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Contraceptive effects on the cervicovaginal microbiome: recent evidence including randomized trials

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Abstract

Until recently, most data regarding the effects of non-barrier contraceptives on the mucosal microbiome have derived from observational studies, which are potentially biased due to behavioral confounders that may mask their true biological effects. Overall, good quality data describe that initiation of long-acting progestin-only contraceptives, including levonorgestrel (LNG)-implant and the injectables depot-medroxyprogesterone acetate (DMPA-IM) and norethisterone enanthate (NET-EN) do not alter the mucosal microbial environment. Likewise, no strong evidence exists that the use of oral contraceptive pills (OCPs) is associated with alterations of the vaginal microbiome or increased risk of bacterial sexually transmitted infections (STIs). While there are limited data on the effect of intravaginal rings (IVRs) on the mucosal environment, those that exist show conflicting effects on the vaginal microbiota. Copper intrauterine device (Cu-IUD) initiation has been associated with bacterial vaginosis (BV) acquisition, including in a large, randomized trial. LNG-IUDs may have similar affects but need to be evaluated further. Different synthetic hormones have divergent effects on the microbiome and therefore novel hormonal methods need to be rigorously evaluated. Furthermore, the addition of antiretrovirals into multipurpose technologies may alter the effects of the hormonal component. There is thus a critical need to improve our understanding of the biological effects of contraceptive hormones and delivery methods with different pharmacokinetic and chemical properties on the mucosal microbiome in rigorous trials, to inform the development of novel contraceptives and improve individual family planning guidance.

Keywords

hormonal contraception; sexual health; reproductive health; mucosa; microbiota

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INTRODUCTION

One of the most important successes in reproductive health has been the development of cost-effective and reversible family planning methods and the expansion of their use in low- and middle-income countries (1). Non-barrier contraceptives, including hormonal contraceptives (HCs), have become an important tool in preventing unintended pregnancies and associated sequelae. However, despite their contraceptive benefits, concerns regarding the potential effects of non-barrier contraceptives on the female genital tract (FGT) mucosal environment and risk of vaginal infections have been raised. Until recently, most of the data linking non-barrier contraceptive use to changes in the mucosal environment have derived from observational studies (Table 1), which are potentially biased due behavioral confounders that may mask the true biological effects of non-barrier contraceptives (2, 3). Furthermore, much research has combined different contraceptive methods into groups (e.g., injectables, any HC) and compared these to no non-barrier contraceptive use, rather than to alternative non-barrier contraceptives methods in women seeking effective contraception. Identifying safe contraceptive options is an important public health priority, particularly in adolescent and young women in sub-Saharan Africa, as they are at high risk of both vaginal infections and unintended pregnancies (4, 5). There is thus an urgent need to evaluate a broad range of available contraceptive options, both individually and compared to each other, to understand their impact on the genital mucosa. Here, we have reviewed the current data, particularly those from randomized clinical trials (RCT), on the effect of reversible non-barrier contraceptives on the mucosal microbiota and their association with vaginal health. Although weight should be placed on randomized data, it is important to note that although randomized trials remove selection bias, it does not overcome bias introduced by potential behavioral changes following assignment to a specific contraceptive modality in these largely open-label trials.

IMPACT OF CONTRACEPTIVES ON THE VAGINAL MICROBIAL COMMUNITY

Bacterial Microbiome

Observational data (Table 2)—The composition of the vaginal bacteriome plays a key role in women's sexual and reproductive health. While certain vaginal bacterial species have been associated with an optimal mucosal environment and protection against sexually transmitted infections (STIs), others have been associated with inflammation, poor reproductive health outcomes and susceptibility to bacterial and viral cervicovaginal infections (6–9). In general, risk of certain cervicovaginal infections has been associated with highly diverse communities comprised of bacterial vaginosis (BV)-associated bacteria, including *Gardnerella vaginosis*, *Prevotella*, *Fannyhessea vaginae* (previously *Atopobium vaginae*) and *Sneathia* (6, 8). In contrast, low-diversity communities dominated by lactobacilli, particularly non-*iners Lactobacillus* spp. such as *L. crispatus*, have been associated with vaginal health and lower risk of infections (6, 8, 10). To date, the majority of studies investigating the effect of non-barrier contraceptives on the vaginal microbiota have primarily been based on either clinical signs of BV, such as Amsel criteria, or the Nugent score (based on Gram staining), or on levels of limited members of the bacterial community

as measured by quantitative polymerase chain reaction (qPCR) or culture-based methods (reviewed by (11, 12)).

Depot-medroxyprogesterone acetate—Several observational studies have described a lower BV prevalence in women using the trimonthly intramuscular injectable depot-medroxyprogesterone acetate (DMPA-IM) compared to non-contracepting women in both high- and lower-middle income countries (11–16). Accordingly, increases of *Lactobacillus* species or reductions in BV-associated bacteria have been reported in women initiating DMPA-IM (17–20). In one observational study, in which the bimonthly injectable norethisterone enanthate (NET-EN) was evaluated separately to DMPA-IM, a reduction in BV prevalence was also found with NET-EN use (21). In the Zim CHIC study, a longitudinal observational study among Zimbabwean women choosing to initiate either DMPA-IM, NET-EN, or medroxyprogesterone acetate/ethinyl cypionate (MPA-EC) injectables, levonorgestrel (LNG) or etonogestrel (ETG) subdermal implants, or a copper T intrauterine device (Cu-IUD), Achilles *et al.* found no change in the genital concentrations of BV-associated species *G. vaginalis* and *F. vaginae* as measured by qPCR in women using DMPA-IM, despite a significant decrease in Nugent score among the DMPA-IM users (22).

With the development of next-generation sequencing (NGS) methods, a deeper insight into the impact of non-barrier contraceptives on the vaginal bacteriome has been gained. In a retrospective 16S rRNA gene sequencing survey of vaginal samples from a subset of the Vaginal Human Microbiome Project that included participants who reported using either condoms, oral contraceptive pills (OCP), DMPA-IM, or LNG intrauterine system (IUS) as their contraceptive method, women reporting DMPA-IM use were less likely to have vaginal microbiota dominated by BV-associated bacteria relative to women who reported condom use (23). However, DMPA-IM use was not associated with a concurrent increased relative abundance of beneficial *Lactobacillus* species (23). In a cross-sectional study of Kenyan women, DMPA-IM usage was not associated with changes in bacterial community profiles or diversity as inferred from bacterial proteins (24), in contrast to another cross-sectional cohort of Kenyan sex workers, in which DMPA-IM correlated with increased diversity of the vaginal microbiota as assessed by 16S rRNA gene sequencing (25). The latter agrees with longitudinal studies reporting decreasing concentrations of *Lactobacillus* species in women initiating DMPA-IM (26–28). However, many of the reported outcomes of these studies could be a result of behavioral differences between women choosing DMPA-IM over other hormonal or non-hormonal non-barrier contraceptives (2) or methodological differences such as relative or absolute abundance measurements.

IUD/IUS—In the aforementioned Zimbabwean cohort, Achilles *et al.* observed an increase in the genital concentration of *G. vaginalis* and *F. vaginae* in women choosing to initiate Cu-IUD (22). Any IUD use has been previously described as an independent predictor of BV (29, 30) and the prevalence of BV and the amount of BV-associated bacteria in women using IUDs were found to be higher than in women using estrogen-containing HC methods (23, 31) or condoms (32). Yet, the US-based CHOICE study found no difference in vaginal microbiota stability or BV rates between Cu-IUD and LNG-IUS users (31, 33), and one study comparing BV prevalence in Thai women did not find any differences between women

using Cu-IUD and those not using Cu-IUD (34). One study suggested that an initial increase in BV after LNG-IUS insertion may be reversed with long-term use (35), but this was not found to be true after 18 months of Cu-IUD use in African women (36), suggesting that there may be differences between hormonal and non-hormonal IUDs.

