HHS Public Access

Author manuscript

Eur J Contracept Reprod Health Care. Author manuscript; available in PMC 2016 April 01.

Published in final edited form as:

Eur J Contracept Reprod Health Care. 2015 April ; 20(2): 149–153. doi:10.3109/13625187.2014.957826.

The effect of protease inhibitors on the cervical mucus of HIV-positive women taking norethindrone contraception

Jessica ATRIO[a], **Alice STEK**[a,b], **Hita VORA**[c], **Lorraine SANCHEZ-KEELAND**[d], **Ferdous ZANNAT**[e], and **Melissa NATAVIO**[a]

[a]Department of Obstetrics and Gynecology, Los Angeles, CA 90033

[b]Department of Maternal Child and Adolescent Center for Infectious Diseases, Los Angeles, CA 90033

[c]Southern California Clinical and Translational Science Institute, Los Angeles, CA 90033

[d]University of Southern California Keck School of Medicine, Los Angeles, CA 90033

[e]Albert Einstein College of Medicine, Bronx, NY 10461, USA

Abstract

Objective—To compare cervical mucus score (CMS) with and without protease inhibitors (PI) before and after taking norethindrone (NET).

Study Design—This two-arm, researcher blinded, non-randomized, prospective study was conducted to evaluate cervical mucus quality in HIV-positive women taking progestin only pills. The study group was taking a PI, and compared to women taking ARV regimens that have demonstrated no significant interaction with NET in prior pharmacokinetic studies with combined oral contraceptives. Women had a cervical mucus score prior to NET administration. Mucus collection was repeated after 21 days of steady state exposure to oral NET 0.35 milligrams, the POP available in the US. Cervical mucus quality, was quantified according to the World Health Organization criteria, which included: volume, consistency, cellularity, spinnbarkeit, and ferning.

Results—Sixteen women took PI and 17 were controls. Baseline CMS were similar ($p \geq 0.1$). After 21 days CMS were similar between the two groups ($p = 1$).

Conclusions—HIV-positive women taking PI demonstrated thickened cervical mucus with oral norethindrone 0.35mg and are similar to HIV-positive women taking no PI therapy, this may suggest no difference in contraceptive efficacy of progestin only pills in HIV positive women taking PI.

Keywords

AIDS; drug interaction; hormonal contraception; progestin only pills; antiretroviral medication; contraceptive efficacy

Corresponding author: Tel. (917) 721-6155; jessicaatrio@gmail.com.

Financial conflicts of interest: none to declare

ClinicalTrials.gov Identifier: NCT01667978

INTRODUCTION

Providing reproductive health services with antiretroviral (ARV) therapy is crucial to improving health outcomes of HIV positive women. Protease inhibitors (PI) inhibit hepatic enzymes systems such as cytochrome P450 3A4, which in turn alter the bioavailability of other medications such as hormonal contraceptives [1,2]. Trials with a limited number of HIV negative subjects have demonstrated that combined oral contraceptives (COC) and PI result in decreased ethinyl estradiol levels with concern for decreased contraceptive efficacy [1,2]. Based on these findings the U.S. Center for Disease Control Medical Eligibility Criteria for Contraceptive Use state that women taking ritonavir-boosted PI should be advised against taking progesterone only pills (POP), as the risks outweigh the benefits (3). However, COC studies have also demonstrated there is no decrease in serum levels of progestins with ARVs (1, 2). This trial assesses a surrogate marker of POP contraceptive efficacy, cervical mucus score (CMS) among HIV-positive women with and without PI therapy. It was a secondary outcome in a pharmacokinetic drug interaction clinical study (4).

METHODS

Design

This is a prospective, non-randomized, researcher blinded trial to assess cervical mucus in HIV-1-positive women. CMS of women taking PI was compared to controls taking ARVs without PI, which have demonstrated no significant interaction with norethindrone in previous COC trials at the time of enrolment into the clinical trial. Both groups then began taking norethindrone 0.35 mg daily, after 21 days of norethindrone CMS of the PI group was compared to the controls. University of Southern California (USC) Institutional Review Board approval was obtained.

