraceptive vaginal ring in comparison to other methods?

Search Terms
Contraceptives, combined contraceptive vaginal ring, NuvaRing®, efficacy, effectiveness

Citation

Object of Research
Combined contraceptive vaginal ring

Research Outcome
Efficacy

Study Features
Standard medical databases were searched for published articles with objective to identify studies reporting contraceptive efficacy which included the Pearl Index. Reports that recruited less than 400 subjects per study group
and those covering less than six cycles/six months were excluded. In addition, unlicensed products or those not internationally available, (e.g. emergency contraception), and male or female sterilization studies were excluded. Information was identified and extracted from 139 studies.

(Level 2 Evidence)

The Evidence

One-year Pearl Indices (# pregnancies per 100 women years of use) reported for combined contraceptive vaginal ring ranged from 0.25 to 1.23 under typical use. Short-acting user-dependent hormonal methods were generally less than 2.5 (combined oral contraceptives: 0-1.26, progesterone only pill: 0.14,). Pearl indices for long-acting hormonal methods (single rod etonogestrel implant and the levonorgestrel releasing-intrauterine system [LNG-IUS]) generally ranged between 0–0.6 per 100 at one year, but wider ranges (0.1–1.5 per 100) were observed for the copper intrauterine devices (0.1–1.4 per 100 for Cu-IUDs with surface area ≥300mm² and 0.6–1.5 per 100 for those with surface area<300mm²). Pearl indices for the male condom ranged between 2.5-5.9, natural methods ranged between 3.8-20.4.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update by: 4 March 2016
There is a high level of user and partner acceptability for the combined contraceptive vaginal ring

Conclusion
There is a high level of user and partner acceptability for the combined contraceptive vaginal ring. The majority of women found the instructions for use to be clear, felt comfortable with the ring during intercourse, were very satisfied with the ring, and would recommend it to others.

Clinical Question
What is the level of user and partner acceptability of the combined contraceptive vaginal ring?

Search Terms
Combined contraceptive vaginal ring, NuvaRing®, contraceptive, acceptability.

Citations

Object of Research
Combined contraceptive vaginal ring

Research Outcome
User and partner acceptability.

Study Features
Two large-scale open-label, non-comparative, multi-center studies of the combined contraceptive vaginal ring’s efficacy, cycle control, tolerability and acceptability were included in this review
One study was in the United States and Canada, and the other was carried out in 12 European countries. The participants were asked to assess their acceptability of the combined contraceptive vaginal ring by completing a 21-item questionnaire after cycles 3, 6 and 13 or on early withdrawal from the studies. The women were also asked to indicate what, in their opinion, was the best method of contraception at baseline and again as part of the questionnaire assessments.

The questionnaire contained 21 questions (items) in total, of which 17 related to the following six domains: clarity of instructions, ease of use, sexual comfort, satisfaction, cycle-related characteristics and compliance. Cross-cultural differences were compared between countries.

(Received Evidence)

The Evidence
A total of 1950 women (82% of those recruited) completed a questionnaire at cycle 3. At baseline, 66% of participants preferred oral contraceptives, but after three cycles of ring use 81% preferred the ring. On study completion, 97% agreed that the instructions for use were clear; 85% of women and 71% of their partners never/rarely felt the ring during intercourse and 94% of their partners never/rarely minded that the woman was using the ring. Overall acceptance was high, 96% were satisfied with the ring and 97% would recommend the ring to others. Similar responses were seen for women who prematurely discontinued from the studies, except that slightly fewer women were satisfied (60%) and would recommend the ring (75%) for use by others. Reasons for liking the ring included “not having to remember anything” (45%) and “ease of use” (27%).

Appraised by: The Jordan Evidence Based Medicine-Reproductive Health Group

Update by: 4 March 2016
Resumption of ovulation after removal of the combined contraceptive vaginal ring (NuvaRing®) is rapid.

