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Effect of contraceptive methods on the vaginal microbiome and host immune factors☆,☆☆

Myrna G. Serrano [a,b,4], David Edwards [a,b,c,4], Khatija Ahmed [d,e], Veronique C. Bailey [d], Mags Beksinska [f], Laahirie Edupuganti [a,b], Rushil Harryparsad [g], Florence L. D'Hellencourt [h,1], Bahiah Meyer [g], Celia Mehou-Loko [g], Nina Radzey [g], Ongeziwe Taku [g], Anna-Lise Williamson [g], Jennifer Smit [f], Katherine Spaine [a,b], Bin Zhu [a,b], Kimberly K. Jefferson [a,b], Kavita Nanda [h], Jerome F. Strauss III [i,2], Charles S. Morrison [h], Jennifer Deese [h,1], Lindi Masson [g,j,k,3,5], Gregory A. Buck [a,b,*,5]

[a] Microbiology and Immunology Department, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA
[b] Center for Microbiome Engineering and Data Analysis, Virginia Commonwealth University, Richmond, VA, USA
[c] Statistical Science, College of Humanity and Sciences, Virginia Commonwealth University, Richmond, VA, USA
[d] Setshaba Research Centre, Tshwane, South Africa
[e] Department of Medical Microbiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa
[f] MatCH Research Unit (MRU), University of the Witwatersrand, Durban, South Africa
[g] Institute of Infectious Disease and Molecular Medicine (IDM), University of Cape Town, Cape Town, South Africa
[h] FHI 360, Cary, NC, USA
[i] Department of Obstetrics and Gynecology, School of Medicine, Virginia Commonwealth University, Richmond, VA, USA
[j] Centre for the AIDS Programme of Research in South Africa, Durban, South Africa
[k] Central Clinical School, Monash University, Melbourne, Australia

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ABSTRACT

Objective: The objective of this study was to assess alterations in vaginal microbiota and immune markers over the first 3 months following initiation of copper intrauterine device (copper IUD), levonorgestrel (LNG) implant, and intramuscular depot medroxyprogestone acetate (DMPA-IM).
Study design: We included 162 participants from the Evidence for Contraceptive Options and HIV Outcomes (ECHO) trial, which enrolled healthy, HIV-negative women seeking contraception and randomized them to a copper IUD, LNG implant, or DMPA-IM. Microbiome and immune profiles in vaginal swab samples collected at enrollment, 1 month and 3 months were analyzed. We categorized microbiome profiles as "optimal", "intermediate", or "non-optimal" based on established criteria [1]. We compared microbiome and immune markers across contraceptive groups and evaluated changes to 1 and 3 months.
Results: Copper IUD users had a more diverse vaginal microbiome and generally increased inflammatory cytokines and antimicrobial peptides over the 3-month follow-up, compared to LNG-implant and DMPA-IM users [2]. LNG-implant users had less complex vaginal microbiomes with reduced inflammation, while DMPA-IM showed little change in either microbiome composition or inflammatory markers. Copper IUD users exhibited lower microbiome stability and a higher likelihood of transitioning to less optimal profiles. In contrast, LNG-implant users showed greater stability and a higher probability of transition to optimal microbiome and immune marker profiles.
Conclusions: Contraceptive methods affect the vaginal microbiome differently. Copper IUD use may lead to less favorable profiles and increased levels of some immune markers, indicating potential adverse health effects. Conversely, LNG-implant usage promotes a more favorable microbiome and immune marker balance.
Implications: Our findings suggest that copper IUDs are associated with decreased prevalence of Lactobacillus-dominated microbiomes, higher transition rates towards less optimal microbiome and increased inflammatory profiles, which may lead to negative implications for gynecologic and reproductive health, the LNG-implant may offer positive health benefits with increased prevalence of L. crispatus-dominated microbiomes.
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1. Introduction

Of nearly 2 billion reproductive aged women worldwide, almost half use contraception [3]. However, its impact on the vaginal microbiome remains unclear. In recent years, consensus is that *Lactobacillus* species (*L. crispatus, L. gasseri* and *L. jensenii*) are considered protective against bacterial vaginosis (BV) and sexually transmitted infections (STIs) including HIV [4]. Conversely, *Gardnerella vaginalis*, *Ca.* Lachnocurva vaginae (BVAB1), *Atopobium vaginae.* and other anaerobes are linked to BV, cervicovaginal inflammation, reduced epithelial barrier integrity, and increased risk of adverse gynecological and obstetric outcomes [5–8]. Lastly, *Lactobacillus iners* is often considered intermediate impact because of its association with greater microbial diversity and a higher probability of transition to a less protective vaginal microbiome [9,10].

Recent studies suggest that estrogen-containing contraceptives have a positive effect on the vaginal microbiome, favoring *Lactobacillus*-dominant profiles [11–14], whereas copper intrauterine devices (IUDs) are linked to increased microbial diversity and BV [15,16]. The impact of progestin-only contraceptives, including intramuscular depot medroxyprogesterone acetate (DMPA-IM) - used by nearly 23 million women and the most used contraceptive among African women [3] - has yielded inconsistent findings [11].