Population

HIV-positive women 18 to 44 years of age, with no recent exposure to hormonal contraception, no change in medication or lifestyle, CD4+ cell counts ≥200 cells/mm^3, and no liver or renal disease. Regular menstrual cycles and a body mass index (BMI) less than 40 kg/m^2. Participants abstained from CYP3A4 interacting substances.

Procedures

Following screening and informed consent, baseline endo-cervical mucus was collected from the external os by the Aspirette Endocervical Aspirator (Cooper Surgical, Inc., Trumbull, CT), with a non-lubricated vaginal speculum. These specimens were collected at different times during the menstrual cycle for the various participants. World Health Organization Laboratory Manual for the Examination of Human Semen was used to assess CMS, maximum score is fifteen, a score greater than ten is indicative of mucus favouring sperm penetration (Table 1) (5). The research team considered nine as the a priori cut off. Volume, consistency, and spinnbarkeit were assessed within thirty minutes of aspiration. Cellularity and ferning were assessed in four microscopic high power fields (40x) on slides that had dried for two hours.

After 21 consecutive days of norethindrone 0.35 mg (Jolivette, Watson Pharmaceuticals, Inc. Corona, CA) women presented for a repeat cervical mucus collection. The same investigator, blinded to ARV treatment, performed all collections and scoring.

Statistics and Sample Size

CMS values were analysed as a dichotomous categorical variable using a cut point of (<9 and >= 9) and as an ordinal (continuous) variable. Data are presented as medians and interquartile range for ordinal and continuous variables and n (%) for categorical data. Differences between groups were compared using Wilcoxon Rank Sum, non-parametric test. The chi square test was used for nominal categorical data. Fisher's exact test was used when the expected counts were less than 5. Assessments were two-tailed and P-values <0.05 were considered significant. Analyses were performed using SAS, version 9.3 statistics software (SAS Institute, Inc., Cary, NY).

The sample size calculation was based on the primary pharmacokinetic outcome of the trial, a projected change of 40% in serum norethindrone area under the curve between the two groups; details are addressed in Atrio, et al. (4). This research was not powered to assess changes in cervical mucus.

RESULTS

Both groups had similar demographics with regard to age, parity, ethnicity, CD4, and history of opportunistic infections ($p \geq 0.1$). In the PI group (n=16): 15 women were taking ritonavir, 11 atazanavir, 3 darunavir, and 2 lopinavir. Four women in the control group (n=17) were not taking ARV therapy, 13 were taking a combination of ARV medications including: etravirine, rilpivirine, tenofovir, emtricitabine and raltegravir.

Baseline CMS were similar in both groups: PI median score was 6, and 5 for the controls, as shown in Table 2. In the PI group 75% (n=12) had a baseline CMS less than 9 compared to 53% (n=9) in the controls (p=0.28). After norethindrone, CMS were similar among the groups (p=1); 94% (n=15) of the PI and 94% (n=16) of controls had a score less than 9. Median scores were 3.5 for PI and 4 for controls. Results were unchanged when cervical mucus was treated as continuous variable at baseline (p=0.28) and post exposure (p=1). Thickened cervical mucus that would be unfavourable to sperm penetration was observed in both groups taking oral norethindrone.

DISCUSSION

The cervical mucus score before and during norethindrone 0.35mg exposure are not statistically different among women taking PI therapy as compared to women taking ARV without PI or no ARV. CMS was devised to predict conception; there is no standard score for contraceptive efficacy (6, 7, 8). These data suggest contraceptive efficacy is maintained among women who are HIV-positive and taking PI based therapy with POP. However, the small sample size of this pilot clinical trial is a significant concern and may limit the validity of these findings. Additionally, due to limited resources additional clinical testing such as sperm penetration studies were not employed.

