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Original Research Article

Comparative study of cervical-vaginal microbial flora changes in women using Cu-T380A contraceptive device and LNG-IUS in Ibadan: a two-centre clinical cohort study

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ABSTRACT

Background: Intrauterine devices cause various changes in the female genital tract which might result in altered microbial flora and risk of genital infections. The aim of this study was to determine the change in bacterial flora of women using Copper-bearing T380A and levonorgestrel intrauterine system and the risk of genital infections.

Methods: This was a two-center clinical cohort study of women using Cu-T380A IUD and LNG-IUS in Ibadan, Nigeria. The study was conducted from March to August, 2016 and it involved 130 women (66 Cu-T380A and 64 LNG-IUS) at 2 family planning clinics in Ibadan, Nigeria. The clients were clinically assessed before admission into the study and high vaginal and endocervical swabs were taken before insertion of the devices, and at 3 and 6 months after insertion.

Results: Fifty-seven clients with LNG and 63 with copper T380A completed the study. The mean age in LNG-IUS was 34.4 years (SD= 6.3) and Cu-T380A was 35.4 years (SD=5.6). All participants had one sexual partner. There was no previous or current STIs/PID at recruitment. The organisms isolated included coagulase negative *Staphylococcus* (CNS), *Staphylococcus aureus*, *Streptococcus* spp, *Escherichia coli*, *Candida* spp, *Neisseria gonorrhoeae* and *Klebsiella* spp. Cu-T380A women had an increase or persistence of CNS, Staphylococci, Klebsiella and Candida at 3 months while in the LNG-IUS group only CNS increased. The HVS revealed that participants with Cu-T380A had higher risks (33.3%) for asymptomatic genital infections than the LNG-IUS (5.3%) group at 6 months (p value <0.001).

Conclusions: Cu-T380A has a higher likelihood of altering the microbial flora in the cervix and vagina and therefore encouraging the growth of a variety of other organisms compared to LNG-IUS.

Keywords: Cervical, Vaginal, Microbial flora, Contraceptive device

INTRODUCTION

The intrauterine device (IUD) is a birth control method inserted into uterus which prevents fertilization and implantation of a fertilized egg. Two IUDs are currently available in Nigeria the copper-bearing T380A and the

levonorgestrel bearing intrauterine system (LNG-IUS). Both are effective methods of contraception while the LNG-IUS also provides various non-contraceptive benefits. Despite the numerous advantages of the copper IUD and LNG-IUS, there are a few concerns about the adverse effects and complications associated with its use,

especially the probability of vaginal infections. Understanding the impact of contraceptive initiation and use on vaginal microbiota is important to alleviate the anxiety and/or mental uneasiness and distressing symptoms that may be associated with occurrence of such infections. It is widely accepted that microbes present in or on the human body can impact immunity, nutrition and physiology.¹ The human vagina is unique in that in healthy states, it is most often characterized by reduced diversity and the dominance of *Lactobacillus* spp. Compared to other microbiota.^{1,2} *Lactobacillus* spp. are known to produce copious amounts of lactic acid which is directly correlated with acidic vaginal PH. This driven acidity of the vaginal fluid has been strongly correlated with the protection against cervical-vaginal infections including HIV and other sexually transmitted infections.³⁻⁷ There are few published longitudinal studies assessing the impact of contraceptives on vaginal microbiota but those that have been published suggested that women with copper IUDs may have a modest increased risk of bacterial vaginosis⁸ and women using the LNG-IUS had no increased risk of BV and no changes in the microbiome consistent with BV.⁸⁻¹⁰ Some scientific studies definitively have proven that IUD users consistently have more yeast cells in the vagina, leading researchers to believe that the IUD predisposes the woman to infections by yeast cells due to the tail of the IUD picking up yeasts from the vagina. The findings of a study that analyzed the presence of biofilm (complex community of surface associated cells in a polymer matrix) on the surfaces of IUDs in patients with recurrent vulvo-vaginal infections revealed the presence biofilm on the surface of IUDs as an important risk factor for recurrent vulvo-vaginal candidiasis.¹¹ The levonorgestrel IUS is known to decrease the risk of pelvic inflammatory disease (PID) caused by STIs by causing the cervical mucus to thicken, creating a barrier against bacteria, however such benefit may not have been reported with copper-bearing T380A. Both CuT380A and LNG-IUD are intrauterine devices, and such factors are known to disturb the natural balance in the vagina, if these changes become too intense, the vaginal flora can no longer adapt and may result in a vaginal infection. The number of lactobacilli in the vagina is usually then reduced and the pH is also often raised to values above 4.4. The presence of foreign body such as an IUD/IUS in the female genital tract has been linked with various types of cervical-vaginal infections. Cervical-vaginal infections arise when the natural balance of the vagina is altered giving rise to an environment prone to the proliferation of excessive fungi, bacteria, and parasites causing female genital infections. Such complications as STIs and PID pose threats to fertility and reproductive health.^{12,13} Previous research suggested that after the first month of use, IUDs do not increase the risk of PID.¹⁴ The first month carries an increased risk of PID due to the possibility of introducing bacteria during insertion. However, a mode of action of the levonorgestrel intrauterine system is to thicken cervical mucus and suppress or reduce endometrial bleeding and may offer some protection