OCP—Data on the influence of OCPs on the vaginal bacteriome have mainly reported increased *Lactobacillus* levels and a reduction of BV-associated taxa (20, 23) corresponding to a decrease in BV incidence (11, 12, 37, 38) and recurrence (13, 39). A small number of longitudinal studies have reported that the vaginal microbiota was unchanged following OCP initiation, albeit the duration of OCP use may have been too short to identify any potential shifts in the bacterial community (40–43). Furthermore, OCPs are varied in their hormonal constituents and dosage, which might explain the differences found in studies.

Vaginal rings—In two studies comparing use of contraceptive intravaginal rings (IVR) containing diethylstilbesterol (DES)/EE and ETG/EE, respectively, to OCP use, no significant differences in incident BV were observed within or between groups (31, 44). In a study assessing the long-term impact of a cyclic nestorone (NES)/EE IVR use on the vaginal microbiota, a non-significant increase in H_2O_2-positive *Lactobacillus*-dominated vaginal microbiota at cycle thirteen was observed, yet the Nugent scores did not differ over time (45).

Randomized data—In a substudy of the recently completed randomized open-label Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial, the effect of DMPA-IM, Cu-IUD and LNG-implant on the FGT bacteriome was analyzed using 16S rRNA gene sequencing (46). Participants randomized to Cu-IUD had significantly elevated vaginal bacterial diversity, Nugent score and abundance of multiple BV-associated taxa after one and six months of use relative to baseline, and by six months of use participants assigned Cu-IUD had significantly higher bacterial alpha diversity compared to those assigned to DMPA-IM or LNG-implant (46). Women randomized to DMPA-IM regularly transitioned from a *L. iners* to a *L. crispatus* dominated community during the first six months of use. Total 16S rRNA gene copies increased significantly for both DMPA-IM and Cu-IUD users, but whereas this increase was predominately due to an increased in *Lactobacillus* bacterial load in DMPA-IM users, women randomized to Cu-IUD had significant increases in *G. vaginalis*, *Prevotella* and *Sneathia* species, among other BV-associated bacteria. Similarly, in an RCT in which the impact of the NET-EN, OCPs and ETG/EE IVR on the vaginal microbiota of South African adolescent females was evaluated, NET-EN injectable users displayed a tendency to shift from an *L. iners*-dominated community towards either a *L. crispatus*-dominated or a more diverse community after 16 weeks of HC use (47). In this study, adolescents assigned to OCP had more lactobacilli, particularly *L. iners*, and lower bacterial alpha diversity after 16 weeks of HC use compared to those assigned to either NET-EN or ETG/EE IVR (47). Furthermore, the use of OCP was associated with a non-significant decrease in BV by Nugent scoring (47). However, among Australian women randomized to OCP versus no OCP use following antibiotic treatment for BV, OCP exposure did not improve BV cure, although the authors note that their results may be limited by sample size and attrition (39).

There have been multiple small, randomized trials of contraceptive IVRs which measured their effects on the vaginal microbiota with contrasting results. In a recently conducted RCT, the impact of cyclic versus continuous use of ETG/EE IVR on BV incidence and concentrations of key vaginal bacteria was investigated in a population of Rwandan women with a high BV prevalence (48). In both study groups, a decrease in mean Nugent score was observed after 12 weeks of contraceptive IVR use and while the concentration of *Lactobacillus* species increased significantly, the concentration of *G. vaginalis* and the presence of *F. vaginae* decreased, suggesting that the contraceptive IVR favored optimal vaginal microbe colonization over BV-associated anaerobes (48). In the CONRAD A15–138 study, a placebo-controlled RCT, US and Dominican women were randomized to an IVR delivering either the antiretroviral drug tenofovir (TFV) alone, or together with LNG, or a placebo IVR. The vaginal microbiota of the TFV/LNG IVR users did not differ from that of the placebo IVR users in terms of diversity, bioburden and community composition after two weeks of use, but the sample size was small (49). Similar results were found in Kenyan women after 90 days of use, although the women in the TFV/LNG IVR arm either maintained stable microbiota or shifted to a *Lactobacillus*-dominant state (50). In Kenyan women treated for BV there was a non-significant increase in BV incidence/recurrence two months post-initiation among women randomized to either continuous or intermittent use of ETG/EE IVR, and BV prevalence returned to a level compared to baseline after three to six months of use (51). In US women randomly assigned to either ETG/EE IVRs or norelgestromin/EE patches for four months, there was also no significant change in Nugent score among contraceptive IVR users (52). Similar results have previously been reported in another North American RCT comparing ETG/EE and OCP use, in which no change in positive *Lactobacillus*-culture results or BV prevalence was found within or between HC groups (53). In contrast, in the South African UChoose study, the relative abundance of BV-associated species implicated in HIV risk (such as *Prevotella, Mycoplasma* and *Parvimonas*) was significantly higher in adolescents randomized to the ETG/EE IVR compared to those assigned to OCP use (47). Yet, the BV prevalence did not significantly increase (54). This may be due to the shift from *L. iners* dominance to *L. crispatus* dominance in some IVR users. Studies have shown the formation of biomass on used contraceptive IVRs with a composition mirroring the vaginal bacteriome, suggesting that the composition of the starting vaginal bacterial community could influence the formation of biofilm on contraceptive IVRs and/or *vice versa* (48, 55), and explain the different microbiota outcomes in IVR and possibly IUD studies. (56, 57). A high proportion of participants in the UChoose study had high diversity, BV-associated vaginal microbiota at baseline, whereas women in Rwanda and Kenyan studies were older with more optimal baseline vaginal microbiota. Larger RCTs are needed to confirm the effect of contraceptive IVRs on vaginal microbiota in diverse populations.

Bacterial STIs and Trichomoniasis

Observational Studies—Globally, the most prevalent bacterial STIs include *Chlamydia trachomatis, Neisseria gonorrhoeae*, and *Mycoplasma genitalium*. Bacterial STIs can result in serious complications including pelvic inflammatory disease, ectopic pregnancy, infertility (58) and increased risk of HIV acquisition (59, 60). *Trichomonas vaginalis* is a protozoan STI that is fairly prevalent worldwide. HCs may alter susceptibility to STI

acquisition or clearance due to alterations in mucosal immunity, or via changes in the microbiota. On the other hand, contraceptives such as IVR or IUD may alter susceptibility due to changes in mucosal integrity or the presence of a biofilm. Observational data suggest that the use of non-barrier contraceptives may influence women's susceptibility to certain bacterial STIs, including *C. trachomatis* (61–63). In recent systematic reviews in which these collective observational data were thoroughly described (61, 62), no association was found between use of OCP and risk of *N. gonorrhoeae* or *T. vaginalis* acquisition although data on *C. trachomatis* acquisition risk in OCP users was conflicting. A more recent systematic review and metanalysis found long-acting reversible contraception users had two-fold increased odds of trichomoniasis compared with OCP users, possibly due to decreased condom use (63), with no association between non-barrier contraceptives and *N. gonorrhoeae* or *C. trachomatis*. While no evidence of an association between DMPA-IM use and *N. gonorrhoeae* was found in any of these analyses, the evidence regarding risk of *T. vaginalis* and *C. trachomatis* overall suggested a reduced incidence with DMPA-IM use (60–64). A recent analysis of the VOICE trial comparing South African women choosing DMPA-IM versus NET-EN found no differences in *C. trachomatis*, *N. gonorrhoeae* or *T. vaginalis* incidence between the two groups (65). Very few studies have evaluated implant, contraceptive IVR and IUD use on bacterial STI risk and generally, no association has been found (58, 59). However, in two recent longitudinal studies evaluating STI incidence in users of difference contraceptive methods in sub-Saharan African women and US adolescents, respectively, Cu-IUD use was a significant risk factor for trichomoniasis (64, 66, 67).

