

Contraceptive use and the risk of sexually transmitted infection: systematic review and current perspectives

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Purpose: Evidence on the association between contraceptive use and risk of sexually transmitted infections (STIs) and bacterial vaginosis (BV) is lacking, with few prospective studies. We systematically reviewed the last 10 years' evidence on the association between contraception and STI/BV, building on the most recent systematic reviews published in 2006 and 2009.

Methods: We searched the MEDLINE and POPLINE databases for peer-reviewed articles published between January 1, 2008 and January 31, 2018 reporting prospective studies that assessed the association between contraceptive use and incident STI and/or incident or recurrent BV.

Results: We identified 33 articles that evaluated combined oral contraceptives (COC), depot medroxyprogesterone acetate (DMPA), the copper intrauterine device (Cu-IUD), the levonorgestrel intrauterine system (LNG-IUS) and other methods. The strength of the evidence for many specific contraceptive method/STI associations is limited by few prospective studies with comparably defined exposures and outcomes. Available data suggest no association of COCs and *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, HSV-2 or syphilis, and mixed evidence on the association with HPV, *Chlamydia trachomatis*, and BV. For DMPA, none of the studies identified found an association with *N. gonorrhoeae* or syphilis, and data on *C. trachomatis*, *T. vaginalis*, HPV and BV were mixed. Two large studies showed a highly clinically significant increased risk of HSV-2 infection with DMPA use. Data on the effect of Cu-IUD and the LNG-IUS on the acquisition of *C. trachomatis*, *N. gonorrhoeae* and *T. vaginalis* are sparse, and data on HPV and BV are mixed.

Conclusion: Few data are available from prospective studies, including randomized trials, to draw strong conclusions about the relationships between contraceptive methods and specific STIs. The overall evidence on the association between contraceptive use and STI/BV risk is limited by the lack of any randomized trials, few published prospective studies designed to analyze these associations, wide variability in exposure definitions and comparator groups, potential for confounding due to inaccurate sexual behavior data, differential confounder adjustment and differences in study populations and sizes. Despite these limitations, new evidence is supportive of a significantly increased risk of HSV-2 infection among DMPA users which warrants additional research to better understand this association.

Keywords: combined oral contraceptives, depot medroxyprogesterone acetate, intrauterine device, intrauterine system, sexually transmitted infections, chlamydia, gonorrhea, trichomonas, herpes simplex virus, bacterial vaginosis

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Introduction

Fifty-seven percent of reproductive aged married or in-union women worldwide use a modern method of family planning including female and male sterilization, oral contraceptive pills, the intrauterine device (IUD), male and female condoms, injectables, implants, vaginal barrier methods and emergency contraception.¹ Moreover, in an effort to meet the Sustainable Development Goal of ensuring universal access to sexual and reproductive health services by 2030, Family Planning 2020 aims to enable 120 million more women and girls to use contraceptives by 2020.² However, women using or in need of contraception are also at risk of sexually transmitted infections (STIs). The World Health Organization estimates that over 357 million new cases of curable STIs, including chlamydia, gonorrhea, syphilis and trichomoniasis, and a similarly high burden of viral STIs (417 million prevalent herpes simplex virus [HSV] and 291 million prevalent human papillomavirus [HPV] infections), not including HIV, occur among individuals aged 15–49 each year.³

Both increasing access to contraceptives, and preventing STIs, are critical to ensuring women's sexual and reproductive health. However, the evidence base on potential associations between use of specific contraceptive methods and STI risk is lacking, with few prospective studies designed to assess these associations. Moreover, any true association between contraceptive use and STIs could be due to behavioral and/or biological risk factors. Behaviorally, women who use modern methods of contraception may have different condom use patterns, sexual frequency and numbers of sexual partners as compared to women not using modern contraception.^{4–7} Uncontrolled and/or residual confounding due to inaccurate measurement of sexual behavior is a significant concern in evaluating the results of observational studies on the topic – results may be biased toward or away from the null depending on the type and frequency of misreporting or lack of adjustment for salient variables – and studies which randomize women to contraception are lacking.⁶ Possible biological mechanisms linking contraceptives and STIs include alteration of the vaginal epithelium, changes in mucus production and in multiple immune responses (eg, production and availability of cytokines, chemokines and relevant cell types in the upper and lower female reproductive tract and alteration of the vaginal microbiota).^{8–13}

Women and providers need the best available information on potential associations between contraceptive use and STI risk. We conducted a systematic review of the recent literature (past 10 years), following published systematic reviews in 2006 and 2009, to summarize the current evidence.^{14,15}

Methods

We report our findings in accordance with the Preferred Items of Reporting for Systematic Reviews and Meta-Analyses (PRISMA).¹⁶ We searched the MEDLINE and POPLINE databases for articles published in peer-reviewed journals between January 1, 2008 and January 31, 2018 for prospective studies with data on the association between use of contraceptives and incident protozoan/bacterial (*Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *sypillis*), and incident and persistent viral (HPV, HSV), STI. We also included studies that evaluated incident and recurrent bacterial vaginosis (BV) due to recent evidence that suggests sexual transmission is an important mechanism of BV recurrence in women, and because BV represents a significant health burden for women.^{17,18} The search strategy is provided in the Appendix. We identified 1,147 unique articles using the aforementioned search strategy. While we did not decide a priori to exclude articles that were not in English, all 1,147 articles identified were in English. We then systematically reviewed abstracts from the 1,147 articles to identify the study design and to determine the contraceptive methods and STIs evaluated in each study. Abstract review data, including author, title, journal, study design and reason for exclusion were recorded, as well as classification for inclusion in the review (ie, include, exclude, defer to senior author for decision). The specific contraceptive methods and STIs evaluated in each article were abstracted. We included articles which were prospective, in humans, specified the hormone (or at a minimum classified exposure by estrogen-containing vs progesterone-containing) under study if evaluating a hormonal method, and had laboratory results for incident STI and/or incident or recurrent BV outcomes (not including HIV). Additionally, we excluded articles that only evaluated the STI/BV outcome in a subset of participants without defining how the subset was selected. Where these criteria could not be ascertained from the abstract, we reviewed the full manuscript to determine inclusion status. A second reviewer confirmed that all included articles met inclusion criteria. This review resulted in 33 manuscripts which included the following number of studies by contraceptive method: 21 combined oral contraceptives (COC), 17 depot medroxyprogesterone acetate (DMPA), nine levonorgestrel intrauterine system (LNG-IUS), six copper intrauterine device (Cu-IUD), one non-specified IUD type, three contraceptive vaginal ring (CVR), one contraceptive patch, four implant (levonorgestrel or etonogestrel [ENG]), two norethisterone enanthate (NET-EN), one medroxyprogesterone acetate-ethinyl estradiol (MPA-EE) injectable and one that was categorized only by estrogen- or progesterone-containing.

Results

Combined oral contraceptives

We identified 21 studies which evaluated the association between COC use and chlamydia, gonorrhea, trichomoniasis,

HPV, HSV-2, BV and/or syphilis. We provide summary data (author, year, population, sample size, study design, STI/BV outcome, variables adjusted for in analyses and results) in Table 1.

Table 1 Combined oral contraceptive use and risk of STI/BV summary

Study	Reference #	n, population	Design	STI/RTIa	Estimate adjusted for	Result Estimate (95% CI)
Borgdorff 2015	22	397 female sex workers aged 18–49 in Rwanda	Prospective observational cohort	CT, NG, TV, HPV, HSV-2, BV, syphilis	Duration of time since last follow-up, age, educational level, years worked as sex worker, baseline breast-feeding status, consistent condom use, antibiotic use in the past 14 days, ever having used antibiotics before the outcome assessment date	CT incidence: • OC use vs not using HC aOR 6.13 (1.58–23.8) NG incidence: • OC use vs not using HC aOR 2.57 (0.78–8.45) TV incidence: • OC use vs not using HC aOR 0.61 (0.20–1.84) HPV incidence: • OC use vs not using HC aOR 1.08 (0.21–5.44) HSV-2 incidence: • OC use vs not using HC aOR 4.28 (0.07–262.1) BV incidence: • OC use vs not using HC aOR 0.73 (0.32–1.67) Syphilis incidence: • No incident cases
Brahmbhatt 2014	24	2,374 sexually active women aged 15–49 in Uganda	Prospective observational cohort	TV	Age, education, number of non-marital sex partners in last 12 months, socio-economic status, Nugent score, HIV status, syphilis serology	TV incidence: • COC use vs no HC/condom use aIRR 1.02 (0.40–2.59)
Bradshaw 2013	37	404 women aged 18–50 in Australia	A secondary analysis of a double-blind BV treatment trial to identify factors associated with BV recurrence	BV	Age, sex frequency	BV recurrence by recent use of an estrogen-containing contraceptive (ECC): • Current/recent use of ECC vs not current/not recent use of ECC aHR 0.51 (0.33, 0.78) Note: ECC group consisted of 108 COC users and 2 NuvaRing users.
De Seta 2012	33	30 new COC users and 30 new CVR users aged 18–45 in US	Prospective observational cohort	TV, BV	Not adjusted	No significant difference in BV between CVR and COC users over 6 months' follow-up (no effect estimate provided). No trichomoniasis infections were identified in either group.
De Seta 2014	34	60 new COC users	Prospective observational cohort	BV	Not adjusted	Significant decrease in BV in women using 17β-estradiol/norgestrel regimen over 6 months. No differences observed among women using estradiol valerate/dienogest regimen.
Francis 2016	35	1,027 female sex workers in aged ≥18 in Uganda	Prospective observational cohort	BV	Age, level of education, number of lifetime partners, frequency of condom use with clients, any use of alcohol, intravaginal insertion, HIV, HSV-2, vaginal yeast, TV, NG, syphilis	BV prevalence during follow-up: • COC use vs no contraceptive use aOR 0.81 (0.56–1.17)

