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Comparison of cervical mucus of 24/4 vs. 21/7 combined oral contraceptives☆

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Abstract

Background: Few studies have examined the action of combined oral contraceptives (COCs) on cervical mucus. We hypothesized that midcycle cervical mucus of women taking COCs is of poor quality when compared to their own midcycle mucus prior to initiating COCs. We sought to compare the effect upon quality and sperm penetration of the cervical mucus on the last hormone-free day with a 24/4 regimen to a 21/7 regimen.

Methods: This is an open-label, investigator-blinded, randomized, controlled, crossover equivalency study. All subjects received, in random order, 2 months of a 21/7 regimen and 2 months of a 24/4 regimen, each containing 20 mcg ethinyl estradiol and 1 mg norethindrone acetate. Analysis of cervical mucus quality (CMQ) and sperm penetration took place midcycle and on the last day of the hormone-free interval during the second month of each COC treatment.

Results: From April 2010 to November 2011, 18 subjects completed all study visits. Mean midcycle CMQ was poor (mean CMQ=1) and did not differ between 24/4 and 21/7 regimens (p=.92). On the last day of the pill-free interval, the quality and sperm penetration were poor with both regimens.

Conclusion: This study indicates that thickening of cervical mucus is a major mechanism of contraceptive action of COCs and that both 21/7 and 24/4 regimens result in poor quality and impenetrable mucus on the last day of the pill-free interval.

Keywords: Cervical mucus; Oral contraceptives; Sperm penetration test

1. Introduction

The main contraceptive effect of combined oral contraceptives (COCs) is inhibition of the midcycle lutenizing hormone (LH) surge to prevent ovulation. However, several studies have shown that the percentage of ovulatory cycles in women using low-dose COCs ranges between 1.5% and 16.8% [1–8]. With this high rate of ovulatory cycles in women taking COCs, we would expect the pregnancy rate with COC use to be much higher than the perfect use failure rate of 0.3% [9] were there not other effective mechanisms of contraceptive action in addition to ovulation inhibition.

Another potential mechanism of contraceptive action is the suppression of follicle-stimulating hormone secretion during the follicular phase of the cycle, thereby preventing follicular maturation; however, follicular development has been shown to occur in 23%–90% of cycles in women using COCs [1,5,9]. There are also many progestin-related mechanisms that likely contribute to the overall efficacy of the combined contraceptives, such as thickening of cervical mucus, impairment of tubal mobility and peristalsis, and effects on the endometrial lining, making it less suitable for implantation.

It is known that sperm transport from the vagina to the oviducts is greatly dependent on the properties of human cervical mucus, including mucus quantity, thickness and hydration [10]. Beginning at approximately the ninth day of an ovulatory menstrual cycle, increasing estradiol levels cause an increase in the amount of cervical mucus [11]. The mucus quality changes, it becomes thin and watery, and it allows sperm penetration from the endocervix into the endometrial cavity. The effect of sperm penetrability increases and reaches a peak just prior to ovulation.

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Progesterone is then secreted from the corpus luteum and causes the cervical mucus to become scant in amount, thick, opaque and unfavorable to sperm penetration [12].

Prior studies have examined the changes in cervical mucus quality (CMQ) and sperm penetrability in women using progestin-only oral contraceptives. Moghissi et al. [13] demonstrated that microdose norgestrel (75 mcg daily) causes alterations of physical and chemical properties of cervical mucus such that it becomes highly viscous, cellular and scanty; exhibits reduced ferning and spinbarkeit; and inhibits sperm transport. Barbosa et al. [14] examined time to contraceptive effectiveness in users of the single implant containing 55 mg nomegestrol acetate. Cervical mucus and sperm penetration tests were altered in all subjects within 48 h after insertion of the implant. Another study of the same design enrolled 30 women receiving an injection of 150 mg depot medroxyprogesterone acetate (DMPA) and measured the same parameters of cervical mucus changes [15]. This study showed all subjects to have CMQ scores of 0, as determined by the World Health Organization (WHO) criteria, and sperm penetrability test sufficient to prevent pregnancy by day 7 after the injection. Lewis et al. [16] demonstrated that midcycle mucus of users of the levonorgestrel intrauterine system is of poor quality and prevents endocervical sperm transport in vitro.

