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HIV and Hormonal Contraception: Bench and Bedside

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To the Editors

While results from observational studies have been inconsistent, the preponderance of clinical data indicates the risk of acquiring HIV is modestly increased among women using progestin-only injectable hormonal contraceptives such as depot medroxyprogesterone acetate (DMPA; Depo-Provera).¹ In a recent review, Hickey et al. postulated that DMPA promotes acquisition of HIV by reducing integrity of the vaginal epithelium.² Offering support for this possibility, we found that DMPA administration reduced cell-cell adhesion molecule expression in murine and human genital epithelial tissues, and significantly increased permeability of these tissues.³ We also found that mice concomitantly administered DMPA and systemic or intravaginal estrogen displayed reduced genital mucosal permeability and were protected from acquiring genital herpes simplex virus type 2 (HSV-2) infection.³

Here, we extend these findings by similarly assessing genital mucosal permeability in 7 healthy women 18–24 years of age before and after they initiated levonorgestrel-releasing intrauterine system (LNG-IUS) (Mirena®) use for pregnancy prevention. Worldwide, LNG-IUS is the most popular long-acting reversible contraceptive (LARC), and is identified as a first-line choice for LARC by the American College of Obstetrics and Gynecology.⁴ Using methods described in detail previously,³ we obtained ectocervical biopsy tissue specimens from women using no form of hormonal contraception and again approximately 1 month after they initiated LNG-IUS use. Biopsy tissues were incubated in 20 µl of a PBS solution that contained 62.5 µg of dextran Texas-Red (MW = 70,000 Da) and 50 µg of Lucifer yellow CH, lithium salt (MW = 457 Da). Forty-five minutes later, specimens were formaldehyde-fixed, agarose-embedded, and DAPI-stained to visualize the fluorescently tagged molecules by confocal microscopy. Analysis of these images revealed increased tissue penetration of Lucifer yellow CH in biopsy specimens collected after LNG-IUS insertion (representative results shown in Figure 1A). Congruent with this increased permeability, we detected significantly reduced expression of the desmosomal cadherin desmoglein-1 in ectocervical tissues collected after LNG-IUS initiation (Figure 1B).

These new results are consistent with the decreased cell-cell adhesion molecule expression and increased genital mucosal permeability and susceptibility to genital HSV-2 infection we previously observed in LNG-treated mice.³ As ectocervical mucosal permeability is increased in women initiating use of DMPA or LNG-IUS, our results also imply both progestins may similarly affect genital mucosal barrier protection. Because uncompensated hypoestrogenism is thought to occur with DMPA but not LNG-IUS use,² our results also provide novel indication that the increased ectocervical permeability seen in women initiating LNG-IUS use was not sequelae to reduced circulating estradiol concentrations.

In their review, Hickey et al. specified that DMPA enhanced susceptibility of rhesus macaques (RM) to genital infection with simian immunodeficiency virus (SIV), but that concomitant use of exogenous estrogen was shown to abrogate this effect.² While our mouse model results imply that concomitant estrogen treatment would protect DMPA-treated RM from SIV,³ to date, there are no published reports from studies comparing SIV transmission in RM administered progestin vs. progestin and estrogen. Conversely, Preston Marx and colleagues have shown exogenous estrogen administration protected ovariectomized RM from SIV transmission.^{5, 6} Therefore, as exogenous estrogen use may offer an effective adjuvant approach for reducing genital mucosal permeability in women using progestin-only compounds for LARC, defining the utility of this approach in experimental infection models seems warranted. It also seems useful to perform clinical studies to more fully define the effects of LNG-IUS use on anti-pathogen host defense.

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Figure 1. LNG-IUS use increased permeability and decreased desmoglein-1 (DSG1) expression levels in human ectocervical mucosal tissue

Ectocervical biopsy specimens were obtained from 7 healthy young women at enrollment (i.e., using no form of hormonal contraception) and 1 month after LNG-IUS use was initiated. These specimens were used to define permeability to a fluorescently-tagged low molecular weight molecule and expression levels of the cell-cell adhesion molecule DSG1. (A) Representative images display increased permeability to Lucifer yellow CH, lithium salt (LY) with LNG-IUS use (L denotes vaginal lumen); (white bar = 20 μ m); (LY, green); dextran Texas-Red (red); DAPI, 4,6-diamidino-2-phenylindole (blue). (B) LNG-IUS use significantly reduced DSG1 expression (panel displays relative gene expression levels before and after LNG-IUS insertion) (relative gene expression was defined using glucose-6-phosphate isomerase as a housekeeping reference gene); a paired Student *t*-test provided statistical comparison; $p < 0.05$ were considered statistically significant.