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Injectable Progestin Contraceptive Use and Risk of STI Infection amongst South African Women

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Abstract

Objective—The study was conducted to determine the association between the use of injectable progestin contraception (IPC) and risk of infection with *Neisseria gonorrhoea* (GC), *Chlamydia trachomatis* (CT), bacterial vaginosis (BV) and *Trichomonas vaginalis* (TV) among women in South Africa.

Methods—From August 1999 through May 2001, 643 HIV-1 negative women were recruited from family planning clinics in Orange Farm, South Africa. IPC users (NET-EN and DMPA) and non-hormonal contraception users were recruited in approximately equal numbers. Eligible participants were seen at enrolment and four follow-up visits over a 12 month period; 567 returned for at least one follow up visit. Multivariable Poisson regression models with generalized estimating equations (GEE) were used to compute the incidence rate ratio for infection with GC, CT, BV and TV by use of NET-EN or DMPA relative to non-use during follow-up.

Results—In multivariable models, the use of DMPA slightly increased the risk of infection with CT (IRR 1.24; 95% CI 0.80–1.94) and GC (IRR 1.30; 95% CI 0.58–2.98), although these associations were not statistically significant. In contrast, DMPA appeared to be protective for TV (IRR 0.35; 95% CI 0.12–1.01), although this estimate was very imprecise. Use of both DMPA and NET-EN were associated with a decreased risk of BV.

Conclusions—Use of DMPA among women in this study population was associated with an increased, but not statistically significant, risk of cervical infection with chlamydia and gonorrhea and a decreased risk of TV and BV. Given the inconsistencies and limitations of the data describing an increased risk for CT and GC with IPC use, the potential risk of STIs must be balanced against the risk of unintended pregnancy and its health consequences, especially in developing countries. Women opting to use IPC should be counselled to use condoms to protect against STIs and HIV.

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1. Introduction

The prevalence of HIV infection in South Africa is among the highest in the world; more than 30% of women attending antenatal clinics are infected with HIV [1]. In addition, other sexually transmitted infections (STI), such as chlamydial infection and gonorrhea, are very common in the general population. In one population-based study of young people age 15–24 years in South Africa, chlamydial infection was over 9% in young women and more than 3% were infected with gonorrhea [2].

One of the factors thought to increase the risk of STIs in women is the use of hormonal contraception [3,4]. Use of hormonal contraception is extremely prevalent with more than 100 million women using them worldwide [5]. In South Africa, an estimated 57% of all women aged 15 to 49 years have used injectable progestin-only contraception (IPC) at some point in their lives [6]. Depot medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-EN) are the two IPCs available in South Africa. Both are available free of charge at public sector primary health care facilities and are on the South African Essential Drugs List [7]. DMPA is administered once every 12 weeks while NET-EN is provided every 8 weeks. Although the active ingredients in the two methods are different, the World Health Organization's Medical Eligibility Criteria for Contraceptive Use classifies DMPA and NET-EN together with the same safety and efficacy profile [8].

The use of IPCs may increase the risk of cervical infection with chlamydia and gonorrhea in women [3,4,9]. Three prospective studies have been conducted to date to examine the association between use of IPC and STI acquisition [3,4,9]. Among U.S. family planning clinic attendees, the use of DMPA increased the risk of cervical infection with gonorrhea and/or chlamydia [4]. Among sex workers in Kenya, the use of DMPA was associated with an increased risk of chlamydial infection but not gonorrhea and a decreased risk of bacterial vaginosis (BV) and *Trichomonas vaginalis* (TV) [3]. In a large cohort study among family planning clinic attendees in Uganda, Zimbabwe and Thailand, DMPA was found to increase the risk of gonorrhea but not chlamydia [9].

