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Hormonal contraceptive use and risk of sexually transmitted infections: a systematic review

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Abstract

Previous research has suggested that hormonal contraceptive users, compared with nonusers, may be at increased risk for acquiring sexually transmitted infections (STIs). We searched the MEDLINE and EMBASE databases for all articles from January 1966 through February 2005 for evidence relevant to all hormonal contraceptives and STIs (including cervical chlamydial and gonococcal infection, human papillomavirus, trichomoniasis, herpes and syphilis). We used standard abstract forms and grading systems to summarize and assess the quality of 83 identified studies. Studies of combined oral contraceptive and depot medroxyprogesterone use generally reported positive associations with cervical chlamydial infection, although not all associations were statistically significant. For other STIs, the findings suggested no association between hormonal contraceptive use and STI acquisition, or the results were too limited to draw any conclusions. Evidence was generally limited in both amount and quality, including inadequate adjustment for confounding, lack of appropriate control groups and small sample sizes. The observed positive associations may be due to a true association or to bias, such as differential exposure to STIs by contraceptive use or increased likelihood of STI detection among hormonal contraceptive users.

Keywords: Hormonal contraception; Sexually transmitted infections; Systematic review

1. Introduction

During 1999, the World Health Organization (WHO) estimated that there were 340 million new cases worldwide of sexual transmitted infections (STIs) in men and women aged 14 to 59 years, with 92 million cervical chlamydial infections, 62 million gonococcal infections and 174 million cases of trichomoniasis, the most common STI [1]. In many geographic areas with a high prevalence of STIs, hormonal contraceptive methods are commonly used. Based on estimates of married women of reproductive age during the year 2000, more than 75 million women worldwide use oral contraceptives and more than 27 million women use hormonal injectables or implants [2].

Questions have been raised regarding whether hormonal contraceptives may increase a woman's risk of acquiring STIs, perhaps by inducing cervical ectopy and, thereby, increasing susceptibility to cervical infection [3–5]. Cervical ectopy has been associated with human papillomavirus (HPV), HIV and chlamydial infection [5–8], but not with gonococcal infection [5–9].

We conducted this systematic review in preparation for an Expert Working Group of international family planning experts convened by the WHO in October 2003 to develop and revise medical eligibility criteria for contraceptive use. In this report, we describe the evidence obtained through our systematic review regarding whether hormonal contraceptive use is associated with the risk of STI acquisition (including cervical chlamydial and gonococcal infections, HPV, trichomoniasis, herpes and syphilis), as well as provide the WHO recommendations that were derived in part from this evidence. This review also includes evidence identified since the 2003 meeting through February 2005.

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2. Materials and methods

We searched the MEDLINE and EMBASE databases for all articles (in all languages) published in peer-reviewed journals from January 1966 through February 2005 for evidence relevant to hormonal contraceptives and STIs. The following search strategy was performed in MEDLINE: (hormonal adj contracept: or (Medroxyprogesterone 17-Acetate/ and (contracept: or depo or depot)) or depot medroxyprogesterone or depo medroxyprogesterone or depotmedroxyprogesterone or depomedroxyprogesterone or dmpa or net en or norethisterone enantate norethisterone–enantate or norplant: or uniplant or jadelle or implanon or ((levonorgestrel or etonogestrel) and implant:) or (exp contraceptives, oral/ and contracept:) or (exp Contraceptive Devices, Female/ and ring) or NuvaRing or (exp Contraceptive Agents, Female/and patch) or orthoevra or ortho evra) AND (sexually transmitted infections or sti or stis or sexually transmitted disease$ or std$ or gonorrhea or chlamydia: or trichomon: or syphilis or chancre or neurosyphilis or Papillomavirus, Human/or exp Papillomavirus Infections/or HPV or genital warts or condylomata acumina or HPV or Herpesvirus 1, Human/or exp Herpes Simplex/or Herpesvirus 2, Human/or herpesvirus or HSV or herpes). The EMBASE search was identical with the exception of the subject headings. We limited search results to studies of humans.

We searched key review articles and reference lists from articles identified by the database searches to identify additional articles. We did not attempt to identify unpublished articles or abstracts from scientific conferences. In one instance, we contacted one of the authors of a published article for clarification purposes [10].

2.1. Selection of studies

We identified 1147 articles through the initial search strategy. We then reviewed the titles and abstracts of each of these articles, as well as the full article when necessary, in order to identify and then categorize them by the STI studied. We included studies identified by one metaanalysis on chlamydial infection (29 cross-sectional studies and 2 prospective studies), plus an additional 20 cross-sectional studies and 6 prospective studies published since that analysis [4–6,9–61]. For gonorrhea, we identified 5 cohort or case-control studies [5,10,60–63] and 20 cross-sectional studies [13,16,26,30,37–39,47,53,54,64–73]. For HPV, we identified one systematic review of 19 primarily cross-sectional studies [74]. Because the review was recent, we used it as our primary source of evidence, but also searched for articles published subsequent to the review, using the same inclusion criteria as described in the review (at least 200 controls, adjusting for age). We identified one additional cross-sectional study and three prospective studies, which we have included in this review [75–78]. For herpes, we located 5 studies [79–83]; for trichomoniasis, 11 cross-sectional studies [13,37,38,47,53,68,73,84–87] and 2 prospective studies [60,88]; and for syphilis, 1 cross-sectional study [73] and 1 prospective study [60].

2.2. Assessment of study quality and synthesis of data

We summarized and systematically assessed the evidence using standard abstract forms [89] and appraised the quality of each study using the system for grading evidence developed by the United States Preventive Services Task Force (Appendix A) [90]. In addition, we assessed heterogeneity by examining the characteristics of our study participants. Because of the heterogeneity of the studies, we did not estimate summary odds ratios.