Randomized data—Few randomized data exist on bacterial STI incidence risk and contraception. In a secondary analysis of the ECHO Trial, the prevalence of *C. trachomatis* did not differ between the DMPA-IM and Cu-IUD arms or between the Cu-IUD and LNG-implant arms after 18 months of contraceptive use (68). However, DMPA-IM use was associated with a 20% lower risk of *C. trachomatis* detection compared with LNG-implant use and a 30% lower risk of *N. gonorrhoeae* detection compared to the Cu-IUD. *N. gonorrhoeae* prevalence was also lower in the DMPA-IM arm compared to the LNG-implant arm, albeit not significantly so (68). Additionally, *T. vaginalis* was significantly more prevalent among Cu-IUD users than DMPA-IM or LNG-implant users at 18 months, although the baseline prevalence across the arms is unknown (69). This may be due to the evidence of less condomless sex in the DMPA-IM arm (70). In the UChoose cohort, lower *N. gonorrhoea* incidence but a higher incidence of *M. genitalium* was found in adolescents after 16 weeks of NET-EN use compared to adolescents randomly assigned to the ETG/EE IVR and OCP arms (54). Furthermore, the incidence of any bacterial STI was found to be higher in adolescents using ETG/EE IVR compared to those using NET-EN or OCP (54). Given the possible relationship between STI susceptibility and the vaginal microbiota, these findings require further investigation.

Vaginal Candidiasis

Observational data—Vulvovaginal candidiasis (VVC) is a symptomatic fungal infection due to any species in the genus *Candida*, most commonly *C. albicans*. Women using estrogen-containing HC methods may be more prone to vaginal *Candida* infections compared to progestin-only users as elevated estrogen levels promote a glycogen-rich

environment in which *Candida* thrives (71–73). Accordingly, some observational studies have observed increased prevalence and incidence of VVC among OCP users compared to non-HC users (12, 38, 74), yet other studies including one evaluating women before and after initiation of OCP have found no significant increase in vaginal candidiasis with OCP use (14, 41). While one cross-sectional study found DMPA-IM to be a risk factor for vaginal candidiasis (75), another found DMPA-IM use to be protective against candidiasis (14). Further, a reduction in *Candida* colony forming units/ mL six months after initiation of DMPA-IM and decrease in symptomatic candidiasis has been observed (76). Several studies have reported an association between non-hormonal and hormonal IUD use and vaginal *Candida* colonization as measured by microscopy, qPCR or culture (40, 77–80) and some have shown that *C. albicans* can adhere to contraceptive IUD devices (81, 82).

Randomized data—The impact of contraceptive use on VVC has mainly been assessed in RCTs evaluating contraceptive IVRs. In a RCT of intermittent versus continuous use of the ETG/EE IVR in Rwandan women, there was a high incidence of vaginal yeast with 22% in the intermittent contraceptive IVR group and 27% in the continuous contraceptive IVR group (83). In agreement with this, the incidence of *Candida* colonization in women using ETG/EE IVR in the South African UChoose study, was 1.8-fold and 1.5-fold higher compared to those randomized to NET-EN and OCP, respectively, albeit these differences were not statistically significant (84). As for IUDs, *in vitro* data have shown that *Candida* is capable of adhering to the contraceptive IVR (85, 86). Any association of candidiasis with IUD or contraceptive IVR use may thus be related to the physical presence of an inert surface for *Candida* to grow on.

Vaginal Virome

In addition to bacteria and fungi, the vaginal ecosystem also contains a diverse community consisting of eukaryotic RNA and DNA viruses and bacteriophages, collectively referred to as the ‘virome’. The vaginal virome remains poorly characterized. This is partly because no marker gene exists to deeply sequence viruses, and therefore shotgun metagenomics of purified viral particles has to be performed. Furthermore, there is a discrepancy between the diversity of viruses and the number of viral genomes available in public databases (reviewed in 87). In the few studies of the vaginal virome published to date, only DNA viruses have been identified (possibly due to methodology) and include many bacteriophages, as well as eukaryote-infecting viruses such as papillomaviruses and anelloviruses (88). Using shotgun metagenomics on bacterial DNA, no relationship between contraceptive arm and prophage numbers was found amongst a subset of the randomized UChoose participants but the sample size was small (89). Since prophages can be induced into lytic cycle by stress or antibiotic use, the potential association between HC use and the total vaginal virome should be assessed.

Viral STIs

Although Human Immunodeficiency Virus is often a sexually transmitted, the recently completed ECHO Trial (90) found no significant difference in HIV risk among women randomized to DMPA-IM, Cu-IUDs, or LNG-implants. Since then, multiple recent metanalyses and reviews (63, 91, 92) have sufficiently covered this topic, and thus will not

be discussed herein. Other viral STIs include Herpes Simplex Virus, Human Papillomavirus and likely some as yet undescribed viruses of the vaginal virome.

Observational data

Herpes Simplex Virus: Recent systematic reviews examining the data on HC use and risk of genital herpes simplex virus type 2 (HSV-2) acquisition found some observational evidence suggesting that progestin-only injectable use, specifically DMPA-IM, increases risk of HSV-2 acquisition while no study has specifically looked at the association between HSV-2 risk and NET-EN (61, 62). No association between OCP use and HSV-2 acquisition risk has been described, and no studies have investigated the impact of IUDs or implant use (61, 62). Only one study, conducted in a cohort of US adolescents, has looked at contraceptive IVR use and HSV-2 acquisition risk. Here, contraceptive IVR use was found to be a risk factor for genital herpes (66). Given the possibility that sex hormones may alter T cell immunity (93), observational studies have explored the association between HCs and HSV shedding with conflicting results (94–96).

Human Papillomavirus: Increased risk for human papillomavirus (HPV) acquisition or decreased HPV clearance with contraceptive use could have important implications, such as increased potential to develop cancer. The bulk of the research conducted on the influence of HC on HPV acquisition and clearance has focused on OCP use, partly due to the association of long-term use with cervical cancer (98). Recent systematic reviews examining the observational data on HC use and HPV acquisition risk, persistence and clearance highlighted inconsistent results regarding OCPs, which may be due to differences in the duration and timing of OCP use, reference groups, duration of follow-up and/or HPV subtype evaluated (61, 62). One recent study, conducted in US adolescents, found contraceptive IVR use to be a significant risk factor for HPV acquisition (66). The available observational evidence does not support an association between DMPA-IM use and HPV acquisition risk and clearance, although injectable contraceptive users may have increased risk of persistent HPV infection (61, 62). Data on HPV acquisition, persistence and/or clearance among implant and IUD users are sparse (61, 62) and the results mixed (97–99). Likely, given the large number of different HPV types, there may also be a difference between high and low risk HPV types.

