Population-level impact of hormonal contraception on incidence of HIV infection and pregnancy in women in Durban, South Africa

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Objective To estimate the potential impact of using hormonal contraceptives on rates of infection with human immunodeficiency virus type 1 (HIV-1) and pregnancy by theoretically removing the use of hormonal contraceptives from a study population.
Methods A prospective cohort study included 3704 HIV-negative women who were enrolled in two biomedical trials that tested two vaginal microbicides (PRO 2000 and Carraguard®) for the prevention of HIV-1 in Durban, South Africa, in 2004–2009. Cox proportional hazards regression models along with partial population attributable risks (PARs) and their 95% confidence intervals (CIs) were calculated to assess the relative population-level impact of the use of hormonal contraceptives on HIV-1 seroconversion rates and on pregnancy rates.
Findings Women who reported using hormonal contraceptives at enrolment in the trial had a higher risk of HIV-1 seroconversion (adjusted hazards ratio: 1.24; 95% CI: 0.97–1.58) than women who reported using other types of contraceptives at enrolment. At the population level, the use of hormonal contraceptives (pills or injectables) at baseline and during study follow-up accounted for approximately 20% (95% CI: 16–22) of HIV-1 seroconversions. However, the partial PAR indicated a relative impact of 12% (95% CI: 9.0–15.7). On the other hand, 72% (95% CI: 66–77) of the pregnancies could have been avoided if all women had used hormonal contraceptives.
Conclusion Women using hormonal contraceptives need comprehensive counselling on simultaneous prevention of HIV-1 infection.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

In sub-Saharan Africa, an estimated 22.5 million people live with human immunodeficiency virus type 1 (HIV-1) infection.[1] In the province of KwaZulu-Natal, the prevalence of HIV-1 infection is estimated to be 39% among women who attend antenatal clinics.[2] Poor socioeconomic conditions, sexual networking, multiple concurrent partnerships, low level of condom use and high rates of sexually-transmitted infections are factors that contribute to the high local prevalence of HIV-1 infection.[2,3] Trials for the prevention of HIV-1 infection have been heavily focused on developing biomedical interventions under female control.[4–6] Typically these trials recruit sexually active, non-pregnant women of childbearing age and, since the teratogenic effects of the products they test are seldom known, the women are required to use an effective birth control method. Furthermore, if a trial participant falls pregnant, she is usually taken off the product under study, a practice that reduces the trial's statistical power and its ability to demonstrate the product's efficacy.

Hormonal contraception has been reported to increase susceptibility to HIV-1 infection by promoting cervical ectopy, increasing vulnerability to sexually-transmitted infections and altering the flora of the genital tract and the structure of the vaginal epithelium.[7] In South Africa, hormonal contraceptives, particularly injectables, are reported to be the most common contraceptive method because they are highly effective and safe.[8–10] Contraceptives play a key role in efforts to prevent HIV-1 infection by reducing the number of unintended pregnancies and, hence, the number of potential cases of mother-to-child transmission of HIV-1.[11]

Several epidemiological studies have provided evidence, although inconsistent, that the use of hormonal contraceptives (injectables and pills) increases the risk of HIV-1 infection.[12–17] These findings were supported by a subsequent study by Heffron et al. that provided new evidence suggesting an increased risk of contracting and transmitting HIV-1 infection associated with the use of hormonal contraceptives, particularly injectables.[18] Durban data from the MDP301 trial confirmed this.[19] Morrison et al. combined the multisite data from the Carraguard® trial, including the Durban site data, and showed a moderately increased risk of HIV-1 seroconversion with the use of the injectable progestin depo-medroxyprogesterone acetate, but no effect with other types of hormonal contraceptives.[20] Based on available data, in 2012 the World Health Organization released a technical statement clarifying that the data on hormonal contraceptives was inconclusive and that women should continue to use hormonal contraceptives to prevent unwanted pregnancy. Nonetheless, it advised women using progesterone-only contraception to use condoms and other methods for preventing HIV-1 infection.[21]

The data on hormonal contraceptives and an increased risk of HIV-1 infection makes it critically important to understand the dynamics of HIV-1 transmission, the relative risk and population attributable risk (PAR) associated with the use of hormonal contraceptives. Standard epidemiological methods that quantify risk relative to exposure through metrics such as relative risks are suitable for establishing a causal link between exposure to a given risk factor and a particular disease outcome. However, they provide no information about the population-level impact of removing the risk factor – hormonal contraceptives in our case – from the target population. Doing so yields the PAR, which quantifies the theoretical reduction in disease rates if the target population were not exposed to the risk factor at all.

After three decades of research, we have arrived at a good understanding of the behavioural and biological drivers of the

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HIV-1 epidemic.[22,23] However, we still have a poor understanding of the impact of the use of family planning methods, particularly hormonal contraceptives, on the incidence of HIV-1 infection. Studies are urgently needed to determine the association between hormonal contraceptive use and the risk of HIV-1 infection and, most importantly, the population-level impact of hormonal contraceptives, not just on HIV-1 seroconversion but also on pregnancy rates.