3. Results

3.1. Combined oral contraceptives

3.1.1. Cervical chlamydial infection

We identified six prospective studies that examined the association between combined oral contraceptive (COC) use and acquisition of cervical chlamydial infection (Fig. 1). Three of the studies reported statistically significant increased risks of chlamydial infection with COC use [5,59,60]. A study on the use of nonoxynol 9 for preventing chlamydial and gonococcal infections enrolled 818 participants from an STD clinic in the United States and followed participants for 6 months [5]. After adjusting for coital frequency, number of partners, age, number of pregnancies and number of live births, participants using COCs had an increased risk of chlamydial infection [hazard ratio (HR), 1.73; 95% confidence interval (CI), 1.08–2.77] compared with women who either used intrauterine devices (IUDs) or had undergone tubal sterilization. Among 123 IUD users and 108 COC users in Belgium, the COC users had an almost ninefold risk of chlamydial infection compared with the IUD users after 2 years of follow-up [crude relative risk (RR), 8.8; 95% CI, 1.3–59.0]; potential confounders were not included in the model [59]. A study of sex workers in Kenya that followed participants at monthly intervals (median total follow-up of 421 days) found an elevated risk for chlamydial infection among 147 COC users compared with 615 women who either had undergone tubal ligation or did not use any contraceptive method, after adjusting for several sexual behaviors (HR, 1.8; 95% CI, 1.1–2.9) [60]. Three other prospective studies, however, found no significant associations between COC use and cervical chlamydial infection: two of them reported elevated point estimates, and one reported a decreased point estimate [6,10,61]. A study of 301 teenage girls in Sweden, who were tested for chlamydial infection and then followed up at 6 and/or 12 months [6], found that COC use at the initial visit was not associated with chlamydial infection during follow-up compared with no COC use (crude RR, 0.67; 95% CI, 0.27–1.68); adjusted analyses were not conducted. An evaluation of 819 women who were attending either an inner city or suburban family planning

Author	Year	COC users/ comparison group (n)	Comparison group	Adjusted for sexual behaviors	Quality
Chlamydia					
Avonts	1990	108/123	IUD	No	II-2, poor
Lavreys	2004	37/124	No contraceptives or tubal ligation	Yes	II-2, fair
Morrison	2004	354/351	Non-hormonal	Yes	II-2, fair
Baeten	2001	213/not stated	No contraceptives or tubal ligation	Yes	II-2, fair
Louv	1989	617/201	IUD or tubal ligation	Yes	II-2, fair
Rahm	1991	251/17	Non-COC use	Not stated	II-2, poor
Gonorrhea					
Jick	1982	60/119 (cases/controls)	Spermicide	No	II-2, poor
Jick[1]	1982	73/116 (cases/controls)	Tubal ligation	No	II-2, poor
Louv	1989	617/201	IUD or tubal	Yes	II-2, fair
Baeten	2001	213	No contraceptives or tubal ligation	Yes	II-2, fair
Austin	1984	735/958 (cases/controls)	Never	Yes	II-2, poor
Lavreys	2004	37/351	No contraceptives or tubal ligation	Yes	II-2, fair

[1] Calculated for systematic review.

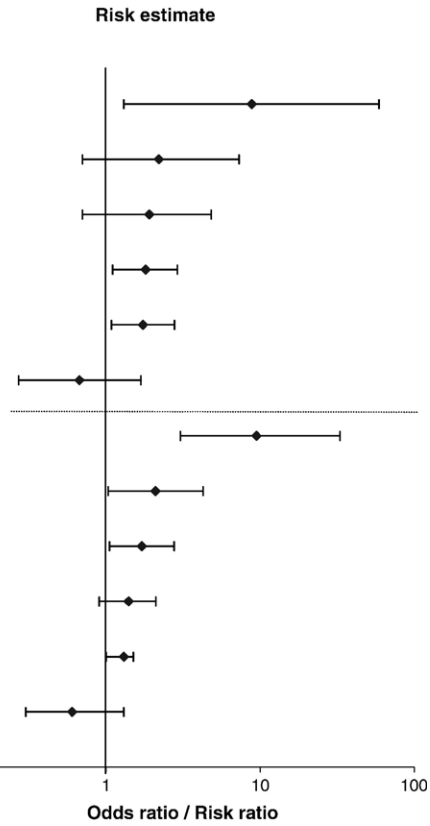

Fig. 1. Cohort and case-control studies of association between oral contraceptive use and chlamydial infection or gonorrhea.

center in the United States compared women who were initiating COCs or depot medroxyprogesterone acetate (DMPA) use with women who were either initiating or continuing use of a nonhormonal method of contraception [10]. Participants were followed at 3, 6 and 12 months for incident cervical chlamydial or gonococcal infection, and contraceptive use and behavioral factors were measured at all follow-up visits for inclusion in the model as time-varying covariates. After adjusting for age, ethnicity, clinic site, number of sex partners and condom use, the researchers found increased HRs for COC users compared with those women who were not using hormonal methods; these results, however, were not statistically significant (HR for chlamydial infection or gonorrhea combined, 1.5; 95% CI, 0.6–3.5; HR for chlamydial infection only, 1.9; 95% CI, 0.7–4.8). The third study followed 242 commercial sex workers in Kenya for a median duration of 35 months and a total of 7999 person-years after diagnosis of HIV infection [61]. The median number of follow-up visits was 8 (range, 7–9), and the median interval between visits was 40 days (range, 28–81). After adjusting for age, education, duration of prostitution, parity, number of sex partners per week and condom use, the researchers found that the women using COCs had a nonsignificant increased risk for chlamydial infection compared with women who either used no contraception or had undergone tubal ligation (HR, 2.2; 95% CI, 0.7–7.3).