We previously reported that users of copper IUDs and LNG implants in this cohort South African women had higher levels of pro-inflammatory and chemotactic markers at month 3 compared to baseline [2]. In the present study, we evaluated the same cohort, randomized to contraceptive methods including the copper IUD, the levonorgestrel implant (LNG-implant), and DMPA-IM. We assessed vaginal microbiome profiles alongside cytokine and antimicrobial peptide levels to test the hypothesis that these contraceptive methods may exert distinct effects on the vaginal microbiome and host immune responses.

2. Materials and methods

The following is a summary of Methods; full details are provided in Appendix A: Supplemental Materials.

2.1. Participants and samples

We selected participants from the Evidence for Contraceptive Options and HIV Outcomes (ECHO) Trial, in which individuals were randomized to receive either copper IUD, LNG-implant, or DMPA-IM. The trial was conducted across four African countries between December 14, 2015, and September 12, 2017 [17]. We collected lateral vaginal wall swabs at baseline, 1 month, and 3 months post-contraceptive initiation from participants at the Setshaba Research Centre (SRC) in Tshwane (n = 53) and the MatCH Research Unit (MRU) in the eThekwini District, South Africa (n = 109). We obtained all baseline samples immediately before contraceptive initiation. All participants were HIV-seronegative at baseline, and none had been using HIV pre-exposure prophylaxis (PrEP). We stored samples dry at −80 °C.

2.2. 16S rRNA taxonomic surveys

We performed 16S rRNA gene surveys as previously described [18] and deposited sequences in the Sequence Read Archive under BioProject SUB12094402. We assigned vagitypes as described previously, categorizing vaginal 16S rRNA profiles into community state types (CSTs) according to the taxon with the highest proportion of reads (≥30%). We classified samples with no single dominant taxon (< 30% of reads) as “No Type” [18]. Alternatively, we designated vagitypes dominated by *L. crispatus, L. gasseri* or *L. jensenii* as “optimal”, those dominated by *L. iners* as “intermediate” and those lacking *Lactobacillus* species as “non-optimal” [1].

2.3. Diversity analysis

We assessed alpha diversity using the Shannon and Inverse Simpson indices. To evaluate beta diversity, we used Non-Metric Multi-Dimensional Scaling and Bray-Curtis distances via the vegan package in R [19]. We also analyzed beta diversity using centered log ratio (clr) transformation and visualized it with t-distributed stochastic neighbor embedding (t-SNE) using Rtsne package [20,21]. We tested statistical differences using the Wilcoxon and Adonis tests [19].

2.4. Longitudinal analysis

We applied Poisson regression models to assess associations between vaginal microbiome composition and contraceptive method over time. We modeled vaginal microbiome counts (optimal, intermediate, non-optimal) as a function of contraceptive method, time point, and vaginal microbiome class. To compare homogeneous and non-homogeneous association models, we used an analysis of deviance Chi-square test in R [19].

2.5. Transition analysis

We used a continuous-time Markov chain model to analyze vagitype transitions, employing the msm and markovchain packages in R [22]. We estimated transition probabilities among the three vaginal microbiome states (optimal, intermediate, or non-optimal) and calculated 95% confidence intervals to assess statistical differences between groups.

2.6. Mixed effects modeling of cytokine and vaginal microbiome associations

We previously measured cytokines and immune markers - including MIP-1α (CCL3), MIP-1β (CCL4), MIP-3α (CCL20), IP-10, CXCL10, RANTES, CCL5, IL-6, IL-8, IL-1β, TNF-α, IFN-α, and SLPI using customized Human Magnetic Luminex Screening Assays (R&D Systems, Minneapolis, USA) as previously described [2]. HBD-1 and HBD-2 were quantified using ELISA kits (Novus Biologicals, Colorado, USA). In the current study, we conducted a new analysis combining these previously reported cytokine and antimicrobial peptide profiles with vaginal microbiome profiles using mixed effect models.

(*footnote continued*)
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* Corresponding author.
E-mail address: Gregory.buck@vcuhealth.org (G. Buck).
[1] Present address: Pfizer, Inc., Pennsylvania, PA, USA.
[2] Present address: Department of Obstetrics and Gynecology, Center for Research on Reproduction and Women's Health, University of Pennsylvania, Philadelphia, PA, USA.
[3] Present address: Disease Elimination Program, Life Sciences Discipline, Burnet Institute, Melbourne, Australia.
[4] Myrna G. Serrano and David Edwards contributed equally to this work.
[5] Lindi Masson and Gregory A. Buck are co-senior authors of this work.