Using data from a prospective study designed to examine the association between the use of IPC and HIV infection, we examined the association between use of two different IPCs (NET-EN and DMPA) and STI among South African women. To date, the association between NET-EN and STI infection has not been examined prospectively, despite the widespread use of NET-EN, particularly among young women in South Africa [7]. In addition, prospective data on the association between IPC use and STIs, particularly infections with TV and BV, among 'low-risk' populations in sub-Saharan Africa are limited.

2. Materials and methods

From August 1999 through May 2001, HIV-1 negative women were recruited from family planning clinics in Orange Farm, a large settlement 60 km from Johannesburg. The main findings from this study have been published elsewhere [10]. Criteria for inclusion in the study included age 18–40 years, sexually active (meaning they had sex) in the past 3 months, not pregnant or planning to become pregnant for 12 months, consenting to HIV testing and other study procedures, willing to be contacted at home for follow-up, and not using or planning to use oral contraceptive pills. IPC users (NET-EN and DMPA) and non-hormonal or non-contraceptive users were recruited in approximately equal numbers. The main study was approved by the University of the Witwatersrand Research Ethics Committee and the secondary data analysis for the present study was approved by the University of North Carolina at Chapel Hill. Informed consent was conducted in the main trial.

Eligible participants were seen at enrolment and months 2, 6, 8 and 12 (NET-EN users) or months 3, 6, 9 12 (DMPA users and controls). Participants were interviewed by means of a structured questionnaire to collect information on demographics, STI/HIV prevention knowledge and sexual history at enrolment and at all visits on sexual practices, condom use, and current contraceptive method. At each visit, a pelvic examination was performed, vaginal specimens were collected, and STIs were treated using the syndromic approach (using standard algorithms based on signs and symptoms of STIs). STI and HIV testing were performed at each visit.

2.1. Laboratory methods

Infections with *Chlamydia trachomatis* (CT) and *Neisseria gonorrhoea* (NG) were detected from urine using ligase chain reaction (LCx; Abbot Laboratories) at enrolment and each follow-up visit. Five mL of clean-catch urine was collected at each study visit, transported daily to the laboratory, an aliquot tested by LCR for gonorrhea and chlamydia and the remainder frozen at -70%, and shipped to the CDC for batch testing. Vaginal swabs were cultured in Diamond's media for detection of *Trichomonas vaginalis* (TV). Bacterial vaginosis (BV) was assessed from a gram stained smear of a vaginal swab using Nugent's criteria. A score ≥ 7 was categorized as positive. A proportion of Gram-stain slides were sent to the CDC in the US for re-assessment of Nugent's scoring and diagnosis of BV. All specimens were tested at the Contract Laboratory Services which is a joint partnership between the National Health Laboratory Service and the School of Pathology at the University of the Witwatersrand in South Africa. All laboratory procedures and validations met with CDC approval.

2.2. Statistical analysis

To assess the association between use of IPCs and incident STI infection, we used multivariable Poisson regression models with generalized estimating equations (GEE) to compute incidence rate ratios for infection by use of hormonal contraception (HC), relative to non use. Separate models were constructed for each of the four STIs examined. We defined an incident infection as the first positive test following a negative test. Therefore, a woman could have multiple incident infections. For BV, we examined both incident infections and any infection after the first negative result given the long time between follow-up visits and the relatively high recurrence of BV, thus a positive BV test following a previous BV test could well be an incident case of BV [11].

We examined the use of IPC as a three-part variable coded as: use of DMPA, use of NET-EN or no HC use. Use of IPC was determined based on self report at each visit. Any visit where the woman tested positive for pregnancy or HIV was excluded from analysis due to the fact that pregnancy is more likely amongst those women not using HC [4] and HIV may affect the risk of STI acquisition [3].