Randomized data—In contrast to observational studies, the ECHO Trial found that DMPA-IM users had a significantly lower incidence of HSV-2 compared to Cu-IUD users but not LNG-implant users, but the difference was very small (101). Subgroup analysis revealed that this relationship was stronger among younger women (<25 years) (101). To our knowledge, no randomized data exists on HPV risk and contraception, but given the high prevalence and relationship with sexual activity, the relationship between HPV acquisition, clearance and progression to dysplasia would be important to evaluate.

CONCLUSIONS

Overall, good quality data describe that initiation of long-acting progestin-only contraceptives, including LNG-implant and the injectables DMPA-IM and NET-EN, do

not have a major impact on the mucosal microbial environment. While there are generally very limited data on the effect of contraceptive IVRs on the mucosal environment, many different IVRs, including multi-purpose rings containing microbicides against HIV and hormones for pregnancy prevention, are currently in clinical trials and show promising results with few contraindications. Yet, the potential for increased risk of bacterial STIs and candidiasis should be taken into consideration when evaluating these. Additionally, Cu-IUD use has been shown in multiple studies, including a large RCT, to be associated with higher prevalence of BV. Whether LNG-IUS has similar affects needs to be evaluated further. Contraceptives containing different hormones have divergent effects on the FGT ecosystem, leading to differential impact on vaginal health. The high variability in the effect on mucosal immune factors of specific contraceptive methods may be attributed to sub-group effects, whereby different women respond differently to contraceptive initiation due to differences in populations, demographics, age, presence of STIs or bacterial community. These differences may also partly be due to the timing of sampling, duration of contraceptive use, dosage, delivery methods, data analysis methods, and/or to methods used for specimen collection, processing, and analysis. There is thus still a critical need to improve our understanding on the biological effects of contraceptive methods with different pharmacokinetic properties and delivery systems on the mucosal environment, aiding in the development of novel contraceptives and improving individual family planning guidance and recommendations for women.

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Table 1.

Overview of randomized studies evaluating the impact of non-barrier contraceptives on the vaginal mucosal environment

Study details	Randomization	Target group	Methodology	Summary of findings
Bacterial microbiome				
Balle et al, (2020) (Balle et al., 2020a), UChoose trial	NET-EN, OCP or ETG/EE CVR [1:1:1] for 32 weeks.	HIV negative, nonpregnant, adolescent girls; 15–19 years old; single center; South Africa (n=130).	16S V4 sequencing of vaginal swab and Gram staining of vaginal smear collected at baseline and at 16-weeks follow-up visit.	Adolescents randomized to OPCs had lower vaginal microbial diversity and relative abundance of HIV risk-associated taxa compared to those assigned to NET-EN or ETG/EE CVR and were less likely to have BV by Nugent scoring.
Brown et al (2023) ECHO trial	DMPA-IM, Cu-IUD, LNG-implant [1:1:1] for 18 months.	HIV negative, nonpregnant, reproductive age women; 16–35 years old; multi center; South Africa, eSwatini, Zambia and Kenya (n=216/N=7,829).	16S V3V4 sequencing of vaginal swab and Gram staining of vaginal smear collected at enrolment and at 1- and 6-month follow-up.	Participants randomized to Cu-IUD, and not DMPA-IM nor LNG implant, had significantly elevated vaginal bacterial diversity after one and six months of use, relative to baseline. Participants randomized to Cu-IUD also displayed significantly elevated Nugent scores after six months of contraceptive use.
Creinin et al (2008) (Creinin et al., 2008)	ETG/EE CVRs or norelgestromin/EE patches [1:1] for four cycles.	HIV negative, nonpregnant, reproductive aged women; multi center; USA (n=479).	Gram staining of vaginal smear collected at baseline and during the first week of the fourth cycle of product use.	Baseline and follow-up Nugent scores did not vary between groups after three consecutive cycles of use.
Crucitti et al (2018) (Crucitti et al., 2018)	Intermittent or continuous use of ETG/EE CVR [1:1] for 12 weeks.	HIV negative, nonpregnant, reproductive age women; 18–35 years old; single center; Rwanda (n=120).	Gram staining of vaginal smear and qPCR assays of common genital bacteria in vaginal swab collected at baseline and at 12 weeks follow up visit.	In both study arms, a mean decrease in Nugent score was observed after 12 weeks of CVR use and the concentration of *Lactobacillus* species increased significantly while the concentration of *G. vaginalis* and the presence of *A. vaginae* decreased.
Dabee et al (2022)	TFV IVR, TFV/LNG IVR or placebo IVR [2:2:1] for 90 days.	HIV negative, nonpregnant, 18–34 years old; single center; Kenya (n=27)	16S rRNA V3-V4 sequencing and Candidal qPCR of vaginal swab collected prior to IVR insertion and after 90 days of use.	In the TFV/LNG IVR arm; community state types remained unchanged or shifted towards higher Lactobacillus abundance.
Marrazzo et al (2019) (Marrazzo et al., 2019)	Intermittent or continuous use of ETG/EE CVR [1:1] for 7 months.	Nonpregnant, BV-treated reproductive age women, 18–40 years old, single center; Kenya (n=151).	Gram staining of vaginal smear collected at baseline and 2 months (immediate post-CVR) and 3–6 months (sustained post-CVR) follow-up visits.	Over a median duration of follow-up of 4.7 months, BV incidence/recurrence was 10.2% at the immediate post-CVR visit and 7.1% over the sustained post-CVR visits. In a model combining CVR arms, a non-significant increase in BV incidence/recurrence immediate post-CVR (aOR = 2.5 [95% CI 0.9–7.2]), after which BV returned to a level comparable to before CVR initiation (aOR = 1.2 [95% CI 0.8–1.9]).
Thurman et al (2019) (Thurman et al., 2019), CONRAD A13–128 trial	TFV IVR, TFV/LNG IVR or placebo IVR [2:2:1] for 15 days.	HIV negative, nonpregnant, reproductive age women; 18–45 years old; multi center; USA and Dominican Republic (n=51).	16S rRNA V3-V4 sequencing of vaginal swab collected prior to IVR insertion and after 15 days of use.	The vaginal microbiota in participants randomized to active IVRs (TFV/LNG and TFV) did not differ from that of the placebo IVR users in terms of diversity, bioburden and community composition after ~15 days of use. The majority of IVR users maintained their CST throughout the study and there was no increased the incidence of BV in either arm.
Veres et al (2004) (Veres et al., 2004)	ETG/EE CVR or OCP [1:1] for 3 cycles, followed by 3 cycles of the other contraceptive method.	HIV negative, nonpregnant, reproductive age women, 18–45 years old, single center; USA (n=80).	Vaginal swabs were collected at baseline and during cycle 2, 3 and 7 for Gram staining and culture.	At baseline, 83.8% of women were positive for any *Lactobacillus* by culture, and this percentage was similar at subsequent visits and did not differ by contraceptive method. However, the concentration of *Lactobacillus* CFUs positive for H_2O_2-production

