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Misreporting of contraceptive hormone use in clinical research participants

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Abstract

Objective: Researchers traditionally rely on participant self-report for contraceptive use. We hypothesized that self-reported contraceptive use by clinical research participants may disagree with objectively measured hormonal status.

Study design: We enrolled women in Harare, Zimbabwe, aged 18–34, who by self-report had not used hormonal or intrauterine contraception for >30 days, or depot medroxyprogesterone acetate for >10 months, into a study designed to assess biologic changes with contraceptive initiation and use. Blood samples obtained at enrollment and each follow-up visit (N=1630 from 447 participants) were evaluated by mass spectrometry for exogenous hormones. We individually interviewed a subset of participants (n=20) with discrepant self-reported and measured serum hormones to better understand nondisclosure of contraceptive use.

Results: Discrepant with self-reported nonuse of hormonal contraception, synthetic progestogens were detectable in 120/447 (27%, 95% confidence interval 23%–31%) enrolled women. Measured exogenous hormones consistent with use of contraceptive pills (n=102), injectables (n=20) and implants (n=3) were detected at enrollment, with 7 women likely using >1 contraceptive. In-depth interviews revealed that participants understood the requirement to be hormone free at enrollment (100%). Most (85%) cited partner noncooperation with condoms/withdrawal and/or pregnancy concerns as major reasons for nondisclosed contraceptive use. All interviewed women (100%) cited access to health care as a primary motivation for study participation. Of participants who accurately reported nonuse of hormonal contraception at enrollment, 41/327 (12.5%) had objective evidence of nonstudy progestin use at follow-up that disagreed with self-reported nonuse.

Conclusions: Women joining contraceptive research studies may misrepresent their use of nonstudy contraceptive hormones at baseline and follow-up. Objective measures of hormone use are needed to ensure that study population exposures are accurately categorized.

Implications statement: Among Zimbabwean women participating in a contraceptive research study, 27% had objective evidence of use of nonstudy contraceptives at enrollment that disagreed with self-report. Studies that rely on self-report to identify contraceptive hormone exposure could suffer from significant misclassification.

Keywords: Self-report; Hormonal contraception; LARC; Misreporting; Oral contraceptive pills

1. Introduction

Clinical research investigators traditionally rely on participant self-report for important variables including last menstrual period (LMP) and contraceptive use. Many published studies have relied on these self-reported variables to critically classify participants into analysis cohorts on which outcomes are determined [1–11]. Objective biomarkers of exposure have rarely been evaluated. Recently, several authors have described significant discrepancies between self-report and objective biomarker exposure data for sexual activity [12,13], history of *Chlamydia trachomatis* infection [14], tobacco use [15] and contraceptive use [16–18]. Misreported contraceptive use could bias results in studies examining the effects of specific

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contraceptives, for instance, studies of contraceptive injectables and human immunodeficiency virus (HIV) acquisition risk [19]. Research to validate self-reported contraceptive use is limited [20].

Studies assessing use of hormonal contraception and HIV acquisition risk show mixed outcome data [19]. In order to untangle possible biological links between hormonal status and risk of acquiring sexually transmitted infections (STIs) and HIV, there is a need to understand if self-reported variables are adequate for cohort assignment. We hypothesized that self-reported contraceptive use by clinical research participants may disagree with objectively measured hormonal status. In order to assess accuracy of self-reported LMP and contraceptive use, we compared laboratory evaluation of serum progestogens and estrogens to participant self-report. We also explored reasons for misreporting in a subset of participants with discrepant self-reported and measured serum hormone data.

