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Are hormonal contraceptive users more likely to misreport unprotected sex? Evidence from a biomarker validation study in Zimbabwe

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Abstract

We analyzed biomarker validation data of unprotected sex from women in Zimbabwe to determine whether condom and sexual behavior misreporting differs between users of different contraceptive methods. Self-reported sexual behavior was compared with the presence of prostate-specific antigen (PSA) in vaginal fluid, a biomarker of semen exposure. Of the 195 women who were PSA positive, 94 (48%) reported no sex or only condom-protected sex. Hormonal contraceptive users misreported sexual behavior less than women using non-hormonal methods (45% vs. 67%, P=0.03). This misclassification pattern could have implications on the elevated risk of HIV infection associated with hormonal contraception in some studies.

Keywords

bias; HIV; hormonal contraception; misclassification; women

INTRODUCTION

Understanding whether hormonal contraception (HC) increases women's risk of human immunodeficiency virus (HIV) acquisition is an urgent public health priority. Although observational studies have not generally reported an elevated risk of HIV acquisition among oral contraceptive users,[1] there is a growing body of studies reporting an association between HIV infection and injectable HC methods such as depot medroxyprogesterone acetate (DMPA) and norethisterone enantate.[2–6] Nonetheless, findings have been inconsistent across hormonal methods, study populations, and analytic methods.[1,7] Given that 41 million women worldwide who are married or in union use injectable hormonal contraceptives, including 8.7 million women living in the generalized HIV epidemics in Sub-Saharan Africa, this is a critical issue.[8]

HC prevents unintended pregnancies, reduces maternal and infant morbidity and mortality, and has other significant social and economic benefits.[9] Thus, policymakers are

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understandably cautious not to over-interpret the findings from observational studies where contraceptive methods are self-selected and sexual behaviors, like condom use, are self-reported. [10] One concern is that inadequate control for the confounding and mediating effect of condom use,[11] due in part to imperfect measurement, may contribute to the association between HC and HIV infection.[12] In particular, it has been hypothesized that HC users may *over-report* condom use more than women who rely on condoms or other non-hormonal methods as their primary contraceptive method,[13–15] potentially due to the low use of condoms by women solely for disease prevention.[16,17] Such differential misclassification may be particularly important in the context of HIV prevention trials – the source of data in many analyses of the HC-HIV relationship [2–4,6,18–21] – during which women are typically asked to avoid pregnancy and are counseled extensively to use condoms, which may result in over-reporting of socially desirable behaviors.

We analyzed biomarker validation data of unprotected sexual activity from women in Zimbabwe to determine whether there is evidence to support the hypothesis that differential misclassification of condom use and sexual activity partially explains the association between HC use and HIV infection.

METHODS

Study design

The objective of our analysis was to determine whether condom and sexual behavior misreporting is differential by users of different contraceptive methods. The study sample was a subset of women who participated in the Methods for Improving Reproductive Health in Africa (MIRA) study, a phase III effectiveness trial of the diaphragm and lubricant gel for HIV prevention that enrolled women who intended to avoid pregnancy for the next 24 months.[22] An analysis of 4,913 non-pregnant women in this study found no increased HIV risk associated with oral contraceptives, but a small increased risk associated with injectable HC in some models.[2]

Here, we analyzed data from an ancillary methodological study conducted with a convenience sample of 910 women in Zimbabwe who had recently completed participation in the MIRA trial. The median duration of time between the last MIRA visit and the ancillary study was 8.9 months (range: 2.3–20.6). The study examined sexual behavior and condom reporting validated by prostate-specific antigen (PSA), a biomarker with high positive predictive value, as the reference standard for recent semen exposure.[23,24] Women completed a face-to-face or audio computer-assisted self-interview that included questions about their sexual activity and condom use in the previous 7 days (there was no difference in reporting by interview mode[23]).