Conclusion
The combined contraceptive vaginal ring is a highly effective, reversible method of hormonal contraception. The vaginal ring acts similarly to the combined oral contraceptive and return to ovulation for most is rapid occurring for half or more women within 17-19 days after removal.

Clinical Question
Does the use of combined contraceptive vaginal ring affect return to fertility?

Search Terms
Combined contraceptive vaginal ring, NuvaRing®, return to fertility

Citations
Mulder TMT, Dieben TOM, Bennick HJTC. Ovarian Function with a novel combined contraceptive vaginal ring. Human Reproduction 2002;17(10):2594-2599

Object of Research
Combined contraceptive vaginal ring

Research Outcome
Return to fertility

Study Features
This is an open label, randomized, pharmocodynamic study of the combined contraceptive vaginal ring assessing ovarian function when there are deviations from the recommended usage schedule. The recommended regimen is one in which the ring is used continuously for three weeks followed by one ring free week. Forty-five combined contraceptive vaginal ring users were enrolled in the study and all used the ring continuously for three weeks. Fifteen women (Group A) had a one week ring free period followed by another ring use period of three weeks. Another 15 women (Group B) had a ring free week followed by three days of ring use and a third 15 (Group C) had a ring
free period until a 13 mm follicle was detected by ultrasound. Group C then used the ring for three weeks followed by a one week ring free period.

*(Level 1 Evidence)*

**The Evidence**

Regardless of the length of the second cycle, 3 weeks (group A) versus 3 days (group B), the time to ovulation after ring removal was similar (19 versus 17 days). The median time needed to develop a follicle up to 13 mm in diameter (group C) was 11 days (range 8–21 days); none of the women ovulated after insertion of the second ring. (Note: Median time is the point in which at least half the women returned to ovulation.)

Comment: As there were no research regarding return to fertility after vaginal ring use, and as this current study has limitations regarding the duration of the method, we expect what applies to combined contraceptive pills is the same as combined contraceptive vaginal ring in terms of return to fertility.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group  
**Update by:** 5 March 2016
Assuming that the combined vaginal contraceptive ring is similar to a combined oral contraceptive pill in terms of prevention of pregnancy, there is indirect evidence that the use of the ring may be associated with a significant decrease in the risk of an ectopic pregnancy.

**Conclusion**
There is not enough patient information to determine whether or not the combined vaginal contraceptive ring is associated with a decrease in ectopic pregnancy should there be a method failure. However, combination hormonal contraceptives including the combined contraceptive vaginal ring decrease the number of ectopic pregnancies since fewer pregnancies of any type occur. Based on the results of a review of studies involving combined oral contraceptives and their effect in reducing ectopic pregnancy risk, even if a pregnancy occurs, the combined vaginal contraceptive ring may also have a protective effect against ectopic pregnancy.

**Clinical Question**
Is there a decrease in the risk of ectopic pregnancy among women using the combined vaginal contraceptive ring?

**Search Terms**
Oral contraceptives, combined vaginal contraceptive ring, NuvaRing®, ectopic pregnancy

**Citation**

**Object of Research**
Combined vaginal contraceptive ring
Subject of Research
Ectopic pregnancy

Study Features
The study was a meta-analysis of 12 case control studies and 1 cohort study though only 5 of the case control studies involved combined oral contraceptives. Cases in the control studies were women with an ectopic pregnancy. Controls were non-pregnant or pregnant women actively on COCs or with past use. For the cohort study, women who used COCs were compared to a group of women who had not used them. Note that data for the vaginal ring is not available, but this method is part of the class of combined hormonal contraceptive methods.

(Level 3 Evidence)

The Evidence
Among pregnant women, current users of COCs had a 0.19 odds ratio when compared to non-pregnant controls. This suggests that women users of COCs have less risk of an ectopic pregnancy than those who do not. The chance of past COC users having an ectopic pregnancy showed the risk for an ectopic was no different from non-pregnant or pregnant non-users.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group State University

Update by: 5 March 2016
Users of the combined contraceptive vaginal ring were found to have better cycle control than users of combined oral contraceptives.