(Continued)

Table 1 (Continued)

Study	Reference #	n, population	Design	STI/RTIa	Estimate adjusted for	Result Estimate (95% CI)
Goodman 2008	26	972 women aged 18–85 years in the US	Prospective observational cohort	HPV	Age at study entry	HPV acquisition by baseline COC use: • Ever vs never aHR 0.81 (0.65–1.01) • Past vs never aHR 0.74 (0.57–0.97) • Current vs never aHR 0.86 (0.68–1.09) HPV acquisition by years of COC use: • <2 years vs never aHR 0.78 (0.57–1.06) • 2–4 years vs never aHR 0.70 (0.55–0.89) • 5–9 years vs never aHR 0.61 (0.47–0.79) • ≥10 years vs never aHR 0.65 (0.46–0.90) HPV clearance by baseline COC use: • Ever vs never aHR 1.20 (0.93, 1.57) • Past vs never aHR 1.23 (0.91, 1.66) • Current vs never aHR 1.18 (0.89, 1.57) HPV clearance by years of COC use: • <2 years vs never aHR 1.03 (0.73, 1.46) • 2–4 years vs never aHR 1.16 (0.87, 1.56) • 5–9 years vs never aHR 0.75 (0.56, 1.00) • ≥10 years vs never aHR 0.99 (0.69, 1.40)
Grabowski 2015	32	682 women aged 21–29 in Uganda	Prospective observational cohort	HSV-2	Age, educational status of female and male partners, number of lifetime sexual partners, male partner circumcision status, coital frequency, self-reported condom use, non-marital partners in past year	HSV-2 incidence: • OC use vs no HC use aHR 0.49 (0.08, 3.01)
Kapiga 2009	21	958 women at risk of STIs aged 16–62 years in South Africa, Zambia, and Tanzania	Prospective observational cohort	CT, NG, TV, syphilis	TV analysis adjusted for site, anal sex in past 3 months, DMPA use, NG, BV, abnormal vaginal discharge, otherwise not adjusted	CT incidence by site: • Durban/Hlabisa OR 1.4 (0.7, 3.1) • Moshi/Lusaka OR 0.9 (0.3, 2.6) NG incidence by site: • Durban/Hlabisa OR 0.9 (0.4, 2.3) • Moshi/Lusaka OR 1.6 (0.7, 4.0) TV incidence all sites: • aOR 0.6 (0.3, 1.0) Syphilis incidence all sites: • OR 1.0 (0.5, 2.1)
Louvanto 2011	25	329 pregnant women in Finland	Prospective observational cohort	HPV	Age, mother seroconverted to HR-HPV, age at onset of sexual activity, lifetime number of sexual partners, practices of anal sex, age COC initiation, age of smoking initiation, second pregnancy during follow-up, change in marital status during follow-up	Incident HPV species 7 and 9-type infection by timing of COC use: • <20 years vs >20 years aIRR 1.13 (1.02–1.26) • never vs ever use a IRR 1.01 (0.74, 1.37)

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Table 1 (Continued)

Study	Reference #	n, population	Design	STI/RTIa	Estimate adjusted for	Result Estimate (95% CI)
Madden 2012	47	90 new IUD users, 59 new LNG-IUS users, 31 new Cu-IUD users and 63 new COC/ring/patch users aged 18–45 in the USA	Prospective observational cohort	BV	Age, race, condom use over the study period, douching in the 6 months before enrollment, baseline intermediate flora, irregular bleeding, and IUD use	BV incidence by contraceptive method, not adjusted: • COC 15.0% vs CVR 16.7% vs patch 22.4%, $P=0.24$
Marks 2011	28	376 COC users, 331 DMPA users, and 428 NHC users in Thailand	Prospective observational cohort	HPV	Age, study site, number of lifetime sexual partners, cytology, incident vs prevalent HPV infection, and duration of COC and DMPA use	HPV incidence: • COC vs NHC aOR 1.27 (0.93, 1.74) HPV clearance: • COC vs NHC aHR 0.67 (0.49, 0.93)
Masese 2013	20	865 women aged 18–50 reporting transactional sex in Kenya	Prospective observational cohort	CT	Age, contraceptive method, sexual risk behavior, HIV-I status, presence of candida/TV/NG	CT incidence: • COC use vs non-HC use aHR 0.2 (0.0–1.7)
Maucourt-Boulch 2010	31	2,408 women with abnormal or equivocal cervical cytology in the USA	Prospective observational cohort	HPV	Age stratified by prevalence/incidence status group, study center, randomization arm, community cytology interpretation and observed duration of infection	HPV persistence at 6 months: • COC users vs non-COC user aOR 0.98 (0.89–1.08)
McClelland 2008	36	151 female sex workers in Kenya	Prospective observational cohort	BV	Age, vaginal washing frequency, vaginal washing substance, cloth to clean inside vagina, bathing frequency, vaginal lubricant for sex, number of sex partners in the last week, unprotected sex in the last week, new partner in the past month, candidiasis, TV	BV incidence: • OC use vs no contraceptive use/tubal ligation aHR 1.20 (0.96, 1.50)
Rezk 2017	23	236 new COC users and 194 new LNG-IUS users in Egypt	Prospective observational cohort	TV, BV	Not adjusted	BV: COC vs LNG-IUS • at 6 weeks OR 1.25 (0.79, 1.98) • at 6 months OR 1.16 (0.70, 1.91) • at 12 months OR 1.41 (0.80, 2.48) TV: COC vs LNG-IUS • at 6 weeks OR 0.91 (0.46, 1.76) • at 6 months OR 0.69 (0.31, 1.53) • at 12 months OR 0.82 (0.30, 2.22)

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Table 1 (Continued)

Study	Reference #	n, population	Design	STI/RTIa	Estimate adjusted for	Result Estimate (95% CI)
Russell 2016	19	225 women aged 15–35 with NG/CT or male partner treated for NG/CT in the US	Prospective observational cohort	CT	Not adjusted	CT incidence: • COC use vs no COC use HR 0.75 (0.40, 1.38)
Schmeink 2010	27	2,065 women aged 18–29 years in the Netherlands	Prospective observational cohort	HPV	Not adjusted	No significant difference in HPV incidence or persistence between COC users and nonusers (no effect estimate provided)
Shew 2015	30	146 adolescent women aged 14–17 in the USA	Prospective observational cohort	HPV	CT, NG, TV, number of sex partners in the last 3 months, new sex partner in the last 3 months, COC use in last 3 months	All HPV type redetection: • COC use last 3 months vs no COC use last 3 months aHR 2.00 (1.28, 3.15) High risk HPV type redetection: • COC use last 3 months vs no COC use last 3 months aHR 1.31 (0.73, 2.35) Low risk HPV type redetection: • COC use last 3 months vs no COC use last 3 months aHR 2.73 (1.52, 4.90)
Stensen 2016	29	2,874 women with high-risk HPV in Denmark	Prospective observational cohort	HPV	Age and time between samples	High risk HPV persistence 2.5 years before baseline: • COC current vs not current use aOR 1.23 (1.02, 1.48) High risk HPV persistence 1 year after baseline: • COC current vs not current use aOR 1.35 (1.13, 1.63)
Van de Wijgert 2013	38	6,109 women aged 18–35 using COCs, DMPA or no hormonal contraception in Thailand, Uganda and Zimbabwe	Prospective observational cohort	BV	Adjusted but final model not specified	Incident/prevalent BV: • COC vs no hormonal contraceptive use aIRR 0.90 (0.84, 0.97)

Notes: ^aResearch articles may have included infections other than those listed; however, our review extracted only information for CT, NG, TV, HSV-2, HPV and BV.

Abbreviations: STI, sexually transmitted infection; RTI, reproductive tract infection; CT, *C. trachomatis*; NG, *N. gonorrhoeae*; TV, *T. vaginalis*; HSV-2, herpes simplex virus-2; HPV, human papilloma virus; BV, bacterial vaginosis; OC, oral contraceptive; HC, hormonal contraceptive; aOR, adjusted odds ratio; COC, combined oral contraceptives; aHR, adjusted hazard ratio; aIRR, adjusted incidence rate ratio; ECC, estrogen-containing contraceptive; CVR, contraceptive vaginal ring; IUD, intrauterine device; LNG-IUS, levonorgestrel intrauterine system; NHC, non-hormonal contraceptive; DMPA, depot medroxyprogesterone acetate.