Exposure assessment

At each visit in the MIRA study, women were asked about their current contraceptive method including combined oral contraceptive pills, progestin-only pills, injectable hormonal contraceptives, male and female condoms, intrauterine devices, implants, and other methods. (Due to the small number women testing positive for PSA who were also

using hormonal implants (n=3), we excluded these women from the analysis.) We first classified women into three mutually exclusive groups based on their reported contraceptive method at their last MIRA visit: 1) oral contraceptives (OC); 2) injectables; and 3) condoms and other non-hormonal methods (the same comparison group used in most analyses of the HC-HIV relationship). Women who reported use of oral contraceptives or injectables in addition to a non-hormonal method (e.g., condoms) were classified into the oral contraceptive and injectable groups, respectively. We also created a binary variable indicating use of any hormonal contraceptive method (oral contraceptives and injectables) versus non-hormonal methods.

Outcome assessment

There were two primary outcomes in the analysis. The first was condom misreporting, defined as detection of PSA and the self-report of no unprotected sex (e.g., no sex without condoms) in the previous two days. PSA detection methods used to test women's self-collected vaginal fluid specimens have been previously described.[25] PSA concentrations greater than 1.0 ng/mL were considered evidence of semen exposure within the past 2 days. (Due to rapid PSA clearance, the sexual behavior of women who were PSA-negative is unknown; these women are therefore excluded from the analysis given that they are non-informative.) The second outcome was a combined category of sexual behavior misreporting, defined as detection of PSA and the self-report of no sex or no unprotected sex in the previous two days. We repeated the analysis using an indicator for no sex or only protected sex without report of condom breakage, slippage, or spillage of semen and the results did not qualitatively change; thus, we present the results with the broader category alone.

Statistical analysis

Consistent with previous biomarker validation studies using PSA,[23] the analysis was restricted to the subset of women who tested positive for PSA (>1 ng/mL) in vaginal eluate and who had contraceptive use data available from their last MIRA follow-up visit. We first present descriptive statistics of the study population using data provided at the baseline MIRA visit. Then we examined the proportion of women who, based on PSA results, misreported condom use or sexual activity within each contraceptive group (both the 3-level and binary categorizations), and tested the null hypothesis of no association with a two-sided Fisher's exact test with α=0.05.

Sensitivity analyses

We conducted three sensitivity analyses. We first examined the sensitivity of our findings to the gap between the last MIRA visit, when contraceptive type was measured, and the ancillary PSA study. To do this, we examined the relationship between contraception type and sexual behavior misreporting only among those women with delays that were equal to or less than the median delay of 8.9 months.

We also examined the relationship between contraceptive type and sexual behavior misreporting when the sample was restricted to women who reported the same contraceptive type at both their final and penultimate MIRA quarterly visit (consistent method use over 3–

6 months). The motivation for this analysis was to increase the likelihood that women were using the same method at the time of the ancillary PSA study. Finally, we examined the relationship between contraceptive type and sexual behavior misreporting with both sample restrictions, including only women with gaps equal to or below the median *and* those who were consistent method users.

RESULTS

Of the 195 PSA-positive women, the mean age was 28 years (range 18–48), 189 (97%) were married, 192 (98%) lived with their husband or regular partner, 99 (51%) had less than a high school education, and 158 (81%) had one lifetime sexual partner. At their last MIRA study visit, 128 (66%) reported using OCs, 37 (19%) used injectables, and 30 (15%) used non-hormonal methods. Seventeen (56.7%) of the 30 non-hormonal method users reported using condoms as their contraceptive method.

Overall, 94 (48%) women misreported sexual behavior, reporting no sex or only condom-protected sex in the previous 2 days (Table 1). Of these women, 71 (36% of all PSA-positive women) women misreported condom use and 23 (12% of all PSA-positive women) women reported no sex in the previous 2 days. There was no statistical difference in condom misreporting by contraceptive method group: protected sex only was reported by 36%, 27%, and 50% of PSA-positive women using OCs, injectables, and other methods, respectively (Fisher's exact test P=0.16). Likewise, the combined category of sexual behavior misreporting (no sex or no unprotected sex) was not statistically different across the three contraceptive groups (P=0.09). The binary categorization suggested that HC users were less likely to misreport sexual behavior than users of non-hormonal methods (45% vs. 67%, P=0.03). The results were qualitatively similar in the sensitivity analyses (Table 2) when the sample was restricted to women with a shorter contraceptive measurement gap (n=102), those who were consistent method users (n=173), or both (n=93).