Study details	Randomization	Target group	Methodology	Summary of findings
				increased during CVR use and increased over baseline values. BV was rare and did not differ between contraceptive methods.
Vodstrcil et al (2019) (Vodstrcil et al., 2019) SToPBV trial	OCPs (intervention) or current non-hormonal contraceptive practices (control) [1:1], followed for 6 months (or BV-recurrence).	HIV negative, nonpregnant, reproductive age women treated for BV, 18–45 years old, single center; Australia (n=95).	Participants were assessed for BV using both the Amsel method and Nugent scoring of vaginal smears collected at baseline and at day 8 and 1-, 2-, 4-, 5- and the 6-month follow-up visits.	BV-recurrence rates were similar in participants randomized to the OCP (10/100 person years [95% CI: 6–19/100 person years]) compared to controls (14/100 person years [95% CI: 9–21/100 person years], *P*=0.471).
Bacterial STIs and trichomoniasis				
Balle et al, (2020) (Balle et al., 2020b) UChoose trial	NET-EN, OCP or ETG/EE CVR [1:1:1] for 32 weeks.	HIV negative, nonpregnant, adolescent girls; 15–19 years old; single center; South Africa (n=130).	PCR detection of CT, NG and MG in vaginal swab collected at baseline and at 16-weeks follow-up visit.	Adolescents randomized to NET-EN had an increased risk of MG compared to adolescents assigned to oestrogen-containing contraceptives (IRR 16.0 (95% CI 2.96–400), P=0.001) but not an overall increased risk of bacterial STIs (0.96 (0.41–2.07), P=0.915). OCP use was associated with a decreased risk any STI relative to ETG/EE CVR (IRR 2.15 [95% CI 0.84–6.23], P=1.112).
Deese et al (2021) (Deese et al., 2021) ECHO trial	DMPA-IM, Cu-IUD, LNG-Implant [1:1:1] for 18 months.	HIV negative, nonpregnant, reproductive age women, 16–35 years old, multi center; South Africa, eSwatini, Zambia and Kenya (n=7,829).	PCR detection of CT, NG, MG and TV in vaginal swab collected at enrolment and at 18-month follow-up visit.	Participants randomized to DMPA-IM showed a 30% lower risk of NG (PR 0.7 (95% CI 0.5–0.9), P=0.002) compared with Cu-IUD and a 20% lower risk of *CT* (PR 0.8 (95% CI 0.7–0.9), P=0.005) compared with the LNG-Implant users. TV was significantly more prevalent among Cu-IUD (15.3%) than DMPA-IM users (5.6%) (OR 3.29 [95% CI 1.42–7.64]) and LNG implant users (6.5%) (OR 2.72 [95% CI 1.25–5.93]). No significant associations were observed between MG and contraceptive method.
Candidiasis				
Balle et al, (2020) (Balle et al., 2020a) UChoose trial	NET-EN, OCP or ETG/EE CVR [1:1:1] for 32 weeks.	HIV negative, nonpregnant, adolescent girls; 15–19 years old; single center South Africa (n=130).	Candidiasis screening of vaginal smear by microscopy (*Candida* hyphae and spores) at baseline and 16- and 32-weeks follow-up visits.	Women using ETG/EE CVR had a higher number of *Candida* infections (27.0%) compared to the NET-EN (16.4%, P=0.146) and OCP users at follow up (8.7%, P=0.035).
Dabee et al (2022)	TFV IVR, TFV/LNG IVR or placebo IVR [2:2:1] for 90 days.	HIV negative, nonpregnant, reproductive age women; 18–34 years old; single center; Kenya (n=27)	Candidal qPCR of vaginal swab collected prior to IVR insertion and after 90 days of use.	No difference in *Candida* load between arms.
Kestelyn et al., 2018 (Kestelyn et al., 2018)	Intermittent or continuous use of ETG/EE CVR [1:1] for 12 weeks.	HIV negative, nonpregnant, reproductive age women; 18–35 years old; single center Rwanda (n=120).	Vaginal swabs were collected to prepare KOH wet mounts to visualize yeasts at baseline and at follow-up visits (every 4 (intermittent) or 3 (continuous) months)).	The incidence of vaginal yeasts during CVR use increased to 22% for intermittent CVR users and 27% for continuous CVR users, and symptomatic vaginal yeast cases were more common in the continuous than intermittent users (P=0.031).
Marrazzo et al (2019) (Marrazzo et al., 2019)	Intermittent or continuous use of ETG/EE CVR [1:1] for 7 months.	Nonpregnant, BV-treated reproductive age women, 18–40 years old, single center; Kenya (n=151).	Vaginal swabs were collected at baseline and 2 months (immediate post-CVR) and 3–6 months (sustained post-CVR) follow-up visits.	An increased incidence of vulvovaginal candidiasis was observed with CVR use.
Veres et al (2004) (Veres et al., 2004)	ETG/EE CVR or OCP [1:1] for 3 cycles, followed by 3 cycles of the other contraceptive method.	HIV negative, nonpregnant, reproductive age women, 18–45 years old, single center; USA (n=80).	Vaginal swabs were collected at baseline and during cycle 2, 3 and 7 for wet mount preparation to perform	At baseline, 15% of women had *Candida* on culture; during CVR use 18.8% and with OCP use 22.5% of samples were positive for *Candida* by culture. There was a nonsignificant increase in the estimated average concentrations of yeast with OCP use.

Study details	Randomization	Target group	Methodology	Summary of findings
			KOH microscopy for the detection of *Candida*.	
Viral STIs				
Ahmed et al (2019) (Ahmed *et al.*, 2019), ECHO trial	DMPA-IM, Cu-IUD, LNG-Implant [1:1:1] for 18 months.	HIV negative, nonpregnant, reproductive age women; 16–35 years old; multi center; South Africa, eSwatini, Zambia and Kenya (n=7,829).	HIV serological testing performed at every follow-up visit every 3 months to 18 months.	Overall HIV incidence was 3.81 per 100 woman-years (95% CI 3.45–4.21): 4.19 per 100 woman-years (3.54–4.94) in the DMPA-IM group, 3.94 per 100 woman-years (3.31–4.66) in the Cu-IUD group, and 3.31 per 100 woman-years (2.74–3.98) in the LNG-Implant group. The HRs for HIV acquisition were 1.04 (96% CI 0.82–1.33, P=0.72) for DMPA-IM compared with Cu-IUD, 1.23 (0.95–1.59, P=0.097) for DMPA-IM compared with LNG-Implant, and 1.18 (0.91–1.53, P=0.19) for Cu-IUD compared with LNG-Implant.
Hofmeyer *et al* (2017) (Hofmeyr et al., 2017)	Progestin-only injectable (DMPA-IM or NET-EN) or Cu-IUD [1:1] for 12 months	HIV-negative, nonpregnant, reproductive age women, 16–45 years old; multi center; South Africa (n=1,290)	HIV serological testing performed at baseline and at the 12-month follow-up visit.	HIV acquisition occurred in 3.0% women in the injectable arm and 3.5% women in the Cu-IUD arm (injectable vs. Cu-IUD, RR 0.88 [95% CI 0.48–1.59], P= 0.7). Of the DMPA-IM users 3.4% acquired HIV (DMPA-IM vs Cu-IUD, RR 1.01 [95% CI 0.55–1.86], P=1.0) and of the NET-EN users, 1.9% acquired HIV (DMPA-IM vs. Cu-IUD, RR 0.58 [95% CI 0.14–2.42], P=0.4).
Mugo et al (2021) (Mugo et al., 2021), ECHO trial	DMPA-IM, Cu-IUD, LNG-Implant [1:1:1] for 18 months.	HIV negative, nonpregnant, reproductive age women; 16–35 years old; multi center; South Africa, eSwatini, Zambia and Kenya (n=4,062).	HSV-2 serologic testing performed by ELSA on serum at baseline and at the 18-month follow-up visit. Confirmation of HSV-2 was performed by Western blot analysis on those with equivocal ELISA results.	Overall, 614 (15.8%) acquired HSV-2 with an incidence of 12.4/100 person years. Among women assigned to DMPA-IM the incidence rate was 10.9/100 person years, among those assigned to the Cu-IUD it was 13.7/100 person years, and among those assigned to the LNG implant it was 12.7/100 person years. IRR for HSV-2 acquisition were 0.80 (95% CI 0.65–0.97) for DMPA-IM compared with CU-IUD, 0.86 (95% CI 0.71–1.05) for DMPA-IM compared with LNG implant, and 1.08 (95% CI 0.89–1.30) for Cu-IUD compared with LNG implant.