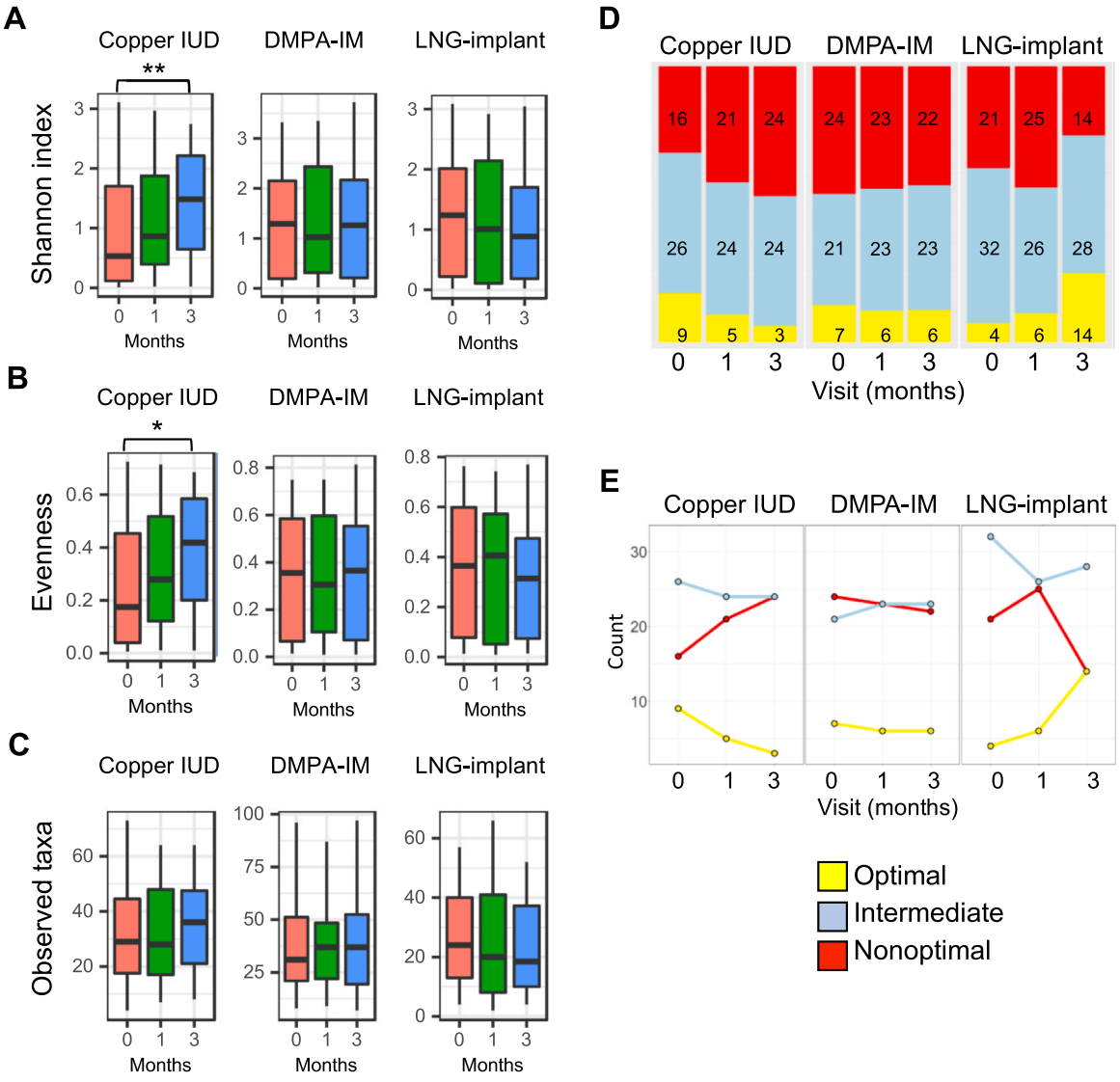

Fig. 1. Transitions over time of vagitypes in response to different contraceptive methods (Tshwane and in the eThekwini District, South Africa, 2015–2017). (A) Alpha diversity was quantified by calculating the Shannon index. (B) Evenness of taxa distribution. (C) The number of observed taxa. * Indicates $p = 0.05$ and ** $p = 0.01$ after adjusting for multiple comparisons. (D) Longitudinal changes in Optimal, Intermediate and Non-optimal vaginal microbiome. (E) Vaginal microbiome counts across time with respect to contraceptive method.

3. Results

3.1. Baseline vaginal microbiome similarity across study sites

We recruited participants for this ECHO sub-study from women's health clinics and the general community in Tshwane and eThekwini, South Africa, and randomized into copper IUD group (n = 51), DMPA-IM group (n = 53) and LNG implant group (n = 58). Baseline characteristics were comparable across sites and contraceptive groups, closely resembled the full ECHO cohort, except that 99% of the individuals in this sub-cohort had never been married, compared to 80% in the ECHO cohort.

The majority of participants exhibited low-diversity vaginal microbiomes dominated by a single species with *L. iners* being the most common (around 49% of samples), followed by *L. crispatus* (around 12%), BVAB1 (around 11%), *G. vaginalis* (around 6%), and *A. vaginae* (around 4%) (Supplemental Fig. 1A). Only around 9% of samples were classified as "no type" (Supplemental Figs. 1A–C). No significant differences in baseline vaginal microbiome diversity or composition were observed between sites or contraceptive groups (Supplemental Figs. 2A–D).

3.2. Copper IUD use associated with less protective vaginal microbiome

Our taxonomic analysis using 16S rRNA profiles showed that copper IUD use was associated with a trend toward a less protective vaginal microbiome with decreased prevalence of *L. crispatus* and increased prevalence of *G. vaginalis,* BVAB1, *A. vaginae* and other anaerobes, although these changes did not remain significant after adjustment for multiple comparisons (Supplemental Figs. 3A–D). Profiles of copper IUD users showed increased Shannon index (within sample) taxonomic alpha diversity (p = 0.01), evenness (taxa become more similar in relative abundance, (p = 0.01) and decreased beta diversity (between sample taxonomic diversity, p = 0.28) by M3 (Figs. 1A–C, and Supplemental Fig. 3E). In contrast, among women using the LNG-implant, there was an increase in the proportion with optimal *L. crispatus*-dominated vaginal microbiomes and a reduction in *G. vaginalis* and other non-optimal vagitypes, with diversity trending toward optimal states. Taxonomic profiles of DMPA-IM users were largely unaltered.