Chlamydia

Four of the included studies evaluated the association between chlamydia and COC use. Russell et al¹⁹ evaluated factors associated with incident and ascending *C. trachomatis* infection among 48 women with current or prior diagnosis of gonorrhea and/or chlamydia. In the analysis of incident *C. trachomatis* infection, no association with COC use was observed in univariate analysis, therefore COC use was not further analyzed in the final multivariate model. A study of Kenyan women reporting transactional sex, which included over 2,000 person-years of follow-up with monthly follow-up

visits, found no association between COC use and incident *C. trachomatis* infection.²⁰ Similarly, a study conducted among 958 South African, Tanzanian, and Zambian women at risk of STIs and followed monthly for 1 year found no association with baseline oral contraceptive (OC) use and subsequent *C. trachomatis* infection.²¹ It is unclear as to whether or not changes in contraceptive methods during follow-up were accounted for in the two aforementioned studies which found no significant association in multivariate analyses. However, a study among 397 Rwandan sex workers, which followed women quarterly for 1–2 years and controlled for time-

varying contraceptive use, found a significant association between COC use and *C. trachomatis* incidence (adjusted odds ratio [aOR] 6.13, 95% CI 1.58–23.8).²²

Gonorrhea

Only two of the included studies – the aforementioned studies of 958 South African/Tanzanian/Zambian women and 397 Rwandan sex workers – evaluated the association between COC use and gonorrhea, and found no significant association.^{21,22}

Trichomoniasis

We identified five studies which evaluated the association between COC use and trichomoniasis, none of which identified a significant association. Rezk et al²³ enrolled 452 Egyptian women seeking contraception who agreed to COC or LNG-IUS use. Two-hundred and thirty-six women opted to use COCs (194 opted to use the LNG-IUS; 22 participants dropped out and were not included in analyses) and attended follow-up visits at 6 weeks, 6 months and 12 months; *T. vaginalis* testing was conducted at each follow-up visit by wet mount. The authors found no significant difference in *T. vaginalis* infection between COC and LNG-IUS users.²³ The aforementioned study among Rwandan sex workers also found no association between COC use and trichomoniasis incidence.^{21,22} A large study among 2,374 Ugandan women participating in the Rakai Community Cohort Study (RCCS), which included annual follow-up with assessment of contraceptive method use, found no significant association between COC use and incident *T. vaginalis*.²⁴ However, the study of 958 South African/Tanzanian and Zambian women found a reduced risk of *T. vaginalis* among women using COCs (OR 0.4, [95% CI 0.2–0.7]).²¹

Human papillomavirus

We identified eight studies which evaluated the association between COC use and incident and/or persistent HPV infection. A Finnish prospective study included 255 HPV-negative pregnant women in their third trimester. Among ever COC users, those who initiated COC use at <20 years of age had a significantly increased risk of incident infection by HPV types 7 and 9 compared to those who initiated COC use at ≥20 years of age (aIRR 1.13, [95% CI 1.02–1.26]).²⁵ Another study among 972 women in Hawaii found that the risk of acquiring any HPV infection varied by baseline COC use as well as by duration of COC use.²⁶ Women using COC at baseline were not at increased risk of incident high-risk HPV (HR-HPV), although past COC users were protected (ever users: adjusted hazard ratio [aHR] 0.81 [95% CI 0.65–1.01],

past users: aHR 0.74 [95% CI 0.57–0.97], current user: aHR 0.86 [95% CI 0.68–1.09]). The study also showed significantly decreasing HPV incidence with number of years of past COC use. However, three other studies – all of which incorporated time-varying exposure control in analyses – found no association between COC use and incident HPV infection. Schmeink et al²⁷ followed 2,065 Dutch women over 1 year, classifying women as consistent vs never COC users in analyses; Marks et al²⁸ followed 1,135 women for 18 months, classifying each follow-up interval as non-hormonal contraceptive (NHC) use, DMPA use or COC use; and Borgdorff et al²² followed 397 women for up to 2 years, classifying each follow-up interval as no hormonal contraceptive use, DMPA use, COC use or pregnant.

Among the studies which evaluated HPV, five evaluated persistent infection. A Danish cohort study among 2,874 HR-HPV positive women found significantly increased risk of HPV persistence with current COC use at baseline, as well as with COC use during the first year of follow-up (aOR 1.23 [95% CI 1.02–1.48] and aOR 1.35 [95% CI 1.13–1.63], respectively).²⁹ Similarly, a cohort study among 150 US adolescent women showed a significant association between COC use in the last 3 months and HPV re-detection compared to women who had not used COCs in the last 3 months (aHR 2.0 [95% CI 1.28, 3.15]).³⁰ Another study among 1,135 Thai women found a significant association between COC and reduced risk of HPV clearance compared to NHC use (aHR 0.67 [95% CI 0.49–0.93]).²⁸ However, the aforementioned study by Schmeink, as well as a study among 2,408 women with low-grade or equivocal cytological abnormalities followed for 2 years, found no association between COC use and HPV persistence.^{27,31}

Herpes simplex virus type 2

Two of the included studies, including the aforementioned study of 397 Rwandan sex workers, evaluated the association between COC use and HSV-2 and found no significant association.^{22,32} The second study was conducted among 682 Ugandan women who were partners of male participants in a randomized trial of male circumcision and were followed up annually, with assessment of time-varying contraceptive method use, over a 2-year follow-up period.

Bacterial vaginosis

We identified nine studies which evaluated the association between COC use and risk of incident and/or recurrent BV; six identified no significant association and three found a significant decrease in BV associated with COC use.

Among 153 US women who were BV-negative at baseline in a sub-study of the CHOICE study,⁴⁷ no association was observed between COC use and risk of BV over 6 months. Similarly, a study among 60 Italian women, 30 who agreed to COC use and 30 who agreed to CVR use, found no difference in incident BV or intermediate vaginal flora over 6 months between the two groups.^{33,34} In both of the aforementioned studies, women were analyzed according to chosen/assigned contraceptive method, allowing for discontinuations. Two studies among 151 Kenyan and 1,027 Ugandan female sex workers followed for ~1 to ~2 years respectively, found no significant difference in BV among women using COCs as compared to women using no contraception/(had tubal ligation, Kenya study only) while controlling for time-varying contraceptive use.^{35,36} Lastly, the aforementioned studies of 194 Egyptian and 397 Rwandan women found no differences in BV risk in COC users relative to LNG-IUS users, or relative to NHC users, respectively.^{22,23}

Three studies observed a significant protective effect of COCs and BV. In a study among 60 COC users, women using a 17 β -estradiol/norgestrel regimen had a significant decrease in BV over time, though no information is provided on whether or not BV treatment was administered for women who were determined to have BV at baseline, or during the follow-up period.³⁴ A sub-study within a BV-treatment trial of 400 women found that current/recent users of estrogen-containing contraceptive (ECC) (n=110, among which 108 were oral contraceptive users and two were NuvaRing users) had significantly lower risk (aHR 0.51 [95% CI 0.33–0.78]) of BV recurrence over 6 months compared to women not reporting current/recent ECC use.³⁷ Lastly, a study among 6,109 women aged 18–35 in Zimbabwe, Uganda and Thailand, which included 15–24 months of follow-up per woman and time-varying control of contraceptive method, also observed a protective association (aHR 0.90, [95% CI 0.84, 0.97]) as compared to women not using hormonal contraception.³⁸

Syphilis

Only two of the included studies – the aforementioned studies of 958 South African/Tanzanian women and 397 Rwandan sex workers – evaluated the association between COC use and *T. pallidum* and found no association.^{21,22}

COC summary

We found no evidence of any significant association between use of COCs and the risk of trichomoniasis, gonorrhea, HSV-2 or syphilis. There is mixed evidence on COC use

and incident chlamydia and HPV infection. One study showed a significant association between COC use and increased incident *C. trachomatis* as compared to women not using hormonal contraception, whereas three other studies found no association.^{19–22} Two of eight studies identified modified HPV incidence with COC use. One study showed a significant association between the timing of COC use initiation and HPV incidence, with women initiating COC use before 20 years of age having a slightly higher HPV incidence.²⁵ A second study showed an inverse association between the number of years of COC use and HPV incidence, whereas three other studies found no association with HPV incidence.²⁶ Findings were similarly inconsistent among studies which evaluated HPV persistence/re-detection. There is also conflicting evidence of an association between COC use and BV – six studies found no effect, whereas three studies found reduced risk of BV recurrence associated with COC use.

Depot medroxyprogesterone acetate

We identified 17 studies which evaluated the association between DMPA use and chlamydia, gonorrhea, trichomoniasis, HPV, HSV-2, BV and/or syphilis. Summary data are provided in Table 2.