We identified a total of 49 cross-sectional studies that examined COC use and chlamydial infection, including 29 studies from a previously published metaanalysis [4,9,11–58]. Results from these 49 cross-sectional studies are shown in Figs. 2–5, stratified by comparison group. Despite differences in contraceptive use among the comparison groups, most of these studies reported a positive association between COC use and chlamydial infection. Nearly all the studies failed to adjust for confounders, had relatively small sample sizes and were given a “poor” quality rating.

The published metaanalysis of 29 cross-sectional studies and 2 prospective studies concluded that COC use elevated the risk of chlamydial infection (pooled odds ratio [OR], 1.93; 95% CI, 1.77–2.11) [11]. When compared with use of barrier contraceptives, the risk of infection increased with COC use (pooled OR, 2.91; 95% CI, 1.86–4.55). Most of the studies did not adjust for confounders, particularly sexual behavior. In a sensitivity analysis, however, the pooled estimate of the 13 studies that controlled for age and number of sex partners did not differ from the pooled estimate of all the studies.

3.1.2. Gonorrhea

Three cohort studies [5,60,61] and two case-control studies [62,63] that evaluated the association between COC use and gonorrhea reported inconsistent results (Fig. 1). The three cohort studies were described in the previous section

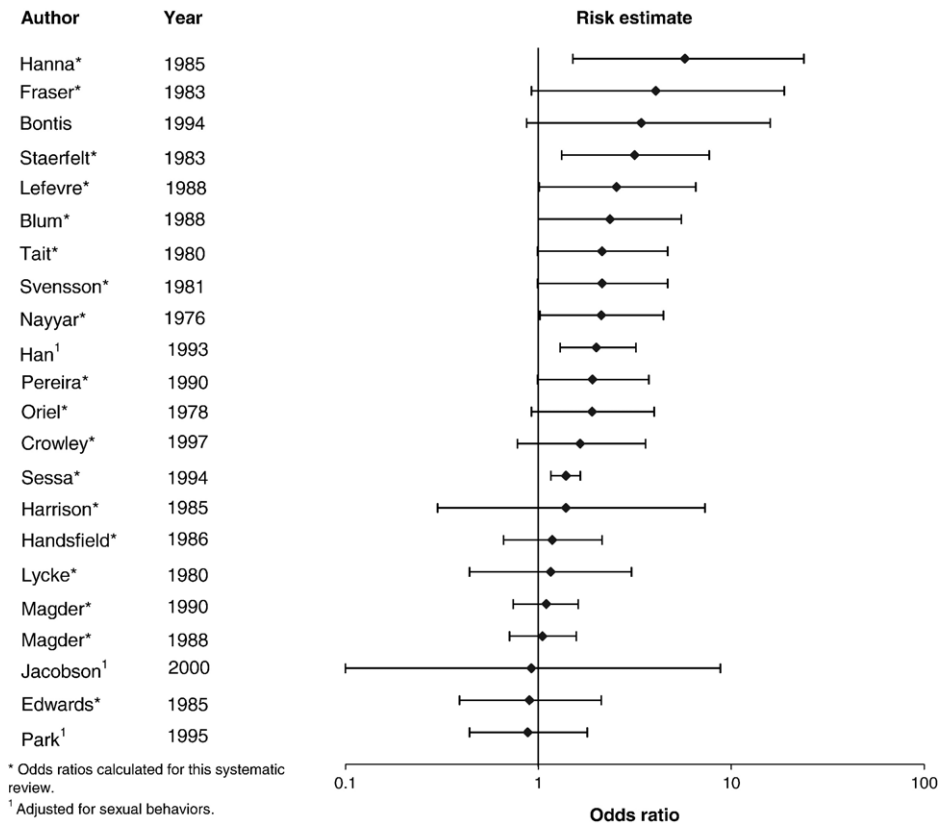

Fig. 2. Cross-sectional studies of association between chlamydial infection and oral contraceptive use compared with no contraceptive use.

on COC use and chlamydial infection. The study on the use of nonoxynol 9 for preventing gonococcal and chlamydial infections reported an HR of 1.70 (95% CI, 1.05–2.76) for gonorrhea for COC users compared with nonusers [5]. However, neither of the two studies conducted among commercial sex workers in Kenya reported a statistically significant increased risk of gonorrhea among COC users compared with women who either had undergone tubal ligation or did not use contraception (HR, 1.4; 95% CI, 0.9–2.1 for commercial sex workers [60]; HR, 0.6; 95% CI 0.3–

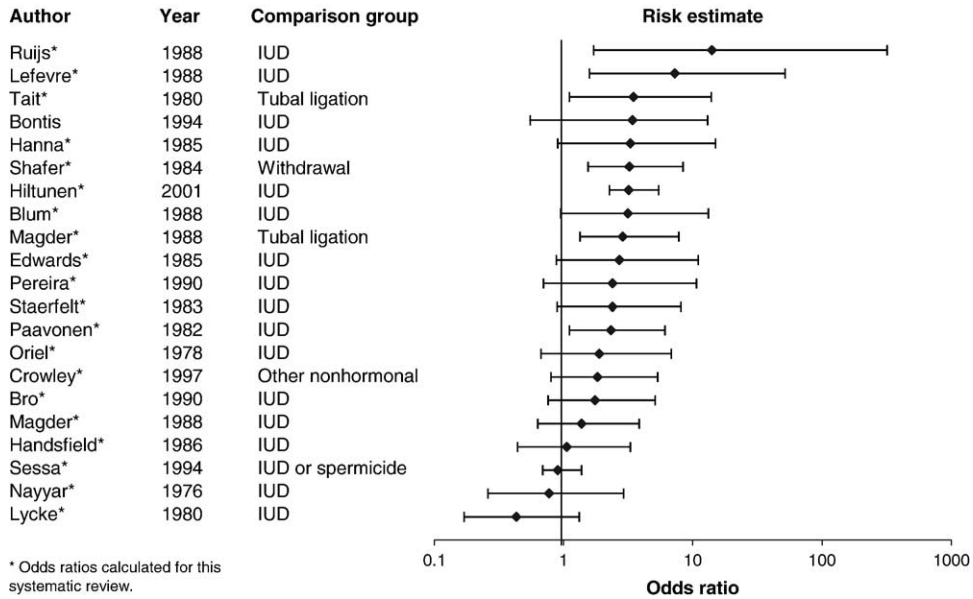

Fig. 3. Cross-sectional studies of association between chlamydial infection and oral contraceptive use compared with nonhormonal contraceptive use.