Conclusion
Compared to users of combined oral contraceptives, there is some evidence that users of the combined contraceptive vaginal ring had better cycle control as measured by the number of bleeding episodes and length of menstrual periods.

Clinical Question
Is the use of the combined contraceptive vaginal ring associated with abnormal uterine bleeding?

Search Terms
Combined contraceptive vaginal ring, NuvaRing®, abnormal uterine bleeding

Citation

Object of Research
Combined contraceptive vaginal ring

Research Outcome
Cycle control, bleeding, spotting
Study Features
This is a systematic review of randomized controlled trials which includes studies involving the combined contraceptive vaginal ring. Eleven studies involving the ring were found comparing this method to different combined oral contraceptives (COCs). Of these, seven studies reported bleeding data. Five of these obtained bleeding data from diaries, one from reported adverse events, and one from a questionnaire about bleeding. Included in the analysis are studies conducted in European, North and South America, and Egypt. 

(Level 1 Evidence)

The Evidence
The significant differences found in these studies include the following:

• European multicenter: The mean number of breakthrough bleeding or spotting days was higher for the ring group at cycle 6.
• European/South American multicenter: Breakthrough bleeding was less likely for ring users at cycle 6, but not at cycle 13.
• USA Single Center: Prolonged bleeding (bleeding or spotting lasting at least 10 days) was less likely for ring users than COC users. Frequent bleeding (4 or more episodes of bleeding or spotting) was also less likely for the ring users.
• European study: Spotting and breakthrough bleeding were less common among ring users. Also early or late withdrawal bleeding was less likely among ring users than COC users.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update by: 5 March 2016
The use of combined contraceptive vaginal ring (NuvaRing®) is associated with an increased risk of thromboembolism

Conclusion
The use of the combined contraceptive vaginal ring (NuvaRing®) is not associated with an increased risk of thromboembolism compared with women using standard combined low dose oral contraceptive pills.

Clinical Question
Is the use of the combined contraceptive vaginal ring associated with increased risk of venous thromboembolism?

Search Terms
Combined contraceptive vaginal ring, etonogestrel/estradiol vaginal ring, NuvaRing®, thromboembolic disorders, cardiovascular disorders.

Citations

Object of Research
Combined contraceptive vaginal ring

Subject of Research
Thromboembolic disorders

Study Features
This was a prospective, controlled, cohort study performed in the United States and five European countries with two cohorts; new users of the vaginal ring and new users of combined oral contraceptives (COCs). The study included 33,295 users of the vaginal ring or a COC recruited by 1,661 study centers. Follow-up for study participants occurred for 2 to 4 years. The primary clinical outcomes of interest were cardiovascular outcomes, particularly venous and arterial thromboembolism. Outcomes were validated by attending physicians and further adjudicated by an independent board.

(Level 2 Evidence)
**The Evidence**

Follow up for the study participants included 66,489 women-years of use and loss to follow-up was 2.9 percent. Only 34 occurrences of venous thromboembolism (VTE) were found during the four years of follow-up and the rate of VTE was similar in users of the vaginal ring and uses of combined oral contraceptives. The rates of VTE for the ring and COC groups were 8.8 and 9.9 per 100,000 women years, respectively.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 8 March 2016
Women using the combined contraceptive vaginal ring (NuvaRing®) as contraceptive showed no significant changes in either systolic or diastolic blood pressure after 12 months of usage

Conclusion
Blood pressure is not altered by the usage of a combined contraceptive vaginal ring.

Clinical Question
Is the use of the combined contraceptive vaginal ring associated with an increase in blood pressure?

