Comparison of uterine concentrations of ethinyl estradiol and etonogestrel after use of a contraceptive vaginal ring and an oral contraceptive

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Objective: To compare uterine tissue concentrations of ethinyl estradiol (EE) and etonogestrel (ENG) after one cycle of use of a contraceptive vaginal ring (NuvaRing; NV Organon, Oss, The Netherlands) or a combined oral contraceptive (COC).
Design: Randomized, open-label, pharmacokinetic study.
Setting: Obstetrics and gynecology unit.
Patient(s): Eight premenopausal women about to undergo hysterectomy but otherwise healthy.
Intervention(s): One cycle (17–21 days) of NuvaRing or COC treatment that ended with surgical hysterectomy.
Main Outcome Measure(s): Tissue concentrations of EE and ENG in uterine tissue samples taken from the upper myometrium and mid-myometrium, the cervical region, and the endometrium.
Result(s): In both groups, concentrations of EE and ENG were similar in uterine tissue taken from the upper myometrium and mid-myometrium and the cervical region. However, compared with the COC group, concentrations of both hormones were markedly lower in tissue samples from the endometrium of women who had been treated with NuvaRing.
Conclusion(s): Vaginal administration of hormones with NuvaRing did not produce elevated uterine concentrations of EE and ENG, compared with an oral contraceptive. (Fertil Steril® 2006;85:57–62. ©2006 by American Society for Reproductive Medicine.)

Key Words: NuvaRing, oral contraceptive, ethinyl estradiol, etonogestrel, uterus, tissue concentration, hysterectomy

The search for new methods of hormonal contraception has focused on alternative routes of administration to traditional oral dosing that allow longer dosage regimens. Non-daily formulations are likely to be more convenient for users (1, 2), particularly for those wishing to use hormonal contraceptives for a reasonable period of time.

The contraceptive vaginal ring (NuvaRing; NV Organon, Oss, The Netherlands) is a monthly contraceptive method that releases 15 μg of ethinyl estradiol (EE) and 120 μg of etonogestrel (ENG) per day over 3 consecutive weeks. One of the main advantages of NuvaRing over oral contraceptives is the release of hormones directly into the systemic circulation. This avoids gastrointestinal metabolism and allows the use of low doses of contraceptive hormones. Furthermore, the controlled-release delivery results in stable and precise therapeutic concentrations of contraceptive hormones and avoids the daily hormone fluctuations that occur with combined oral contraceptives (COCs).

Large-scale studies have previously demonstrated NuvaRing's efficacy, tolerability, and acceptability and remarkable cycle control with a low daily dose of EE (3–5). Further studies have shown that cycle control with Nuva-Ring was superior to that with a COC containing 30 μg EE (6, 7). The reason for this attribute is not known but might be linked to local hormone administration and local hormone concentrations and/or stable serum hormone levels resulting from NuvaRing's continuous dosing. Studies with several other therapeutic agents, including misoprostol and indomethacin, have demonstrated increased efficacy with vaginal administration over the oral route (8). The basis for the increased efficacy of these agents is uncertain but might also be related to increased local concentrations of the agents in uterine tissues.

To investigate whether uterine contraceptive steroid levels might be higher after vaginal compared with oral administration, in the present study we compared uterine steroid

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concentrations of ENG and EE after administration of NuvaRing with those after administration of a COC containing 20 μg EE and 150 μg desogestrel. It should be noted that ENG is the active metabolite of desogestrel, so the same active contraceptive hormones are being compared in this study. Notably, in this trial we used a unique approach by studying uterine contraceptive hormone levels in a population of premenopausal women undergoing hysterectomy.

MATERIALS AND METHODS

This phase III, randomized, open-label, group-comparative, pharmacokinetic trial was conducted at the Atrium Medisch Centrum, Heerlen, The Netherlands, between October 2002 and October 2003. The trial protocol was approved by the independent ethics committee of the trial center and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guideline for Good Clinical Practice. All subjects provided written informed consent.