against an already low risk of PID.¹⁵ Some scientific studies definitively have proven that IUD users consistently have more yeast cells in the vagina, leading researchers to believe that the IUD predisposes the woman to infections by yeast cells due to the tail of the IUD picking up yeasts from the vagina.¹¹ Disturbed vaginal microflora, with decreased numbers of lactobacilli, leading to bacterial vaginosis and/or aerobic vaginitis is a risk factor for acquisition of sexually transmitted infections, pre-term birth and can have a major impact on the development of human papilloma virus-induced cervical lesions into cancer.¹⁶⁻¹⁸ A study conducted in 2003 reported that the prevalence of cervical-vaginal infections was 29.1% and that bacterial vaginosis was frequently found in 19.7% of IUDs users 6 months after insertion.¹⁹ Negative perceptions of the copper IUD and the struggles to establish even moderate levels of use in most African countries naturally dampen interest in another intrauterine product such as the LNG-IUS.²⁰ The reduced bleeding associated with the use of LNG-IUS may suggest a lower prevalence of organisms in the cervical-vaginal region and the introduction of the LNG-IUS may provide a new opportunity for family planning providers to promote intrauterine contraceptive services. Data evaluating the impact of intrauterine contraceptive devices on vaginal microbiota in Nigeria are limited while those on levonorgestrel intrauterine system are non-existent. Therefore, this study was conducted to compare the pattern of changes in the cervical-vaginal flora of women who used CuT380A and LNG-IUS over a period of 6 months.

METHODS

This was a two-center, prospective, comparative study conducted over a period of 6 months. It was a clinical cohort study design conducted at two family planning clinics in Ibadan - the family planning clinic of the department of obstetrics and gynecology, at the university college hospital (UCH), and Adeoyo maternity teaching hospital (AMTH). The study population included healthy women scheduled for insertion of either CuT380A IUD or LNG-IUS for the purpose of contraception were included in the study. All the women who agreed to participate in the study provided written informed consent and completed a baseline questionnaire collecting demographic information as well as clinical and sexual history, hygiene, and infection history. Women who were less than 18 years, pregnant women and those with clinical features of untreated cervical-vaginal infections were excluded. Other exclusion factors include history of having been treated for cervical-vaginal infections in the last 3 months or presence of risk factors (multiple sexual partners), immunocompromised state, use of antibiotics 4 weeks prior to study, previous insertion of IUD and failure to adhere to study protocol. Additionally, women who were on anti-viral or immunosuppressive drugs, HIV drugs, or practice douching or use of vaginal suppository were excluded from the study.