We examined the following variables as potential confounding factors based on a priori hypotheses: age (15–24 years vs. 25–40 years), relationship status, education (less than high school vs. greater than high school), frequency of sex in past 3 months (one or more times a week vs. less than one time a week), number of partners in past 3 months (one vs. more than one), condom use in past 3 months (always vs. sometimes/never), cleaning inside the vagina (douching) in past 3 months (yes vs no), and age of first sex (14 or younger vs. older than 14). For multivariable models, variables were kept in the final model based on a backward elimination procedure (10% change in effect estimate) and based on a priori hypotheses; age, education and condom use consistency were forced into the final model. Effect modification of age on use of IPC was assessed.

Among women reporting switching contraceptive methods during the study (N=181), we assessed the effect of a 'wash-out' period for switches from NET-EN or DMPA to a non-hormonal method during the study follow-up period in a sensitivity analysis. We imposed a lag time which counted the first non-exposed visit as 180 days from the last visit where HC use was reported [12]. We also conducted an analysis where we excluded all women who reported switching methods. Point estimates generated from the analysis conducted allowing for switching and the wash-out period were similar to the main analysis that did not take these factors into account (data not shown).

3. Results

A total of 567 HIV negative women returned for at least one follow-up visit of 643 enrolled. At baseline, 4.0% tested positive for GC, 14.0% for CT, 7.8% for TV and 35.6% for BV. In the study population, 45.3% of women were not using any HC, 19.9% were using DMPA and 34.7% NET-EN at baseline (Table 1). The mean age was 27.7 years. Over one-third (37.3%) of women reported that they were married and cohabiting at baseline, 38.5% reported that they had a boyfriend that they were not living with, and 17.7% reported having a boyfriend that they were living with (Table 1). The majority of women (76.5%) reported having at least a high school education. Internal vaginal washing (douching) was reported by 43% of women and of these women, 87% reported douching every time she had sex. Dry sex was not common in this population, only 3% of women reported using anything to dry their vagina for the purpose of having dry sex. Any condom use in the past 3 months was reported by 54.6% of women who had ever used condoms and 79% of women stated that they only had one sex partner in the past 12 months.

Among the women with at least one follow-up visit, we observed 45 incident infections with gonorrhea, 119 with chlamydia, and 47 with TV yielding incidence rates of 9.9/100 person-years, 28.2/100 person-years, and 10.2/100 person-years, respectively, (Table 2). We observed a higher incidence of BV (n=281 episodes; incidence rate = 93.5/100 person-years) (Table 2).

In multivariable models adjusting for age, education, and condom use consistency in the past 3 months, use of DMPA was associated with a slightly increased risk of infection with chlamydia (IRR 1.24; 95% CI 0.80–1.94) and gonorrhea (IRR 1.30), the latter observation had very wide confidence intervals (95% CI 0.58–2.98). In contrast, a protective effect was observed with DMPA and TV (IRR 0.35; 95% CI 0.12–1.01), although this estimate was somewhat imprecise. NET-EN use was not clearly associated with CT or GC.

Considering incident infections (defined as a positive test following a negative test), DMPA and NET-EN were not strongly associated with BV. However, when all instances of BV in follow-up visits were considered, including those episodes that followed a previous positive result after the first negative test, both DMPA and NET-EN demonstrated protective effects (DMPA: incidence rate ratio (IRR) 0.74; 95% CI 0.59–0.93; NET-EN: IRR 0.78; 95% CI 0.64–0.94).

4. Discussion

We found that use of DMPA in this population of South African family planning clinic attendees was associated with similar slight increases in risk for chlamydial infection and gonorrhea, although the associations were not statistically significant. In contrast, DMPA appeared to be protective for TV, although this estimate was imprecise. Use of both DMPA and NET-EN were associated with a decreased risk of BV, although these associations were only statistically significant when considering all cases of BV.

Three other prospective studies have explored the relationship between use of IPCs and STI acquisition. In a study of sex workers in Kenya, the use of DMPA was associated with a significant increased risk of chlamydia but not gonorrhea [3]. Among family planning clinic attendees in Zimbabwe, Uganda, and Thailand, use of DMPA was associated with an increased risk of gonorrhea but not chlamydia [9], while use of DMPA increased the risk of cervical infection with either gonorrhea or chlamydia among family planning clinic attendees in the US [4]. Only one other study has examined the associated between use of IPC and TV or BV, and this study found a decreased risk of both with the use of IPC [3].

