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Injectable and oral contraception and the incidence and progression of cervical disease in HIV-infected women in South Africa☆

Daniel Westreich[a,*], Naiomi Jamal[b], Jennifer S. Smith[c], Doreen Schulze[d], Sophie Williams[e], Pam Michelow[f], Simon Levin[e,g], Cynthia Firnhaber[d,e]

[a]Department of Obstetrics and Gynecology and Duke Global Health Institute, Duke University, Durham, NC, USA
[b]Department of Family Medicine, University of Texas Medical Branch, Galveston, TX, USA
[c]Department of Epidemiology, Gillings School of Global Public Health and Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA
[d]Clinical HIV Research Unit, Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[e]Right to Care, Johannesburg, South Africa
[f]Cytology Unit, National Health Laboratory Service and Department of Pathology, University of Witwatersrand, Johannesburg, South Africa
[g]Department of Obstetrics and Gynecology, Rahima Moosa Mother and Child Hospital, University of Witwatersrand, Johannesburg, South Africa

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Abstract

Background: Few data exist regarding the effect of hormonal contraception (HC) on incidence and progression of cervical disease (e.g., cervical dysplasia, squamous intraepithelial lesions, cervical intraepithelial neoplasia) in HIV-infected African women.
Study Design: We conducted an observational study of HIV-seropositive women in Johannesburg, South Africa. The effect of individual HC types on the incidence and progression of cervical disease was determined using Poisson regression to obtain adjusted incidence rate ratios.
Results: We evaluated 594 HIV-infected women, with median follow-up time of 445 days; 75 of these women were receiving some form of HC (largely DMPA, NET-EN, or COCs) at baseline. Risks of incidence and progression of cervical disease were similar comparing women not receiving HCs to women receiving DMPA, NET-EN, or COCs both individually by HC-type and considering all HC together.
Conclusions: There was no statistically significant effect of particular HC methods or of HC use in general on rates of incidence or progression of cervical disease in this study. These results should reassure us that use of HC is unlikely to substantially increase risks of cervical disease among HIV-positive women.

Keywords: Cervical disease; Combined oral contraceptives; DMPA, HIV, NET-EN

1. Introduction

Cervical cancer is currently the third most common cancer in women globally [1] and the most common in sub-Saharan Africa [2]. Up to 85% of the disease burden is in the less-developed world, and large parts of the African continent including southern Africa are considered to be high-risk regions. In South Africa, the age-standardized incidence rate is 26.6 per 100,000 women per year, making it the second most common female cancer [1]. Within South Africa the prevalence of HPV infection is approximately 21% in the general female population; the majority of diagnosed invasive cervical cancer cases are attributed to high-risk human papillomavirus (HPV) types, particularly 16 and 18 [3].

South Africa is also home to the highest number of people living with HIV/AIDS, approximately 5.7 million people, the majority of whom are women [4]. High-risk HPV is seen in 60-90% in HIV positive women with HPV-16 being the most common cause of invasive cervical cancer [5–7]. Studies from across the globe suggest the progression of cervical neoplasia to cervical cancer to be higher in HIV positive women [8–11], although progression rates might be

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* Corresponding author. CB 7435 McGavran-Greenberg Hall Department of Epidemiology UNC-Chapel Hill Chapel Hill, NC 27599. Tel.: +1 919 966 7437.
E-mail address: westreic@email.unc.edu (D. Westreich).

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reduced [12–14] and regression improved [15] by use of highly active antiretroviral therapy.

Among young HIV-positive South African women, unintended pregnancy is common [16–19] and use of modern contraceptive methods including hormonal contraception is high [20]. HIV-positive women have an increased incidence of HPV-associated cervical disease (e.g., cervical dysplasia, squamous intraepithelial lesions (SIL), cervical intraepithelial neoplasia) [8–11]. But unfortunately, hormonal contraceptives - critical in this setting not only to prevent unintended pregnancy and attendant maternal morbidity and mortality, and also to prevent mother-to-child transmission of HIV - may increase the risk of high-risk cervical disease including invasive cervical cancer, possibly due to effects of estrogens and progestins on key HPV proteins (e.g., HPV-16 E2 and E7) [21–23]. This may be a particular concern with oral contraceptives. Women who use oral contraceptives over a longer duration [24] may be at higher risk, and risk may be reduced after discontinuation of HC for several years [24]. For example, a collaborative reanalysis of 24 previous studies found a near-doubling of risk of invasive cervical cancer after five years use [2]. In contrast, a South African case–control study found no association between recent users of oral contraceptives (compared to never users) and cervical cancer [25]. Other studies have found associations of oral contraceptives with increased prevalence [26,27] and persistence [28] of HPV.