The primary aim of this study was to examine the population-level impact of hormonal contraceptives (injectables and pills) with respect to HIV-1 seroconversion and the incidence of pregnancy during follow-up in two combined cohorts of HIV-1-negative, non-pregnant women who participated in two biomedical trials conducted in Durban, South Africa, in 2004–2009 to test the effectiveness of two vaginal microbicides in preventing HIV-1 infection: the MDP 301 trial, which tested PRO 2000, and the Carraguard® trial, which tested the potential microbicide, Carraguard. ®[5,6]

Methods

Participants and design

A total of 3704 study participants were included in our analysis: 1456 from the Carraguard® trial and 2248 from the MDP301 trial.[5,6] The two Durban cohorts were broadly similar in terms of sociodemographic and behavioural characteristics and prevalence of HIV-1 infection and pregnancy rates, except that the proportion of women who reported use of a condom by their partners in their most recent sexual act was significantly higher in the MDP301 trial.

The MDP301 trial followed women every 4 weeks for 52 weeks, and women's HIV-1 status was assessed at weeks 12, 24, 40 and 52. Serostatus was confirmed by means of parallel HIV-1 rapid tests, and discordant/positive test results were confirmed by enzyme-linked immunosorbent assay.[5] The Carraguard® trial had visits at screening, enrolment, at months 1 and 3, and every 3 months thereafter. Rapid HIV-1 blood testing was conducted at all visits except at enrolment. Serostatus was confirmed with parallel HIV-1 rapid tests, and positive/discordant tests were confirmed by third-generation enzyme immunoassay or polymerase chain reaction (PCR) for the detection of HIV-1 ribonucleic acid (RNA).[6]

In Durban, the MDP301 and the Carraguard® trial were both approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee and the South African Medical Research Council.

Risk factors

We assessed commonly-reported risk factors for HIV-1 seroconversion, such as being less than 25 years old, being unmarried or not living with a regular sex partner, having multiple sex partners, having frequent sex, being unemployed and having a sexually-transmitted infection.[24,25] To this end we used the following data, as collected across the two trials: age, marital status, patterns of contraceptive use, diagnosis of a sexually-transmitted infection, condom use, educational level, employment status, number of sex partners and average number of sex acts per week. Data that were not common to both trials, such as being abused by partner or forced to have sex (which were collected in the Carraguard® trial but not in the MDP301 trial), were not included. Women were categorized according to their self-reported type of contraceptive use: hormonal methods (injectables or pills) and other methods (male condoms, hysterectomy, female sterilization and traditional methods such as abstinence and rhythm).

Age at baseline was based on self-reported date of birth and verified by examining each woman's local identification card. Women were categorized by self-reported level of education (lower than high school versus high school or higher), employment status (employed with a regular income versus unemployed and having an irregular income or none) and religion (Christian versus others). Cohabitational status (married or living with a sexual partner versus not married or not living with a sexual partner), multiple sexual partners (two or more) in the three most recent months, average weekly number of sexual acts (three or more versus less than three) and diagnosis of a sexually-transmitted infection (at baseline) were used as binary variables. Since more than 90% of the women reported having a regular partner, having a regular sex partner was not among the risk factors considered in the analyses.

In the current study, hormonal contraception was treated as a theoretically modifiable risk factor, whereas age was assumed to be non-modifiable. The remaining variables (cohabitational status, number of sexual partners, average weekly number of sexual acts and presence or absence of a sexually-transmitted infection) were assumed to be background risk factors (or potential confounders) and hence non-modifiable and unchanged. All decisions regarding risk factor classification were made before conducting the analyses.

Statistical analyses

Demographic characteristics and sexual behaviour, including cohabitational status, number of sexual partners, average weekly number of sexual acts during the 2 weeks immediately preceding the study visit and diagnosis of a sexually-transmitted infection, were compared across contraceptive groups using χ^2 analyses. Kaplan–Meier survival analyses were carried out to estimate time to infection among women who became infected with HIV-1 and time to pregnancy among women who became pregnant during trial follow-up, with stratification by contraceptive groups (i.e. hormonal injectables or pills versus other contraceptives). Calculation of the time to seroconversion in each of the two trials is described in detail elsewhere.[5,6] Briefly, the seroconversion date was imputed as the midpoint between the date at which the participant first tested positive for HIV-1 and the date of the previous negative test. Time to seroconversion was then calculated as the difference between the seroconversion date and the date of enrolment in the trial.[5,6]

In unadjusted analyses, univariate Cox proportional hazard regression models were used to determine the association between baseline and follow-up use of contraceptives and risk of HIV-1 infection and pregnancy. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox regression models. Results with a $P < 0.05$ were considered significant. We also adjusted for age, number of sexual partners, condom use by partner during the most recent sexual act (at trial baseline and follow-up) and pregnancy status after baseline. To accommodate missing data, we applied the last-observation-carried-forward convention, a method used to impute unknown values from existing data, to all time-varying covariates (e.g. condom use), except for pregnancy status.

Table 1. **Selected characteristics of study women at enrolment, by type of contraceptive, South Africa, 2004–2009**