Chlamydia

We identified six studies that reported an association between DMPA use and chlamydia, only one of which found a significant association. A study of Kenyan women reporting transactional sex, which included over 2,000 person-years with monthly follow-up visits, found that DMPA was significantly associated with increased incident *C. trachomatis* infection in adjusted analyses (aHR 1.8 [95% CI 1.1–3.0]), including adjustment for time-varying contraceptive method use when compared to women not using a hormonal contraceptive.²⁰ However, five other studies, also with relatively frequent follow-up assessments, found no significant association. These include: 1) a study of 342 young US women which conducted 3-monthly follow-up visits for a median of 42 months and compared women using DMPA in the current or previous 3-month period to women not reporting DMPA use in those periods; 2) a study among 225 US women with follow-up visits at months 1, 4, 8 and 12 which included 2,058 person-months and compared women reporting DMPA use at any visit to women never reporting DMPA use; 3) a study among 397 Rwandan sex workers that followed women for up to 2 years and compared women reporting DMPA use by follow-up interval to women reporting no hormonal

Table 2 Depot medroxyprogesterone acetate use and risk of STI/BV summary

Study	Reference #	n, population	Design	STI/BV ^a	Estimate adjusted for	Result Estimate (95% CI)
Achilles 2018	43	41 new DMPA users, 44 new NET-EN users, 40 new MPA-EE users, 45 new LNG implant users, 48 new ENG implant users, 48 new Cu-IUD users in Zimbabwe aged 18–35	Prospective observational cohort	BV	Not adjusted	BV prevalence over time following DMPA initiation ($P=0.77$): - Enrollment 29.3% 30 days 30.0% 90 days 31.7% 180 days 30.8%
Borgdorff 2015 ^b	22	397 female sex workers aged 18–49 in Rwanda	Prospective observational cohort	HSV-2, HPV, TV, CT, NG, BV, syphilis	Duration of time since last follow-up, age, educational level, years worked as sex worker, baseline breast-feeding status, consistent condom use, antibiotic use in the past 14 days, ever having used antibiotics before the outcome assessment date	CT incidence: - Injectable use vs not using HC aOR 2.24 (0.69–7.29) NG incidence: - Injectable use vs not using HC aOR 0.80 (0.28–2.31) TV incidence: - Injectable use vs not using HC aOR 0.44 (0.17–1.10) HPV incidence: - Injectable use vs not using HC aOR 0.79 (0.34–1.83) HSV-2 incidence: - Injectable use vs not using HC aOR 6.34 (0.25–158.5) BV incidence: - Injectable use vs not using HC aOR 0.73 (0.32–1.67) Syphilis incidence: - Injectable use vs not using HC aOR 1.43 (0.11–19.1)
Brahmbhatt 2014	24	2,374 women aged 15–49 in Uganda	Prospective observational cohort	TV	Age, education, number of non-marital sex partners in last 12 months, socio-economic status, Nugent score, HIV status, syphilis serology	TV incidence: DMPA use vs no HC/condom use aIRR 0.54 (0.30–0.98), $P<0.05$
Francis 2016	35	1,027 female sex workers aged ≥ 18 in Uganda	Prospective observational cohort	BV	Age, level of education, number of lifetime partners, frequency of condom use with clients, any use of alcohol, intravaginal insertion, HIV, HSV-2, vaginal yeast, TV, NG, syphilis	BV prevalence during follow-up: DMPA use vs no contraceptive use aOR 0.66 (0.50–0.86)
Grabowski 2015	32	682 women aged 21–29 in Uganda	Prospective observational cohort	HSV-2	Age, educational status of female and male partners, number of lifetime sexual partners, male partner circumcision status, coital frequency, self-reported condom use, non-marital partners in past year	Incident HSV-2 incidence: - Discontinued DMPA use vs no HC use aHR 0.58 (0.13–2.51) - Initiated DMPA use vs no HC use aHR 0.75 (0.29–1.92) - Consistent DMPA use vs no HC use aHR 2.26 (1.09–4.69) HSV-2 incidence among women with HSV-2 positive partners: - Discontinued DMPA use vs no HC use aHR 2.42 (0.29–20.1) - Initiated DMPA use vs no HC use aHR 1.42 (0.25–8.08) - Consistent DMPA use vs no HC use aHR 6.23 (1.49–26.3)

(Continued)

Table 2 (Continued)

Study	Reference #	n, population	Design	STI/BV ^a	Estimate adjusted for	Result Estimate (95% CI)
Kapiga 2009	21	958 women at risk of STIs aged 16–62 years in South Africa and Tanzania	Prospective observational cohort	CT, NG, TV, syphilis	Adjustment varies by STI and site	CT incidence by study site: • Durban/Hlabisa injectable use vs no injectable use aOR 1.8 (1.0, 3.3) • Moshi/Lusaka injectable use vs no injectable use OR 1.9 (0.8, 4.4) NG incidence by study site: • Durban/Hlabisa injectable use vs no injectable use OR 0.9 (0.5, 1.4) • Moshi/Lusaka injectable use vs no injectable use OR 0.9 (0.4, 2.0) Syphilis incidence all sites: • injectable use vs no injectable use OR 0.9 (0.5, 1.6) TV incidence all sites: • injectable use vs no injectable use aOR 0.7 (0.5, 1.0)
Marks 2011	28	376 COC users, 331 DMPA users, and 428 NHC users in Thailand	Prospective observational cohort	HPV	Age, study site, number of lifetime sexual partners, cytology, incident vs prevalent HPV infection, and duration of COC and DMPA use	HPV incidence: • DMPA vs NHC aOR 0.90 (0.63, 1.31) HPV clearance: • DMPA vs NHC aHR 0.75 (0.50, 1.13)
Masese 2013	20	865 women aged 18–50 reporting transactional sex in Kenya	Prospective observational cohort	CT	Age, sexual risk behavior, HIV-1 status, presence of candida/TV/NG	CT incidence: • DMPA use vs non-HC use aHR 1.8 (1.1–3.0)
Maucourt-Boulch 2010	31	2,408 women with abnormal or equivocal cervical cytology in the USA	Prospective observational cohort	HPV	Age stratified by prevalence/incidence status group, study center, randomization arm, community cytology interpretation and observed duration of infection	HPV persistence at 6 months: • Injectable user vs not injectable user aOR 1.15 (1.01, 1.32)
McClelland 2008	36	151 Kenyan female sex workers	Prospective observational cohort	BV	Age, vaginal washing frequency, vaginal washing substance, cloth to clean inside vagina, bathing frequency, vaginal lubricant for sex, number of sex partners in the last week, unprotected sex in the last week, new partner in the past month, candidiasis, TV	BV incidence: • DMPA use vs no contraceptive use/tubal ligation aHR 0.59 (0.48–0.73)
Pettifor 2009	40	647 women aged 18–40 in South Africa	Prospective observational cohort	CT, NG, TV, BV	Age, education, and condom use consistency within the past 3 months	CT incidence: • DMPA use vs no HC use aIRR 1.24 (0.80, 1.94) NG incidence: • DMPA use vs no HC use aIRR 1.30 (0.58, 2.98) TV incidence: • DMPA use vs no HC use aIRR 0.35 (0.12, 1.01) BV incidence: • DMPA use vs no HC use aIRR 0.77 (0.56, 1.06)

(Continued)

Table 2 (Continued)

Study	Reference #	n, population	Design	STI/BV ^a	Estimate adjusted for	Result Estimate (95% CI)
Rifkin 2009	42	330 US new users of COC, CVR, patch, DMPA or no hormonal contraceptive (HC)	Historical cohort	BV	Pregnancy in last year, condom use, douched in last month, days since last sexual intercourse, days since last menstrual period, days since first study visit, number of partners in the last 30 days, race, current smoking status at baseline, history of chlamydia and BV	BV diagnosis by type of contraception: • Combined hormone use vs no HC use aOR 0.66 (0.39, 1.10) • Progestin-only use vs no HC use aOR 0.42 (0.20, 0.88)
Romer 2013	39	342 women aged 14–17 in the US	Prospective observational cohort	CT, NG, TV	DMPA use during the diary period, DMPA use during previous 3-month period, age, positive STI test at start of diary period, number of lifetime sexual partners, number of sexual partners in past 3 months, number of sexual events and number of unprotected sexual events during diary period	Incident CT: • DMPA use in current period vs no DMPA use in current period aOR 0.76 (0.45, 1.31) • DMPA use in previous period vs no DMPA use in previous period aOR 1.17 (0.69, 1.96) Incident NG: • DMPA use in current period vs no DMPA use in current period aOR 1.19 (0.57, 2.48) • DMPA use in previous period vs no DMPA use in previous period aOR 1.12 (0.54, 2.32) Incident TV: • DMPA use in current period vs no DMPA use in current period aOR 0.66 (0.32, 1.36) • DMPA use in previous period vs no DMPA use in previous period aOR 1.04 (0.52, 2.08)
Russell 2016	19	225 women aged 15–35 with NG/CT or male partner treated for NG/CT in the USA	Prospective observational cohort	CT	Age, education, NG infection during follow-up, site of CT infection at enrollment, partner STI infection during follow-up, number sex partners, new sex partner(s) since last visit, recent sex with uncircumcised male, sex during last menstrual period	CT incidence: • DMPA use vs no DMPA use aHR 1.03 (0.59, 1.78)
Shew 2015	30	146 adolescent women aged 14–17 in the USA	Prospective observational cohort	HPV	CT, NG, TV, number of sex partners in the last 3 months, new sex partner in the last 3 months, unprotected coital event last 3 months, COC use in last 3 months	All HPV type redetection: • DMPA use last 3 months vs no DMPA use last 3 months aHR 0.96 (0.67, 1.38) High risk HPV type redetection: • DMPA use last 3 months vs no DMPA use last 3 months aHR 0.80 (0.54, 1.19) Low HPV type redetection: • DMPA use last 3 months vs no DMPA use last 3 months aHR 1.57 (0.90, 2.75)
Socias 2017	41	149 sex workers aged ≥14 in Canada	Prospective observational cohort	HSV-2	Primary place of servicing clients	Incident HSV-2: • DMPA use in past 6 months vs no report of DMPA use past 6 months aHR 4.43 (1.90, 10.35)

(Continued)

Table 2 (Continued)

Study	Reference #	n, population	Design	STI/BV ^a	Estimate adjusted for	Result Estimate (95% CI)
Van de Wijgert 2013	38	6,109 women aged 18–35 using COCs, DMPA or no hormonal contraception in Thailand, Uganda and Zimbabwe	Prospective observational cohort	BV	Adjusted but final model not specified	Incident/prevalent BV: • DMPA vs no hormonal contraceptive use 0.82 (0.77, 0.87)

Notes: ^aResearch articles may have included infections other than those listed; however, our review extracted only information for CT, NG, TV, HSV-2, HPV and BV.