To reduce the complexity of the data, we grouped vaginal microbiome profiles into (1) optimal (dominated by *L. crispatus, L. gasseri* and *L. jensenii*); (2) intermediate (dominated by *L. iners*); and (3) non-

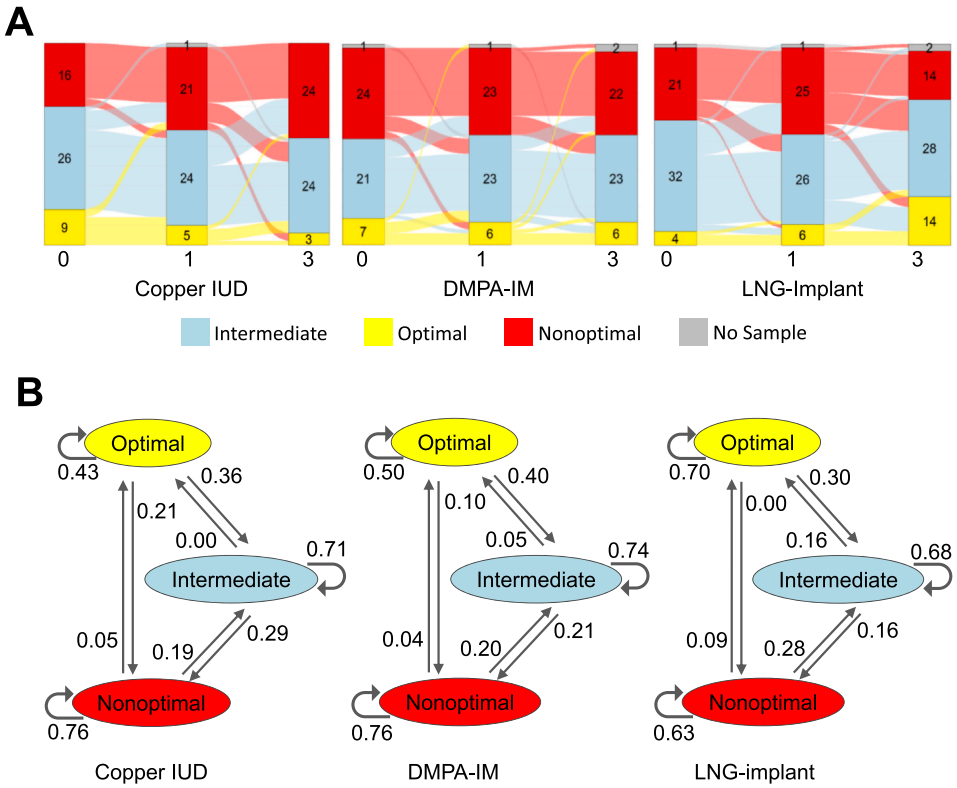

Fig. 2. Vaginal microbiome transitions in women using different contraceptive methods (Tshwane and in the eThekwini District, South Africa, 2015–2017). We assessed the probability of transition of the vaginal microbiomes in each contraceptive group longitudinally across the three month period using a simplified Markov model. (A) Alluvial diagram illustrating the transitions among vaginal microbiome profiles among women using different contraceptive methods. The numbers of women in each transitional group are indicated. (B) Transition frequencies among women using different contraceptive methods.

Table 1
Relevant baseline characteristics of the ECHO cohort[a] and sub-study cohort from Setshaba Research Centre (Tshwane) and MatCH Research Unit (eThekwini District), South Africa, 2015–2017

	Copper IUD *n* (%)		DMPA-IM *n* (%)		LNG implant *n* (%)	
	ECHO[a]	Sub-study	ECHO[a]	Sub-study	ECHO[a]	Sub-study
	2609	51	2607	53	2613	58
Age (y)						
16–17	26 (1)	0 (0)	17 (1)	0 (0)	21 (1)	0 (0)
18–20	684 (26)	11 (21.5)	695 (27)	8 (15)	683 (26)	12 (21)
21–24	913 (35)	23 (45)	953 (37)	26 (49)	956 (37)	22 (38)
25–30	752 (29)	11 (21.5)	719 (28)	11 (21)	735 (28)	20 (34)
31–35	232 (9)	6 (12)	225 (9)	8 (15)	218 (8)	4 (7)
Marital status						
Never married	2090 (80)	51 (100)	2087 (80)	53 (100)	2085 (80)	57 (98)
Married[b]	517 (20)	0 (0)	522 (20)	0 (0)	528 (20)	1 (2)
BMI ≤ 30	1946 (75)	29 (57)	1958 (75)	39 (74)	1913 (73)	41 (71)
BMI > 30	663 (25)	22 (43)	649 (25)	14 (36%)	700 (27)	17 (29)
STI status[c]						
C. trachomatis	486 (19)	7 (14)	454 (17)	8 (15)	480 (18)	16 (28)
N. gonorrhoeae	124 (5)	2 (4)	117 (4)	2 (4)	127 (5)	3 (5)
HSV−2-serology	1020 (39)	14 (27)	1001 (38)	21 (40)	967 (37)	18 (31)

