

# NuvaRing: new combined hormonal contraceptive device

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## KEY POINTS

- NuvaRing is a combined hormonal contraceptive ring
- it delivers 15µg ethinylestradiol and 120µg etonogestrel per 24 hours
- it is inserted once per cycle for 3 weeks; 3 rings cost £27
- in studies lasting one year, NuvaRing was as effective as a combined oral contraceptive (COC) and user acceptability appears to be similar
- systemic adverse effects are similar to those of the COC
- NuvaRing is also associated with increased vaginal discharge in 3-4 per cent of women
- it is particularly suitable for women who are poor pill-takers, shift-workers, suffer from poor GI absorption, or want a contraceptive device that does not require the intervention of a healthcare professional



**NuvaRing is a new contraceptive device that delivers ethinylestradiol and etonogestrel and is inserted once every cycle for three weeks. In our New products review, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects and Dr Tina Peers comments on its place as a birth control option.**

The National Institute for Health and Clinical Excellence (NICE) guideline on long-acting contraception recommends that women should be given information about and offered a full choice of different methods.<sup>1</sup> This guideline excluded combined oestrogen/progestogen vaginal rings because none were available in the UK at the time. NuvaRing, a vaginal contraceptive ring, is the first to be introduced.

### The technology

NuvaRing is a flexible, transparent plastic ring 5.4cm in diameter and 0.4cm thick (see Figure 1). After insertion into the vagina, it releases 120µg etonogestrel (the active metabolite of desogestrel) and 15µg ethinylestradiol per 24 hours over a period of three weeks.

The ring is then removed, provoking withdrawal bleeding, and a new one is inserted one week later. The *Summary of Product Characteristics* (SPC) explains when to start use following previous or no contraception and details the actions to take if the ring is not inserted at the correct time, is expelled or left out.<sup>2</sup>

NuvaRing acts systemically and its positioning is not critical. Vaginal absorption of etonogestrel and desogestrel achieves blood levels that are comparable with those associated with a combined oral contraceptive (COC)<sup>2</sup> and NuvaRing inhibits ovulation to a comparable extent.<sup>3</sup>

The precautions and contraindications to its use are similar to those for COCs. Insertion or retention may be impossible for

women with a prolapsed cervix, a cystocele or rectocele, or severe or chronic constipation.<sup>2</sup>

### Clinical trials

The efficacy of NuvaRing has been evaluated in two one-year non-comparative trials<sup>4,5</sup> and two one-year comparative trials;<sup>6,7</sup> none were blinded. Contraceptive efficacy was estimated by the Pearl index (PI; number of pregnancies per 100 woman-years of use) for the intent to treat (ITT) population (including method failures) and the per protocol (PP) population (used the method correctly). Pooled data from these trials and other studies provide a total of 37 977 woman-years of ITT use and a PI of 0.96; there were 28 723 woman-years of PP use, giving a PI 0.64.<sup>2</sup>

NuvaRing has been compared with a daily COC pill containing ethinylestradiol 30µg and 150µg levonorgestrel in 1030 women.<sup>6</sup> Seventy-one per cent of women in each group completed the trial; the commonest reason for discontinuation was adverse events – 39 per cent of discontinuations with the ring and 30 per cent with the COC.

After 13 cycles there was no significant difference in contraceptive efficacy: five pregnancies occurred in each group (ITT PI 1.23 for NuvaRing and 1.19 for the COC); three and two pregnancies respectively were associated with non-compliance, giving PP PIs of 0.96 and 0.53. Overall compliance was 87 per cent in both groups.

In a one-year trial, 983 women were randomised to use a daily COC pill containing ethinylestradiol 30µg and drospirenone 3mg (Yasmin; see Table 1).<sup>7</sup> Twenty-nine per cent of women discontinued NuvaRing prematurely (42 per cent due to adverse effects) and 25 per cent discontinued the COC (39 per cent due to adverse effects). There was one pregnancy among women using NuvaRing;

this was not associated with non-compliance (ITT PI 0.25, PP PI 0.31). Of the four pregnancies associated with COC use, two were linked with poor compliance (ITT PI 0.99, PP PI 0.55). These differences were not statistically different. Overall compliance was 89 per cent with NuvaRing and 86 per cent with the COC.

Breakthrough bleeding or spotting was reported by 2-7 per cent of NuvaRing users;<sup>2</sup> vaginal bleeding (spotting in half to three-quarters of cycles) occurred outside the ring-free interval in 30-40 per cent of women,<sup>2</sup> more frequently after the interval (20-27 per cent of cycles) rather than before (5-8 per cent).<sup>5</sup>

User acceptability was not reported in the trial comparing NuvaRing with the ethinylestradiol/levonorgestrel COC; compared with ethinylestradiol/drospirenone, the proportion of women satisfied/very satisfied was 84 per cent with NuvaRing and 87 per cent with the COC. Among ring users, most reported no problems with insertion (96 per cent) or removal (97 per cent).