Characteristic	No. (%) of women by type of contraceptive				*P*[c]
	None	Hormonal[a]	Condom	Other[b]	
Age, years					< 0.001
< 25	299 (36.2)	667 (49.6)	447 (45.5)	65 (11.8)	
25–29	102 (12.3)	278 (20.7)	169 (17.2)	62 (11.3)	
≥ 30	426 (51.5)	399 (29.7)	367 (37.3)	423 (76.9)	
Education					< 0.001
High school or more	214 (26.0)	450 (33.5)	348 (35.4)	103 (18.8)	
Less than high school	613 (74.0)	894 (66.5)	635 (64.6)	447 (81.2)	
Occupation					0.061
Employed and with regular income	173 (21.0)	206 (15.3)	171 (17.4)	116 (21.0)	
Unemployed/having no regular income	654 (0.79)	1138 (84.7)	812 (82.6)	434 (79.0)	
Cohabitational status[d]					< 0.001
Married or living with regular sex partner	118 (26.6)	90 (18.3)	44 (15.3)	130 (56.0)	
Neither married nor living with regular sex partner	326 (73.4)	403 (81.7)	244 (84.7)	102 (44.0)	
Condom used in most recent sexual act					< 0.001
No	553 (66.9)	695 (51.7)	107 (10.9)	319 (57.9)	
Yes	274 (33.1)	649 (48.3)	876 (89.1)	232 (42.1)	
Multiple sex partners[e]					< 0.001
No	715 (86.5)	1212 (90.2)	839 (85.3)	478 (86.8)	
Yes	112 (13.5)	132 (9.8)	144 (14.7)	73 (13.2)	
Average no. of sexual acts per week					< 0.001
< 3	650 (78.6)	915 (68.1)	664 (67.6)	386 (70.2)	
≥ 3	177 (21.4)	429 (31.9)	319 (32.5)	164 (29.8)	
Presence of an sexually-transmitted infection at screening					0.577
Yes[f]	178 (21.5)	303 (22.5)	226 (23.0)	109 (20.0)	
No	649 (78.5)	1041 (77.5)	757 (77.0)	441 (80.0)	
All women	827 (22.3)	1344 (36.3)	983 (26.5)	550 (14.9)	

[a] Injectables and pills.
[b] Includes intrauterine devices, spermicides and traditional methods such as rhythm and abstinence.
[c] *P*-value for χ^2 test.
[d] This variable was only considered in the Carraguard® trial.
[e] This variable was measured by combining two variables: having had a sexual partner other than the regular partner (MDP301 trial) or at least two sexual partners (Carraguard® trial) in the three most recent months.
[f] At least one test positive for *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Trichomonas vaginalis* or syphilis at baseline.

Population attributable risk

We used a novel method to estimate the PARs,[26,27] which reflect the proportion of HIV-1 seroconversions that would not have occurred had all women been using a low-risk family planning method (i.e. any non-hormonal method), under the assumption that the observed associations were causal. When calculating PARs, we used Cox regression models to analyse how much individual risk factors and their various combinations affected the rate of HIV-1 seroconversion. The prevalence of different combinations of variables for all risk factors were estimated as multinomial probabilities using the empirical fraction of person–time of follow-up in the cohort. This approach to calculating PARs is intended to determine the joint impact of several theoretically modifiable risk factors on HIV-1 transmission while keeping non-modifiable and/or background risk factors unchanged. The result is known as the partial PAR, which is based on the estimated relative risk associated with each risk factor of interest and the estimated population prevalence of each factor. Analyses were performed using SAS statistical software version 9.2 (SAS Inc., Cary, United States of America).

Results

At enrolment in the study, approximately 78% of the women reported using at least one type of contraceptive (Table 1). Hormonal contraceptives (injectables and pills) were the most commonly reported method, followed by condoms and other types of contraceptives (36.28%, 26.53% and 14.87%, respectively). Hormonal contraceptives were most often used by women that were younger and unmarried. Reported use of a condom during the most recent sexual act was highest (89.11%) among women who indicated that condoms were their preferred contraceptive method.

HIV-1 seroconversion

Table 2 gives crude incidence rates and unadjusted and adjusted HRs for HIV-1 seroconversion in association with the use of hormonal contraceptives at enrolment and during trial follow-up. A total of 272 HIV-1 seroconversions were observed in the cohort as a whole. Compared with women who reported

using other contraceptives, those who were using hormonal contraceptives at study enrolment had a significantly higher risk of HIV-1 seroconversion. This association was slightly attenuated when the analysis was adjusted for age, consistent condom use in the most recent sexual act, average number of sexual acts per week during the two weeks immediately preceding the study visit, and incidence of pregnancy. When pattern of contraceptive use was included as a time-dependent covariate (i.e. updated at each visit), use of hormonal contraceptives was significantly associated with an increased risk of HIV-1 infection in both unadjusted and adjusted analyses.

Pregnancy incidence

The incidence of pregnancy was 3.7 per 100 woman–years and 10.1 per 100 woman–years for women who reported using hormonal contraceptives and other methods, respectively (Table 2). The use of hormonal contraceptives at enrolment and during the study was associated with a significantly decreased risk of pregnancy. These strong protective associations were sustained but slightly attenuated in adjusted analyses.

Partial population attributable risk

The partial PARs and their 95% CIs are presented in Table 3. In analyses without adjustments (crude PAR), the use of hormonal contraceptive pills or injectables at baseline and during study follow-up accounted for approximately 20% of the HIV-1 seroconversions. When adjustments were made for other risk factors, such as multiple sex partners, no condom use by partner during the most recent sexual act and younger age (< 25 years), the partial PAR was 12%. Although the use of hormonal contraceptives at enrolment was reasonably high (36.28%), relatively small effect sizes were responsible for this small percentage. Meanwhile, if women who reported using non-hormonal contraceptive methods (at baseline and during study follow-up) had used hormonal contraceptives instead, 72% (adjusted) of all pregnancies could have been avoided. High rates of use of other types of contraceptives (64%) having a strong protective effect accounted for this large impact on pregnancy incidence. Only a small percentage of women reported having changed the type of contraceptive during the study (data not shown).