Sample size calculation

The sample size was calculated using the formula by Kirkwood and Stearn for comparing proportions to determine a difference of 20% in prevalence of post insertion cervical-vaginal infection between copper T380A IUD and LNG-IUS users at 5% level of significance and 90% power.²¹ Allowing for 10% loss to follow-up, approximately 60 subjects were recruited in each group thus making a total of 120 subjects. The women who had selected IUD as preferred method of contraception were counselled and admitted into the study after an informed written consent was obtained. They were then requested to select their preferred type of IUD, either the Cu-IUD or LNG-IUS. Prior to insertion of the IUD, the clients were thoroughly assessed to be suitable for the preferred IUD. Each participant was placed in lithotomy position and a general pelvic examination was conducted under sterile aseptic condition. The vulva was cleansed with sterile water and a speculum was passed. Swabs were taken from the posterior vaginal fornix and endocervical region. The Copper-bearing IUD or LNG-IUS was inserted after the swab has been taken and the post-insertion instructions were given, as well as the next appointment. At the 3-month and six-month follow-up visits, the participants were reviewed for any clinical features of cervical-vaginal infections and follow-up questionnaires were administered to elicit possible complications or adverse events. Swab specimens of high vaginal (HVS) and endocervical swabs (ECS) were taken from the genitals of the participants.

Laboratory methods

The high vaginal and endocervical swabs collected from each participant were transported to the laboratory for processing within 30 minutes to 1 hour after collection. The swabs were processed in the laboratory at the

department of medical microbiology and parasitology and processed by a specialist medical microbiologist. A direct Gram staining was carried out on each sample following standard procedures.

Each sample was inoculated onto Mac-Conkey and chocolate/blood agar plates and incubated for 18-24 hours in a CO₂ enriched environment. Isolates were identified by indirect gram staining and biochemical tests following standard procedures.²² A wet preparation was also conducted on each specimen for detection of any parasitic organism especially *Trichomonas vaginalis*.

Data assessment and statistical analysis

The data was coded and analyzed using SPSS for windows version 18.0.1. The demographic data and clinical characteristics were summarized as the mean \pm standard deviation for continuous variables and as frequency counts (percentages) for categorical variables. The chi-square and t-test were used to investigate associations between categorical variables, p value less than 0.05 was considered statistically significant.

RESULTS

Sixty-three participants completed the study for copperT380A group as three were excluded at 3 months. Of the 64 participants recruited in the LNG-IUS group, 57 completed the study. Four participants were excluded at 3 months and an additional 3 were lost to follow up at 6 months. Baseline characteristics of the women in the two groups are shown in (Table 1). The mean age of participants in the Copper T380A group of 35.4 ± 5.6 years (range = 23-48 years) was not statistically different from the mean age of those in the LNG-IUS group 34.4 ± 6.3 years (range=22-48 years).

Table 1: Background characteristics between the groups.

Characteristics	Copper T380A %	LNG IUS %	Total	χ^2/t	P value
Age (years)					
Mean (SD)	35.4 (5.6)	34.4 (6.3)	34.5 (5.9)	0.045	0.964
Number of children					
1	7 (10.6)	11 (17.2)	18 (13.8)	4.095	0.129
2	8 (12.1)	14 (21.9)	22 (16.9)		
3+	51 (77.3)	39 (60.9)	90 (69.2)		
Religion					
Christianity	27 (40.9)	41 (64.1)	68 (52.3)	6.982	0.008
Islam/others	39 (59.1)	23 (35.9)	62 (47.7)		
Educational level					
Primary	8 (12.1)	11 (17.2)	19 (14.6)	44.159	<0.001
Secondary	52 (78.8)	15 (23.4)	67 (51.5)		
Tertiary/post-graduate	6 (9.1)	38 (59.4)	44 (33.8)		
Occupation					
Artisan/trader	62 (93.9)	37 (57.8)	99 (76.2)	23.352	<0.001
Others/Professionals	4 (6.1)	27 (42.2)	31 (23.8)		

Table 2: Bacterial flora in both devices over 6 months period.