BMI, body mass index; *C. trachomatis, Chlamydia trachomatis*; DMPA-IM, intramuscular depot medroxyprogesterone acetate; ECHO, Evidence for Contraceptive Options and HIV Outcomes; HSV-2, herpes simplex virus type 2; IUD, intrauterine device; LNG, levonorgestrel; *N. gonorrhoeae*, *Neisseria gonorrhoeae*; STI, sexually transmitted infection.
[a] Samples from the ECHO cohort were collected across 12 research sites in eSwatini, Kenya, South Africa, and Zambia, 2015-2017 [17].
[b] Includes married and previously married participants.
[c] STI results from the sub-study cohort were previously reported by Radzey et al. [2].

optimal (all other vagitypes). The numbers of women in each category or visit for each contraceptive group in the study are indicated in Figure 1D. This analysis revealed a significant association ($p = 0.029$) between visit and vaginal microbiome among LNG-implant users; i.e., a shift toward increased optimal and decreased non-optimal vagitypes (Fig. 1D). However, copper IUD users shifted toward increased non-optimal and decreased optimal vagitypes over time, although the association was not statistically significant ($p = 0.29$). Poisson regression analysis comparing transitions between the three vagitype groups in copper IUD and LNG-implant users showed a significant ($p = 0.015$) non-homogenous association between the longitudinal vagitypes across the two groups (Fig. 1E). In contrast, we observed no non-homogenous association in pairwise analyses of the DMPA-IM group compared to the copper IUD or LNG-implant groups.

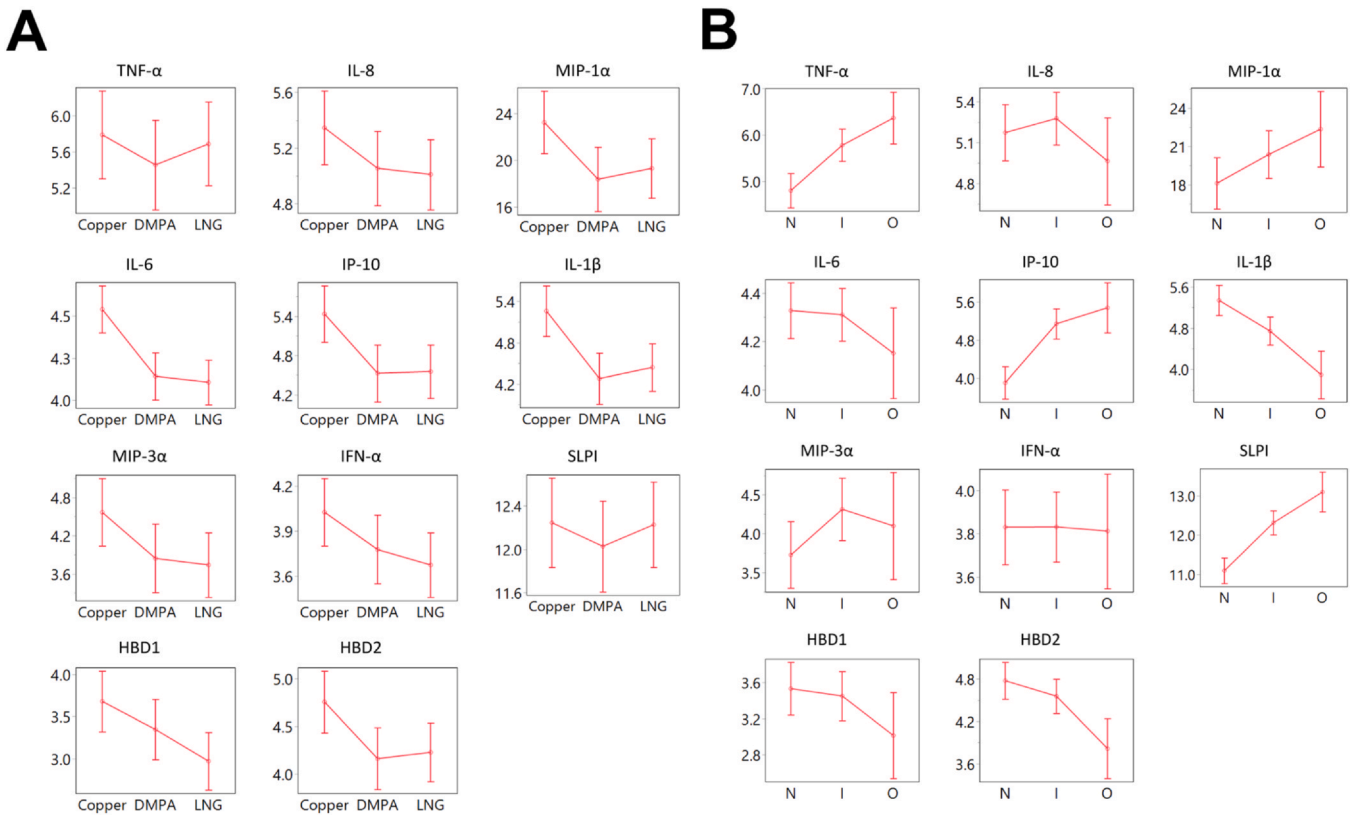

Fig. 3. Effect of contraceptive method on cytokine and antimicrobial peptide expression levels (Tshwane and in the eThekwini District, South Africa, 2015–2017). A mixed effect model was fit using JMP version 16 to each cytokine and antimicrobial peptide including a random subject effect and covariates for (A) Contraceptive method (copper IUD, DMPA-IM, LNG-implant), visit (baseline, M1 or M3), BMI, active STI, and (B) Vaginal microbiome profile (Optimal, Intermediate, Nonoptimal). BMI = body mass index; DMPA-IM = intramuscular depot medroxyprogesterone acetate; IUD = intrauterine device; LNG = levonorgestrel; STI = sexually transmitted infection.