The observed relationships between IPC and STIs are biologically plausible. Although the differences in the effects of progestogens (natural progesterone versus synthetic progestins) are not well defined, progestogens could reduce lactobacilli, thus increasing vaginal pH and susceptibility to cervical infections [13–15]. They may also depress the immune system, thereby increasing risk to cervical infections [4]. Progestogens support the growth and persistence of *C trachomatis* whereas they may suppress the growth of *N gonorrhoeae* [16]. A decreased risk of trichomoniasis may be the result of growth inhibition as a result of “exogenous hormones of estrogen and androgen receptors on *T vaginalis*” [3,17]. Another possible causal mechanism for the decreased risk of TV and also for BV may be the result of amenorrhea, a common side effect of IPC. TV growth has been found to be most predominant immediately following menses when lactoferrin concentrations are highest and thus iron availability from lactoferrin is greatest [18]. Increased iron has been found to enhance the adherence and cytotoxicity of trichomonads [19]. Reduced BV rates could be due to progestin-induced amenorrhoea; menses have been shown to destabilize the vaginal flora resulting in high concentrations of non-lactobacillus species that favor BV [20].

From a public health perspective, questions have arisen as to the messages that should be conveyed to clinicians and users of IPCs with regard to the potential risk of cervical infection with gonorrhea or chlamydia. There are now four longitudinal, observational studies that have found an increased risk of cervical infection with either GC or CT among women who use DMPA. These findings come from different populations that include sex workers in Kenya, and family planning clinic attendees in the US, South Africa, Zimbabwe, Uganda and Thailand. Currently, the 2004 WHO Medical Eligibility Criteria states “limited evidence suggests that there may be an increased risk of chlamydial cervicitis among DMPA users at high risk for STIs” [8]. For other STIs, they state that there is either no evidence of an association or too limited evidence to draw any conclusions. Certainly, women using HC, including IPCs, should continue to be counselled to use condoms to reduce their risk of STIs and HIV. Nevertheless, given that many women using IPC are likely in long-term relationships and may be using HC because they cannot use male condoms, the likelihood of using condoms for some women is slim. Currently, women at high risk of STIs do not need to be discouraged from using IPCs. Given the inconsistencies and limitations of the data describing an increased risk for CT and GC with IPC use, the potential risk of STIs must be balanced against the risk of unintended pregnancy and its health consequences, especially in developing countries.

The main limitation of this and other studies is that residual and unmeasured confounding related to women who chose to use IPCs may explain the observations. Women using IPCs are less likely to use condoms and may have other behaviors or characteristics that differ from women who do not use HC [5]. Although we adjusted for condom use in our analysis, measurement error with regard to over- or under-reporting of condom use may have resulted in our inability to adequately adjust for differential use between IPC users and non-users. In addition, factors such as education, gender power dynamics within relationships, partner characteristics, condom use self-efficacy, and other factors that are associated with use of IPCs and STI risk may not be adequately measured or adjusted for.

5. Conclusion

Use of DMPA among women in this study population was associated with a slight, but not significant, increase in the risk of cervical infection with Chlamydia and gonorrhea. A randomized, controlled trial may be necessary to adequately determine whether IPCs, and other HC, increase STI and HIV risk. Although the evidence is not conclusive with regard to cervical infection and use of IPC, women opting to use IPC should be counselled that sex without condom use may place them at continued risk of STIs and HIV.