^bAuthors report injectable type was not documented but noted that most family planning programs in Rwanda mostly offer DMPA and only occasionally NET-EN.

Abbreviations: STI, sexually transmitted infection; CT, *C. trachomatis*; NG, *N. gonorrhoeae*; TV, *T. vaginalis*; aHR, adjusted hazard ratio; HSV-2, herpes simplex virus-2; HPV, human papilloma virus, BV, bacterial vaginosis; DMPA, depot medroxyprogesterone acetate; NET-EN, norethisterone enanthate; MPA-EE, medroxyprogesterone acetate-ethinyl estradiol; LNG, levonorgestrel; ENG, etonogestrel; Cu-IUD, copper intrauterine device; HC, hormonal contraceptive; aOR, adjusted odds ratio; COC, combined oral contraceptives; aIRR; ECC, estrogen-containing contraceptive; NHC, non-hormonal contraceptive.

contraceptive use; 4) a study among 958 Tanzanian, Zambian and South African women followed monthly for 1 year; and 5) a study among 567 South African family planning clinic attendees.^{19,21,22,39,40}

Gonorrhea

We identified four studies which evaluated gonorrhea as an outcome, all of which identified no significant association. The aforementioned study of 342 young US women found no association between DMPA use and incident *N. gonorrhoeae* infection as compared to non-DMPA users.³⁹ Similarly, the studies among Rwandan sex workers, Tanzanian, Zambian, and South African women and South African family planning clinic attendees found no significant association between DMPA use and incident *N. gonorrhoeae*.^{21,22,40}

Trichomoniasis

We identified five studies which evaluated trichomonas as an outcome. Three of these studies identified no significant association with DMPA use, including the study of 342 young US women, the study of 397 Rwandan sex workers and the study of 567 South African family planning clinic attendees.^{21,22,39,40} However, the study among 2,374 Ugandan women and the study of 958 Tanzanian, Zambian, and South African women found significantly decreased risk of *T. vaginalis* incidence among DMPA users (aIRR 0.54, [95% CI 0.30–0.98] and OR 0.6 [95% CI 0.4, 0.8], respectively).²⁴

Human papillomavirus

Four studies analyzed the association between DMPA use and incident HPV infection and/or HPV persistence; three of these studies identified no association and one identified a marginally significant association. One prospective study, which evaluated HPV incidence and persistence

among 1,135 Thai COC, DMPA and NHC users followed up every 6 months for 18 months, found that DMPA use, as compared to NHC use, was not significantly associated with incident HPV infection or clearance of prior infection in adjusted analyses.²⁸ Similarly, a smaller study among 146 US young women, followed for an average of 5.8 years, found no association between DMPA use in the prior 3 months and HPV re-detection.³⁰ The study among 397 Rwandan sex workers also found no association between DMPA use and incident HPV.²² However, another study among 2,408 women with baseline HPV infection and cytological abnormalities followed up every 6 months for 2 years found that injectable contraceptive use was marginally significantly associated with HPV persistence relative to no injectable contraceptive use (aOR 1.5 [95% CI 1.01–1.32]).³¹

Herpes simplex virus type 2

Three of the included studies evaluated the association between DMPA use and HSV-2.^{22,32,41} The study among Rwandan sex workers found no association, though the total number of DMPA users was small, which may have limited study power. Two larger studies identified significant increases in HSV-2 incidence among DMPA users. A study among 682 women in Uganda found increased risk of HSV-2 acquisition (aHR 2.26, [95% CI 1.09, 4.69]) as compared to women who were not using hormonal contraceptive and were not pregnant. A sensitivity analysis among women with known HSV-2 positive partners strengthened the conclusion with an observed aHR of 6.23 (95% CI 1.49, 26.3) among consistent DMPA users. A second study among 149 Canadian female sex workers with a median follow-up period of 19 months found significantly higher HSV-2 incidence among DMPA users (aHR 4.43 [95% CI 1.90, 10.35]).⁴¹

Bacterial vaginosis

Four of seven studies which reported on the association between BV and DMPA found significantly reduced BV detection among women using DMPA. A study among 330 US women attending STI clinics, 105 of which used DMPA at least once during the study period, found DMPA to be protective against BV diagnosis as compared to NHC (aOR 0.42 [95% CI 0.20–0.88]).⁴² A second large study among 1,027 Ugandan sex workers followed over 24 months, among which 1,309 visits were during reported DMPA use, also found DMPA use to be associated with a reduction in BV (aOR 0.66, [95% CI 0.50, 0.86]).³⁵ Notably, the Ugandan cohort was at high risk of BV as evidenced by high baseline (56%) and follow-up (54%–63%) BV prevalence. Another study among sex workers in Kenya also found DMPA use to be associated with reduced BV prevalence (aHR 0.60, [95% CI 0.48, 0.74]).³⁶ Lastly, the large study among 6,109 women in Zimbabwe, Uganda and Thailand, also observed a protective association (aHR 0.82, [95% CI 0.77, 0.87]) as compared to women not using hormonal contraception.³⁸ Three other studies found no significant change in BV – one which followed 41 new DMPA users for 6 months, another which followed 397 Rwandan sex workers and controlled for time-varying contraceptive use for up to 2 years, and another which followed 567 South African family planning clinic attendees for 1 year.^{22,40,43}

Syphilis

Only two of the included studies – the aforementioned studies of 958 South African/Zambian/Tanzanian women and 397 Rwandan sex workers – evaluated the association between DMPA use and *T. pallidum* and found no significant association.^{21,22}

DMPA summary

We found no evidence of any association between the use of DMPA and the risk of gonorrhea or syphilis. A single study among Kenyan women did find a significant association between DMPA use and increased *C. trachomatis* infection, whereas two US-based studies found no association. This may suggest a potential for population-level differences in risk associated with DMPA use. Two studies identified a decreased risk of *T. vaginalis* infection with DMPA use; while one did not control for potential confounding variables, the study conducted among 2,374 Rwandan women was large and controlled for time-varying contraceptive use as well as other important variables. The available evidence suggests no association between DMPA use and HPV infection, though one study did identify a marginally significant increased risk of HPV persistence among injectable contraceptive users. In

regards to HSV-2, one study found no association while two large studies found significantly increased risk of HSV-2 with DMPA use. The large study size and robust sensitivity analyses in the study by Grabowski et al³² provides supporting evidence to a positive association between risk of HSV-2 and DMPA use. Lastly, though there are studies that show both no and negative associations with BV, the weight of the evidence, particularly as evidenced by studies with large sample sizes, suggests that DMPA use is associated with a reduced risk of BV. Notably, several of the studies which identified protective effects were among women at high risk of STI, suggesting that any true protective effect may be population-specific, or may not have been detected in other studies due to overall low risk of BV among the study population.

Levonorgestrel intrauterine systems and copper intrauterine devices

We identified eleven studies which evaluated the association between the LNG-IUS and/or the Cu-IUD and chlamydia, gonorrhea, trichomoniasis, HPV and BV; we did not identify any published studies that met our inclusion criteria which evaluated IUD use and HSV or syphilis. Summary data are provided in Table 3.

Chlamydia

We identified one study that compared chlamydia diagnoses before and 1 year after insertion of an LNG-IUS (n=42) and the Cu-IUD (n=108) in Turkey.⁴⁴ No chlamydia infections were identified in either group either before or after IUD insertion.

Gonorrhea

The same study conducted in Turkey also evaluated the incidence of gonorrhea among women before and after insertion of an LNG-IUS (n=42) and the Cu-IUD (n=108).⁴⁴ Again, no gonococcal infections were identified in either group either before or after IUD insertion.