Search Terms
Combined contraceptive vaginal ring, NuvaRing®, blood pressure

Citation

Object of Research
Combined contraceptive vaginal ring

Research Outcome
Blood pressure

Study Features
This is randomized, open-label study which included 600 women who attended the contraception clinic at Kasr El-Aini Hospital in Cairo, Egypt, between May 1, 2008, and July 31, 2010. The women were 17–42 years of age, had regular menstrual cycles and were randomly divided into 2 groups, with 300 women per group at the beginning of treatment. The women were randomized to receive the combined contraceptive vaginal ring or a combined oral contraceptive (COC) containing 30 μg of ethinyl estradiol and
3 mg of drospirenone. Only 239 women in the ring group completed the study compared with 251 women in the combined coral contraceptive. All participants received treatment for 12 consecutive cycles. Each treatment cycle consisted of 3 weeks of ring/pill treatment followed by a 1-week ring-free/pill-free period. Blood pressure, height, and weight were recorded at each clinic visit 3, 6, 9, and 12 months.

*Level 1 Evidence*

**The Evidence**
In the combined contraceptive vaginal ring group, baseline systolic blood pressure was 114.6 ± 10.7, at 3 months it was 114.3 ± 10.7, at 6 months it was 113.9 ± 10.4 and at 12 months it was 114.4 ± 10.6 mmHg. In women received combined oral contraceptive, baseline systolic blood pressure in was 117.3 ± 10.9, at 3 months it was 125.4 ± 13.1, at 6 months it was 125.6 ± 12.9 and at 12 months it was 126.2 ± 13.2 mmHg.

In the combined contraceptive vaginal ring group, baseline diastolic blood pressure was 72.4 ± 9.1, at 3 months it was 71.7 ± 8.4, at 6 months it was 73.2 ± 8.2 and at 12 months it was 71.8 ± 8.4 mmHg. In women received combined oral contraceptive, baseline diastolic blood pressure in was 71.5 ± 8.1, at 3 months it was 78.5 ± 9.9, at 6 months it was 81.5 ± 10.1 and at 12 months it was 79.7 ± 10.3 mmHg.

The differences in systolic or diastolic blood pressure, either at baseline or 3, 6 and 12 months for either method were not statistically significant. Women who used combined oral contraceptives tended to have higher systolic and diastolic blood pressure compared with women who used the combined contraceptive vaginal ring at 3, 6 and 12 months, but the differences were not statistically significant.

**Appraised by:** The Jordan Evidence-Based Medicine Reproductive Health Group

**Update by:** 7 March 2016
The use of the combined contraceptive vaginal ring (NuvaRing®) is associated with increased incidence of headache

Conclusion
Occurrence of headaches is often associated with the use of hormonal contraceptives including combined oral contraceptives as well as the combined contraceptive vaginal ring. The occurrence of these headaches may lead to discontinuation of the method.

Clinical Question
Is the use of the combined contraceptive vaginal ring associated with increased incidence of headache?

Search Terms
Combined contraceptive vaginal ring, NuvaRing®, headache, tolerability

Citation

Object of Research
Combined contraceptive vaginal ring

Research Outcome
Headache

Study Features
This is an open-label, randomized, multicenter trial study comparing the tolerability of combined contraceptive vaginal ring with a low dose, combined oral contraceptive (COC). The study was conducted in 11 countries in Europe and South America with 512 women randomly assigned to use the ring and 518 to the COC. (Level 1 Evidence)
The Evidence
Headache was the most commonly reported adverse effect in both groups. In the combined contraceptive vaginal ring group there were 37 (7.2%) who reported a headache which was classified by the investigators as drug-related. The corresponding number for the COC group was 30 (5.8%). Overall, 97 (18.9%) combined vaginal contraceptive ring users and 77 (14.8%) of the COC users reported a headache during the study. Four (0.8%) of the ring users and 8 (1.5%) of the COC users discontinued their method because of a headache.

Appraised by: The Jordan Evidence Based Medicine-Reproductive Health Group

Update by: 7 March 2016
The use of combined contraceptive vaginal ring is not associated with increased risk of migraine headaches.

**Conclusion:**
Use of an extended-cycle combined contraceptive vaginal ring was associated with a reduced frequency of migraine aura and with resolution of menstrual related migraine. Given the small sample size of the study and the use of the extended use of the ring, generalization of results to all ring users should be made with caution.