Table 2. **Use of hormonal contraceptives and risk of HIV-1 seroconversion and pregnancy during study follow-up, Durban, South Africa, 2004–2009**

Outcome	Crude incidence[a]	Unadjusted HR (95% CI)	Adjusted[b] HR (95% CI)
HIV-1 seroconversion			
At baseline			
Hormonal contraceptive[c]	8.15 (6.91–9.61)	1.41 (1.11–1.75)	1.24 (0.97–1.58)
Other[d]	5.70 (4.80–6.76)	1	1
During study			
Hormonal contraceptive[c]	–	1.49 (1.16–1.89)	1.30 (1.01–1.66)
Other[d]	–	1	1
Pregnancy			
At baseline			
Hormonal contraceptive[c]	3.7 (3.0–4.6)	0.39 (0.28–0.54)	0.34 (0.24–0.48)
Other[d]	10·1 (9·0–11·4)	1	1
During study			
Hormonal contraceptive[c]	–	0.43 (0.33–0.57)	0.36 (0.27–0.48)
Other[d]	–	1	1

CI, confidence interval; HIV-1, human immunodeficiency virus type 1; HR, hazard ratio.
[a] Per 100 woman–years.
[b] Adjusted for age (< 25, 25–34, 35+ years); multiple sex partners; incidence of pregnancy during study; no condom use by partner in most recent sexual act; average of three or more sexual acts per week, and having been diagnosed with an sexually-transmitted infection (at least one test positive for *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Trichomonas vaginalis* or syphilis) at baseline.
[c] Injectables and pills.
[d] Includes intrauterine devices, spermicides and traditional methods such as rhythm and abstinence.

Table 3. **Population-level impact of use of hormonal and other contraceptives, at baseline and follow-up, in terms of HIV-1 seroconversion and pregnancy rates during study, Durban, South Africa, 2004–2009**

Outcome	Crude PAR% (95% CI)	Partial PAR%[a] (95% CI)
HIV-1 seroconversion		
Hormonal contraceptives[b] (at baseline only)	12 (10–16)	6 (4–8)
Hormonal contraceptives[b] (during follow-up only)	15 (12–18)	7 (5–10)
Hormonal contraceptives (at baseline and follow-up)	20 (16–22)	12 (9–16)
Pregnancy		
Other types of contraceptives[c] (at baseline only)	54 (48–59)	58 (52–63)
Other types of contraceptives[c] (during follow-up only)	36 (26–48)	44 (35–54)
Hormonal contraceptives (at baseline and follow-up)	63[d] (55–70)	72 (66–77)

CI, confidence interval; HIV-1, human immunodeficiency virus type 1; PAR%, population-attributable risk per cent.
[a] Adjusted for age (< 25, 25–34, 35+ years); multiple sex partners; no condom use by partner in most recent sexual act, and having been diagnosed with an sexually-transmitted infection (at least one test positive for *Neisseria gonorrhoea*, *Chlamydia trachomatis*, *Trichomonas vaginalis* or syphilis) at baseline.
[b] Injectables and pills.
[c] Includes intrauterine devices, spermicides and traditional methods such as rhythm and abstinence.
[d] In other words, if women who reported using non-hormonal contraceptive methods (at baseline and follow-up) had used hormonal contraceptives instead, 63% of all pregnancies could have been avoided.

Discussion

The use of hormonal contraceptives, which are highly effective, is known to directly benefit women by reducing the physical, emotional and social consequences of unintended pregnancies and by indirectly reducing cases of mother-to-child transmission of HIV-1. This was shown by a study in sub-Saharan Africa in which the use of hormonal contraceptives reduced the number of neonates becoming positive for HIV-1 by an annual 22%.[11] Our data concurs with those from previous studies in which the use

of hormonal contraceptives was found to be associated with an increased risk of HIV-1 infection.[12–15] The relatively small effect size in our study was statistically significant in both the adjusted and unadjusted analyses because of the study's high statistical power (> 90%). However, the population-level impact of the use of hormonal contraceptives on HIV-1 infection rates was determined to be only 12% in adjusted analyses. Alternatively, using non-hormonal contraceptives or no contraception at all accounted for 72% of the incident pregnancies during the trials. In short, removing all use of hormonal contraceptives from the target population would result in 12% fewer HIV-1 seroconversions but 72% more pregnancies. These findings provide an idea of the risk-benefit and cost-effectiveness ratios – both beyond the scope of this study – associated with the use of hormonal contraceptives among women targeted by HIV-1 prevention efforts. These assumptions can be more accurately assessed using mathematical modelling. Our study established that hormonal contraceptives were most commonly used by young, unmarried women, and this may have contributed to their increased risk of HIV-1 seroconversion in our setting.[28]

Heffron et al. reported a significant association between use of hormonal contraceptives and HIV-1 seroconversion with a reasonably large effect size (adjusted HR: 1.98; 95% CI: 1.06–3.68).[18] The study reported that almost 15% of women were using hormonal contraceptives at enrolment and 21% at follow-up. Given this data, determining the population-level impact is critical. Based on our results, the population level impact would be estimated to be in a range of 10–20%, suggesting that if the exposure to hormonal contraceptives was removed from the study population, 10––20.0% of the HIV-1 seroconversions could have been prevented. Heffron et al. also reported pregnancy rates of 5.2% and 16.0% among women who did and who did not report using hormonal contraceptives, respectively.[18] Since the adjusted hazard ratio was not presented, the percentage of pregnancies attributed to the use of other types of contraceptives in adjusted analyses could not be estimated. However, a large absolute difference between rates of HIV-1 seroconversion and pregnancy rates may indicate that hormonal injectable contraceptives have a large population-level impact in terms of preventing pregnancies in the target population.