Trichomoniasis

We identified three studies that evaluated trichomoniasis among LNG-IUS and Cu-IUD users. The aforementioned Turkish study found no trichomoniasis among either group before or after IUD/IUS insertion.⁴⁴ A second previously described study conducted among 194 LNG-IUS users in Egypt again found no significant difference in *T. vaginalis* infection between LNG-IUS and COC users.²³ Additionally, in a study among 187 new LNG-IUS users in Brazil, no significant alteration in TV was found over 7 years following insertion ($P=0.67$).⁵⁰

Table 3 Copper intrauterine devices and levonorgestrel intrauterine systems and risk of STI/BV summary

Study	Reference #	n, population	Design	STI/RTIa	Estimate adjusted for	Result Estimate (95% CI)
Achilles 2018	43	41 new DMPA users, 44 new NET-EN users, 40 new MPA-EE users, 45 new LNG implant users, 48 new ENG implant users, 48 new Cu-IUD users in Zimbabwe aged 18–35	Prospective observational cohort	BV	Not adjusted	BV prevalence over time following Cu-IUD initiation) ($P=0.005$): - Enrollment 27.1% 30 days 35.4% 90 days 39.6% 180 days 48.9%
Alice 2012	46	38 new Cu-IUD users and 32 new LNG-IUS users aged 18–48 in the US	Prospective observational cohort	BV	Not adjusted	Overall BV prevalence: 9% (4 of 43 tested) at month 1 Note: no analyses by IUD/IUS type were conducted.
Donders 2018	49	252 new LNG-IUS users in Belgium	Prospective observational cohort	BV	Not adjusted	BV prevalence before and after insertion: - Before insertion 7.8% 3 months post-insertion 14.0% 1-year post-insertion 4.8% 5-years post-insertion 7.4%
Erol 2014	44	108 new Cu-IUD users and 42 new LNG-IUS users in Turkey	Prospective observational cohort	BV, CT, TV, NG	Not adjusted	BV prevalence at 1 year post insertion: - LNG-IUS $n=3/42$ (7.1%) vs Cu-IUD $n=5/108$ (4.6%), $P=0.537$ - No significant differences in BV prevalence within groups before vs after IUD insertion Note: No CT, TV or NG infections observed.
Lessard 2008	50	187 new LNG-IUS users in Brazil	Prospective observational cohort	BV, TV	Not adjusted	- No significant difference in BV over 7 years of LNG-IUS use ($P=0.65$) - No significant difference in TV over 7 years of LNG-IUS use ($P=0.67$)
Lekovich 2015	45	150 new Cu-IUD and 152 new LNG-IUS users in the USA	Retrospective cohort	HPV	Not adjusted	Incident high-risk HPV after insertion: - Cu-IUD 1.7% vs LNG-IUS 6.9%, $P=0.056$ Persistent high-risk HPV after insertion: - Cu-IUD 30% vs LNG-IUS 58%, $P=0.02$ Clearance of high-risk HPV after insertion: - Cu-IUD 70% vs LNG-IUS 42%, $P=0.04$
Madden 2012	47	90 new IUD users, 59 new LNG-IUS users, 31 new Cu-IUD users and 63 new COC/ring/patch users aged 18–45 in the USA	Prospective observational cohort	BV	Age, race, condom use over the study period, douching in the 6 months before enrollment, baseline intermediate flora, irregular bleeding, and IUD use	BV incidence by contraceptive method, not adjusted: - IUD 37.0% vs COC/CVR/patch 19.3%, HR 2.18 (1.04, 4.54) $P=0.03$ BV incidence by IUD use, adjusted: - IUD use vs non-use aHR 1.19 (0.48, 2.92)
McClelland 2008	36	151 female sex workers in Kenya (number of IUD users and type of IUD not specified)	Prospective observational cohort	BV	Age, vaginal washing frequency, vaginal washing substance, cloth to clean inside vagina, bathing frequency, vaginal lubricant for sex, number of sex partners in the last week, unprotected sex in the last week, new partner in the past month, candidiasis, TV	BV incidence: IUD use vs no contraceptive use/tubal ligation aHR 1.59 (0.74, 3.40)

(Continued)

Table 3 (Continued)

Study	Reference #	n, population	Design	STI/ RTIa	Estimate adjusted for	Result Estimate (95% CI)
Neale 2009	48	78 new Cu-IUD and 94 LNG-IUS in the UK	Prospective observational cohort	BV	Not adjusted	BV prevalence 4–6 weeks post-insertion: • Cu-IUD vs LNG-IUS OR 2.86 (0.25–32.39) BV prevalence 6 months post-insertion: • Cu-IUD vs LNG-IUS OR 2.73 (0.44–17.02)
Rezk 2017	23	236 new COC users and 194 new LNG-IUS users in Egypt	Prospective observational cohort	TV, BV	Not adjusted	BV: COC vs LNG-IUS • at 6 weeks OR 1.25 (0.79, 1.98) • at 6 months OR 1.16 (0.70, 1.91) • at 12 months OR 1.41 (0.80, 2.48) TV: COC vs LNG-IUS • at 6 weeks OR 0.91 (0.46, 1.76) • at 6 months OR 0.69 (0.31, 1.53) • at 12 months OR 0.82 (0.30, 2.22)
Stensen 2016	29	2,874 women with high-risk HPV in Denmark	Prospective observational cohort	HPV	Age and time between samples	High risk HPV persistence 2.5 years before baseline: • LNG-IUS vs not current use aOR 1.08 (0.56, 1.98) High risk HPV persistence 1 year after baseline: • LNG-IUS current vs not current use aOR 1.32 (0.75, 2.27)

Notes: *Research articles may have included infections other than those listed; however, our review extracted only information for CT, NG, TV, HSV, HPV and BV.

Abbreviations: STI, sexually transmitted infection; RTI, reproductive tract infection; CT, *C. trachomatis*; NG, *N. gonorrhoeae*; TV, *T. vaginalis*; aHR, adjusted hazard ratio; HSV-2, herpes simplex virus-2; HPV, human papilloma virus, BV, bacterial vaginosis; DMPA, depot medroxyprogesterone acetate; NET-EN, norethisterone enanthate; MPA-EE, medroxyprogesterone acetate-ethinyl estradiol; LNG, levonorgestrel; LNG-IUS, levonorgestrel intrauterine system; ENG, etonogestrel; Cu-IUD, copper intrauterine device; aOR, adjusted odds ratio; COC, combined oral contraceptives.

Human papillomavirus

We identified two studies that considered HPV acquisition, persistence and/or clearance among Cu-IUD and LNG-IUS users. A US study followed 150 new Cu-IUD users and 152 new LNG-IUS users. At a 1-year follow-up there were two (1.7%) new HR-HPV infections in the Cu-IUD group compared with 8 (6.9%) in the LNG-IUS group ($P=0.06$).⁴⁵ Clearance of HR-HPV infections was significantly higher in the Cu-IUD group (70% [95% CI 53.6–86.4]) than in the LNG-IUS group (42% [95% CI 25.6–57.8]). A Danish study of type-specific persistence of HR-HPV found that neither LNG-IUS use prior to baseline nor during the 1-year period after baseline resulted in increased HPV persistence.²⁹

Bacterial vaginosis

We identified nine studies that examined LNG-IUS and Cu-IUDs and the prevalence, incidence and/or persistence of bacterial vaginosis; eight of these studies found no significant association. In a study conducted among women

in Zimbabwe, BV prevalence significantly increased in women initiating Cu-IUD use from 27% at baseline, to 35% at 30 days, 40% at 90 days, and 49% at 180 days ($P=0.005$ compared to prevalence at enrollment).⁴³ Another study among 70 Canadian women found 9% BV incidence at 1 month (4/43 women BV negative at enrollment) following IUD placement (either Cu-IUD or LNG-IUS), though no comparisons were done between women using the Cu-IUD or LNG-IUS, and BV history among those women is not reported.⁴⁶ Among the 153 US women who were BV-negative at baseline in a sub-study of the CHOICE study, no significant association was observed.⁴⁷ Among 78 new Cu-IUD users and 94 LNG-IUS users, Neale et al⁴⁸ observed no significant differences in BV at 1 month or 6 months post-insertion between Cu-IUD and LNG-IUS users. Among 252 new LNG-IUS users in Belgium, Donders et al⁴⁹ found no significant differences in BV pre-insertion to 3-months, 1-year and 5-years after insertion. Similarly, Lessard et al⁵⁰ found no difference in BV prevalence over 7 years of LNG-IUS use. Rezk et al²³ reported no significant

difference in BV between LNG-IUS and COC users during follow-up, as did McClelland et al,³⁶ though the type of IUD used, and the number of IUD users during follow-up, was not specified but is presumed to be low based on the small number of IUD users at baseline (n=2). Finally, in the aforementioned Turkish study, there were no significant differences in BV rates before vs 1 year after insertion for 108 new Cu-IUD users and 42 new LNG-IUS users as well as no difference in BV detection at 1 year between the two IUD groups.⁴⁴

Levonorgestrel IUS and the copper IUD: summary

The available data on the association between Cu-IUD and LNG-IUS use and chlamydia, gonorrhea and trichomoniasis are sparse, but suggest no significant association. The data on IUD use and HPV acquisition and persistence are mixed, with one study suggesting somewhat higher HPV acquisition and persistence among LNG-IUS users than Cu-IUD users, while another study suggested no significant difference in HPV persistence associated with the LNG-IUS compared with non-users, a majority of whom used COCs.^{29,45} Eight of nine studies which evaluated BV incidence, recurrence and/or persistence found no significant association, with only one study reporting increasing BV over 6 months following Cu-IUD insertion. Additionally, although several studies did not differentiate between Cu-IUD and LNG-IUS users, those that did suggest no difference in BV between the two types of IUDs.