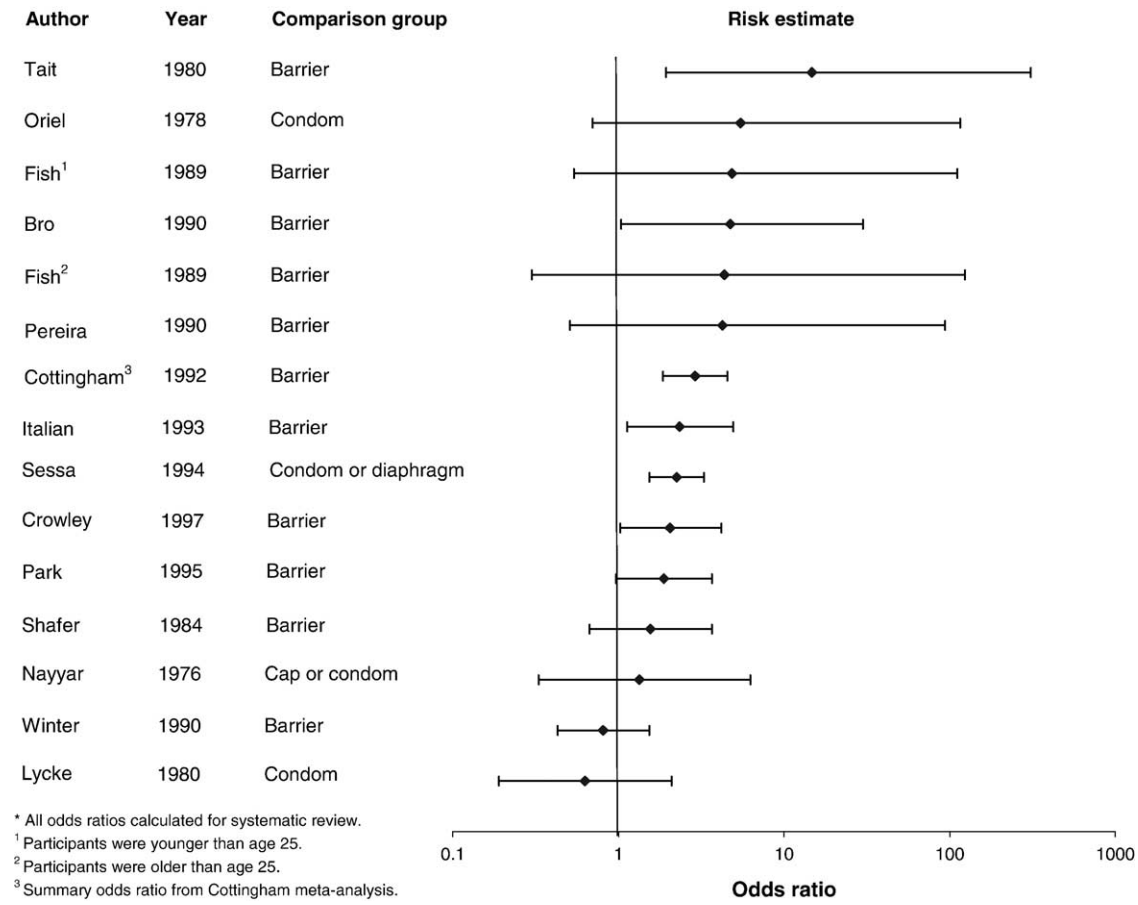

Fig. 4. Cross-sectional studies of chlamydial infection and oral contraceptive use compared with use of barrier methods.

1.3 for HIV-infected commercial sex workers [61]). Of the two case-control studies, one reported an OR of 1.3 (95% CI, 1.0–1.5) for COC use compared with "never use" among 735 gonorrhea cases and 958 controls [62]; the other study examined 77 cases and 164 controls, and reported proportions of contraceptive use from which we calculated separate ORs for COC use compared with spermicide use (OR, 9.46; 95% CI, 3.03–32.96) and tubal ligation (OR, 2.09; 95% CI, 1.03–4.26) [63].

Twenty-one cross-sectional studies examined COC use and the presence of gonorrhea (Fig. 6) [13,16,26,28,30,37–39,47,53,54,64–73]. Seventeen of the cross-sectional studies found no association between COC use and gonorrhea for any of the comparison groups, although none of the studies controlled for behavioral factors. Four of the studies observed statistically significant positive associations between COC use and gonorrhea [30,64,65,73], with ORs ranging from 1.53 to 5.25 (95% CI range, 1.09–26.25); one study adjusted for sexual behaviors [73].

3.1.3. Human papillomavirus

A systematic review of COC use and risk of HPV included 19 cross-sectional studies published through 2002 [74]. Seven of the studies were conducted in developing countries, and 15 studies adjusted for sexual behaviors. The authors of the systematic review concluded that there was no evidence for a strong association between having ever used COCs and presence of HPV; however, given the limited amount of data, the heterogeneity among studies and the potential for bias and confounding, caution is warranted when interpreting these results [74].