Our study was not designed to assess the association between contraceptive use and the risk of HIV-1 infection. Therefore, the results presented here may not be generalizable. Additionally, since the questions on behavioural and sociodemographic characteristics differed between trials, we were unable to include in the analysis some key risk factors (such as young age at sexual debut). Similarly, since a common protocol was not used across both trials, we cannot be sure that all categorizations were the same. Also, contraceptive methods were self-reported and therefore subject to misclassification due to recall bias. In the cohorts described, some women were given contraceptives at the research sites, whereas others received them from their local family planning clinics. However, the significantly lower pregnancy rate among women who reported using hormonal contraceptives provided strong biological evidence of good adherence to the method. Our results cannot be generalized because of the selected population targeted in the HIV-1 prevention trials. Importantly, our findings, which are based on behavioural data, do not constitute biological evidence that hormonal contraception per se facilitates disease transmission. What they suggest, rather, is that the partners of women on hormonal contraceptives are less likely to use condoms than the partners of women who do not use contraceptives of this type (the assumption being that women with a steady partner have sex with no one else).

The impact of using hormonal contraceptives, particularly injectables, on HIV-1 transmission is a public health question that remains unanswered, yet understanding such impact is vital.[12–14,29–31] Conflicting study outcomes have triggered doubts regarding the role of injectable contraceptives and their use in developing countries.[12–18] It is critical to determine to what degree hormonal contraceptives increase the risk of HIV-1 infection. Although studies designed to address this question may be complex and difficult to implement, such difficulty must be weighed against their potential impact on HIV-1 acquisition.

In our study setting, condom use among the partners of women on hormonal contraceptives was low, a finding that underscores the importance of establishing comprehensive programmes that integrate both family planning and HIV-1 prevention for women and their partners. Our data points to the urgent need to develop methods for simultaneously protecting women against HIV-1 infection and pregnancy. Furthermore, there is an urgent need to expand women's contraceptive choices in areas of high HIV-1 endemicity, by providing access to safe and effective long-acting, non-hormonal contraceptives, such as intrauterine devices and low-dose hormonal implants. To our knowledge, the current study is the first to have explored the population-level impact of the use of hormonal contraceptives in a large combined cohort of women in Durban. Our results confirm an urgent need to adopt innovative health-care strategies and to educate women and health-care workers on the importance of dual counselling on pregnancy and the prevention of HIV-1 infection.

Thirty years of risk factor research has provided us with a good understanding of how HIV-1 is acquired. The current challenge is to interpret risk factor analyses in terms of prioritizing prevention strategies. The findings of our study and of previous studies suggest that the use of hormonal contraceptives is a speculative risk factor for HIV-1 seroconversion. However, its population-level impact in terms of the risk of HIV-1 infection is lower than its population-level benefit in preventing unintended pregnancies and, indirectly, HIV-1 infection among neonates. Integration of family planning and HIV-1 counselling and testing programmes may be the key to promoting a multi-pronged approach to a healthy, HIV-1-free reproductive life for women. ■

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ملخص

أثر منع الحمل الهرموني على مستوى السكان على حدوث عدوى فيروس العوز المناعي البشري والحمل لدى النساء في ديربان بجنوب أفريقيا

الغرض تقدير الأثر المحتمل لاستخدام وسائل منع الحمل الهرمونية على معدلات الإصابة بعدوى فيروس العوز المناعي البشري من النمط الأول (HIV-1) والحمل من خلال استبعاد استخدام وسائل منع الحمل الهرمونية من الخاضعين للدراسة من الناحية النظرية.

الطريقة تضمنت دراسة استباقية استطلاعية 3704 سيدة من غير المصابات بعدوى فيروس العوز المناعي البشري اشتركن في تجربتين من التجارب الطبية الحيوية فحصتا نوعين من مبيدات الميكروبات المهبلية (PRO 2000 وCarraguard®) للوقاية من فيروس العوز المناعي البشري من النمط الأول في ديربان، بجنوب أفريقيا، في الفترة من 2004–2009. وتم حساب نماذج ارتداد الأخطار التناسبية لكوكس إضافة إلى المخاطر الجزئية التي تنسب إلى السكان (PAR) وفواصل الثقة الخاصة بها والتي بلغت نسبتها 95 ٪ بغية تقييم الأثر النسبي على الصعيد السكاني لاستخدام وسائل منع الحمل الهرمونية على معدلات انقلاب تفاعلية المصل الخاصة بفيروس العوز المناعي البشري من النمط الأول وعلى معدلات الحمل.

النتائج وفق التقارير الواردة، كانت النساء اللاتي استخدمن وسائل منع الحمل الهرمونية لدى تسجيلهن في التجربة أعلى عرضة لمخاطر انقلاب تفاعلية المصل الخاصة بفيروس العوز المناعي البشري من النمط الأول (نسبة الأخطار المعدلة: 1.24؛ فاصل الثقة: من 0.97 إلى 1.58) مقارنة بالنساء اللاتي استخدمن أنواعاً أخرى من وسائل منع الحمل لدى التسجيل. وعلى الصعيد السكاني، تنسب نسبة 20 ٪ تقريباً من انقلابات تفاعلية المصل الخاصة بفيروس العوز المناعي البشري من النمط الأول (فاصل الثقة 95 ٪، من 16 إلى 22) إلى استخدام وسائل منع الحمل الهرمونية (الحبوب أو الحقن) عند خط الأساس وأثناء متابعة الدراسة. إلا أن المخاطر الجزئية التي تنسب إلى السكان أشارت إلى أثر نسبي بقيمة 12 ٪ (فاصل الثقة 95 ٪، من 9.0 إلى 15.7). ومن ناحية أخرى، كان من الممكن تجنب 72 ٪ (فاصل الثقة 95 ٪، من 66 إلى 77) من حالات الحمل لو استخدمت جميع النساء وسائل منع الحمل الهرمونية.

