Ovarian function with a novel combined contraceptive vaginal ring. Mulders TMT, Dieben TOM, Coelingh Bennick HJT. *Hum Reprod* 2002; **17**: 2594–2599

NuvaRing® (NV Organon) is a new contraceptive vaginal ring that releases 120 µg etonorgestrel and 15 µg ethinyloestradiol per day. It is designed for 3 weeks' use with a 1-week ring-free period. This open label randomised pharmacodynamic study aimed to assess ovarian function in women who used NuvaRing in different schedules.

Fifty-one women were recruited to the study between January 1999 and June 1999. Women were excluded if they had: contraindications to sex steroid use: cervicitis; vaginitis; a bleeding erosion; abnormal smears; cystocoele, rectocoele or other prolapse; severe or chronic constipation; or dyspareunia. All subjects had a pretreatment cycle with Marvelon® (NV Organon) with 30 µg ethinyloestradiol and 150 µg desogestrel. Six women did not receive NuvaRing and 45 women were randomised to one of three groups. Women in Group A used the ring according to the recommended regime for two cycles. Women in Group B used the ring according to the recommended regime for one cycle and in the second cycle used the ring for only three consecutive days. Women in Group C used the ring according to the recommended regime for one cycle and in the second cycle the ring was inserted only after a follicle of 13 mm was identified. Restoration of ovarian activity was determined in each woman by serum hormone levels (follicle-stimulating hormone, luteinising hormone, oestradiol and progesterone) and vaginal ultrasound scans. Compliance with the regime was recorded on diary cards and temporary ring removal was not allowed. Condoms were used as additional contraception in women with ovarian follicles measuring greater than 13 mm. There were no significant demographic differences between women in each group.

This study indicated that as little as 3 days of ring use was sufficient to suppress the hypothalamo-pituitary-ovarian axis. Irrespective of the length of the second ring treatment (3 days or the usual 3 weeks) ovulation required a similar time to occur. The median time to ovulation after removal of the ring was 17 days (Group A, 3 weeks use) or 19 days (Group B, 3 days use). The first ovulation was documented at 12 days (Group A) or 13 days (Group B). Ovulation was blocked by the NuvaRing even when follicles up to 13 mm in diameter were identified.

If women deviate from the standard regime of 3 weeks' use and 1 week ring-free, the NuvaRing is still a robustly effective method of contraception. Importantly, this study also highlighted that ovulation was inhibited after as little as 3 days' use in contrast to the 7 days which has previously been proposed as the time it takes to suppress ovulation with combined oral contraceptive pills. Follicles up to 13 mm could be suppressed by use of the ring and this inhibition of ovulation may suggest a potential role for research into its use as an emergency contraceptive. Large efficacy studies have previously confirmed that this vaginal ring is a highly effective and reversible method of contraception, which will provide women with an alternative contraceptive choice.

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Prolonged use of oral contraception before a planned pregnancy is associated with a decreased risk of delayed conception. Farrow A, Hull MGR, Northstone K, et al. *J Hum Reprod* 2002; **17**: 2754–2761

This large study investigated the impact of oral contraceptive OC use on the time to conception in fertile women. The Avon Longitudinal Study of Parents and Children (ALSPAC) aims to define environmental and genetic factors, which may influence pregnancy outcome and the development and health of children. Couples were eligible for recruitment of the study if they had an expected date of delivery between 1 April 1991 and 31 December 1992. Almost 85% of couples eligible to take part were recruited. This was a prospective study of fertile couples for birth outcome but was retrospective in the identification of the time taken to conceive the index pregnancy. The couples completed questionnaires at 18 weeks' gestation to try to avoid recall bias. Specific fertility factors were identified such as obstetric and gynaecological history; use of contraception; if the pregnancy was planned; and the length of time to conceive (less than 6 months up to over 3 years). Other information such as age, smoking, alcohol consumption and ethnic origin were also obtained. Logistic regression analyses identified factors associated with conception within 12 months and analyses were also performed separately for women who had never previously conceived.

A total of 12 106 couples were eligible: 8497 had conceived intentionally, 3545 had conceived accidentally, and 64 did not answer the question. Most of those whose pregnancies were planned indicated the time it had taken to conceive. For these the proportions were as follows: 74.2% within the first 6 months; 13.9% within the second 6 months; 8.5% in Year 2 or 3; and 3.4% after Year 3.

Interestingly, in women with planned pregnancies, an increasing duration of previous OC use was significantly associated with an increased proportion of conceptions in the first 6 months. Use of OC for over 5 years was used as the reference group [odds ratio (OR) 1.0] because of the small sample size of never or very short-term users. Use of OC for less than 5 years was associated with an OR of conception in the first 12 months of 0.83 (95% CI 0.63–1.09); for never users OR 0.61 (95% CI 0.44–0.85). The type of OC used was not identified but is likely to be mainly the combined oral contraceptive (COC) (over 95% in 1991–1992). A number of suggestions have been proposed as to why this improvement in conception may be biologically plausible: improved iron stores due to reduction in the incidence of menorrhagia seen with the COC; perhaps a reduction in endometriosis; a lower rate of chromosomal abnormalities and age-related miscarriage associated with the COC.

Findings from this large study of women in the South West of England may be reassuring for other British women using OC. It does not suggest a reduction in fertility with OC use regardless of duration of use. Among fertile women, prolonged use of OC is actually associated with a shorter time to conception. This association is strongest after 5 or more years' use, is also the case for women who have never been pregnant, and is independent of other factors.

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Long-term use of contraceptive depot medroxyprogesterone acetate in young women impairs arterial endothelial function assessed by cardiovascular magnetic resonance. Sorensen MB, Collins P, Ong PJ, et al. *Circulation* 2002; **106**(13): 1646–1651

A majority of women using depot-medroxyprogesterone acetate (DMPA) have low circulating oestrogens that theoretically could put them at risk of arterial disease. A mechanism for this could be a blunting of the positive effect of oestrogen on arterial endothelium, which is thought to inhibit atheroma formation. This study found that the endothelium in the arteries of 13 long-term users of DMPA was less responsive to increased blood flow compared to 10 non-hormone-using controls.

This is a novel use of magnetic resonance imaging (MRI) and if is satisfying that it gets its first application in a contraception study. The report, however, should be treated with caution as it was small cross-sectional study, scanning not blinded, although measurements were, and there was a large overlap between DMPA and control values.

Further studies are required to determine whether the arteries in women who are long-term DMPA users are truly dysfunctional. If confirmed, cardiovascular MRI will lend support to the World Health Organization (WHO) advice against using DMPA in women with cardiovascular diseases (WHO Class 3), which so far gets little support in epidemiology, although ultimately it is epidemiology rather than studies of intermediate endpoints that will guide best practice.

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QUESTIONS TO ASK WHEN READING A PAPER

1. Was the study original, why was the study done, and what hypotheses are being tested?
2. What type of study was done and was the design appropriate?
3. Was the study ethical?
4. Who was the study about and how were the subjects recruited?
5. What were the inclusion and exclusion criteria and were the subjects studied in real-life situations?
6. What specific intervention or other manoeuvre was being considered and what was it being compared with?
7. What outcomes were measured and how was systematic bias avoided or minimised?
8. Has the outcome been objectively validated and was the assessment of outcome carried out blind?
9. Was the statistical question dealt with, the size of the sample, the power of the study and the duration and completeness of follow-up?