Cervical mucus serves as a physical and chemical barrier to or facilitator of sperm penetration. Effect on cervical mucus is the most immediate protection against pregnancy provided by POPs (9). Sperm transport from the endocervix into the endometrial cavity is affected by cervical mucus, which increases and becomes thin and watery under the influence of estrogen beginning on approximately day nine of the menstrual cycle. The effect peaks just prior to ovulation. Under the influence of progesterone mucus becomes scant, thick, opaque and unfavourable to sperm penetration (10, 11). POPs effect on cervical mucus leads to decreased production at mid-cycle, increased cell content, greater viscosity, altered molecular architecture, and changes in protein concentration/composition (8). Sperm penetration is greatly reduced as early as three hours after ingestion of POPs (6). Changes in cervical mucus also effect sperm motility, respiration, and capacitation (12–14).

In a regularly menstruating woman the probability of observing cervical mucus favourable for sperm penetration and intercourse that results in fertilization spans approximately seven out of 28 days each cycle (15). For this reason it was expected that a quarter of the 16 enrolled women would have cervical mucus favourable for penetration (or greater than 10) at enrolment. This was observed in both the control and study group.

Strengths of this trial include its prospective design, no inter-examiner variation, and blinding. A limitation of this study was that baseline assessment did not involve peri-ovulatory cervical mucus scoring for all women and sperm penetration testing was not done. Researchers were unable to maintain enrolment through a confirmed follicular cycle of ovulation due to limited resources, support and strict protocol design, which was intended to maximize retention and completion.

The demographic at our California site may not reflect that of other regions. It may be difficult to generalize these results to women who are immunocompromised, who do not have access to clinicians, or who are unable to maintain strict adherence. It is not well understood why ethinyl estradiol levels have been noted to be decreased with PI, it may be secondary to changes in sex hormone binding globulin and other complex pharmacodynamic interactions. Ritonavir is the most potent CYP inhibitor in the PI class and there is biologic plausibility that inhibition of this enzyme, which contributes to the metabolism of steroid hormones, would increase serum norethindrone in combination with other PIs (1). Increased systemic norethindrone may result in maintained tissue levels and impenetrable cervical mucus. Research regarding safety, efficacy, non contraceptive benefits and physiologic impact of hormonal contraception among our HIV positive women is desperately needed. Clinical trials and population-based data will help guide recommendations to optimize safety and access.

Acknowledgments

Funding Sources: Society of Family Planning, Southern California Clinical and Translational Science Institute (The National Institutes of Health, National Center for Research Resources, National Center for Advancing Translational Sciences) through Grant UL1TR000130, Building Interdisciplinary Research Careers in Women's Health Grant K12 HD043488 Research was conducted at the University of Southern California Keck School of Medicine, Los Angeles, CA 90033

