

## GENERAL GYNECOLOGY

# The effects of reproductive hormones on the physical properties of cervicovaginal fluid

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**OBJECTIVE:** The purpose of this study was to determine the impact of contraception, menopause, and vaginal flora on the physical and biochemical properties of cervicovaginal fluid (CVF).

**STUDY DESIGN:** Vaginal swabs, CVF, and cervicovaginal lavage (CVL) were collected from a total of 165 healthy asymptomatic women including: postmenopausal women ( $n = 29$ ), women in the proliferative ( $n = 26$ ) or follicular ( $n = 27$ ) phase, and women using the levonorgestrel intrauterine device ( $n = 28$ ), depomedroxyprogesterone acetate ( $n = 28$ ) or combined oral contraceptives ( $n = 27$ ). Vaginal smears were evaluated using the Nugent score. The osmolality, viscosity, density, and pH of CVL samples were measured.

**RESULTS:** CVL from postmenopausal women and women with abnormal vaginal flora was less viscous and had higher pH than premenopausal women and women with normal flora, respectively. Women using hormonal contraceptives had more viscous CVL as compared with premenopausal women not using hormonal

contraceptives, but this increase in viscosity was mitigated in the presence of bacterial vaginosis. Women using depomedroxyprogesterone acetate had less total protein in the CVL as compared with women using the levonorgestrel intrauterine device, and had similar protein content when compared with postmenopausal women.

**CONCLUSION:** The differences in CVL protein content between depomedroxyprogesterone acetate and levonorgestrel intrauterine device suggest that type of progesterone and route of delivery impact the vaginal environment. Contraceptive hormone users had more viscous CVL than women not using contraceptives. However, the presence of bacterial vaginosis impacted both the pH and viscosity (regardless of hormonal contraceptive use), demonstrating that vaginal flora has a greater impact on the physical properties of CVF than reproductive hormones.

**Key words:** bacterial vaginosis, cervicovaginal fluid, contraceptives

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Cervicovaginal fluid (CVF) is comprised of transudate from the vaginal epithelium as well as cervical mucus and secretions from the uterus and fallopian tubes. The mucin gel layer that coats the vaginal epithelium is one of the first line defenses in protection against pathogens of the genital tract.<sup>1</sup> In order for sexually transmitted pathogens, such as HIV, to establish infection, they must penetrate the mucus layer and attach to receptors on target cells in the

cervical or vaginal epithelium. In a recent study, CVF, collected using a catamenial cup, slowed the diffusion of HIV-1 particles more than 200-nm PEGylated beads, which was dependent on the presence of HIV-1 envelope proteins. This demonstrates an important protective interaction between the CVF and HIV-1 particle.<sup>2</sup> In another study, the movement of HIV-1 through the CVF has been reported to be significantly slower at a pH of 4 and more rapid

when the CVF was buffered to a pH of 6.<sup>3</sup> Thus, the physical properties of the CVF impact how efficiently virus particles can traverse CVF and infect the vaginal or cervical epithelium. Decreased viscosity of CVF may render the mucin gel layer more permissive to penetration. In addition, CVF serves as a carrier for a broad array of antimicrobial peptides<sup>4</sup> and proteins including lysozyme,<sup>5</sup> lactoferrin,<sup>6</sup> secretory leukocyte protease inhibitor,<sup>7,8</sup> and human beta-defensins.<sup>9</sup> Therefore, the protein content of the CVF is also a key component in the innate mucosal defense.

One mechanism of progestin-dependent contraceptive efficacy is believed to be thickening of cervical mucus and preventing the transport of sperm from the vagina into the uterus and fallopian tubes.<sup>10</sup> The quality of the cervical mucus is dependent on reproductive hormones. Without the use of exogenous hormones, the first half of the menstrual cycle is characterized by

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increased estradiol levels and an increased amount of cervical mucus that is thin and watery to allow sperm penetration. In the second half of the menstrual cycle, predominated by increased progesterone levels, the cervical mucus becomes scant in amount, thick and opaque.<sup>11</sup> Several studies have reported a thickening of cervical mucus associated with progestin-only contraceptive methods using subjective measures of cervical mucus quality such as ferning and spinbarkeit.<sup>12-15</sup> Progestins subjectively thicken the cervical mucus within the cervical canal. However, less is known about the impact of reproductive hormones on cervicovaginal fluid, which provide a protective barrier over the vaginal epithelium. In addition to affecting the physical properties of the CVF, reproductive hormones mediate the biochemical content. Specifically, immunoglobulins, human beta-defensins, and secretory leukocyte protease inhibitor are lowest at midcycle when estradiol levels are elevated.<sup>16-18</sup>

The effects of exogenous reproductive hormones on CVF could have clinical consequences. A few prospective, well-controlled studies have linked progestin-only injectable use to increased HIV risk.<sup>19-22</sup> The effect of reproductive hormones on the physical or biochemical composition of the CVF has not been completely characterized, but changes in the mucin gel layer covering the vaginal epithelium is one possible biologic mechanism by which hormonal contraceptives could impact the risk of HIV acquisition.