3.3. Transition probabilities explain differences between contraceptive groups

A Markov chain model analysis was utilized to probabilistically quantify the frequency of vagitype transitions. Stratifying the vaginal microbiomes into optimal, intermediate and non-optimal groups, we found that transitions in copper IUD users were more frequently toward non-optimal profiles than transitions in the other two groups (Figs. 2A and B, and Table 1). Vaginal microbiome profiles of copper IUD users tended to frequently transition away from the optimal group (57%; i.e., 36% to intermediate and 21% to non-optimal), and only rarely (around 5%) transitioned toward an optimal profile. Conversely, optimal vaginal microbiomes of women using LNG-implant were more stable, transitioning away from the optimal profile at a lower rate (around 30% to intermediate vaginal microbiomes). Transitions to the optimal state from other states in the LNG users were not uncommon (i.e., 9% from non-optimal and 16% from intermediate) and observed in a higher rate compared to copper IUD and LNG-implant users, 5% and 9%, respectively. Transition rates among women using DMPA-IM were intermediate in frequency compared to the copper IUD and LNG-implant groups.

3.4. Cytokine and antimicrobial peptide expression is correlated with vaginal microbiome composition and contraceptive method

When we evaluated the vaginal microbiome profiles alongside cytokine and antimicrobial peptide profiles using mixed-effect models - which incorporated covariates such as contraceptive method, visit (M1 and M3), BMI, active STI status, and a random subject effect - with found that levels of IL-6, IL-1β, MIP-1α, MIP-3α, IP-10 and HBD-1 & -2 were significantly higher in copper IUD users compared to the those using LNG-implant and DMPA-IM. IL-8 and IFN-α showed a similar, though statistically non-significant increase in copper IUD users. In contrast, TNF-α and SLPI levels were similar in all three contraceptive groups in this model (Fig. 3A and Supplemental Table 1).

The mixed effect model showed that IL-1β and IL-6 (pro-inflammatory), IL-8 (chemokine), and HBD-1 & -2, were elevated in women with non-optimal or intermediate vaginal microbiomes, with statistically significant differences observed for IL-1β and HBD-2 (Fig. 3B and Supplemental Table 2). Chemokines IP-10, MIP-1α and MIP-3α, as well as the antimicrobial protein, SLPI, were elevated in women with optimal vaginal microbiomes; all associations except for MIP-3α were statistically significant. In addition, elevated levels of the pro-inflammatory cytokine TNF-α were observed among women with optimal vaginal microbiomes.

Additionally, vaginal microbiome profiles were grouped into non-optimal, intermediate, and optimal. Pairwise comparisons of immune factor levels across contraceptive methods at baseline, M1, and M3 showed consistently significantly higher TNF-α, IP-10, and SLPI levels at M1 and M3 in LNG-implant users, with SLPI also elevated in DMPA-IM users (Supplemental Table 3). Women with non-optimal and transitional vaginal microbiomes at baseline generally had higher IL-1β levels, except copper IUD users at M1 and M3, suggesting that IL-1β may be expressed at higher levels in response to this contraceptive device.

Finally, we analyzed longitudinal fold changes in immune markers associated with microbiome transitions (Fig. 4). IL-6, IL-1β, IL-8 and HBD-2 significantly decreased with transitions to more optimal vaginal microbiomes but increased with shifts to a less protective state. Conversely, SLPI and IP-10 decreased in women whose vaginal microbiomes transitioned to a less optimal state and increased in women