References

1. Tsend A, Hills-Nieminen C. Drug interactions between antiretrovirals and hormonal contraceptives. Expert Opinion on Drug Metabolism & Toxicology. 2013; 9:559–72. [PubMed: 23425052]
2. Robinson J, Jamshidi R, Burke A. Contraception for HIV-positive women: a review of interaction between hormonal contraception and antiretroviral therapy. Infectious Disease in Obstetrics and Gynecology. 2012; 2012:1–15.
3. Center for Disease Control. U.S. medical eligibility criteria for contraceptive use. Morbidity and Mortality Weekly Report. 2010; 59(RR-4)
4. Atrio J, Stanczyk F, Neely M, Cherala G, Kovacs A, Mishell D. Effect of protease inhibitors on steady state pharmacokinetics of oral norethindrone contraception in HIV infected women. Journal of Acquired Immune Deficiency Syndromes. 2014; 65:72–77. [PubMed: 24025339]
5. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5. Geneva, Switzerland: WHO Press; 2010.
6. Barbosa I, Coutinho E, Hirsch C, Ladipo O, Olsson S, Ulmsten U. Temporal relationships between Uniplant insertion and changes in cervical mucus. Contraception. 1996; 54:213–217. [PubMed: 8922874]
7. Adamopoulos D, Kapolla N, Abrahamian A, Dessypris A, Nicopoulou S, Giannacodemos G. Sex steroids in cervical mucus of spontaneous or induced ovulatory cycles. Steroids. 2000; 65:1–7. [PubMed: 10624830]
8. Linford E. Cervical mucus: an agent or a barrier to contraception? Journal of Reproduction and Fertility. 1974; 37:239–250. [PubMed: 4131608]
9. McCann M, Potter L. Progestin-only oral contraceptive: a comprehensive review. Contraception. 1994; 50(6 Suppl 1):S1–195. [PubMed: 10226677]
10. Moghissi K, Marks C. Effects of microdose of norgestrel on endogenous gonadotropic and steroid hormones, cervical mucus properties, vaginal cytology, and endometrium. Fertility & Sterility. 1971; 22:424–434. [PubMed: 5104921]
11. Steward R, Melamed A, Granat A, Mishell D. Comparison of cervical mucus of 24/4 vs. 21/7 combined oral contraceptives. Contraception. 2012; 86:710–715. [PubMed: 22682723]
12. Korhonen T, Turpeinen M, Tolonen A, Laine K, Pelkonen O. Identification of the human cytochrome P450 enzymes involved in the in vitro biotransformation of lynestrenol and norethindrone. Journal of Steroid Biochemistry and Molecular Biology. 2008; 110:56–66. [PubMed: 18356043]
13. Chi I. The safety and efficacy issues of progestin-only contraceptives-an epidemiologic perspective. Contraception. 1993; 47:1–21. [PubMed: 8435997]
14. Graham S, Fraser I. The progestogen-only mini-pill. Contraception. 1982; 40:337–388.
15. Wilcox A, Weinberg C, Baird D. Time of sexual intercourse in relation to ovulation-effects of the probability of conception, survival of the pregnancy, and sex of the baby. New England Journal of Medicine. 1995; 333:1517–1521. [PubMed: 7477165]

Table 1

Reference Chart for Scoring of Cervical Mucus World Health Organization Criteria for Cervical Mucus Evaluation

Score	0	1	2	3
Volume	0mL	0.1mL	0.2mL	0.3+mL
Consistency	Thick, highly viscous	Intermediate viscosity	Mildly viscous	Normal mid-cycle pre-ovulatory mucus
Ferning	No crystallization	Atypical ferning	Primary and secondary stem ferning	Tertiary and quaternary stem ferning
Spinnbarkeit	<1cm	1 to <5cm	5 to <9cm	≥9cm
Cellularity	≥21cells/HPF	6–20cells/HPF	1–5cells/HPF	0 cells/HPF

Scoring: ≥ 10 indicative of good cervical mucus favoring sperm penetration, a more stringent cut off of 9 was used for analysis in this trial

World Health Organization: laboratory manual for the examination of human semen and sperm cervical mucus interaction (4)

Table 2

Total Cervical Mucus Score* before and after 21 days of exposure to Norethindrone 0.35 mg

	PI** (n 16)	Control** (n 17)	P value***
Categorical analysis			
Baseline			
≥9	4 (25)	8 (47)	
<9	12 (75)	9 (53)	0.28
Follow up****			
≥9	1 (6)	1 (6)	
<9	15 (94)	16 (94)	1
Continuous variable analysis			
Baseline			
Median (IQR)	6 (2.5–8.5)	5 (3–11)	0.28
Follow up****			
Median (IQR)	3.5 (2–6)	4 (2–6)	1

*World Health Organization scoring criteria, see Table 1

**Study group took protease inhibitor (PI) therapy, control group took no PI

***Wilcoxon rank sum test

****After 21 days of norethindrone ingestion daily