aOR; adjusted odds ratio

ART; antiretroviral therapy

BV; bacterial vaginosis

CI; confidence interval

CST; community state type

CT; *Chlamydia trachomatis*

Cu; copper

CVR; combined vaginal ring

DMPA; depot-medroxyprogesterone acetate

EE; ethinyl estradiol

ECHO; Evidence for Contraceptive Options and HIV Outcomes

ECL; electrochemiluminescence

ETG; etonogestrel

IRR; incidence rate ratio

IUD; intrauterine device

IUS; intrauterine system

HR; hazard ratio

KOH; potassium hydroxide

LNG; levonorgestrel

MG; *Mycoplasma genitalium*

NET-EN; norethisterone enanthate

NG; *Neisseria gonorrhoea*

OCP; oral contraceptive pills

RR; risk ratio

RT-PCR; Real-time polymerase chain reaction

PR; point prevalence ratios

TFV; tenofovir

TV: Trichomonas vaginalis

Table 2.

Overview of non-randomized studies evaluating the impact of initiation of non-barrier contraceptives on the vaginal mucosal environment

Study details	Contraceptive method	Target group	Methodology	Summary of findings
Bacterial microbiome				
Recently reviewed by Bastianelli et al, 2021				
Achilles et al (2018) (Achilles et al., 2018)	Choice of DMPA-IM (n=41), NET-EN (n=44) or MPA/EE (n=40) injection, LNG (n=45) or ETG (n=48) implants or Cu-IUD (n=48), followed for six months.	HIV-negative, nonpregnant, reproductive age women; 18–45 years old; single center; Zimbabwe (n=266).	qPCR analyses for assessment of specific microbiota (including *Lactobacillus* ssp., *G. vaginalis*, *A. vaginae*, and *Megasphaera*-like bacterium phylotype I) in swabs collected at baseline and after 30, 90, and 180 days of use.	BV prevalence increased after Cu-IUD initiation (from 27% to 49%) at 180 days (P=0.005) and the mean increase in Nugent score was 1.2. The frequency and density of beneficial lactobacilli did not change in Cu-IUD users but the concentration of *G. vaginalis* (4.5–5.9; P=0.046) and *A. vaginae* (3.0–5.1; P=0.002) increased between baseline and follow-up. Initiation of hormonal contraceptives did not lead to change in BV prevalence over 180 days or any change in beneficial lactobacilli concentration but women using DMPA had decreased concentrations of *L.iners* (mean decrease 0.8; P=0.004).
Alice *et al* (2012) (Alice et al., 2012)	Requesting either Cu-IUD (n=38) or LNG-IUD (n=32), followed for one month.	HIV-negative, nonpregnant, reproductive age women; 18–48 years old; multi center; Canada, (n=70).	Gram staining and culturing of vaginal samples collected before and one month after IUD insertion.	The prevalence of BV (7.1%) was lower in this study than that described in other populations. Of 43 BV-negative patients who had cultures performed at their one-month follow-up visit, four (9.3%) shifted from being BV negative to being BV positive.
Bassis et al (2017) (Bassis et al., 2017)	Choice of Cu-IUD (n=36) or LNG-IUS (n=40), followed for 12 months.	HIV-negative, nonpregnant, reproductive age women; years old; single center; Brazil (n=76).	DNA extraction and 16S rRNA sequencing of vaginal swabs collected at baseline and 6- and 12-months after contraceptive initiation.	Changes in the vaginal bacterial community composition were not associated with the use of Cu-IUD or LNG-IUS. No observed difference in vaginal microbiota stability with Cu-IUD versus LNG-IUS use.
Ferraz do Lago *et al* (2003) (Ferraz do Lago et al., 2003)	Requesting Cu-IUD insertion, followed for six months.	HIV-negative, nonpregnant, reproductive age women; year range not specified; single center: (n=223).	Gram staining and culturing of vaginal samples collected at after one and six months of contraceptive initiation.	After one month of Cu-IUD insertion, BV was found in 44 women (19.7%) a rate which is similar to what have been observed in similar populations. The authors did not screen the women for BV prior to inserting the Cu-IUD.
De Seta et al (2012) (De Seta et al., 2012)	Requesting either OCPs (n=30) or ETG/EE CVR (n=30), followed for six months.	HIV-negative, nonpregnant, reproductive age women; 18–45 years old; single center; Italy (n=60).	Gram staining and culturing of vaginal samples collected at baseline and after 3 and 6 months of contraceptive initiation.	There was a little change of vaginal milieu in both groups at follow-up. However, an increase in lactobacilli was observed in the CVR users and an increase of Group B *Streptococcus* was observed in OCP users.
Donders *et al* (2011) (Donders et al., 2011)	Requesting LNG-IUS, followed for one to two years.	HIV-negative, nonpregnant, reproductive age women; age range not specified; single center; Belgium (n= 286).	Microscopic analysis pf on pap smears collected prior to and 1–2 years after contraceptive initiation.	After one year of contraceptive use, LNG-IUS users did not have different rates of abnormal vaginal flora, BV, aerobic vaginitis and *Candida* vaginitis compared to baseline, but the general risk of developing any infection was increased.
Donders et al (2018) (Donders et al., 2018)	Personal decision to initiate LNG-IUS, followed for three months (short term) and one year (long term).	HIV-negative, nonpregnant, reproductive age women; >18 years old; single site; Belgium (n=252).	Detailed microscopy on vaginal smears obtained by cytobrush collected at baseline and 3- and 12-months after LNG-IUS initiation was used to define lactobacillus grades and detect BV.	A temporary worsening in lactobacillus grades and increased rates of BV was found after three months of LNG-IUS use. After one year, however, these changes were reversed.