**Clinical Question**
Is the use of the combined contraceptive vaginal ring associated with a decreased risk of migraine headaches?

**Search Terms**
Combined contraceptive vaginal ring, NuvaRing®, migraine.

**Citations**

**Object of Research**
Combined contraceptive vaginal ring

**Research outcome**
Migraine

**Study Features**
This is a pilot study based on a retrospective review of a data base of 830 women seen in a menstrual related migraine clinic to identify women who met the inclusion criteria of current history of migraine with aura, a confirmed diagnosis of migraine related menstruation and extended use of a combined vaginal contraceptive ring. Standardized calendars that specifically docu-
mented bleeding patterns, headache details, and occurrence of aura were re-
quired of all patients in this clinic. Twenty-eight (3.4%) of the 830 identified
women met the study criteria, none of whom were smokers.

(Level 3 Evidence)

The Evidence
Of the 28 women, 5 (18%) discontinued use of etonogestrel/ethinyl estradiol
within the first month, leaving 23 evaluable subjects. At baseline, subjects
averaged 3.23 migraine auras/month (range: 0.1-12). With extended dosing of
the vaginal ring contraceptive, median frequency was reduced to 0.23 auras
per month following treatment after a mean observation of 7.8 months (P <
0.0005). No subject reported an increase in aura frequency. Using the ring
continuously, migraine related menstruation was eliminated in 91.3% of the
evaluable subjects. No comparison group (e.g. non users of the ring) was
available

Appraised by: The Jordan Evidence Based Medicine Reproductive Health
Group

Update By: 7 March 2016
The use of combined vaginal contraceptive ring is associated with an increased risk of vaginitis and vaginal discharge.

Conclusion
Vaginitis appears to be associated with the use of the combined contraceptive vaginal ring. In two separate randomized studies, the occurrence of vaginitis thought to be associated with vaginal ring use were less than 5 percent.

Clinical Question
Does the use of the combined contraceptive vaginal ring increase the risk of vaginitis?

Search Terms
Combined contraceptive vaginal ring, NuvaRing®, vaginal infection, vaginitis

Citations


Object of Research
Combined contraceptive vaginal ring

Research Outcome
Vaginal infection
**Study Features**

*Mohamed et al.*
This is a study of women seeking contraception at a family planning clinic in Cairo, Egypt. Three hundred women each were randomly assigned to receive either the combined contraceptive vaginal ring or a combined oral contraceptive (COC) for 12 cycles in this one year, open-label study (*Level 1 Evidence*)

*Oddsson et al.*
This is an open-label, one year, randomized study to compare the efficacy and tolerability of the combined contraceptive vaginal ring to a combined oral contraceptive (COC). A total of 512 ring and 518 COC users received and started their contraceptive method. (*Level 1 Evidence*)

*Camacho DP et al.*
Yeast infections are known to be a source of vaginitis. The purpose of this study was to evaluate the in vitro adherence of different yeasts, isolated from vaginal exudates of patients with vulvovaginal candidiasis to the combined contraceptive vaginal ring. Four isolates of *Candida* sp. and one of *Saccharomyces cerevisiae* were used. (*Level 1 Evidence*)

**The Evidence**

*Mohamed et al.*
Vaginitis was present in 11 (4.6%) ring users and in 3 (1.2%) COC users. This difference was statistically significant (p < 0.05). [Note that the authors use as the denominator all women who completed the study. Assuming that all 300 women in each group had an opportunity to report an adverse effect, 1 percent of the COC users and 3.7 percent of the ring users had vaginitis).
Oddsson et al
For the vaginal ring group, 54 (10.5%) women reported or were diagnosed as having vaginitis. Of these diagnoses, 20 (3.9%) were thought to be definitely, possibly or probably related to the ring use. For the COC users, the corresponding numbers were 24 (4.6%) and 5 (1.0%), respectively.