الاستنتاج تحتاج النساء اللاتي يستخدمن وسائل منع الحمل الهرمونية إلى المشورة الشاملة حول الوقاية الفورية من الإصابة بعدوى فيروس العوز المناعي البشري من النمط الأول.

摘要

激素类避孕方法对南非德班妇女艾滋病毒感染发病率和怀孕率的群体水平影响

目的 通过理论上消除研究人群使用激素类避孕药，估计使用激素类避孕药对1 型艾滋病毒（HIV-1）感染和怀孕率的潜在影响。

方法 2004-2009 年在南非德班将3704 名HIV阴性的妇女纳入前瞻性定群研究，这些妇女参加两种生物医学试验，检测两种预防HIV-1 的阴道杀微生物剂（PRO 2000和Carraguard®）。计算Cox比例风险回归模型及部分人群归因危险度（PAR）及其95%置信区间（CI），用以估计使用激素类避孕药对HIV-1 血清转换率和怀孕率的相对人群影响。

结果 在登记参加试验时报告使用激素类避孕药的妇女比报告使用其他类型的避孕药的妇女的HIV-1 血清转换（调整后的危害比：1.24，95% CI：0.97-1.58）风险更高。就群体而言，在基线水平和随后的研究期间使用激素类避孕药（避孕药或注射）导致大约20%（95% CI：16－22）HIV-1 血清转换。然而，部分PAR指示12%（95% CI：9.0-15.7）的相对影响。另一方面，如果所有妇女使用激素类避孕药，则可用避免72%（95% CI：66-77）的怀孕。

结论 使用激素类避孕药的妇女需要同时预防1 型艾滋病毒感染的全面指导。

Résumé

Impact au niveau de la population de la contraception hormonale sur l'incidence de l'infection par le VIH et sur la grossesse chez des femmes de Durban, en Afrique du Sud

Objectif Estimer l'impact potentiel de l'utilisation de contraceptifs hormonaux sur les taux d'infection par le virus d'immunodéficience humaine de type 1 (VIH-1) et sur la grossesse par suppression théorique de l'utilisation de contraceptifs hormonaux dans une population témoin.

Méthodes Une étude de cohorte prospective comprenait 3704 femmes séronégatives qui étaient inscrites dans deux études biomédicales testant deux microbicides vaginaux (PRO 2000 et Carraguard®) pour la prévention du VIH-1 à Durban, en Afrique du Sud, de 2004 à 2009. Les modèles de régression à risque proportionnel de Cox ainsi que les risques attribuables dans la population (RAP) partielle et leurs intervalles de confiance (IC) de 95% ont été calculés pour évaluer l'impact relatif au niveau de la population de l'utilisation de contraceptifs hormonaux sur les taux de séroconversion du VIH-1 et sur les taux de grossesse.

Résultats Les femmes qui ont déclaré utiliser des contraceptifs hormonaux lors de l'inscription à l'essai clinique présentaient un risque accru de séroconversion du VIH-1 (taux de risque ajusté: 1,24; IC de 95%: 0,97 à 1,58) par rapport aux femmes qui ont déclaré utiliser d'autres types de contraceptifs lors de l'inscription. Au niveau de la population, l'utilisation de contraceptifs hormonaux (comprimés ou injectables) au début et au cours du suivi de l'étude a représenté environ 20% (IC de 95%: 16 à 22%) des séroconversions du VIH-1. Toutefois, le RAP partiel a indiqué un impact relatif de 12% (IC de 95%: 9 à 15,7%). D'autre part, 72% (IC de 95%: 66 à 77%) des grossesses auraient pu être évitées si toutes les femmes avaient utilisé des contraceptifs hormonaux.

Conclusion Les femmes qui utilisent des contraceptifs hormonaux nécessitent des conseils détaillés sur la prévention simultanée de l'infection par le VIH-1.

Резюме

Влияние на уровне популяции гормональной контрацепции на заболеваемость ВИЧ-инфекцией и беременность у женщин в Дурбане, Южная Африка

Цель Оценить возможное влияние использования гормональных контрацептивов на уровень заболеваемости вирусом иммунодефицита человека 1-го типа (ВИЧ-1) и беременность посредством теоретического исключения использования гормональных контрацептивов в исследуемой группе населения.

Методы Проспективное групповое исследование включало 3704 ВИЧ-отрицательных женщин, участвующих в двух биомедицинских исследованиях, в которых испытывались два вагинальных бактерицидных средства (PRO 2000 и Carraguard®) для предотвращения ВИЧ-1 в Дурбане, Южная Африка, в течение 2004–2009 гг. Производился расчет регрессионных моделей пропорциональных рисков Кокса вместе с частичными популяционными добавочными рисками (ПДР) и их 95% доверительными интервалами (ДИ) для оценки относительного влияния использования гормональных контрацептивов на показатели сероконверсии ВИЧ-1 и на уровни беременности, исходя из численности населения.