Bacterial Flora	Baseline		Month 3		Month 6	
	Copper T380A %	LNG IUS %	Copper T380A %	LNG IUS %	Copper T380 A %	LNG IUS %
Isolate ECS						
CNS	9 (13.6)	1 (1.6)	8 (12.7)	14 (23.3)	2 (3.2)	1 (1.8)
<i>Strep. Spp</i>	2 (3.0)	3 (4.8)	1 (1.6)	0	1 (1.6)	0
No growth	47 (71.2)	38 (60.3)	32 (50.8)	40 (66.7)	57 (90.5)	55 (96.5)
<i>Kleb. Spp</i>	0	3 (4.8)	1 (1.6)	0	0	0
<i>S. aureus</i>	1 (1.5)	5 (7.9)	3 (4.8)	0	2 (3.2)	0
<i>E. coli</i>	1 (1.5)	2 (3.2)	0	0	0	0
Insignificant growth	2 (3.0)	8 (12.7)	14 (22.2)	5 (8.3)	0	1 (1.8)
<i>Candida Spp.</i>	3 (4.5)	3 (4.8)	4 (6.3)	1 (1.7)	1 (1.6)	0
<i>Neisseria gono</i>	1 (1.5)	0	0	0	0	0
Isolate HVS						
CNS	7 (10.6)	6 (9.4)	13 (20.6)	26 (43.3)	8 (12.5)	1 (1.8)
<i>Strep. Spp.</i>	2 (3.0)	3 (4.7)	2 (3.2)	0	1 (1.6)	0
No growth	41 (62.1)	29 (45.3)	20 (31.7)	21 (35.0)	43 (67.2)	54 (94.7)
<i>Kleb. Spp.</i>	0	5 (7.8)	2 (3.2)	1 (1.7)	1 (1.6)	0
<i>S. aureus</i>	1 (1.5)	5 (7.8)	5 (7.9)	0	3 (4.7)	1 (1.8)
<i>E. coli</i>	2 (3.0)	3 (4.7)	2 (3.2)	0	3 (4.7)	0
Insignificant growth	6 (9.1)	11 (17.2)	15 (23.8)	11 (18.3)	4 (6.3)	1 (1.8)
<i>Candida Spp</i>	6 (9.1)	2 (3.1)	3 (4.8)	1 (1.7)	4 (6.3)	0
<i>Neisseria Gono</i>	1 (1.5)	0	0	0	0	0

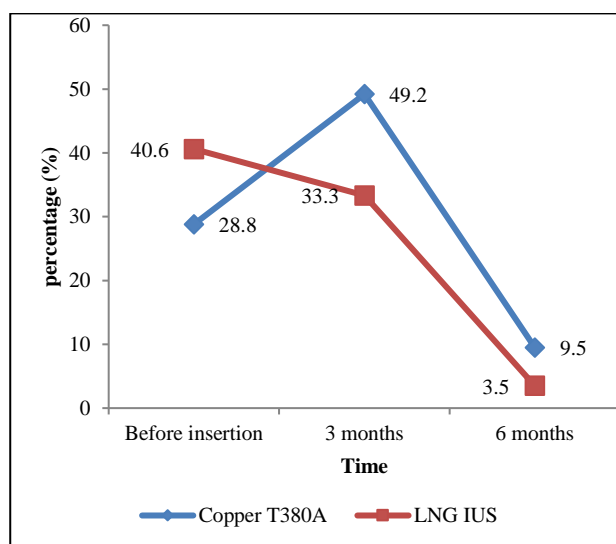


Figure 1: Trends in Cervico-vaginal infection (ECS).

Changes in bacterial flora

Yeast cells were isolated from the ECS and HVS wet preparations in 2 women (3.0%) in the CuT380A group and 4 women (6.1%) in the LNG-IUS group, respectively

at baseline only (Table 2). There was a general drop in the number of isolated organisms over the 6 months period when samples cultured from the ECS and HVS were compared. The table also showed that *Klebsiella* spp. was detected in the LNG-IUS group but had drastically cleared or reduced by 3rd month of review.

Comparing the bacterial flora changes for each device Four organisms were isolated from the participants in the copper-bearing IUD group namely coagulase negative staphylococcus (CNS), *Staphylococcus aureus*, *Klebsiella. spp* and *Candida* compared to one (CNS) in LNG-IUS group. These persisted at the 3rd month while by the 6th month, the specimens from most of the participants cultured no growth. However, participants in the Copper IUD group still had more organisms than LNG-IUS group at the 6th month as depicted in (Table 2).