Camacho et al
All yeast were capable of adhering to the vaginal ring. The adherence of the tested yeasts to the ring could potentially facilitate the development and/or recurrence of vulvovaginal candidiasis in susceptible patients using the contraceptive method.

Appraised by: The Jordan Evidence Based Medicine Reproductive Health Group

Update By: 8 March 2016
The use of antimycotic co-medication is not expected to compromise NuvaRing’s contraceptive efficacy or tolerability.

Conclusion
Antimycotic co-medication slightly increases the amount of hormones released from the combined contraceptive vaginal ring. However, the increases in serum levels observed with different antimycotic formulations are not expected to compromise NuvaRing’s contraceptive efficacy or tolerability.

Clinical question
Does the use of antimycotic co-medications affect the NuvaRing contraceptive efficacy and tolerability?

Search Terms
Combined contraceptive vaginal ring, NuvaRing®. antimycotic co-medications

Citations
C.H.J. Verhoevena, M.W. van den Heuvelb, T.M.T. Muldersa, Th.O.M. Diebena,*
The contraceptive vaginal ring, NuvaRing, and antimycotic co-medication. Contraception 69(20040129-132.

Object of Research:
Combined contraceptive vaginal ring

Research Outcome
Effect of antimycotic co-medications

Study Features.
The effect of antimycotic co-medication on the systemic exposure to etonogestrel (ENG) and ethinylestradiol (EE) released from the contraceptive vaginal ring, NuvaRing was investigated. Different formulations of miconazole nitrate and single as well as multiple dosing were investigated
during two separate randomized, open-label, crossover studies. The first study recruited 12 women to compare the effects of co-use of NuvaRing and a single dose of antimycotic to NuvaRing alone. The second study recruited 14 women to compare the effects of multiple doses of an antimycotic vaginal suppository to an antimycotic vaginal cream equivalent.

The Evidence.
Co-administration of all three antimycotic formulation resulted in a slight increase in systemic exposure to ENG and EE over time, with suppositories having a more pronounced effect than a cream formulation in the multiple-dosing study.

Over 24 and 48 hours no significant effects of co-medication with a single dose of anti mycotic on the systemic exposure to ENG and EE released from vaginal ring were observed. However, over 312 hours, there was significant increase in the systemic exposure to ENG (17%)and EE(16%)released from the ring relative to the control cycle.

The mean ENG and EE serum concentrations showed an increase during treatment with both antimycotic suppositories and cream. After treatment the average concentration of ENG and EE remained elevated compared with the first day of interaction treatment.

In addition, ENG and EE content remaining in the rings after use was determined ex vivo. Less steroids remained in rings from subjects treated with antmycotics plus Nuva-Ring than with NuvaRing alone, indicating that ENG and EE release rates were higher in the presence of the antimycotic. (Miconazole nitrate is lipophilic in nature, which may facilitate the release of the (lipophilic) hormones from the ring). The increase in serum level observed with the different antimycotic formulations are not expected to compromise NuvaRing contraceptive efficacy and tolerability.
The use of tampons is not expected to compromise the combined contraceptive vaginal ring’s (NuvaRing®) contraceptive efficacy or tolerability.

Conclusion
Tampon co-usage did not result in any changes in serum etonogestrel or ethinyl estrodiol concentrations and is thus not expected to compromise the combined contraceptive vaginal ring’s contraceptive efficacy.

Clinical Question
Does the use of tampons affect the NuvaRing contraceptive efficacy?

Search Terms
Combined contraceptive vaginal ring, NuvaRing®, tampon use

Citations:
Carole H.J Verhoeven, Th.M Dieben.
The combined contraceptive vaginal ring, NuvaRing and tampon co-usage.

Object of Research:
NuvaRing

Subject of Research:
Tampon co-usage.

Study Features.
This open-label, randomized, cross-over study assessed systemic exposure to the contraceptive hormones released from the combined contraceptive vaginal ring, NuvaRing with tampon co-usage. One cycle of ring use consists of 3 weeks of ring use followed by a 1-week ring-free period.