**Figure 1.** NuvaRing, a flexible, transparent plastic ring 5.4cm in diameter and 0.4cm thick, is inserted once per cycle for three weeks

#### Adverse effects

The systemic adverse effects associated with NuvaRing are similar to those of a COC (see Table 2).<sup>2,6,7</sup> NuvaRing is also associated with vaginal infection (3.9-4.6 per cent attributed to NuvaRing *vs* 1.0-2.1 per cent with a COC) and discharge (3.5-4.8 *vs* 0.2-1.0 per cent).<sup>6,7</sup> The commonest adverse

|            | Exposure (woman-years) | Pearl index (95% CI) |
|------------|------------------------|----------------------|
| <i>ITT</i> |                        |                      |
| NuvaRing   | 408.8                  | 0.245 (0.006-1.363)  |
| COC        | 404.8                  | 0.988 (0.269-2.530)  |
| <i>PP</i>  |                        |                      |
| NuvaRing   | 318.2                  | 0.314 (0.008-1.751)  |
| COC        | 364.7                  | 0.548 (0.066-1.981)  |

**Table 1.** Contraceptive exposure and Pearl indices for NuvaRing and COC treatment groups<sup>7</sup>

effect in comparative clinical trials was headache, affecting approximately 6-8 per cent of women in each treatment arm.<sup>6,7</sup>

Method-related events were the commonest reason for discontinuation due to adverse events and were attributed to the medication in 5 per cent of women with NuvaRing and 0.4 per cent with the COC.<sup>6,7</sup>

**References**

1. National Institute for Health and Clinical Excellence. *Long-acting reversible contraception*. CG30. October 2005.
2. Organon Laboratories. *NuvaRing summary of product characteristics*. June 2008.
3. Mulders TM, et al. *Fertil Steril* 2001;

|                                   | NuvaRing  |                              | COC       |                              |
|-----------------------------------|-----------|------------------------------|-----------|------------------------------|
|                                   | total (%) | related to study medication* | total (%) | related to study medication* |
| headache                          | 87 (17.4) | 34 (6.8)                     | 89 (18.4) | 37 (7.6)                     |
| upper respiratory tract infection | 63 (12.6) | 0 (0)                        | 49 (10.1) | 0 (0)                        |
| vaginitis                         | 61 (12.2) | 23 (4.6)                     | 33 (6.8)  | 10 (2.1)                     |
| method-related events             | 35 (7.0)  | 33 (6.6)                     | 2 (0.4)   | 2 (0.4)                      |
| pharyngitis                       | 35 (7.0)  | 0 (0)                        | 28 (5.8)  | 0 (0)                        |
| leucorrhoea                       | 24 (4.8)  | 16 (3.2)                     | 8 (1.6)   | 5 (1.0)                      |
| influenza-like symptoms           | 23 (4.6)  | 0 (0)                        | 27 (5.6)  | 0 (0)                        |
| breast pain                       | 17 (3.4)  | 16 (3.2)                     | 25 (5.2)  | 23 (4.7)                     |
| nausea                            | 14 (2.8)  | 4 (0.8)                      | 28 (5.8)  | 18 (3.7)                     |

\* considered to be definitely, probably or possibly related to study drug by the investigator

**Table 2.** Incidence of adverse events (occurring in ≥4 per cent of subjects)<sup>7</sup>

- 75:865-70.
4. Dieben TO, et al. *Obstet Gynecol* 2002;100:585-93.
5. Roumen FJ, et al. *Hum Reprod* 2001; 16:469-75.
6. Oddsson K, et al. *Contraception* 2005;71:176-82.
7. Ahrendt HJ, et al. *Contraception* 2006;74:451-7.

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**Place in therapy**

In spite of having 15 methods of contraception, the unplanned pregnancy rate in the developed world is alarmingly high at just under 50 per cent, with as many as 63 per cent of these pregnancies ending in a termination.

The combined pill is still the most popular method, with 27 per cent of British women requiring contraception choosing it. The PI of the combined pill is <1; however, the failure rate could be as high as 8 per cent due to user error.

Many women confess to missing a pill at least once in each

cycle and many of these missed pills are within the first week of pill-taking.

The introduction of the NuvaRing is an exciting new development that could aid compliance and provides women with another reliable, low-dose, hormonal method.

We now have a three-week hormone delivery system to offer women. NuvaRing is convenient, easy to insert and remove, cannot be felt by the woman or her partner in most users, and is proving to be very popular. It is particularly ideal for women who are poor pill-takers, shift-workers, suffer from

poor GI absorption, or who just want the convenience of a longer-acting, reliable contraceptive that does not require the intervention of a healthcare professional – unlike the intrauterine system (Mirena) or etonogestrel subdermal implant (Implanon).

It is important to remember that all the contraindications that apply to the combined pill also apply to this new hormone delivery system, which undoubtedly will be a useful new method to be able to offer women.

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