Two prospective studies published since the systematic review reported conflicting results. One study of 444 university students, aged 18 to 20 years, who were followed-up every 4 months (mean total follow-up, 41.2 months), reported a positive and statistically significant association between incident HPV and current COC use compared with nonuse (HR, 1.4; 95% CI, 1.01–1.8) [75]. This study adjusted for behavioral risk factors, but did not adjust for other demographics. A study of 253 women, aged 18 to 49 years followed-up at their annual health examination (mean time interval of 14 months; range, 9.0–21.3 months), found no significant association between current COC use and HPV compared with non-COC use (OR, 0.7; 95% CI, 0.2–2.0) after adjusting for risky sexual behaviors and age [76].

3.1.4. Trichomoniasis

Two prospective studies have examined COC use and acquisition of trichomoniasis [60,88]. The study of sex

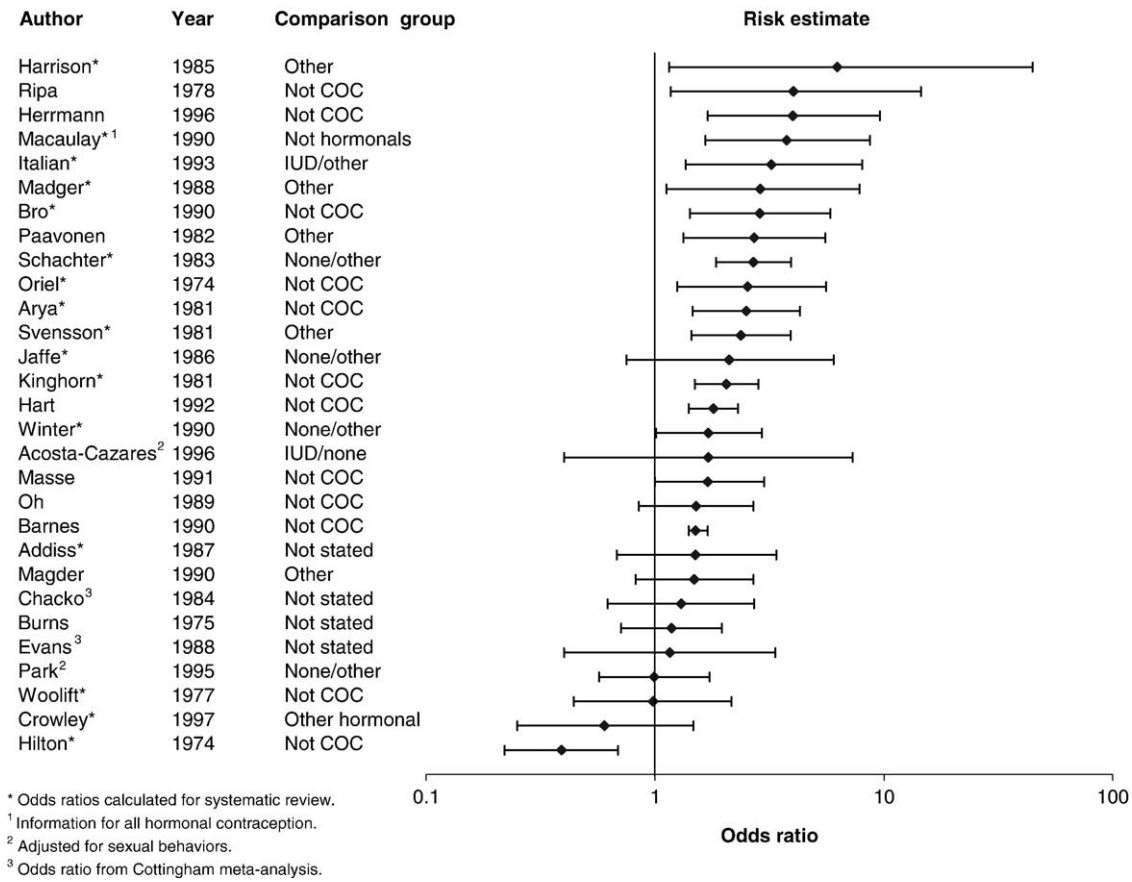

Fig. 5. Cross-sectional studies of association between chlamydial infection and oral contraceptive use compared with non-oral contraceptive methods.

workers in Kenya found no association between COC use and trichomoniasis (HR, 0.9; 95% CI, 0.7–1.3) when compared with women who either had undergone tubal ligation or used no contraception, after adjusting for several sexual behaviors [60]. A study evaluating nonoxynol 9 use for preventing STIs found a decreased risk of trichomoniasis among COC users compared with women who either used an IUD or had undergone tubal ligation (RR, 0.56; 95% CI, 0.39–0.81) after adjusting for spermicide use and sexual activity [90].

Eleven cross-sectional studies found no statistically significant positive associations between COC use and trichomoniasis, with ORs ranging from 0.4 to 3.96 (95% CI range, 0.14–88.65) [13,37,38,47,53,68,73,84–87]. Four of the studies included study participants from STI clinics [47,68,85,86], one was conducted in a developing country [73] and study comparison groups included women who did not use COCs, women who did not use contraceptives, women who used IUDs or women who used diaphragms. Five of the studies found a statistically significant decreased risk of trichomoniasis among COC users (ORs ranging from 0.38 to 0.71; 95% CI, 0.15–0.98) [37,47,68,73,86], but only one study adjusted for confounders [73].

3.1.5. Herpes

Three out of five cross-sectional studies of herpes found no elevated risks for the infection associated with COC use, even when examining different comparison groups (i.e., no contraceptive method, IUD, diaphragm or DMPA) [79–83]. ORs ranged from 0.31 to 3.72 (95% CI, 0.11–76.28), with only one study adjusting for sexual behaviors [82] and only one study including women at very high STI risk (i.e., sex workers) [79]. Calculations from cross-sectional data of 2360 women attending a clinic in New England in the mid-1970s resulted in a positive association between COC use and herpes compared with non-COC use (OR, 2.57; 95% CI, 1.60–4.14); however, there was no adjustment for confounders [81]. After adjusting for sexual behaviors, investigators of a cross-sectional study of women in Brazil and the Philippines found a statistically significant positive association only for women in the Philippines who had used COCs for 4 years or more (OR, 7.4; 95% CI, 2.2–24.9); all other comparisons were statistically nonsignificant [80].