(Level 1 Evidence)
Fourteen healthy women were randomized to use both NuvaRing and tampons (Kotex regular) or NuvaRing alone for one cycle; participants then switched to the alternate treatment regimen for a second cycle of ring use. The first tampon was self-administered on day 8 of the interaction cycle; 4 tampons a day were used for 3 consecutive days.

**The Evidence.**
The mean serum ENG and EE concentrations in the ring–tampon interaction cycle were similar to those observed in the control cycle. There were no statistically significant effects of tampon co-usage on the systemic exposure to ENG released from NuvaRing over the two time periods (24 and 72 h) analyzed.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update By:** March 10, 2016
The use of the combined contraceptive vaginal ring is not associated with greater weight gain than the combined oral contraceptive

Conclusion
Small weight increases for users of the vaginal ring were noted though reports of this as an adverse event were less than two percent of all users.

Clinical Question
Is the use of the combined contraceptive vaginal ring associated with weight gain?

Search Terms
vaginal ring weight gain

Citations
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): 145-146,


Object of Research
Combined contraceptive vaginal ring

Research Outcome
Weight gain, measured and reported.

Study Features
Mohamed et al
This is a study of women seeking contraception seeking contraception at a family planning clinic in Cairo, Egypt. Three hundred women each were
randomly assigned to receive either the combined contraceptive vaginal ring or a combined oral contraceptive (COC) for 12 cycles in this one year, randomized, open-label study  
*(Level 1 Evidence)*

O’Connell et al  
This is a randomized, open label study in which 100 women received a combined oral contraceptive (COC) and 101 received the combined contraceptive vaginal ring. The study was designed to assess acceptability and satisfaction. Study coordinators were blinded to the contraceptive assignment. Ninety-eight ring and 96 pill acceptors were weighed at the time of the initiation of their contraceptive method. The main outcome variable was the mean difference between their measured and perceived weight at entrance though differences in the two groups were also estimated.  
*(Level 1 Evidence)*

**The Evidence**  
Mohamed et al  
Weight increases were reported by 4 (1.7%) of the combined contraceptive vaginal ring users and in 11 (4.5%) of those using a COC. This difference was statistically significant (p < 0.05).

O’Connell et al  
Eight-two of the vaginal ring acceptors were weighed at the time of study initiation and exit compared to 79 COC users. The gains between the COC and ring groups were similar (COC: 3.1 lbs; ring 2.5 lbs). These weight gains were not significantly different though the combined group change from baseline of 2.8 lbs was found to be so.

**Appraised by:** The Jordan Evidence Based Medicine Reproductive Health Group

**Update by:** 8 March 2016
Long-term use of combined contraceptive vaginal ring (NuvaRing®) produces no changes in bone mineral density (BMD) in healthy women

Conclusion
Long use (up to 2 year) of the combined contraceptive vaginal ring in healthy young and pre-menopausal women did not result in any changes in BMD.

Clinical Question
Does the combined contraceptive vaginal ring affect bone mineral density in healthy women?

Search Terms
Combined contraceptive vaginal ring, NuvaRing® and bone mineral density

Citations


Object of Research
Combined contraceptive vaginal ring

Research Outcome
Changes in bone mineral density
**Study Features**  
This was an open-label, multicenter study conducted at 2 centers in Finland and single centers in Chile and The Netherlands. It included 144 healthy women aged 18-35 years followed for two years. The women included combined contraceptive vaginal ring users (n=103) and a control/comparison group (n=39) in a ratio 3:1 respectively. The control group was comprised of women who used a non-hormonal IUD or other non-hormonal methods of contraception. Measurements of bone mineral density were made at the lumber spine (L2-L4) and the proximal femur using dual-energy X-ray absorptiometry at screening and at months 12 and 24 of the study.  
*(Level 2 Evidence)*