Study Population

Healthy, premenopausal, adult female volunteers who were planning to undergo a hysterectomy for curative purposes were included. The reasons for undergoing a hysterectomy were therapy-resistant vaginal bleeding, small fibroids, prolapse, or other indications judged to be necessary by the investigator.

Subjects were excluded if they were pregnant; had used an injectable hormonal contraceptive within 6 months of the study start; had used or were using investigational or certain other drugs (including hydantoins, barbiturates, primidone, carbamazepine, oxcarbazepine, topiramate, felbamate, rifampicin, rifabutin, griseofulvin, sex steroids apart from pretreatment hormonal contraceptives, and St. John's wort). Subjects were also excluded if they had abnormal results on cervical smear at screening or any contraindication for contraceptive steroid use.

Treatment

Eligible subjects were randomly allocated to treatment with a single cycle (17–21 days) of NuvaRing or the COC. For each subject, treatment was scheduled so that it would end when the planned hysterectomy was performed. Subjects visited the Atrium Medisch Centrum at screening and at the end of treatment (when surgery took place). At screening, subjects were allocated to treatment and were issued a medication box containing either a single sachet of NuvaRing, which releases 15 μg EE and 120 μg ENG, or a strip of COC tablets containing 20 μg EE and 150 μg desogestrel (Mercilon; NV Organon) and given instructions on use. Subjects in both groups started treatment according to the instructions on the package leaflet, as outlined below.

NuvaRing Group

Women taking no hormonal contraception inserted the ring between days 1 and 5 of the menstrual cycle. Women using a COC inserted NuvaRing on the day after the usual tablet-free or placebo tablet interval. At the end of the treatment period, the ring was removed by the investigator in the operating room immediately before surgery.

COC Group

Women who had been taking no hormonal contraceptive began taking tablets on day 1 of their natural menstrual cycle. Subjects using another COC switched on the day after the last active tablet or on the day after the usual tablet-free or placebo tablet interval. The final COC tablet was taken 12 hours before surgery, to ensure that contraceptive hormone concentrations in serum would be as similar as possible to those of the NuvaRing group.

Pharmacokinetics

Uterine Assessments. Hysterectomies were performed on treatment days 17–21 with the standard Atrium Medisch Centrum procedures, which included perioperative, subcutaneous heparinization for 5 days. Contrary to routine operating room procedure, uterine specimens were not fixed in formalin. After each hysterectomy, uterine specimens were processed by the Department of Pathology, Atrium Medisch Centrum, Heerlen, The Netherlands. Each uterus was cut in half with a longitudinal, cross-sectional incision, and seven tissue samples of approximately 1 g each were removed (Fig. 1). Four samples of uterine tissue were taken from the myometrium, with two samples (Myo 1 and 2) taken from the upper myometrium and two (Myo 3 and 4) taken from the mid-myometrium. Two samples were taken from the cervical region (Cerv 1 and 2) and one from the endometrium (Endo). Samples were immediately frozen in liquid nitrogen and stored at −80°C. Concentrations of EE and ENG in uterine tissue samples were measured with specific RIAs (PPD Development, Richmond, VA) (9).

Serum Assessments. Blood samples (10 mL) to assess serum EE and ENG concentrations were taken at approximately 12 hours and 1 hour before surgery, 5 minutes after pill intake (if applicable), and at approximately 4 hours after surgery. After samples had been purified by high-performance liquid chromatography, serum concentrations of EE and ENG were measured by RIA (PPD Development).

Other Assessments. At screening, all subjects provided medical and gynecological histories, blood samples for biochemical and hematologic analysis, and underwent physical and cervical cytology examinations. Home pregnancy tests were performed by subjects just before ring insertion or intake of the first COC tablet.

Compliance

Each subject used a daily diary card to record COC tablet intake or the number of hours of ring use. This information

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