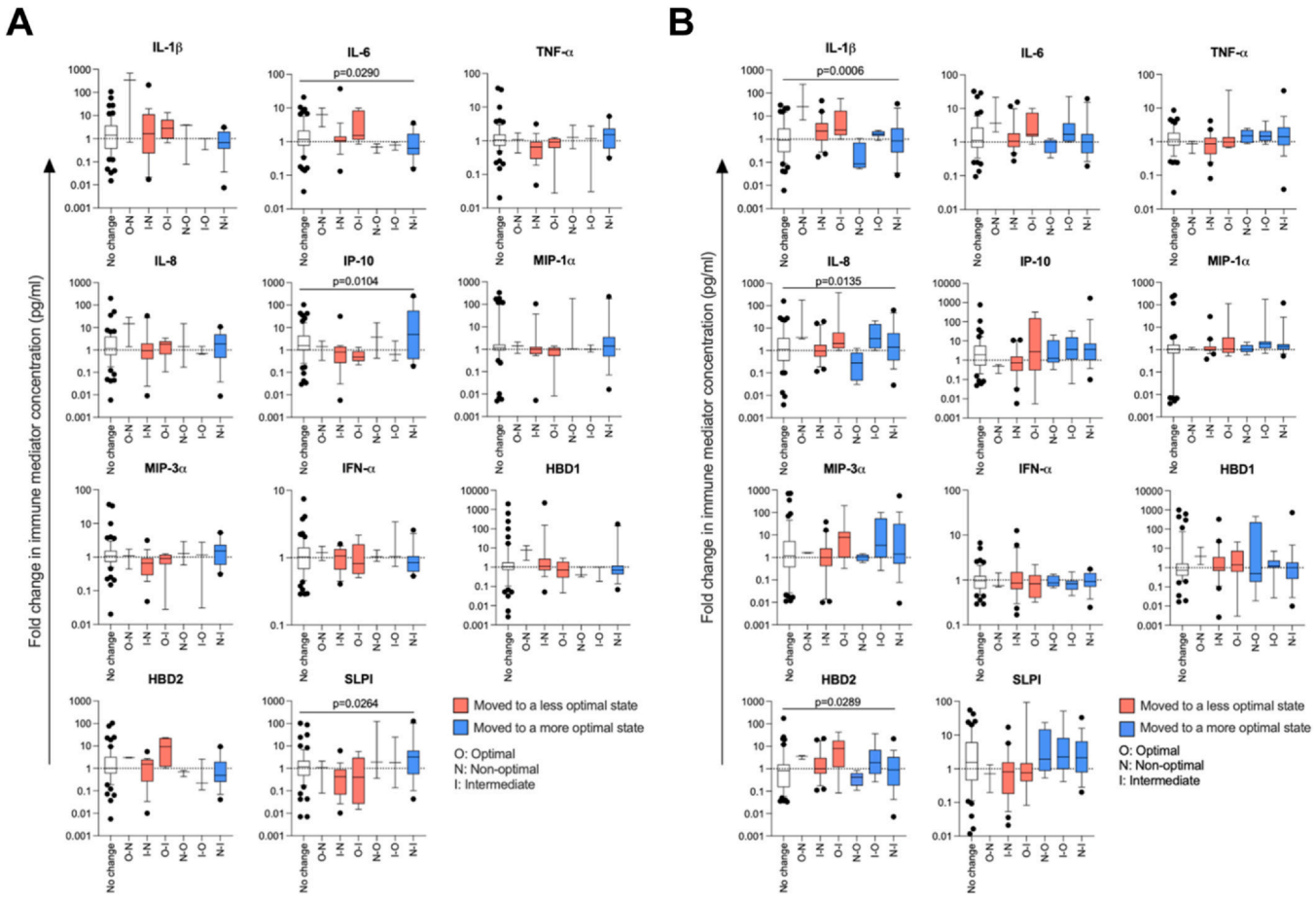

Fig. 4. Changes in cytokine, chemokine and antimicrobial peptide levels (Tshwane and in the eThekwini District, South Africa, 2015–2017). Transitions among Optimal (O), Intermediate (I) and Nonoptimal (N) vaginal microbiome profiles at month 1 (A) and month 3 (B).

whose vaginal microbiomes transitioned to a more optimal state. Similarly, non-optimal vaginal microbiomes were generally associated with increased levels of proinflammatory cytokines (e.g., IL-1β, IL-6), chemokines (e.g., IL-8) and antimicrobial peptides (HBD-1 & -2). Pro-inflammatory cytokine TNF-α was elevated among women with optimal vaginal microbiomes, which were also associated with IP-10, MIP-1α and MIP-3α, and SLPI, as well as use of LNG-implants.

4. Discussion

This study suggests that copper IUD use alters the vaginal microbiome in a way that may be less protective, whereas LNG-implant use supports a more protective state. Copper IUD users exhibited greater alpha diversity but reduced beta diversity, often transitioning from *L. crispatus*-dominated profiles to intermediate or non-optimal profiles. High alpha diversity and low *Lactobacillus* dominance, categorized as non-optimal profiles generally dominated by *G. vaginalis,* Ca. *Lachnocurva vaginae* (BVAB1), *A. vaginae* and other anaerobes [1], are often associated with dysbiosis and linked to BV, increased STI risk (including HIV), and adverse pregnancy outcomes such as preterm birth [1,7,12,18]. In contrast, LNG-implant users maintained stable diversity, trending toward *L. crispatus*-dominant profiles, while DMPA-IM had minimal effects on vaginal microbiome profiles. Categorizing vaginal microbiomes into optimal, intermediate, and non-optimal profiles improved statistical power. Transition patterns varied by contraceptive method: copper IUD users frequently shifted towards less protective compositions, whereas LNG-implant users moved toward optimal profiles.

Cytokines analyses support our previous finding that copper IUD users had elevated immune markers compared to LNG-implant and DMPA-IM users [2]. As previously shown, both SLPI and IP-10 [23,24] are generally associated with optimal vaginal microbiomes. In contrast to previous reports [7,24] but consistent with our observations, TNF-α showed a similar trend as SLPI and IP-10 (i.e., increasing levels in women transitioning to an optimal state).

Variations in TNFα levels across contraception methods and vaginal microbiomes suggest distinct regulatory mechanisms compared to other pro-inflammatory cytokines. TNFα production, influenced by immune and epithelial cells, varies with the local vaginal microbiome environment and systemic contraceptive effects [5,25]. The copper IUD may induce unique immune responses, distinct from hormonal contraceptives. vaginal microbiome-immune interactions further modulate TNFα, as certain bacterial communities can stimulate or suppress its production [24]. Additionally, TNFA-308A carriers exhibit elevated TNFα only with BV-like vaginal microbiome, indicating a gene-environment interaction [26].