Massaro M, Di Cario C, et al.  
This was a prospective, randomized controlled study, conducted in Naples, Italy from May to October 2008. It included 40 healthy women aged 23-34 years, randomly assigned equally to one of two methods of combined contraceptives (patch or vaginal ring). Twenty other women not seeking contraception were used as healthy controls. All studied women had measurements of BMD at the lumber spine (L1-L4) using dual-energy X-ray absorptiometry at screening and after 12 months from initiation of the study.  
*(Level 1 Evidence)*

**The Evidence**  
Out of 144 women, 76 combined contraceptive vaginal ring users completed the study compared to 31 women in the control group. The BMD of the proximal femur and the lumber spine showed no change from baseline in the contraceptive ring users at either the 12 or 24 months follow-up. However, the BMD at 24 months in the control group showed a slight but clinically insignificant increase from the baseline.
Massaro M, Di Cario C, et al.
The BMD values in the three groups at baseline and after 12 months are shown in the following table:

<table>
<thead>
<tr>
<th>Spinal BMD (g/cm²)</th>
<th>NuvaRing® user</th>
<th>Patch user</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.040 ± 0.12</td>
<td>1.042 ± 0.15</td>
<td>1.041 ± 0.08</td>
</tr>
<tr>
<td>After 12 months</td>
<td>1.041 ± 0.09</td>
<td>1.041 ± 0.18</td>
<td>1.042 ± 0.02</td>
</tr>
</tbody>
</table>

There were no significant differences in mean spinal BMD values among the three groups nor in comparison with base line values.

**Appraised by:** The Jordan Evidence Based Medicine – Reproductive Health Group

**Update by:** 8 March 2016
Use of the combined contraceptive vaginal ring (NuvaRing®) as a contraceptive method is not recommended for breastfeeding women less than six months postpartum.

**Conclusion**
Data are not available to assess the effect of the combined contraceptive vaginal ring as used by breastfeeding women. However, based on indirect evidence drawn from studies addressing combined oral contraceptive pills, use by breastfeeding women, the WHO does not recommend the ring for use during the first six months postpartum.

**Clinical Question**
Does the use of combined contraceptive vaginal ring affect milk production while breastfeeding?

**Search Terms**
NuvaRing®, combined contraceptive vaginal ring, combined oral contraceptive, breastfeeding

**Citations**


**Object of Research**
Combined contraceptive vaginal ring

**Research Outcome**
Lactation, breast milk production
Study Features
This is a systematic review of randomized controlled trials. Three studies involving combined oral contraceptives (COCs) were found; a WHO sponsored trial comparing COCs to a progestin-only pill (POP), and two other studies comparing COCs to placebo. For the two placebo-comparator studies, one study used the subjective need for supplemental infant feeds and infant weight as a proxy for milk adequacy while the other was not specified. In the study using a progestin-only pill as a comparator, breast milk volume was determined by pump expression using a standardized process.

(Level of indirect evidence not assessed)

The Evidence
In the WHO trial, at six weeks, the volume of the expressed milk in the COC and POP groups were similar. However, most women in both groups had declines in milk volume over time though the amount for the COC group was greater than that for those using a POP.

In the other two studies, one found inhibitory effects on milk volume in the COC. On the other hand, in the second study, no differences were found between the COC and placebo groups with respect to milk volume, lactation initiation, or infant growth.

Comment
The WHO “Medical eligibility criteria for contraceptive use” makes the following recommendation with respect to the combined contraceptive vaginal ring for breastfeeding women.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks postpartum</td>
<td>Method not to be used</td>
</tr>
<tr>
<td>≥6 weeks and &lt; 6 months</td>
<td>Use of method not recommended unless other more</td>
</tr>
<tr>
<td>postpartum (primarily appropriate methods are not available or not breastfeeding)</td>
<td>Acceptable</td>
</tr>
<tr>
<td>≥6 months postpartum</td>
<td>Generally use method</td>
</tr>
</tbody>
</table>

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Update by:  8 March 2016