Study details	Contraceptive method	Target group	Methodology	Summary of findings
Eschenbach et al (2000) (Eschenbach et al., 2000)	Personal decision to initiate OCPs, followed for two months.	HIV-negative, nonpregnant, reproductive age women; 18–40 years old; single center; USA (n=30).	Vaginal samples collected at baseline and two months after OCP initiation cultured for aerobic and anaerobic bacteria. H_2O_2–producing *Lactobacillus* were identified by blue pigment formation by H_2O_2 oxidation of tetramethylbenzidine in brucella agar base.	The vaginal bacteria remained unchanged after two months of OCP use, except for a small decrease in the number of participants with CFUs of H2O2-producing *Lactobacillus* and in the total number of subjects with *Ureaplasma urealyticum*.
Erol et al (2014) (Erol et al., 2014)	Requesting either Cu-IUD (n=108) or LNG-IUS (n=42) insertion, followed for 12 months.	HIV-negative, nonpregnant, reproductive age women; 18–50 years old); single center; Turkey (n=150).	Gram staining and culturing of vaginal samples collected at baseline and after 12 months of contraceptive initiation.	There were no changes in BV prevalence in either contraceptive group after 12 months of initiation. *Mycoplasma hominis* infections were significantly more common after one year of Cu-IUD use compared to baseline, albeit not with LNG-IUS use.
Fosch et al (2018) (Fosch et al., 2018)	Choice of OCPs, condom use or the rhythm method, followed for six months.	HIV-negative, nonpregnant, reproductive age women; 14–45 years old; single center; Argentina (n=101).	Vaginal swabs were collected at baseline and after 3 and 6 months of contraceptive initiation for MALDI-TOF MS and 16S rRNA sequencing.	A statistically significant association between OCPs and BV-negative microbiota was observed after 3 months ($p<$ 0.01) and after six months (P<0.0001).
Gupta et al (2000) (Gupta et al., 2000)	Personal decision to initiate OCPs (n=103), a cervical cap (35) or diaphragm-spermicide (n=75), followed for one month.	HIV-negative, nonpregnant, reproductive age women; 18–40 years old; single center; USA (n=331).	Vaginal collected at baseline and then weekly for one month for Gram staining and bacterial culturing.	The prevalence of women with lactobacilli, group B streptococci, or *Gardnerella vaginalis,* did not change 4 weeks after initiation of any of the contraceptive methods. However, the prevalence of women with vaginal *Escherichia coli* and anaerobic gram-negative rods colonization and abnormal Nugent scores increased among women using the cervical cap or diaphragm-spermicide but not among women using OCPs.
Huang et al (2015) (Huang et al., 2015)	Phase III trial sub-study of NES/EE CVR, participants followed for 12 months.	HIV-negative, nonpregnant, reproductive age women; 18–40 years old; multi center; USA (n=120).	Vaginal swabs were collected at baseline and after six and 13 cycles for Gram stain and culturing for *Lactobacillus, G. vaginalis, E. faecalis, S. aureus, E. coli* and anaerobic gram-negative rods.	Nugent scores remained stable throughout the 1-year of NES/EE use. Although anaerobic gram-negative rods prevalence increased significantly, the median concentration decreased slightly. There were no significant changes in frequency or concentrations of other pathogens.
Jacobson *et al* (2014) (Jacobson et al., 2014)	Requesting LNG-IUS insertion, followed for 12 weeks.	HIV-negative, nonpregnant, reproductive age women; 21–33 years old; single center; USA (n=13).	Vaginal and cervical samples collected at baseline and 12 weeks after contraceptive initiation for 16S rRNA sequencing.	The vaginal microbiome changes very little in response to LNG-IUS placement. Compared to sampling visits prior to LNG-IUS placement, sampling visits after LNG-IUS insertion were more likely to have *L. crispatus* reads greater than 50% of total reads (OR 2.13, 1.01–4.48).
Lessard et al (2008) (Lessard et al., 2008)	Requesting LNG-IUS, followed for up to seven years.	HIV-negative, nonpregnant, reproductive age women; 20–39 years old; single center; Brazil (n=187).	Cervical smear samples were collected prior to contraceptive initiation and annually thereafter for up to seven years for cytopathological evaluation and BV assessment by presence of clue cells.	No significant results were found with respect to cytopathological abnormalities or other microbiological alterations following insertion of the LNG-IUS.
Madden et al (2012) (Madden et al., 2012)	Choice of either Cu-IUD (n=31), LNG-IUD (n=59), OCPs (n=25), CVR (type not specified) (n=31), or transdermal contraceptive. patch (n=7), followed for 6 months.	HIV-negative, nonpregnant, reproductive age women; 18–45 years old; single center; USA (n=157).	Vaginal swabs were collected at baseline and monthly for up to 6 months for Gram staining and microscopy for Nugent scoring and Amsel criteria determination.	The incidence of BV was higher among IUD users at 37.0% compared to 19.3% in OCP, CVR, and patch users (P=0.03). The incidence of BV did not differ among OCP, CVR and patch users (15.0% vs 16.7% vs 22.4%, P=0.24). There was a trend towards increased BV incidence among LNG-IUS users (41.8%) compared to 28.0% of CU-IUD users (P=0.23). The association between IUD use and BV may be mediated by irregular vaginal bleeding.

Study details	Contraceptive method	Target group	Methodology	Summary of findings
Miller et al (2000) (Miller et al., 2000)	Personal decision to initiate DMPA-IM, followed for six months.	HIV-negative, nonpregnant, reproductive age women; 18–40 years old; single center; USA (n=38).	Vaginal swabs collected at baseline and 3- and 6-months after DMPA-IM initiation were cultured for aerobic and anaerobic bacteria.	The number of participants with any *Lactobacillus* did not change, but the number with H_2O_2–producing *Lactobacillus* decreased from 20% before to 12% after six months of DMPA (P=0.005). The log concentration in CFUs per milliliter of vaginal fluid of H_2O_2–positive *Lactobacillus* decreased in a linear manner from 4.0 ±0.6 at baseline to 2.5 ±0.6 after 6 months of DMPA use (P=0.006).
Neale *et al* (2009) (Neale et al., 2009)	Requesting insertion of either a Cu-IUD (n=78) or a LNG-IUS (n=94), followed for six months.	HIV-negative, nonpregnant, reproductive age women; years old; single center: (n=172).	Symptoms were elicited and a high vaginal smear was obtained for Gram staining and microscopy. BV was graded using the Ison-Hay criteria.	Women were significantly more likely to have developed an abnormal vaginal discharge 4–6 weeks after insertion of a Cu-IUD compared with LNG-IUS (27% vs. 14%; OR 2.29 [95% CI 1.01–5.22], P=0.04). This trend was not significant six months postinsertion (19% vs. 8%; OR 2.63 [95% CI 0.95–7.26], P=0.06). Four to six weeks after insertion, 2/51 (3.9%) Cu-IUD users who had normal vaginal microbiota at baseline had developed BV compared with 1/71 (1.4%) LNG-IUS users (OR 2.86 [95% CI 0.25–32.39], P=0.38). Six months after insertion, 3/41 (7.3%) Cu-IUD users had developed BV compared with 2/71 (2.8%) LNG-IUS users (OR 2.73 [95% CI 0.44 –17.02], P=0.30).
Rifkin *et al* (2009) (Rifkin et al., 2009)	Choice of either a Cu-IUD (n=78) or LNG-IUS (n=94).	HIV-negative, nonpregnant, reproductive age women; age range not specified; single center; UK (n=172).	Vaginal swabs were collected at baseline and after four to six weeks and six months after contraceptive initiation for Gram staining and microscopy.	Women were more likely to develop abnormal vaginal discharge 4–6 weeks after insertion of a Cu-IUD (27%) compared to LNG-IUS (14%, P=0.04). More women with a Cu-IUD developed BV compared with an LNG-IUS at 4–6 weeks (3.9% vs. 1.4%) IUS users (P=0.38) and six months (7.3% vs. 2.8%; P=0.30). However, there were insufficient numbers of women with BV to demonstrate any significant difference between the vaginal microbiota of the two groups.
Roxby et al (2016) (Roxby et al., 2016)	Personal decision to initiate DMPA-IM, followed for one year.	HIV-negative, nonpregnant, reproductive age women; >18 years old); single center; Kenya (n=15).	Vaginal swabs were collected at baseline and monthly after DMPA-IM initiation for up to 1 year for Gram staining, culturing and qPCR assays (*L. crispatus, L. jensenii, L. iners, G. vaginalis* and broad range 16S gene for total bacterial load).	The quantities of *G. vaginalis* and total bacterial load declined significantly after DMPA-IM initiation. *L. iners* was highly prevalent with no significant changes observed after DMPA-IM initiation. *L. crispatus* and *L. jensenii*, were rarely detected at baseline with no changes for either species detected after DMPA-IM initiation. There was also no change in the detection of *Lactobacillus* by culture or Nugent score before and after DMPA-IM initiation.
Whitney et al (2020) (Whitney et al., 2020)	Choice of DMPA-IM (n = 33) or non-HC (condoms, lactational amenorrhea, rhythm) (n = 21).	HIV-negative, 6–14 weeks postpartum, reproductive age women; years old; single center; Kenya (n=54).	Vaginal swabs were collected at baseline and after three months of contraceptive initiation for Nugent score determination and taxon-specific qPCR of eight bacteria.	After three months, significant decreases in the concentrations of *Sneathia* species, *Mycoplasma hominis*, and *Parvimonas* species Type 1 were seen among non-HC users, however concentrations remained stable among DMPA-IM users; contraceptive method was associated with significantly different changes in *M. hominis* concentration between groups (P=0.010).
Yang *et al* (2019) (Yang et al., 2019)	Desire to use DMPA-IM.	HIV-negative, nonpregnant, reproductive age women; 18–35 years old; single center; USA (n=25).	Mid-vaginal swabs were collected at baseline and one and three months after contraceptive initiation for 16S rRNA sequencing.	No significant changes in the vaginal microbiota were observed after DMPA treatment when Hispanic White and Black women were analyzed together. The microbiome in Black women became more diversified and contained more vaginosis-associated bacteria and *Prevotella* than Hispanic