Trends in cervico-vaginal infections (ECS and HVS)

The participants in the study who were without clinical symptoms but whose swab tests cultured pathogenic bacteria were regarded as having asymptomatic infection

(subclinical infection). The trends in bacteria cultured were reviewed from specimens obtained before insertion,

at 3, and 6 months. More participants had asymptomatic genital infections at 3 months and 6 months among those using CuT380A (Figure1). There was an increase in cervical-vaginal infections (asymptomatic infection) among respondents who used the copperT380A IUD (33.3% at six months' post-insertion) than users of LNG-IUS (5.3% at six months' post-insertion).

Comparison of cervical-vaginal infection among groups (HVS)

At 6 months, a slightly higher proportion of copper T380A users (33.3%) had cervical-vaginal infections compared to LNG-IUS users (5.3%) as observed from the high vaginal swabs; this was statistically significant at $p < 0.001$ (Figure 2). The users of Cu T380A had an initial increase in prevalence of cervical-vaginal infections before it dropped at the end of the study while participants who used LNG-IUS had a progressive decrease in the cervical-vaginal infection from before insertion till end of the study. When the results of HVS in the two groups were compared, more clients had cervical-vaginal infections among the Cu T380A group at the end of the study (33.3% compared to 5.3% for LNG-IUS group and it was statistically significant ($p < 0.001$).

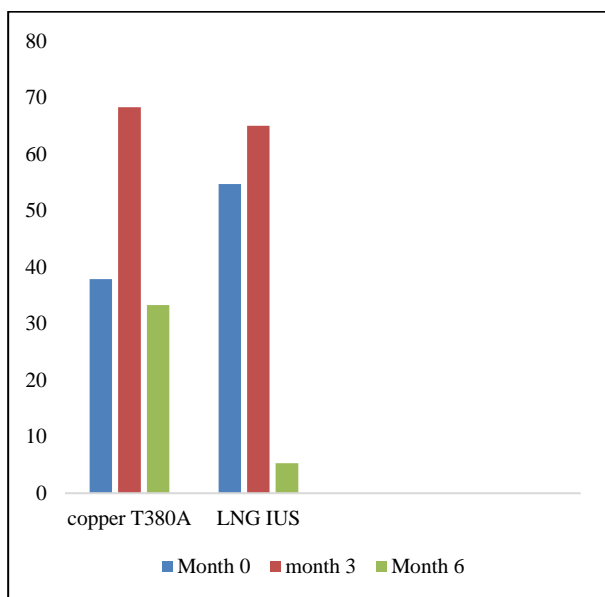


Figure 2: Trends in cervico-vaginal infection (HVS).

The results of the endo-cervical swabs showed that the existence of cervical-vaginal infections dropped gradually and steadily in the LNG-IUS group (from 40.6% prior to insertion, 33.3% at 3 months and 5.3% at 6 months). In the copper IUD group, the values increased at 3 months before dropping at 6 months (28.8% prior to insertion, 49.2% at 3 months and 9.5% at 6 months).

Changes in bacterial flora

The users of Cu T380A had a gradual clearance of the organisms cultured in the vagina over the 6 months'

period. Most of them cultured no growth by the 6th month. More organisms were cultured in the HVS than the ECS specimens. Among the Cu T380A users, there was a spike in the type of organisms cultured by the 3rd month, namely, *Coagulase negative staphylococcus*, *Klebsiella spp*, *Staphylococcus aureus* and *Candida spp*. suggesting that CuT380A encouraged the growth of a wide variety of organisms. However, these were not seen by the 6th month.

The users of LNG-IUS also had a steady clearance of the organisms cultured over the 6 months' period. The proportion of "no growth" from the ECS and HVS specimens over the 6 months' period was about 50%. There was an increase in the number of specimens which did not culture any organism prior to insertion till the 6th month of use suggesting that the organisms were cleared with increase in the duration of use. Coagulase negative staphylococcus was significantly cultured by the 3rd month of use of the device but dropped after 6 months while the other organisms also dropped. *Neisseria gonorrhoea* was not isolated throughout the study among the users.