DISCUSSION

In this study of Zimbabwean women who had recently participated in an HIV prevention trial, we found no evidence to suggest that users of hormonal contraceptive methods were more likely than users of non-hormonal methods to misreport condom use or sexual behavior. Notably, our quantitative results using a binary indicator for hormonal contraception use as well as our assessment of results stratified by the specific type of contraceptive method (positive but non-significant) suggests that women using hormonal contraceptive methods might actually be less likely to misreport condom use and sexual behavior than women using non-hormonal methods (contrary to some prior hypotheses[13–15]). This could occur if women using non-hormonal methods, including condoms and traditional methods, feel pressure to over-report condom use since they provide dual protection against both HIV infection and pregnancy. Thus, although increased condom misreporting by HC users has been cited as one of the potential explanations for the observed association between HC and HIV infection, the results from this study do not support this hypothesis. Our results are similar to another biomarker validation study among HIV infected and uninfected women in the U.S. which found that women using hormonal

contraception were as likely to misreport unprotected sex as women using other methods. In that study, inaccuracies in the reporting of unprotected sex were significantly related to participant characteristics such as study site, age, race, and HIV status, but not related to HC use.[26]

As seen here and as originally reported by Minnis *et al.*,[23] nearly half of women with detectable PSA reported that they had no sex or only condom-protected sex in the previous 48 hours. Because the level of misreporting among women who were negative for PSA is unknown, we do not know if the same proportion and/or pattern of misreporting applies to all women in the MIRA study. Nevertheless, modest condom and sexual behavior misclassification, even if non-differential, could have important implications for interpreting the HIV risk associated with HC in some studies. For example, consider condom use's role as a confounder of the HC-HIV relationship.[11] Unlike non-differential misclassification of an exposure, which predictably biases effect estimates towards the null,[27] non-differential misclassification of a binary confounder can bias either towards or away from the null, depending on the direction of confounding.[28,29] This results in reduced ability to control for confounding, as adjustment for the imperfectly measured confounder produces an effect estimate that lies between the crude and the fully adjusted measure. Indeed, even minimal non-differential misclassification of a strong confounder can quickly render adjustment ineffective, especially when the effect of the exposure is weak, as may be the case with HC and HIV.[29,30]

In addition to the potential for confounding, condom use may also be a mediator of the HC-HIV relationship,[11] and a growing body of methodological research suggests that non-differential measurement error of a mediator can bias estimates of both the direct and indirect effects of the exposure on the outcome.[31,32] Specifically, non-differential misclassification of a binary mediator results in an overestimate of the natural direct effect and an underestimate of the natural indirect effect.[33] Thus, even non-differential misreporting of condom use could affect the observed effect estimate describing the association between HC and HIV infection.

However, our data suggest that the pattern of misreporting might indeed be differential, with non-HC users over-reporting condom use more than HC users. One modeling study reported that this pattern of misreporting could bias the observed effect estimates downward, even if no association were present, depending on the presence of and direction of misreporting in the HC group.[34] However, this model was based on a secondary analysis of the Partners in Prevention HSV/HIV Transmission Study, which consisted of serodiscordant couples who reported high levels of condom use that did not vary significantly by contraceptive method type.[4] In contrast, in the MIRA secondary data analysis and in several other studies,[2,3,18,35] the study population consisted of women in the general population who reported lower condom use that differed significantly between the contraceptive method user groups. In these studies, condom use may be a stronger confounder and/or mediator. Thus, repeating the aforementioned modeling study with different study populations and the condom use reporting patterns we have reported here may be highly valuable.