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References

1. South African Department of Health. Pretoria: South African Department of Health. 2006. National HIV antenatal seroprevalence survey 2005.
2. Pettifor A, Kleinschmidt I, Levine J, et al. A community based study to examine the effect of a youth HIV prevention intervention on young people age 15–24 in South Africa: results of a baseline survey. *Trop Med Internat Health* 2005;10:971–980.
3. Baeten JM, Nyange PM, Richardson BA, et al. Hormonal contraception and risk of sexually transmitted disease acquisition: results from a prospective study. *Am J Obstet Gynecol* 2001;185:380–385. [PubMed: 11518896]
4. Morrison C, Bright P, Wong E, et al. Hormonal contraceptive use, cervical ectopy, and the acquisition of cervical infections. *Sexually Transmitted Diseases* 2004;31:561–567. [PubMed: 15480119]
5. Baeten JM, Lavreys L, Overbaugh J. The influence of hormonal contraceptive use on HIV-1 transmission and disease progression. *Clin Infect Dis* 2007;45:360–369. [PubMed: 17599316]
6. South African Department of Health. South African Demographic and Health Survey 1998. Pretoria: South African Department of Health. 2001
7. Smit J, Gray A, McFadyen L, Zuma K. Counting the costs: comparing depot medroxyprogesterone acetate and norethisterone oenanthate utilisation patterns in South Africa. *BMC Health Serv Res* 2001;1:4. [PubMed: 11401729]
8. World Health Organization. Medical Eligibility Criteria for Contraceptive Use. Geneva: World Health Organization; 2004.
9. Morrison, CS.; Kwok, C.; Chen, P., et al. Hormonal contraception and the acquisition of cervical chlamydial and gonococcal infections; 17th International Society for Sexually Transmitted Diseases Research; Seattle, WA: 2007.
10. Kleinschmidt I, Rees H, Delany S, et al. Injectable progestin contraceptive use and risk of HIV infection in a South African family planning cohort. *Contraception* 2007;75:461–467. [PubMed: 17519153]
11. Wilson J. Managing recurrent bacterial vaginosis. *Sex Transm Infect* 2004;80:8–11. [PubMed: 14755028]
12. Morrison CS, Richardson BA, Mmiro F, et al. Hormonal contraception and the risk of HIV acquisition. *AIDS* 2007;21:85–95. [PubMed: 17148972]

13. Bahamondes L, Trevisan M, Andrade L, et al. The effect upon the human vaginal histology of the long-term use of the injectable contraceptive Depo-Provera. *Contraception* 2000;62:23–27. [PubMed: 11024225]
14. Miller L, Patton DL, Meier A, Thwin SS, Hooton TM, Eschenbach DA. Depomedroxyprogesterone-induced hypoestrogenism and changes in vaginal flora and epithelium. *Obstet Gynecol* 2000;96:431–439. [PubMed: 10960638]
15. Taha TE, Hoover DR, Dallabetta GA, et al. Bacterial vaginosis and disturbances of vaginal flora: association with increased acquisition of HIV. *AIDS* 1998;12:1699–1706. [PubMed: 9764791]
16. Sonnex C. Influence of ovarian hormones on urogenital infection. *Sex Transm Infect* 1998;74:11–19. [PubMed: 9634294]
17. Ford LC, Hammill HA, DeLange RJ, et al. Determination of estrogen and androgen receptors in *Trichomonas vaginalis* and the effects of antihormones. *Am J Obstet Gynecol* 1987;156:1119–1121. [PubMed: 3495180]
18. Ryu JS, Choi HK, Min DY, Ha SE, Ahn MH. Effect of iron on the virulence of *Trichomonas vaginalis*. *J Parasitol* 2001;87:457–460. [PubMed: 11318588]
19. Demes P, Gombosova A, Valent M, Fabusova H, Janoska A. Fewer *Trichomonas vaginalis* organisms in vaginas of infected women during menstruation. *Genitourin Med* 1988;64:22–24. [PubMed: 3257936]
20. Eschenbach DA, Thwin SS, Patton DL, et al. Influence of the normal menstrual cycle on vaginal tissue, discharge, and microflora. *Clin Infect Dis* 2000;30:901–907. [PubMed: 10852812]