Normal vaginal microbiota, characterized by a predominance of lactobacilli, is thought to be protective against sexually transmitted infection. The presence of bacterial vaginosis (BV) is associated with an increased risk of HIV acquisition in an HIV uninfected woman<sup>23</sup> as well as increased risk of HIV transmission by an HIV infected woman to an HIV uninfected male partner.<sup>24</sup> BV is characterized by an overgrowth of anaerobic bacteria and a decreased colonization by *Lactobacillus* species. This overgrowth of anaerobic bacteria is associated with increased levels of bacterial proteases and glycosidase in CVF.<sup>25</sup> Women with BV have higher levels of vaginal sialidases.

Sialidases are considered virulence factor in bacterial vaginosis<sup>26</sup>; they clip the negatively charged sialic acid residues from the terminal end of the mucin oligosaccharides. Sialidase residues protect the oligosaccharide and the protein backbone of the mucin molecule from degradation by mucin-degrading enzymes. The negatively charged mucin molecules keep a rigid structure and trap pathogens, preventing them from reaching the vaginal epithelium. BV may cause thinning of the mucin gel layer thus impeding the capacity of the CVF to serve as a barrier against HIV infection.

To date, there have been few studies that have investigated the impact of reproductive hormones and vaginal flora on the physical and biochemical properties of the CVF. In the present study, we collected both cervicovaginal fluid (CVF) using a catamenial cup as well as cervicovaginal lavage (CVL) by washing the vaginal vault with sterile normal saline. The primary aim of this study was to characterize the impact of reproductive hormones on the viscosity, pH, density, osmolality, and protein content of CVF. Because of the small volume and technical difficulties associated with performance of assays with the CVF, assessment of the physical properties of the CVF samples was not feasible. Therefore, the viscosity, pH, and osmolality and density were measured only in the CVL samples. Because epidemiologic studies have linked BV and exogenous contraceptive use to increased HIV susceptibility, we hypothesized that the use of contraceptives, phase on menstrual cycle, menopausal status, and vaginal flora will impact the physical properties and protein content of CVL.

## MATERIALS AND METHODS

### Study population

Following Institutional Review Board approval by the University of Pittsburgh, informed consent was obtained from healthy, asymptomatic, HIV-negative women who were either between 18-46 years of age or over the age of 50. We enrolled premenopausal women into the study who fell into the 5 following

categories on the basis of contraceptive use by self-report: (1) not contracepting on days 1-14 of the menstrual cycle, (2) not contracepting on days 15-28 of the menstrual cycle, (3) using combined-oral contraceptive pills for at least 6 months, (4) using depot medroxyprogesterone acetate (DMPA) injections for at least 6 months, (5) using the levonorgestrel intrauterine device (LNG-IUD) for at least 1 month. A group of postmenopausal women was also recruited; menopause was defined as age greater than 50 years of age without any vaginal bleeding in the previous 1 year. Women were excluded from the study if they had been pregnant or breastfeeding within the last 90 days, had vaginal symptoms or evidence of vaginitis on clinical examination, had used vaginally applied products in the prior week, had used antibiotics in the 2 weeks prior, had undergone a hysterectomy, or had a positive rapid HIV test. In addition, postmenopausal women taking exogenous estrogen were also excluded. None of the postmenopausal women reported taking supplements containing phytoestrogens.

On enrollment, demographic information, medical, gynecologic, and sexual histories were collected from each participant. A vaginal swab for pH, wet mount microscopy, and Gram stain were collected. The catamenial cup was inserted into the vagina up to the cervix by the clinician and left in place for at least 45 minutes. The catamenial cup was removed and placed into a 50 mL conical vial for transport to the laboratory. The cervicovaginal fluid samples were centrifuged at 2000×g for 10 minutes. The protein laden material was removed and the volume was measured. Because of the small volumes and difficulty working with the CVF samples, we were unable to assess the physical properties of the CVF specimens. Then, these samples were stored at -70°C for future study. For collection of the cervicovaginal lavage (CVL), 10 mL of sterile normal saline was placed into the vagina, a lavage was performed for 1 minute, and placed into 15 mL conical vial with 100 µL of protease inhibitor (Sigma-Aldrich, St. Louis, MO). A cervical swab was collected for

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