Injectable hormonal contraceptive methods (particularly depot-medroxyprogesterone acetate, or DMPA), are more popular than oral contraceptives among prevalent and new users of contraception throughout much of Africa including South Africa [16,19,29–31] (norethisterone oenanthate, also called Nur-sterate, Noristerat or NET-EN is also popular in South Africa). There have been few studies addressing if progesterone-based injectables change risk of the development of cervical disease. A small Latin American case control study [32] found evidence of increased risks of invasive cervical cancer in longer-term users of injectable contraceptives. Two studies in Jamaica found associations between use of hormonal contraceptives (including DMPA in particular) and cervical disease [33,34], while two South African studies found contrasting results: one found no such association [35], while another found that women using DMPA or NET-EN were more likely to be HPV-DNA positive at study enrollment [36]. A Bangladeshi case–control study found a raised risk of cervical cancer with use of oral contraceptives but not injectable methods [37]. A final study which did not distinguish among types of hormonal contraception (including oral contraceptives, injection methods, rings, patches, and progesterone intrauterine devices) found no association between hormonal contraception and high-risk HPV or high-grade cervical disease [38].

None of these studies were conducted primarily among HIV-positive women; some (e.g., [2]) excluded HIV-positive women specifically. Given the significant burden of both HIV and HPV in South Africa, and recommendations of increased integration of hormonal contraception with HIV care [17,19,39], we investigated whether use of hormonal contraception was associated with increased incidence or progression of cervical disease in a cohort of HIV-positive women in Johannesburg, South Africa.

2. Materials and methods

2.1. Study population

We conducted this analysis inside the South Africa Cervical Cancer Cohort, an observational, longitudinal study of HIV-infected women [6]. The cohort included HIV-infected women aged from 18 to 65 who were recruited from an adult HIV outpatient clinic in a teaching hospital affiliated with the University of Witwatersrand in Johannesburg, South Africa (SA). Women were eligible to participate in this study unless they (i) were pregnant; (ii) had undergone a hysterectomy or cone biopsy; (iii) were severely ill per investigator's opinion; or (iv) had signs and/or symptoms suggestive of a sexually transmitted infection (STI). Women were study-eligible following the treatment of any symptomatic STI, and 6 weeks after the end of pregnancy. Women approached for inclusion were given an educational session on cervical cancer screening in English or in an appropriate African language, and then invited for a conventional Pap smear. A medical history was obtained through a participant interview including antiretroviral therapy status, reproductive/menstrual characteristics, sexual history/behaviour, history of STIs, and contraceptive use. Women were treated according to the HIV South African Guidelines on Comprehensive HIV and AIDS Care, Management and Treatment[40], including HAART initiation at WHO stage 4 or CD4 count < 200 cells/mm^3. Women were excluded from the present analysis if they had high grade squamous intraepithelial lesions (HSIL) at baseline.

2.2. Laboratory analysis

Cervical exfoliated cells were collected during a pelvic examination using an endocervical brush for a conventional Pap smear diagnosis. Such conventional cervical smears were performed as standard of care for HIV-positive women in South Africa; liquid-based cytology is currently not available in this setting. Cytology slides were read and analyzed according to Bethesda 2001 guidelines [41]. Women with atypical squamous cells-high (ASC-H) or HSIL were referred for immediate colposcopy, while women with atypical squamous cells of undetermined significance (ASCUS) or low-grade intra-epithelial lesions (LSIL) were followed with a repeat Pap smear after 1 year if their CD4 count was above 200 cells/mm^3, or after 6 months if their CD4 count was 200 cells/mm^3 or below. Women who presented with 2–3 consecutive LSIL results over 18 months were also referred for colposcopic biopsy.