Table 1

Baseline demographics, sexual behaviors and use of IPC amongst women ages 18–40 years in Orange Farm, South Africa, 1999–2001.

	n/N	%
Age (n=567)		
15–24	226	39.9
25–41	341	60.1
Marital status (n=566)		
Married- cohabiting	211	37.3
Married- not cohabiting	9	1.6
Boyfriend- cohabiting	100	17.7
Boyfriend- not cohabiting	218	38.5
Casual partner	23	4.1
No current partner	5	0.9
Education (n=544)		
Less than high school	128	23.5
More than high school	416	76.5
Douche (n=567)		
Yes	243	42.9
No	324	57.1
Frequency of douching in past 3 months (n=243)		
Every time she has sex	212	87.2
Sometimes or never	31	12.8
Used anything to dry vagina for purpose of dry sex in past 3 mo (n=567)		
Yes	17	3.0
No	550	97.0
Condom use in last 3 months (n=383)		
Yes	209	54.6
No	174	45.4
Sexual partners in past 12 months (n=565)		
1	447	79.0
2	76	13.4
≥3	42	7.4
Hormonal contraception use (n=567)		
None	257	45.3
DMPA	113	19.9
NET-EN	197	34.7

Incident STI infections by type of IPC use amongst women ages 18–40 years in Orange Farm, South Africa using IPC (either DMPA or NET-EN) or no hormonal contraception, 1999–2001.

Table 2

Incidence (no./person-year) rate/100 person-years																
NET-EN				DMPA				No hormonal contraception				Total				
Episodes	Person-years	IR	95% CI	Episodes	Person-years	IR	95% CI	Episodes	Person-years	IR	95% CI	Episodes	Person-years	IR	95% CI	
GC	15	124	12.1	7.3, 20.0	8	81	9.9	5.0, 19.8	22	251	8.8	5.8, 13.3	45	456	9.9	7.4, 13.2
CT	30	114	26.4	18.4, 37.7	25	77	32.6	22.0, 48.2	64	232	27.6	21.6, 35.2	119	423	28.2	23.5, 33.7
TV	10	124	8.1	4.3, 15.0	5	82	6.1	2.5, 14.6	32	252	12.7	9.0, 18.0	47	458	10.2	7.7, 13.7
BV	81	88	91.8	74.9, 114.2	42	56	75.5	55.8, 102.1	157	155	101.0	86.4, 118.1	280	299	93.5	83.2, 105.2

Table 3

Unadjusted and adjusted incidence rate ratios and 95% confidence intervals for infection with CT, GC, BV or TV amongst women ages 18–40 years in Orange Farm, South Africa using IPC (either DMPA or NET-EN) compared to those women not using hormonal contraception (HC), 1999–2001

		Unadjusted IRR	Adjusted IRR
<i>CT</i>			
	No HC use	1.0	1.0
	DMPA	1.18 (0.77–1.81)	1.24 (0.80–1.94)
	NET-EN	0.93 (0.60–1.43)	0.91 (0.59–1.43)
<i>GC</i>			
	No HC use	1.0	1.0
	DMPA	1.19 (0.53–2.65)	1.30 (0.58–2.98)
	NET-EN	1.41 (0.70–2.85)	1.11 (0.55–2.25)
<i>TV</i>			
	No HC use	1.0	1.0
	DMPA	0.38 (0.13–1.08)	0.35 (0.12–1.01)
	NET-EN	0.59 (0.28–1.23)	0.63 (0.30–1.29)
<i>BV</i>			
	No HC use	1.	1.0
	DMPA	0.75 (0.55–1.02)	0.77 (0.56–1.06)
	NET-EN	0.89 (0.69–1.14)	0.91 (0.70–1.18)

All models adjusted for age, education, and condom use consistency in the past 3 months.