3.1.6. Syphilis

Two studies assessed COC use and syphilis: one cross-sectional study in a family planning setting compared current COC use with nonuse [73], and one cohort study among prostitutes compared COC users with women who either used IUDs or had undergone tubal ligation [60]. Both studies adjusted for a number of sexual behaviors and found no associations.

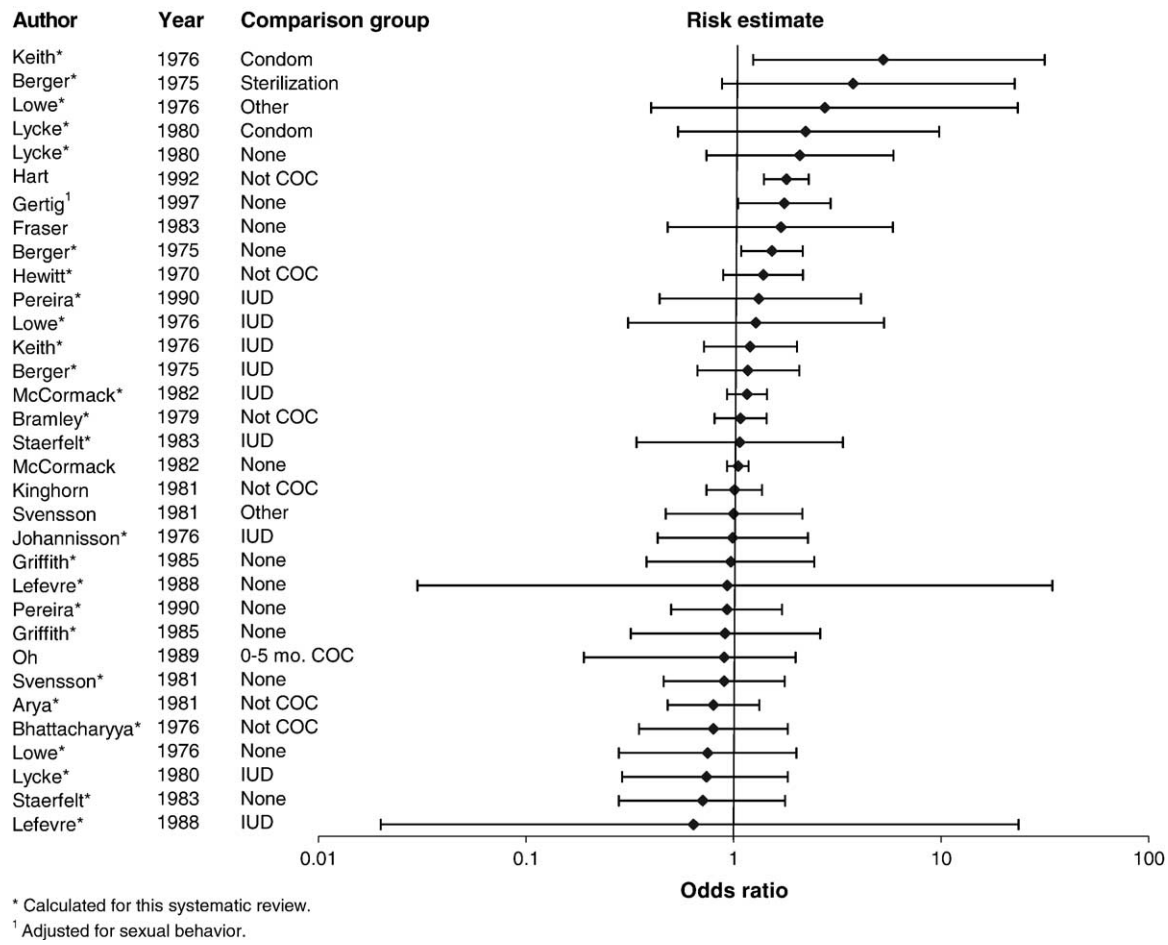

Fig. 6. Cross-sectional studies of association between oral contraceptive use and gonorrhea.

3.2. Depot medroxyprogesterone acetate and Norplant

3.2.1. Cervical chlamydial infection

Three of the prospective studies previously described in the section on COC use and cervical chlamydial infection also examined DMPA use in relation to chlamydial infection (Fig. 7) [10,60,61]. Two prospective studies of sex workers in Kenya reported an increased risk of chlamydial infection with DMPA use compared with women who had undergone tubal ligation or did not use a contraceptive method. One study found an increased risk of 1.6 (95% CI, 1.1–2.4) for DMPA users [60]. The other study, which analyzed HIV-infected sex workers, reported an increased risk of chlamydial infection of 3.1 (95% CI, 1.0–9.4) for DMPA users when adjusting for several demographic and sexual risk behavior factors [61]. A third study reported a statistically significant increased risk of chlamydial infection among DMPA users compared with nonhormonal contraceptive users after controlling for age, ethnicity, clinic site, number of sex partners and condom use (HR, 4.3; 95% CI, 1.7–11.1) [10]. Two cross-sectional studies that examined the association between DMPA use and chlamydial infection did not find any increased risk; however, the studies included few DMPA users and small sample sizes [35,49].

3.2.2. Gonorrhea

Both of the prospective studies of sex workers in Kenya found no association between DMPA use and gonorrhea (HR, 1.1; 95% CI, 0.8–1.6, and HR, 1.0; 95% CI, 0.6–1.7, respectively) among DMPA users, compared with women who either had undergone tubal ligation or did not use contraception, after adjusting for sexual risk behaviors (Fig. 7) [60,61]. One cross-sectional study among family planning clients found no association between DMPA use and gonorrhea among DMPA users compared with either IUD users (OR, 0.23; 95% CI, 0.01–2.37) or women who did not use contraception (OR, 0.32; 95% CI, 0.01–3.65) without adjusting for confounders.