This analysis has important limitations. Data were from a subset of women in an HIV prevention trial; the distribution of contraceptive methods was different from the MIRA study overall (including a higher proportion of oral contraceptive users) and might be different from women in the general population. Contraceptive method was self-reported and was measured, on average, 8.9 months prior to the PSA study. It is feasible that women may have discontinued or switched methods during this time period. However, the findings were robust to several sensitivity analyses, including limiting the sample to women with shorter time gaps between MIRA exit and the PSA study and to those who had used the same method for at least the three- to six-month period before exiting MIRA. Finally, this was a small sample of 195 women with detectable PSA, approximately one-fifth of all women in the PSA study (N=910); thus, we had low power for our primary question of interest. Given that PSA is known to decay rapidly from the vaginal fluid, some women who had recent unprotected intercourse (<2 days prior) but were PSA negative might have been excluded from the analysis.[23,24]

Nevertheless, although the discrepancy between biomarker data indicating recent sexual activity and self-reported sexual behavior has been reported previously,[36] this is the first time a validation study comparing biomarker outcomes with self-reported sexual behavior has been conducted within a study that also reported an increased HIV risk associated with injectable HC. Our results provide no evidence to support the hypothesis that differential over-reporting of condom use by HC users constitutes a primary explanation for the association between hormonal contraception use and HIV infection. However, we cannot rule out the possibility that other patterns of misclassification, including non-differential misreporting of condom use or differential over-reporting of condom use by non-HC users offers a partial explanation, especially given the level of misreporting observed in this study. Larger validation studies in similar populations that include biomarkers like PSA and rapid stain identification of human semen (RSID) are needed to confirm and elaborate on these findings.

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TABLE 1

Reports of sexual activity and condom use among women with detectable PSA, stratified by contraceptive method reported at the last study visit, Zimbabwe, 2006–2007.[a,b]

Contraceptive method	Overall	Reported Sexual Activity During the Past 2 Days		
		No sex	Protected sex only (condom misreporting)	Total: Any sexual behavior misreporting
	N %	N %	N %	N %
Any hormonal method[c]	165 (84.6)	18 (10.9)	56 (33.9)	74 (44.8)
Oral contraceptives	128 (65.6)	11 (8.6)	46 (35.9)	57 (44.5)
Injectables	37 (19.0)	7 (18.9)	10 (27.0)	17 (46.0)
Non-hormonal methods	30 (15.4)	5 (16.7)	15 (50.0)	20 (66.7)
Overall	195 (100)	23 (11.8)	71 (36.4)	94 (48.2)
Fisher's exact test P-value				
OC, injectable, or non-HC methods	---	0.14	0.16	0.09
HC vs. non-HC methods[d]	---	0.36	0.10	0.03

PSA: prostate-specific antigen; OC: oral contraceptives; HC: hormonal contraceptives

[a] PSA concentrations greater than 1.0 ng/mL were considered as providing evidence of semen exposure within the past 2 days.

[b] Analysis was restricted to the subset of women (n=195) who tested positive for PSA (>1 ng/mL) in vaginal eluate and who had contraceptive method data available at their last MIRA study visit.

[c] Oral contraceptives or injectable hormonal contraception.

[d] Binary indicator of hormonal methods versus non-hormonal methods.

TABLE 2

Misreporting of sexual behavior by type of contraception reported at the last study visit among women with detectable PSA, Zimbabwe, 2006–2007. [a,b]

Contraceptive method	Delay ≤8.9 months[c] (n=102)	Consistent method users[d] (n=173)	Delay ≤8.9 months and consistent method users (n=93)
	N %	N %	N %
Any hormonal method[e]	39 (45.9)	67 (44.1)	36 (45.6)
Oral contraceptives	31 (46.3)	51 (42.5)	29 (45.3)
Injectables	8 (44.4)	16 (50.0)	7 (46.7)
Other methods	10 (58.8)	13 (61.9)	7 (50.0)
Overall	49 (48.0)	80 (46.2)	43 (46.2)
Fisher's exact test P-value			
OC, injectable, or non-HC methods	0.62	0.24	0.95
HC vs. non-HC methods	0.43	0.16	0.78

PSA: prostate-specific antigen

[a] PSA concentrations greater than 1.0 ng/mL were considered as providing evidence of semen exposure within the past 2 days.

[b] Analysis was restricted to the subset of women (n=195) who tested positive for PSA (>1 ng/mL) in vaginal eluate and who had contraceptive method data available at their last MIRA study visit.

[c] Median delay between the last measurement of contraceptive method and the PSA study.

[d] Reported the same contraceptive method at the penultimate visit in the MIRA study, typically 3 months prior to the last visit.

[e] Oral contraceptives or injectable hormonal contraception.