Progestin-only contraceptives, like DMPA-IM, have shown inconsistent effects on the vaginal microbiome, likely influenced by individual metabolic and immune factors. For instance, DMPA-IM may increase inflammatory responses only in women with low baseline levels of inflammation. In contrast, the inflammatory potential of LNG implants is largely unknown. LNG implants provide steady progestin release, maintaining lower systemic levels than DMPA injections. This stability may provide a more stable environment in the vaginal microbiota, promoting the growth of protective bacteria. Conversely, the higher systemic concentrations of DMPA

could exert a more pronounced, variable effect on the microbiome and immune system, contributing to inconsistent outcomes.

Our findings align with previous reports that copper IUD users showed increased levels of proinflammatory factors, associated with higher abundance of less protective taxa, suggesting that copper IUD use negatively affects vaginal microbiome composition [15,24,25,27–29]. This effect is potentially due to its antimicrobial properties and induction of inflammatory cytokines. Biofilms formed by non-optimal taxa could be more resistant than lactobacilli to these antimicrobial effects [30,31], leading to sustained inflammation. Elevated levels of antimicrobial peptides HBD-1 & -2 in women with non-optimal vaginal microbiomes suggest compensatory host defense mechanisms.

LNG-implants favor a *L. crispatus*- dominated vaginal microbiome, consistent with reports showing a positive or neutral effect of levonorgestrel-containing contraceptives on the vaginal microbiome [11,13,29,32]. TNF-α, SLPI, IP-10, MIP-1α and MIP-3α were associated with more optimal taxa, supporting a positive effect of this contraceptive method. Our finding that DMPA-IM contraception has minimal impact on the vaginal microbiome and immune marker expression aligns with recent studies indicating that this method does not significantly increase the risk of HIV acquisition [33] when compared to copper IUDs and LNG implants.

Although our findings suggest copper IUDs may transiently disrupt the vaginal microbiota, epidemiologic evidence links long-term use to reduced cervical cancer risk, possibly through enhanced immune surveillance or HPV clearance [34,35]. This underscores a complex relationship between short-term inflammation and longer-term protective effects, warranting further investigation.

Study strengths include the prospective assessment of randomized contraceptive effects on the vaginal microbiome and immune response, with high adherence and follow-up rates. Limitations include small sample size, short contraceptive duration, and single samples per visit. Further studies are needed to confirm immune and microbiome changes with copper IUDs and LNG-implants, assess the durability of these changes, and determine whether they translate into a higher risk of STIs and reproductive health implications. Future research should explore whether copper IUD effects stem from its physical presence and/or copper release [30].

This study finds that LNG-implant use promotes a vaginal microbiome profile dominated by *L. crispatus* in the short term, whereas copper IUD use shifts the vaginal microbiome to a less protective state with increased alpha diversity and non-optimal taxa like *G. vaginalis*, BVAB1, and *A. vaginae*. These profiles, linked to increased inflammatory markers, may potentially lead to elevated risk of BV and STIs, including HIV. These observations may impact the individualized choice of contraceptive methods, considering factors such as efficacy, ease of use, safety, side-effects, and cost.

Although the ECHO study found no increased HIV incidence over 18 months, there were some important limitations such as the lack of a control group and the fact that the trial was only powered to detect a 50% difference in HIV incidence by contraceptive group. A longer follow-up period could potentially reveal an increased incidence of STIs, including HIV, in the copper IUD group. In contrast, DMPA-IM had minimal impact on vaginal microbiome or immune markers. Further research is essential to ensure contraceptives safety and guide future development.

CRediT authorship contribution statement

Serrano Myrna G.: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Formal analysis, Data curation. **Edwards David:** Writing – original draft, Visualization, Formal analysis, Data curation, Writing – review & editing. **Ahmed Khatija:** Writing – review & editing, Supervision, Resources, Project administration, Investigation. **Bailey Veronique C.:** Writing – review & editing, Supervision, Project administration, Investigation. **Beksinska Mags:** Writing – review & editing, Supervision, Project administration, Investigation. **Edupuganti Laahirie:** Formal analysis, Data curation, Writing – review & editing. **Harryparsad Rushil:** Writing – review & editing, Investigation, Data curation. Conceptualization. **D'Hellencourt Florence L.:** Writing – review & editing, Supervision, Project administration. **Meyer Bahiah:** Writing – review & editing, Investigation, Data curation. **Mehou-Loko Celia:** Data curation, Investigation, Writing – review & editing. **Radzey Nina:** Writing – review & editing, Investigation, Data curation. **Taku Ongeziwe:** Writing – review & editing, Investigation, Data curation. **Williamson Anna-Lise:** Writing – review & editing, Resources, Methodology. **Smit Jennifer:** Writing – review & editing, Supervision, Resources, Project administration, Investigation. **Spaine Katherine:** Investigation, Writing – review & editing. **Zhu Bin:** Visualization, Formal analysis, Data curation, Writing – review & editing. **Jefferson Kimberly K.:** Writing – review & editing, Funding acquisition, Conceptualization. **Nanda Kavita:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Strauss III Jerome F.:** Writing – review & editing, Funding acquisition, Conceptualization. **Morrison Charles S.:** Writing – review & editing, Resources, Project administration, Funding acquisition, Conceptualization. **Deese Jennifer:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition. **Masson Lindi:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Buck Gregory A.:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.contraception.2025.110936.

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