3.2.3. Human papillomavirus

In a prospective study of 105 adolescents, aged 13 to 21 years, from family planning clinics, researchers found no association between DMPA use and HPV when comparing DMPA users with nonusers (HR, 0.79; 95% CI, 0.20–3.25) [77]. A cross-sectional study of women at the United States–Mexico border [78] found, after adjusting for a sexual behaviors, that HPV had a positive association with current DMPA use (OR, 2.29; 95% CI, 1.49–3.53), but not with past DMPA use (OR, 1.28; 95% CI, 0.91–1.82), compared

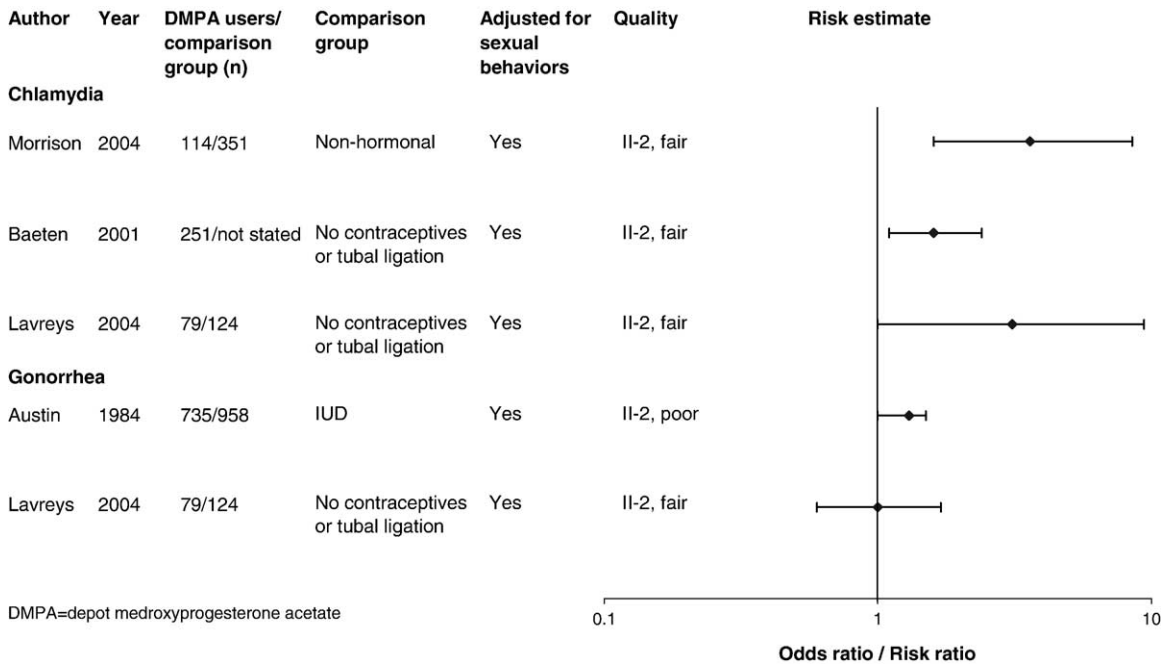

Fig. 7. Cohort and case-control studies of association between DMPA use and chlamydial infection or gonorrhea.

with never use. This study also reported a positive association between ever use of Norplant and prevalent HPV (OR, 2.69; 95% CI, 1.17–6.19).

3.2.4. Trichomoniasis

One prospective study among sex workers [60] and one cross-sectional study among STI clients [91] did not find any statistically significant associations between DMPA use and trichomoniasis when comparing DMPA users with nonusers (HR, 0.6; 95% CI, 0.4–1.0, and OR, 1.00; 95% CI, 0.19–5.14, respectively).

3.2.5. Herpes

A cohort study among sex workers in Kenya found no association between DMPA use and herpes when comparing women using DMPA with women not using either DMPA or COCs (OR, 0.6; 95% CI, 0.4–1.0; not adjusted for sexual behaviors) [79].

3.2.6. Syphilis

One cohort study followed sex workers in Kenya for more than 1 year, and after adjusting for sexual behavior, found no statistically significant association between DMPA use and syphilis after comparing women who used DMPA with women who had undergone tubal ligation or did not use contraception (HR, 0.5; 95% CI, 0.2–1.4) [60].

4. Discussion

Overall, the body of evidence regarding an association between COC use and chlamydial infection included 6 prospective studies of generally "fair" quality and 49 cross-sectional studies of generally "poor" quality. The six prospective studies reported higher risk estimates for chlamydial infection among COC users compared with nonusers, although the findings of the two studies were not statistically significant, and one study reported a nonsignificant negative finding. Results from the cross-sectional studies were generally in a positive direction, although many were not statistically significant. The bodies of evidence regarding the association between COC use and other STIs were more limited and of "fair" to "poor" quality; results from studies of COC use and acquisition of gonorrhea, HPV and herpes were conflicting, whereas studies of trichomoniasis and syphilis suggested no association with COC use. The body of evidence regarding the association between DMPA use and chlamydial infection included three prospective studies of overall "fair" quality and two cross-sectional studies of "poor" quality. All three prospective studies reported positive associations between DMPA use and chlamydial infection, whereas the two cross-sectional studies did not. For trichomoniasis, gonorrhea, syphilis and herpes, limited evidence of "fair" to "poor" quality suggested no association with DMPA use, whereas results on HPV's association with DMPA were inconsistent. One cross-sectional study found a positive association between ever use of Norplant and prevalent HPV infection. We identified no studies of hormonal methods other than COCs, DMPA and Norplant.