Результаты Женщины, пользовавшиеся гормональными контрацептивами при зачислении в исследование, имели более высокий риск сероконверсии ВИЧ-1 (скорректированное соотношение рисков: 1,24; 95% ДИ: 0,97–1,58) по сравнению с женщинами, пользовавшимися другими видами контрацептивов при зачислении в исследование. На уровне численности популяции, использование гормональных контрацептивов (пилюли или инъекционные лекарственные средства) на исходном уровне и во время отслеживания исследования составляло примерно 20% (95% ДИ: 16–22) сероконверсий ВИЧ-1. Тем не менее, частичный ПДР составлял 12% (95% ДИ: 9,0-15,7). В то же время, могло быть предотвращено 72% (95% ДИ: 66–77) беременностей, если бы все женщины пользовались гормональными контрацептивами.

Вывод Женщины, пользующиеся гормональными контрацептивами, нуждаются во всесторонней консультации по одновременному предотвращению инфекции ВИЧ-1.

Resumen

El impacto en el nivel de población de la anticoncepción hormonal en la incidencia de la infección por el VIH y en el embarazo de mujeres de Durban, Sudáfrica

Objetivo Calcular el posible impacto del uso de anticonceptivos hormonales sobre las tasas de infección por el virus de la inmunodeficiencia humana del tipo 1 (VIH-1) y sobre el embarazo bajo el supuesto de eliminar el uso de anticonceptivos hormonales de la población estudiada.

Métodos Entre los años 2004 y 2009, un estudio de cohortes prospectivo incluyó a 3704 mujeres VIH negativas inscritas en dos ensayos biomédicos que evaluaron dos microbicidas vaginales (PRO 2000 y Carraguard®) para la prevención del VIH-1 en Durban, Sudáfrica. Se calcularon los modelos de regresión de Cox junto con los riesgos parciales atribuibles a la población y sus intervalos de confianza (IC) del 95% para evaluar el impacto relativo del uso de anticonceptivos hormonales sobre las tasas de seroconversión del VIH-1 y las de embarazo entre la población.

Resultados El riesgo de seroconversión del VIH-1 fue superior en las mujeres que declararon utilizar anticonceptivos hormonales en el momento de la inscripción en el ensayo (índice de riesgos ajustado: 1,24; IC del 95%: 0,97–1,58) que en las mujeres que declararon utilizar otros tipos de anticonceptivos. Entre la población, el uso de anticonceptivos hormonales (píldoras o inyectables) en el punto de partida y durante el seguimiento del estudio representó aproximadamente el 20% (IC del 95%: 16–22) de las seroconversiones del VIH-1. No obstante, el riesgo parcial atribuible a la población indicó un impacto relativo del 12% (IC del 95%: 9.0–15.7). Por otra parte, el 72% (IC del 95%: 66–77) de los embarazos podría haberse evitado si todas las mujeres hubieran tomado anticonceptivos hormonales.

Conclusión Las mujeres que usan anticonceptivos hormonales necesitan un asesoramiento amplio sobre la prevención de la infección por el VIH.

References

1. *Report on the global AIDS epidemic 2010*. Geneva: Joint United Nations Programme on HIV/AIDS; 2010.
2. *2008 national antenatal sentinel HIV and syphilis prevalence survey, South Africa*. Pretoria: National Department of Health; 2009.
3. Harrison A, Cleland J, Frohlich J. Young people's sexual partnerships in KwaZulu-Natal, South Africa: patterns, contextual influences, and HIV risk. *Stud Fam Plann* 2008;39:295–308. doi:10.1111/j.1728-4465.2008.00176.x PMID:19248716
4. Padian NS, van der Straten A, Ramjee G, Chipato T, de Bruyn G, Blanchard K et al. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. *Lancet* 2007;370:251–61. doi:10.1016/S0140-6736(07)60950-7 PMID:17631387
5. McCormack S, Ramjee G, Kamali A, Rees H, Crook AM, Gafos M et al. PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial. *Lancet* 2010;376:1329–37. doi:10.1016/S0140-6736(10)61086-0 PMID:20851460
6. Skoler-Karpoff S, Ramjee G, Ahmed K, Altini L, Plagianos M, Friedland B et al. Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372:1977–87. doi:10.1016/S0140-6736(08)61842-5 PMID:19059048
7. Baeten JM, Benki S, Chohan V, Lavreys L, McClelland R, Mandaliya K. Hormonal contraceptive use, herpes simplex virus infection, and risk of HIV-1 acquisition among Kenyan women. *AIDS* 2007;21:1771–7. doi:10.1097/QAD.0b013e328270388a PMID:17690576
8. Seiber EE, Bertrand JT, Sullivan TM. Changes in contraceptive method mix in developing countries. *Int Fam Plan Perspect* 2007;33:117–23. doi:10.1363/3311707 PMID:17938094
9. Curtis KM, Chrisman CE, Mohllajee AP, Peterson HB. Effective use of hormonal contraceptives: part I: combined oral contraceptive pills. *Contraception* 2006;73:115–24. doi:10.1016/j.contraception.2005.08.003 PMID:16413842
10. Chrisman CE, Curtis KM, Mohllajee AP, Gaffield ME, Peterson HB. Effective use of hormonal contraceptives: part II: combined hormonal injectables, progestogen-only injectables and contraceptive implants. *Contraception* 2006;73:125–33. doi:10.1016/j.contraception.2005.08.004 PMID:16413843