Few studies have examined CMQ in users of COC regimens. One study published in 1976 by Elstein et al. [17] indicated that contraceptive action of combined low-dose oral contraceptive is mediated through suppression of ovulation and by rendering cervical mucus impenetrable to sperm. Another randomized trial of two low-dose COCs by Winfried et al. [18] found the quality and quantity of cervical mucus to be minimal in the majority of women during treatment cycles.

Another topic that this study aims to address is shortening of the pill-free interval with COCs. A 24/4-day regimen of norethindrone acetate 1 mg/20 mcg ethinyl estradiol was approved for marketing in 2006. This agent has a cumulative pregnancy incidence of 0.9% during the first six cycles of use and a Pearl Index of 1.79 per 100 women-years in women $\leq$35 years old [19]. In addition to a theoretical improvement in efficacy, a shorter hormone-free interval also has the benefits of decreasing symptoms such as pelvic pain, headache, breast tenderness and bloating/swelling, which occur more frequently during this interval than when active pills are ingested [20,21]. Recently, Dinger et al. [22] published a large US cohort study that demonstrated higher contraceptive effectiveness with a 24-day oral contraceptive regimen compared with the 21-day regimen.

2. Material and methods

This was an open-label, investigator-blinded, randomized, controlled, crossover equivalency study comparing the in vitro sperm penetrability and quality of cervical mucus using WHO grading criteria on the last hormone-free day of women assigned to one of two groups. Healthy, reproductive-aged women with regular menses who desired initiation of oral contraceptives were enrolled for participation in this study. They were randomized by a computer-generated system to receive an oral contraceptive containing 20 mcg ethinyl estradiol and 1 mg norethindrone acetate either in a 24/4-day regimen or a 21/7-day regimen and started according to "Quick Start" protocol [23].

Inclusion criteria were healthy women aged 18–39 years desiring to initiate COCs. Exclusion criteria were any contraindications to combined hormonal contraception including pregnancy, breastfeeding, liver disease, vascular or uncontrolled metabolic disorders, smoking greater than 15 cigarettes at age 35 or older, body mass index greater than or equal to 40, migraine headaches with aura or untreated cervical dysplasia. Women were excluded if they had used steroid hormone or intrauterine contraception within 3 months prior to study enrollment or 6 months prior in the case of DMPA. Those currently breastfeeding or patients less than 3 months postpartum of a term pregnancy (or within 6 weeks of a first-trimester loss or termination) were also excluded, as were women who would not refrain from intercourse or the use of vaginal douches during the study period requiring cervical mucus assessment. This study was conducted on women in a primarily underserved population. Our informed consents were in both Spanish and English. The study was approved by the University of Southern California Health Science Campus Institutional Review Board.

2.1. Laboratory measures

As described by Lewis et al. [16], the tests used to determine mucus quality and penetration were the WHO cervical mucus criteria and the sperm–cervical mucus penetration test detailed below.

2.1.1. Collection of cervical mucus

In all subjects, the cervix was exposed using an unlubricated speculum, and the ectocervix was cleansed of debris with a large dry sterile swab. Cervical mucus was then obtained using a specialized endocervical aspirator (Unimar Aspirette, Cooper Surgical, Trumbull, CT, USA). Ring forceps or a cytobrush was used to assist in collecting thick or densely adherent endocervical mucus. Mucus was transported in the collection device to a laboratory where analysis began within 30 min of collection.

2.1.2. Cervical mucus analysis

Cervical mucus was grossly and microscopically examined by an investigator blinded to subjects' hormonal status to determine its volume, consistency, cellularity, spinnbarkeit and ferning, as described in the *WHO Laboratory Manual for the Examination of Human Semen and Sperm–Cervical Mucus Interaction* [24]. A CMQ grading score of 10 or greater of 15 total points favored sperm penetration and