2. Materials and methods

2.1. Study population and sample collection

We performed a parallel cohort study (ClinicalTrials.gov number: NCT02038335) of women initiating contraception with injectable [depot medroxyprogesterone acetate (DMPA), norethisterone enanthate (Net-En), medroxyprogesterone acetate and ethinyl estradiol (MPA/EE)], implant [levonorgestrel subdermal implant (LNG-I) or etonogestrel subdermal implant (ENG-I)] or intrauterine [copper T380A intrauterine device (Cu-IUD)] contraception. The primary objective was to assess the impact of initiation and continued use of contraceptives on HIV target cells in the lower genital tract at 1, 3 and 6 months of use. The study was designed to assess changes compared to baseline with each woman serving as her own control; therefore, being free of exogenous steroid hormones at baseline and in a uniform phase of menses was central to the study design. Given the critical importance of the baseline values, laboratory confirmation by ultra-high-performance liquid chromatography tandem mass spectrometry (UPLC/MS/MS) was performed to evaluate serum progesterone (P4), levonorgestrel (LNG), etonogestrel (ENG), norethindrone (NET) and medroxyprogesterone acetate (MPA) concentrations, which covered the full spectrum of regionally available contraceptive progestins at the time this study was conducted. Baseline sampling was performed at the enrollment visit when all enrolled women were free of hormonal or intrauterine contraceptive use for the preceding 30 days and free of DMPA use for the preceding 10 months by self-report. The University of Pittsburgh Institutional Review Board and The Medical Research Council of Zimbabwe approved this study. All participants were enrolled at Spilhaus Family Planning Centre in Harare, Zimbabwe, and signed informed consent before study participation.

Enrollment consisted of 451 women, age 18–34 years, seeking contraception in Harare, Zimbabwe. Eligible women were healthy, HIV negative and nonpregnant and had regular menstrual cycles. Women were excluded if within 30 days of enrollment they (1) used any hormonal or intrauterine contraceptive; (2) underwent any genital tract procedure (including biopsy); (3) were diagnosed with any urogenital tract infection; or (4) used any oral or vaginal antibiotics, oral or vaginal steroids, or any vaginal product or device except tampons and condoms (such as spermicide, microbicide, douche, sex toys and diaphragms). Women were also excluded if by self-report they used DMPA within 10 months of enrollment, were pregnant or breastfeeding within 60 days of enrollment, or had a new sexual partner within 90 days of enrollment. Exclusion criteria included having a contraindication, allergy or intolerance to use of the contraceptive desired by the participant and having a prior hysterectomy or malignancy of the cervix or uterus.

Screening included urine pregnancy testing; two rapid HIV screening tests to rule out HIV infection; and collection of genital tract swabs for detection of *Neisseria gonorrhoeae*, *Chlamydia trachomatis* (Cepheid, Sunnyvale, CA, USA) and *Trichomonas vaginalis* (OSOM, Sekisui Diagnostics, Lexington, MA, USA).

Eligible participants presented for enrollment on a day when no vaginal bleeding was present and when they were in the follicular phase of menses (day 1–14) by self-reported LMP. Participants were asked to refrain from any vaginal or anal intercourse for 48 h prior to sample collection at enrollment and all follow-up visits. Participants selected their contraceptive group from among the six options (DMPA, Net-En, MPA/EE, LNG-I, ENG-I and Cu-IUD), and the selected contraceptive was administered by a study clinician at the enrollment visit immediately following collection of all study samples. IUDs and implants were inserted per standard clinical practice. All laboratory personnel were masked to clinical status of participants including contraceptive group.

2.2. Laboratory methods

Collection of blood and genital tract samples occurred at enrollment and at follow-up visits on days 30, 90 and 180. Blood was collected in 4-mL tubes (Becton Dickinson, Franklin Lakes, NJ, USA) and transported to the UZ–UCSF Central Laboratory on ice within 90 min. Specimen identifier details were entered into Laboratory Information System (DISA Laboratory Information System, Laboratory System Technologies, version 16.03), and unique identifiers were generated and assigned for subsequent processing. Blood samples were centrifuged at 1100*g* for 10 min at 20°C. Serum was harvested and aliquoted into 2-mL cryo vials (SARSTEDT Aktiengesellschaft & Co., Nümbrecht, Germany) and immediately transferred to −80°C for storage pending shipment for centralized hormonal testing at the University of Pittsburgh. Laboratory Data Management System (Frontier Science Research & Technology foundation, Buffalo, NY, USA) mapped freezer storage positions of