11. Reynolds HW, Steiner MJ, Cates W. Contraception's proved potential to fight HIV. *Sex Transm Infect* 2005;81:184–5. doi:10.1136/sti.2004.012013 PMID:15800107
12. Martin HL, Nyange PM, Richardson BA, Lavreys L, Mandaliya K, Jackson DJ et al. Hormonal contraception, sexually transmitted diseases, and risk of heterosexual transmission of human immunodeficiency virus type 1. *J Infect Dis* 1998;178:1053–9. doi:10.1086/515654 PMID:9806034
13. Bulterys M, Smith D, Chao A, Jaffe H. Hormonal contraception and incident HIV-1 infection: New insight and continuing challenges. *AIDS* 2007;21:97–9. doi:10.1097/QAD.0b013e3280117cb5 PMID:17148973
14. Morrison CS, Pai-Lien C, Cynthia K, Richardson BA, Chipato T, Mugerwa R et al. Hormonal contraception and HIV acquisition: reanalysis using marginal structural modeling. *AIDS* 2010;24:1778. doi:10.1097/QAD.0b013e32833a2537 PMID:20588106
15. Baeten JM, Lavreys L, Overbaugh J. The influence of hormonal contraceptive use on HIV-1 transmission and disease progression. *Clin Infect Dis* 2007;45:360–9. doi:10.1086/519432 PMID:17599316
16. Kiddugavu M, Makumbi F, Wawer MJ, Serwadda D, Sewankambo NK, Wabwire-Mangen F et al. Hormonal contraceptive use and HIV-1 infection in a population-based cohort in Rakai, Uganda. *AIDS* 2003;17:233. doi:10.1097/00002030-200301240-00014 PMID:12545084
17. Kleinschmidt I, Rees H, Delany S, Smith D, Dinat N, Nkala B et al. Injectable progestin contraceptive use and risk of HIV infection in a South African family planning cohort. *Contraception* 2007;75:461–7. doi:10.1016/j.contraception.2007.02.002 PMID:17519153
18. Heffron R, Donnell D, Rees H, Celum C, Mugo N, Were E et al. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. *Lancet Infect Dis* 2012;12:19–26. doi:10.1016/S1473-3099(11)70247-X PMID:21975269
19. Wand H, Ramjee G. The effects of injectable hormonal contraceptives on HIV seroconversion and on sexually transmitted infections. *AIDS* 2012;26:375–80. doi:10.1097/QAD.0b013e32834f990f PMID:22156970
20. Morrison CS, Skoler-Karpoff S, Kwok C, Chen PL, van de Wijgert J, Gehret-Plagianos M et al. Hormonal contraception and the risk of HIV acquisition among women in South Africa. *AIDS* 2012;26:497. doi:10.1097/QAD.0b013e32834fa13d PMID:22156973
21. *Hormonal contraception and HIV* (Technical Statement). Geneva: World Health Organization; 2012.
22. Davis KR, Weller SC. The effectiveness of condoms in reducing heterosexual transmission of HIV. *Fam Plann Perspect* 1999;31:272–9. doi:10.2307/2991537 PMID:10614517
23. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev* 2002;1:CD003255. PMID:11869658
24. Wand H, Ramjee G. Combined impact of sexual risk behaviors for HIV seroconversion among women in Durban, South Africa: Implications for prevention policy and planning. *AIDS Behav* 2011;15:479–86. doi:10.1007/s10461-010-9845-2 PMID:20981479
25. Ramjee G, Williams B, Gouws E, Van Dyck E, Deken B, Karim S. The impact of incident and prevalent herpes simplex virus-2 infection on the incidence of HIV-1 infection among commercial sex workers in South Africa. *J Acquir Immune Defic Syndr* 2005;39:333. doi:10.1097/01.qai.0000144445.44518.ea PMID:15980695
26. Spiegelman D, Hertzmark E, Wand H. Point and interval estimates of partial population attributable risks in cohort studies: examples and software. *Cancer Causes Control* 2007;18:571–9. doi:10.1007/s10552-006-0090-y PMID:17387622
27. Wand H, Spiegelman D, Law M, Jalaludin B, Kaldor J, Maher L. Estimating population attributable risk for hepatitis C seroconversion in injecting drug users in Australia: implications for prevention policy and planning. *Addiction* 2009;104:2049–56. doi:10.1111/j.1360-0443.2009.02704.x PMID:19804463
28. Ramjee G, Wand H, Whitaker C, McCormack S, Padian N, Kelly C et al. HIV incidence among non-pregnant women living in selected rural, semi-rural and urban areas in Kwazulu-Natal, South Africa. *AIDS Behav* 2011:Epub 2011 Sep 25. PMID:21947836
29. Mostad SB, Overbaugh J, DeVange DM, Welch MJ, Chohan B, Mandaliya K et al. Hormonal contraception, vitamin A deficiency, and other risk factors for shedding of HIV-1 infected cells from the cervix and vagina. *Lancet* 1997;350:922–7. doi:10.1016/S0140-6736(97)04240-2 PMID:9314871
30. Myer L, Denny L, Wright TC, Kuhn L. Prospective study of hormonal contraception and women's risk of HIV infection in South Africa. *Int J Epidemiol* 2007;36:166–74. doi:10.1093/ije/dyl251 PMID:17175547
31. Ungchusak K, Rehle T, Thammapornpilap P, Spiegelman D, Brinkmann U, Siraprapasiri T. Determinants of HIV infection among female commercial sex workers in northeastern Thailand: results from a longitudinal study. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996;12:500–7. doi:10.1097/00042560-199608150-00010 PMID:8757428