Study details	Contraceptive method	Target group	Methodology	Summary of findings
				White women after DMPA treatment. The Firmicutes to Bacteroidetes (F/B) ratio and *Lactobacillus* to *Prevotella* (L/P) ratio were lower in Black women than in Hispanic White women after 3 months of contraceptive use.
Bacterial STIs and trichomoniasis				
Recently reviewed by Deese et al, 2018 (Deese et al., 2018) and McCathy et al, 2019 (McCarthy et al., 2019).				
Candidiasis				
Behboudi-Gandevani *et al* (2015) (Behboudi-Gandevani et al., 2015)	Personal decision to initiate Cu-IUD, followed for three months.	HIV-negative, nonpregnant, reproductive age women; 15–45 years old; multi center; Iran (n=101).	Sabouraud's dextrose agar media was used for culturing of *Candida* species from vaginal swabs collected at baseline and 3 months after CU- IUD initiation.	The mean colony counts of *Candida* increased significantly, but the amount of positive *Candida* cultures was not significantly different before and three months after Cu-IUD insertion.
Donders et al (2018) (Donders et al., 2018)	Personal decision to initiate LNG-IUS, followed for three months (short term) and one year (long term).	HIV-negative, nonpregnant, reproductive age women; >18 years old; single site; Belgium (n=252).	Detailed microscopy on vaginal smears obtained by cytobrush collected at baseline and 3- and 12-months after LNG-IUS initiation was used to detect the presence of *Candida*. Cultures for *Candida* were used to back up the microscopy findings.	The number of *Candida*-positive cultures increased significantly after one year of LNG-IUS use compared to before LNG-IUS insertion.
Erol et al (2014) (Erol et al., 2014)	Requesting either Cu-IUD (n=108) or LNG-IUS (n=42) insertion, followed for 12 months.	HIV-negative, nonpregnant, reproductive age women; 18–50 years old); single center; Turkey (n=150).	CHROMagar Candida media used for identification of *Candida* species in vaginal samples collected at baseline and after 12 months of contraceptive initiation.	Colonization by *Candida* was significantly more common after one year of Cu-IUD use compared to baseline, albeit not with LNG-IUS use.
Eschenbach et al (2000) (Eschenbach et al., 2000)	Personal decision to initiate OCPs, followed for two months.	HIV-negative, nonpregnant, reproductive age women; 18–40 years old; single center; USA (n=30).	Vaginal samples collected at baseline and 2 months after OCP initiation for Gram staining and wet-mount analysis.	The presence of *C. albicans* did not change with two months of OCP use.
Gupta et al (2000) (Gupta et al., 2000)	Personal decision to initiate OCPs, a cervical cap or diaphragm-spermicide, followed for one month.	HIV-negative, nonpregnant, reproductive age women; 18–40 years old; single center; USA (n=331).	Vaginal collected at baseline and then weekly for one month for Gram staining and culturing.	The prevalence of women with *Candida* species decreased slightly from 16% at baseline to 5% at week four among those in the OCP group.
Huang et al (2015) (Huang et al., 2015)	Phase III trial sub-study of NES/EE CVR, participants followed for 12 months.	HIV-negative, nonpregnant, reproductive age women; 18–40 years old; multi center; USA (n=120).	Vaginal swabs were collected at baseline and after 6 and 13 cycles for wet mount microscopy, Gram stain and culturing for *Candida*.	Over one year of use, 15% of the participants were clinically diagnosed with vulvovaginal candidiasis, albeit the detection rate did not change significantly from baseline to either cycle six or 13.
Miller et al (2000) (Miller et al., 2000)	Personal decision to initiate DMPA-IM, followed for six months.	HIV-negative, nonpregnant, reproductive age women; 18–40 years old; single center; USA (n=38).	Vaginal swabs collected at baseline and 3- and 6-months after DMPA-IM initiation for Gram stain and wet-mount analysis.	A significant linear decrease in *Candida albicans* colonization was observed over six months of DMPA-IM use.
Moradi et al (2019) (Moradi et al., 2019)	Personal decision to initiate Cu-IUD, followed for three months.	HIV-negative, nonpregnant, reproductive age women; 15–50 years old; single center; Iran (n=95).	Cervicovaginal samples were collected at baseline and 3 months after Cu-IUD initiation for culturing on Sabouraud dextrose agar and CHROMagar Candida. PCR-RFLP was performed for identification of *Candida* species.	The amount of positive *Candida* cultures was significantly increased three months after Cu-IUD insertion from 11.6% to 25.3%. The prevalence of simultaneous infection with both *C. albicans* and *C. glabrata* species increased.
Viral STIs - HIV				

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Study details	Contraceptive method	Target group	Methodology	Summary of findings
Recently reviewed by Curtis et al, 2020 (Curtis et al., 2020).				
Viral STIs - HSV				
Recently reviewed by Deese et al, 2018 (Deese et al., 2018) and McCathy et al, 2019 (McCarthy et al., 2019).				
Viral STIs - HPV				
Recently reviewed by Deese et al, 2018 (Deese et al., 2018) and McCathy et al, 2019 (McCarthy et al., 2019).				

CFU; colony-forming units

Cu-IUD; copper intrauterine device

CVR; combined vaginal ring

DMPA-IM; depot-medroxyprogesterone acetate

EE; ethinyl estradiol

ES; estradiol cypionate

ETG; etonogestrel

HIV; human immunodeficiency virus

KOH; potassium hydroxide

LNG-IUS; levonorgestrel intrauterine system

MPA; medroxyprogesterone acetate

NES; Nestorone

NET-EN; norethisterone enanthate

OCP; oral contraceptive pills

PCR-RFLP; polymerase chain reaction-restriction fragment length polymorphism