Other contraceptive methods

We identified few studies which evaluated the use of other contraceptive methods and risk of STI; we therefore collapsed the findings by method only below, rather than by STI. Summary data are provided in Table 4.

Contraceptive vaginal ring and patch (combined estrogen + progestin)

We identified three studies that examined the association between combined CVR and STI/BV risk. A phase III study of combined Nestorone and ethinyl estradiol (EE) CVR enrolled 120 US women and found no significant differences in BV or *T. vaginalis* detection at ring use cycles six or 13 as compared to baseline (prior to CVR insertion).⁵¹ Similarly, in the Italian study among 60 new COC and CVR containing desogestrel and EE users, there were no significant differences in incident BV or intermediate vaginal flora over 6 months between the two groups.³³

Lastly, in the previously referenced CHOICE sub-study, there were no significant differences in BV incidence among etonogestrel/EE CVR users as compared to women using COCs or the contraceptive patch containing norelgestromin and EE.⁴⁷

Implant (progestin-only)

We identified five prospective studies that examined the association between progestin-only implant use and STI acquisition. One each evaluated Norplant use and HPV persistence and BV and found no association.^{31,36} However, a study among Ugandan women found that Norplant use was associated with a significantly higher rate of trichomonas as compared to women not using hormonal contraception or condoms (aIRR 3.01, [95% CI 1.07–8.49]).²⁴ A study conducted in South Africa, Tanzania and Zambia found increased risk of gonorrhea (OR 5.3, [95% CI 1.4–19.8]) but no significant increased risk of syphilis among Norplant users.²¹ Lastly, a study which evaluated BV prevalence over time among new initiators of the ENG and LNG-IUS implants found no significant associations.⁴³

Other injectables

The study among 567 South African family planning clinic attendees found no significant association between NET-EN and chlamydia, gonorrhea, trichomonas or BV over time when considering only incident infections.⁴⁰ However, when considering all cases of BV, including positive results followed by a previous positive result, NET-EN showed a protective effect (IRR 0.78 [95% CI 0.64–0.94]). A second study among 266 Zimbabwean women, 44 of whom used NET-EN and 40 who used MPA-EE, found no significant associations.^{40,43}

Other contraceptive methods: summary

The data on other contraceptive methods and STI/BV are sparse. Nevertheless the existing evidence suggests no increased risk of trichomonas or BV among users of the CVR and patch (combined estrogen+progestin). Studies of progestin only implants have generally found no association between implants (primarily Norplant) and BV, HPV or syphilis. However, one study each found increased risks of trichomonas and gonorrhea among implant users. The use of other injectables, primarily NET-EN, are sparse with only one study evaluating chlamydia, gonorrhea and trichomonas, and two evaluating BV with mixed results.

Table 4 Other contraceptive methods and risk of STI/BV summary

Study	Reference #	n, population	Design	STI/RTIa	Estimate adjusted for	Result Estimate (95% CI)
Achilles 2018	43	41 new DMPA users, 44 new NET-EN users, 40 new MPA-EE users, 45 new LNG implant users, 48 new ENG implant users, 48 new Cu-IUD users in Zimbabwe aged 18–35	Prospective observational cohort	BV	Not adjusted	BV prevalence over time following NET-EN initiation ($P=0.34$): • Enrollment 40.9% • 30 days 38.6% • 90 days 40.9% • 180 days 46.3% BV prevalence over time following MPA-EE initiation ($P=0.21$): • Enrollment 30.0% • 30 days 35.0% • 90 days 35.0% • 180 days 38.9% BV prevalence over time following LNG implant initiation ($P=0.27$): • Enrollment 35.6% • 30 days 35.6% • 90 days 42.2% • 180 days 39.5% BV prevalence over time following ENG implant initiation ($P=0.97$): • Enrollment 25.0% • 30 days 22.9% • 90 days 25.0% • 180 days 36.2%
Brahmbhatt 2014	24	2,374 sexually active women aged 15–49 in Uganda	Prospective observational cohort	TV	Age, education, number of non-marital sex partners in last 12 months, socio-economic status, Nugent score, HIV status, syphilis serology	TV incidence and implant use • Implant use vs no HC/condom use aIRR 3.01 (1.07–8.49)
De Seta 2012	33	30 new COC users and 30 new CVR users aged 18–45 in USA	Prospective observational cohort	TV, BV	Not adjusted	No significant difference in BV between CVR and COC users over 6 months' follow-up (no effect estimate provided). No trichomoniasis infections were identified in either group
Huang 2015	51	120 women aged 18–40 years in the USA	Phase II study of a nesterone/ethinyl estradiol contraceptive vaginal ring	BV	Not adjusted	BV diagnosis during follow-up: • 3.3% (0.9, 8.3%)
Kapiga 2009	21	958 women at risk of STIs aged 16–62 years in South Africa and Tanzania	Prospective observational cohort	CT, NG, TV, syphilis	Adjustment varies by STI and site	NG incidence in Moshi/Lusaka: • Norplant use vs no Norplant use aOR 4.7 (1.3, 16.5) Syphilis incidence all sites: • Norplant use vs no Norplant use OR 1.7 (0.3, 10.9)
McClelland 2008	36	151 female sex workers in Kenya	Prospective observational cohort	BV	Age, vaginal washing frequency, vaginal washing substance, cloth to clean inside vagina, bathing frequency, vaginal lubricant for sex, number of sex partners in the last week, unprotected sex in the last week, new partner in the past month, candidiasis, TV	BV incidence: • Norplant use vs no contraceptive use/tubal ligation aHR 0.89 (0.60, 1.30)

(Continued)

Table 4 (Continued)

Study	Reference #	n, population	Design	STI/RTIa	Estimate adjusted for	Result Estimate (95% CI)
Madden 2012	47	90 new IUD users, 59 new LNG-IUS users, 31 new Cu-IUD users and 63 new COC/ring/patch users, US women aged 18–45	Prospective observational cohort	BV	Age, race, condom use over the study period, douching in the 6 months before enrollment, baseline intermediate flora, irregular bleeding, and IUD use	BV incidence by contraceptive method, not adjusted: • COC 15.0% vs CVR 16.7% vs patch 22.4%, $P=0.24$
Maucourt-Boulch 2010	31	2,408 women with abnormal or equivocal cervical cytology in the USA	Prospective observational cohort	HPV	Age stratified by prevalence/incidence status group, study center, randomization arm, community cytology interpretation and observed duration of infection	HPV persistence at 6 months: • Norplant users vs non-Norplant users aOR 1.20 (0.75, 1.95)
Pettifor 2009	40	647 women aged 18–40 in South Africa	Prospective observational cohort	CT, NG, TV, BV	Age, education, and condom use consistency within the past 3 months	CT incidence: • NET-EN use vs no HC use 0.91 (0.59, 1.43) NG incidence: • NET-EN use vs no HC use 1.11 (0.55, 2.25) TV incidence: • NET-EN use vs no HC use 0.63 (0.30, 1.29) BV incidence: • NET-EN use vs no HC use 0.92 (0.70, 1.18)

Notes: ^aResearch articles may have included infections other than those listed; however, our review extracted only information for CT, NG, TV, HSV, HPV and BV.

Abbreviations: STI, sexually transmitted infection; CT, *C. trachomatis*; NG, *N. gonorrhoeae*; TV, *T. vaginalis*; aHR, adjusted hazard ratio; HSV-2, herpes simplex virus-2; HPV, human papilloma virus; BV, bacterial vaginosis; DMPA, depot medroxyprogesterone acetate; NET-EN, norethisterone enanthate; MPA-EE, medroxyprogesterone acetate-ethinyl estradiol; LNG, levonorgestrel; LNG-IUS, levonorgestrel; ENG, etonogestrel; Cu-IUD, copper intrauterine device; CVR, contraceptive vaginal ring; HC, hormonal contraceptive; aOR, adjusted odds ratio; COC, combined oral contraceptives; aIRR

Discussion

Overall quality of the evidence

The overall evidence on the association between contraceptive use and STI/BV risk is highly limited by the lack of any randomized trials, few published prospective studies originally designed to analyze this association, wide variability in exposure definitions and comparator groups, potential mismeasurement of self-reported exposure, potential for confounding by inaccurate sexual behavior data and differential confounder adjustment and differences in study populations and sizes.

A major limitation in the comparability of study findings is wide variability in exposure definitions and comparator/reference groups. Exposure classifications range by method type, mode of delivery, hormones contained within, and timing and duration of exposure. In addition, while some studies limit exposure misclassification by employing statistical methods to allow for time-varying contraceptive use, others risk misclassification by defining exposure at baseline only. Similarly, we identified multiple methods of establishing

comparator groups. The most robust method we identified formed discrete time-varying exposure groups by the majority method used during defined and frequent study intervals, whereas other studies used less robust methods, allowing participants to be simultaneously classified in more than one exposure group. This approach results in the formation of comparator groups with different memberships depending on the contraceptive exposure under analysis. Other studies compared women using a specific method to all other women in the analysis, thus allowing the comparator group to consist of a group of women using various methods. Lastly, we excluded several studies due to lumping of contraceptive methods (eg, hormonal vs non-hormonal) which precludes ascertainment of associations between specific contraceptive methods and STI/BVs. Overall, our assessment is that the number of exposure type/timing/duration classification permutations are effectively equivalent to the number of published studies, significantly limiting the comparability of findings and thus the ability to draw robust conclusions from the published evidence base.