Positive associations between hormonal contraceptive use and STIs may be a result of differential exposure to infection, increased susceptibility to infection given exposure or differential likelihood of detection of cervical infection [17]. Many authors have hypothesized that cervical ectopy

may play a role, either by increasing a woman's susceptibility to infection or increasing the likelihood of STI detection. Although we did not specifically examine the interactions between cervical ectopy, oral contraceptive use and chlamydial infection in this systematic review, the previously published meta-analysis [11] concluded that women using oral contraceptives may be more likely to have cervical ectopy, and that women with cervical ectopy may be more likely to have chlamydial infection. However, when oral contraceptive use, cervical ectopy and chlamydial infection were examined together, there were no consistent findings among six studies included in the meta-analysis [11]. In a recent prospective study, cervical ectopy was found to be an independent risk factor for cervical infection (separate analyses were not conducted for chlamydial infection and gonorrhea); however, the presence of cervical ectopy did not change the association between DMPA or COC use and cervical infection risk [10]. Instead of being a risk factor for infection, cervical ectopy may increase the likelihood of detecting cervical infection: some studies of ectopy and cervical chlamydial infection have found that among women with positive cervical chlamydial cultures, *Chlamydia trachomatis* is isolated more frequently when ectopy is present [92]. Cervical ectopy has not been associated with gonococcal infection; therefore, there may be a biological explanation for the observed association of hormonal contraceptive use with chlamydial infection but not gonococcal infection [5,9].

Several key methodological issues should be considered when examining the association between hormonal contraceptive use and STIs. Most of the evidence was obtained from cross-sectional studies, which could not evaluate whether cervical infection occurred prior to contraceptive use. Because researchers generally consider the randomization of women to contraceptive methods to be unethical, the participants in these studies self-selected their contraceptive method of choice. Their chosen method may have been associated with other STI risk factors (e.g., sexual behavior) or had a direct effect on STI risk (e.g., decreased risk with condom use). Many studies were conducted among commercial sex workers and may not be generalizable to contraceptive users with lower STI risk. Other study limitations include small sample sizes, especially for DMPA users, and lack of control for potential confounders, especially STI exposure, sexual behaviors and condom use. Failure to measure and control for potential confounders could at least partially explain the positive study findings, because hormonal contraceptive users may behave differently than women who do not use contraceptives—the former may be more sexually active, more frequently screened for STIs or less likely to use condoms. Given the inability to randomize women to contraceptive method groups and the lack of a direct measure of STI exposure in these studies, it is difficult to assess whether the observed results are true findings or due to differential STI exposure among the groups. However, if the positive associations between hormonal contraceptive use and chlamydial infection were completely due to bias, similar findings might have been expected for the association between hormonal contraception and gonococcal infections.

In 2003, the WHO Expert Working Group reviewed much of this evidence when developing recommendations for whether women at risk for STIs could use hormonal contraceptive methods. Three additional studies reviewed here, but identified subsequent to the 2003 meeting, were not available to the Expert Working Group [6,10,61]. The Expert Working Group determined that there should be no restriction on use of any of the hormonal contraceptives for women who are at high risk for STIs (WHO Category 1) [93]. The guidelines also state that hormonal contraception does not protect against STIs or HIV, and that if there is a risk of STIs or HIV, the correct and consistent use of condoms is recommended, either alone or with another contraceptive method [93]. In October 2004, WHO's Family Planning Guideline Steering Group again reviewed the body of evidence on this topic, including the three new studies that had not been available to the Expert Working Group [6,10,61], and determined that no change in the current guidelines was warranted. A WHO statement regarding this evidence and the WHO guidelines can be found at http://www.who.int/reproductive-health/family_planning/docs/hormonal_contraception_sti_acquisition.pdf.

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Appendix A. Study quality assessment

A.1. Individual study

Each study was given a rating of Level 1, Level II-1, Level II-2, Level II-3 or Level III based on the study design (Table 1). Each study was also given a rating of poor, fair or good based on the criteria for grading the internal validity of a study (Table 2). A good study meets all criteria for that study design, a fair study does not meet all criteria but is judged to have no fatal flaw and a poor study contains a fatal flaw. Also, the type of evidence was either identified as being direct (the evidence was based on the data directly addressing the question) or indirect (the evidence was extrapolated from other relevant data).

A.2. Body of evidence

The quality of the body of evidence was the highest rating given to an individual study. If the results were inconsistent, the quality of the body of the evidence was lowered by one level. If the results were consistent, then the quality of the body of the evidence was left at the original level.

Table 1
Levels of evidence [90]

	Levels of evidence
Level 1	Evidence obtained from at least one properly designed randomized controlled trial.
Level II-1	Evidence obtained from well-designed controlled trials without randomization.
Level II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
Level II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
Level III	Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert communities.

Table 2
Criteria for grading the internal validity of individual studies [90]

Study design	Criteria
Systematic reviews	Comprehensiveness of sources/search strategy used
	Standard appraisal of included studies
	Validity of conclusions
	Recency and relevance
Case-control studies	Accurate ascertainment of cases
	Nonbiased selection of cases/controls with exclusion criteria applied equally to both
	Response rate
	Diagnostic testing procedures applied equally to each group
	Appropriate attention to potential confounding variables
Randomized controlled trials (RCTs) and cohort studies	Initial assembly of comparable groups
	For RCTs: adequate randomization, including concealment and whether potential confounders were distributed equally among groups
	For cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
	Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
	Important differential loss to follow-up or overall high loss to follow-up
	Measurements: equal, reliable and valid (includes masking of outcome assessment)
	Clear definition of interventions
	All important outcomes considered
	Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs
Diagnostic accuracy studies	Screening test relevant, available for primary care, adequately described
	Study used a credible reference standard, performed regardless of test results
	Reference standard interpreted independently of screening test
	Handled indeterminate results in a reasonable manner
	Spectrum of patients included in study
	Sample size
	Administration of reliable screening test

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