In addition to differences in handling of exposure data during the analysis process, concerns about inaccuracy of self-reported hormonal contraceptive (HC) use have recently emerged.^{52,53} Achilles et al⁵² found that 27% of participants reporting no contraceptive use at study enrollment had laboratory evidence of recent HC use inconsistent with their self-report, and 36% of study participants had evidence of HC use which they had not reported during follow-up. Only one of the studies we included in this review included objective assessment of contraceptive use (ie, measurement of specific synthetic hormones). Similarly, in an analysis of 1,102 specimens from 664 African women, Pyra et al⁵³ found that 14% of women reporting no hormonal contraceptive use had detectable exogenous hormones in serum, and varying levels of discordance by reported specific contraceptive method use. Thus, the potential for exposure misclassification is of concern in this body of literature, though may be less of an issue for methods such as the IUD and implant which are not subject to daily dosing and/or routine injections.

None of the studies we evaluated randomized women to different contraceptive methods, and users of different contraceptive methods may differ in ways that are directly, or indirectly, related to the risk of STI/BV in terms of number of sexual partners, frequency of sex, sexual networks and condom use. While most studies included in this review reported adjusted risk estimates, with attempted control of sexual behavior variability, multiple studies have demonstrated self-reported sexual behavior data to be partially inaccurate.^{54–56} Thus, even in the context of robust study design and employment of rigorous analytic approaches, uncontrolled and/or residual confounding may still bias the results due to inaccurate self-reported behavior by study participants.

Lastly, differences in study populations, study size and differential control of confounding variables also reduce the comparability of study results and evidence base. Few studies identified reported a priori power calculations, and many of the studies were of small sample size; these studies may have thus failed to detect true differences in STI/BV risk. Moreover, recent studies have demonstrated important population differences in vaginal mucosal immunologic factors and flora, suggesting that populations may have differential risk of STI/BV, and therefore also potential different risk associated with the use of contraceptives.^{57,58}

Combined oral contraceptives

The evidence for COC use and incident STI remains inconclusive, consistent with the findings reported in prior systematic reviews.^{14,15} We identified four studies which evaluated risk

of chlamydia. Russell et al¹⁹ identified no association with incident *C. trachomatis* infection and COC use. They collected contraceptive use data at each follow-up visit and were therefore able to control for time-varying exposure. Additionally, *C. trachomatis* nucleic acid amplification testing (NAAT) was conducted at months 1, 4, 8 and 12 following enrollment, providing a robust measure of outcome ascertainment. The study by Kapiga et al²¹ followed women monthly with high retention rates and found no association; however, it is unclear whether women were analyzed by their baseline contraceptive method or method switching was considered in analyses. Similarly, the study by Masese et al²⁰ followed women monthly and found no association, but again, it is unknown whether contraceptive method switching was taken into account. The study by Borgdorff et al²² reported control of time-varying contraceptive method and found a statistically and clinically significant increased risk of chlamydia with COC use. Given these conflicting results and study designs, we cannot assess whether the differential findings are due to methodological, analytic and/or population differences. The two studies which evaluated COC use and gonorrhea, four which evaluated trichomonas, and two which evaluated HSV-2, suggest no association. We identified more studies (n=8) evaluating COC use and HPV infection; however, the ability to draw definitive conclusions is limited by several factors. While the cohorts in the reported studies are relatively large, many studies have coarse measures of COC use, and there is variability in COC measurement across all included studies. The study by Louvanto et al²⁵ found that women who initiated COC use at less than 20 years of age had 1.3 times the risk of HPV types 7 or 9; however, women initiating contraception early also represent a population that may be initiating sex earlier, and therefore have an inherently higher lifetime risk of HPV. Similarly, the study by Goodman et al found a significantly reduced risk of BV recurrence among COC users.²⁶ Similarly, Goodman et al²⁶ observed decreasing HPV incidence to be associated with years of COC use. The analysis however only adjusted for age at study entry, leaving open the potential for confounding by other important predictors. The results from published studies on BV risk associated with COC use are weighted toward no association (6 of 8 studies). Among those which found no association, sample sizes were notably smaller, and one specifically noted the inability to enroll the target sample size to achieve planned power, whereas Bradshaw et al³⁷ – who identified reduced risk of BV in COC users – had a comparatively larger sample size. Again, as with the evidence on risk of HPV infection among COC users, the comparability of the evidence is highly limited due to differences in comparator groups, variability in outcome

definitions, varying intervals between outcome measurements and differential confounder control.

DMPA

Similar to the evidence on COC use, there is minimal new evidence on the association between DMPA use and risk of STI/BV. A single study suggests that DMPA use may result in increased risk of *C. trachomatis* infection among Kenyan women, but there is no evidence of increased risk in five other studies. Many of these studies included routine laboratory testing among all cohort participants for *C. trachomatis* infection, and thereby had robust methods for outcome ascertainment. There is no evidence of an association between DMPA use and risk of gonorrhea and syphilis, and mixed evidence suggesting a possible decreased risk of trichomonas among DMPA users. These findings are fairly consistent with prior systematic reviews which concluded a possible association between DMPA and *C. trachomatis* and no evidence of an association with *N. gonorrhoeae* or *T. vaginalis*.^{14,15} The absence of evidence may thus represent a true null effect, or simply lack of sufficient data. While there were more studies on DMPA use and HPV risk, the inconsistency in endpoint definition – ie, any HPV infection, any HR-HPV infection, and re-detection – in addition to differences in exposure classification groups and confounder control, significantly limits the comparability of results. Nonetheless, the weight of the evidence does not suggest an association between contraceptive use and HPV infection at this time. Two new large studies, both of which accounted for contraceptive method switching in analyses, found statistically and clinically significant increases in HSV-2 incidence among DMPA users.^{32,41} The study by Grabowski et al³² included a sensitivity analysis among women with known HSV-2 positive partners which supported the primary finding. The strong associations observed, along with other robust evidence of HSV-2 being a risk factor for subsequent HIV infection, warrants concern and further investigation into this potential association. We identified seven new studies which evaluated the DMPA-BV association, among which four observed a decreased risk of BV among DMPA users. These findings are consistent with the results of prior studies on this topic, including a 2013 systematic review which concluded that COCs and DMPA reduce the prevalence and incidence of BV in women, though the overall results among studies remain mixed.³⁸

Intrauterine devices

Overall, there are fewer studies which have evaluated the association between IUD use and STI/BV risk as compared

to COCs and DMPA. The available new data on the effect of Cu-IUD and LNG-IUS on the acquisition of chlamydia, gonorrhea and trichomoniasis suggests no increased risk for any STI associated with either device, though the data are sparse. The data related to HPV acquisition and persistence are similarly sparse, with one study suggesting somewhat higher HPV acquisition and persistence among LNG-IUS users than Cu-IUD users, while another study suggested no statistically significant increased HPV persistence between LNG-IUS users compared with non-users.^{29,45} The majority of the evidence related to the relationship between Cu-IUD and BV suggests no association between BV and Cu-IUD or LNG-IUS use. However, one well-designed study (among nine identified studies) did observe increased BV levels following Cu-IUD use. Additionally, most current studies comparing the two IUDs have found no difference in BV detection rates when comparing users of the different IUD types, and when comparing IUD users (both Cu-IUD and LNG-IUS) to women using combined estrogen-progestin containing contraceptives (COCs, rings, patches).

Other methods

There is no evidence of any association between use of the contraceptive ring or patch and STI/BV, though the data are very sparse. Studies on STI/BV risk among implant and other injectable users are also sparse with mixed results and not sufficiently comparable to draw firm conclusions.

Conclusion

In conclusion, the evidence base for the association between contraceptive use and STI/BV risk remains highly limited. Prospective studies with the primary objective of understanding STI/BV incidence and persistence as a result of hormonal contraceptive are needed. Randomization to contraceptive method would minimize bias associated with method self-selection, though it is unlikely that funding for randomized controlled trials (RCT) will become available. In the absence of an RCT, additional prospective studies with clear exposure measurement are needed. Validation of participant self-reported contraceptive use with systemic exogenous hormonal levels is recommended. Systematic lab-based outcome (STI/BV) testing should be done during follow-up with clear methods to differentiate prevalent vs incident infection. Lastly, measurement of potential confounders (including but not limited to race/ethnicity, location/geography, sexual behavior, other STI/BV diagnoses and concomitant medication use) should be measured during follow-up at multiple timepoints, and appropriate methods

for inclusion of confounders in statistical models defined a priori. Such robust studies are needed to provide women and providers accurate information, and thereby facilitate fully informed contraceptive choice by women.

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Author contributions

JD managed the overall writing process; all authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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