DISCUSSION

Since 2005, the international contraceptive access (ICA) foundation has been donating limited quantities of free, unbranded LNG-IUS devices for distribution. Several countries, including Nigeria, have used this donated product to support pilot introduction activities.²³ At the time, this study was conducted, there were only 2 intrauterine contraceptive devices available in public health facilities in Nigeria the CuT380A in most and levonorgestrel intrauterine devices (LNG-IUS) in a few facilities. However, recently new, more affordable commercial LNG-IUS products have received regulatory approval suggesting that there may be opportunities in the coming years to further access the method within the country.^{23,24} The common symptoms noted among the users of either device included heavy vaginal bleeds, severe abdominal pains, foul smelling vaginal discharge and fever. More clients had cervical-vaginal infections among the Cu T380A group at the end of the study (33.3% compared to 5.3% for LNG) and it was statistically significant ($p < 0.001$). This was higher than the 29.1% reported in a study by Ferraz do Lago et al. for copper T380A IUD after 6 months of use. The commonest organism that persisted in the genital tract of the copper-bearing IUD participants was coagulase negative staphylococcus. This contrasts with the bacterial vaginosis reported by Ferraz do Lago et al in their study in 2003.¹⁹ *E. coli* was the predominant organism isolated 61.5% by a study conducted by Sabah et al among those women who used copper-bearing IUDs.²⁵ It can be concluded from this study that LNG-IUS use prevents or helps to reduce the prevalence of cervical-vaginal infections. Grimes in 2000 reported that the thickening of the cervical mucous by the hormone in the device maybe the reason LNG IUS have low risk for pelvic infections.¹⁵

The prevalent bacterial or fungal vaginal flora cultured and isolated from the specimens of a few participants recruited in this study prior to insertion of the device included *Coagulase negative staphylococcus*, *Staphylococcus aureus*, *Streptococcus spp*, *Escherichia coli*, *Candida spp*, *Neisseria gonorrhoea* and *Klebsiella spp*. However, the specimens from many participants did not culture any pathogenic bacteria prior to the insertion of the device. Furthermore, in many of those whose specimens cultured micro-organisms, the infection had subsided by the 6th month of use. Hence the use of an IUD in these participants appeared to have caused changes in the cervical-vaginal bacterial flora by producing total clearance or reduction of these micro-organisms from their genital tracts. The findings are similar to the study by Haukkama et al which showed contraceptive devices that contain hormones could alter vaginal bacterial flora just as seen with this study.¹⁵ Kaliterna et al showed that use of IUDs caused growth of opportunistic bacteria particularly *E. coli* and *Ureaplasma urealyticum* in the cervix of the users and the growth of pathogens persisted in some participants.²⁷ They concluded that there is an increased cervical infection with use of IUDs which is similar to the findings associated with the CuT380A group in this study. Wahab et al also have proven that copper IUDs users can have increase in cervical and vaginal flora and increase in culture of anaerobic bacteria. Other studies have also proven that IUDs are most likely to cause growth of various organisms.^{28,30,31}

Use of hormonal forms of contraceptives has been shown to cause significant vaginal bacterial shift in the study conducted by Haukkama et al.²⁶ This may be in keeping with the findings of all forms of pathogenic bacteria among clients who used LNG-IUS in this study. A 7-year study conducted by Lessard et al showed candida was commonly cultured LNG IUS users, this contrasts with findings of no growth of any organism common among LNG-IUS users by 6th month in this study.³²

This study showed the participants with CuT380A rather than LNG-IUS were more likely to grow several organisms in their vagina. Though, with increase in the duration of use most of the clients in both groups had no growth in their cervix or vagina from both cultures. Enrol et al in their study showed that LNG-IUS was superior to copper-T IUD in limiting the prevalence of cervico-vaginal colonization and infections.³³ Even though the participants were not evenly distributed in their study; this study appears to validate their findings. Most recent studies from the literature did not compare both forms of long-acting reversible contraceptives in a longitudinal setting with almost equal client distribution but the assumption was that CuT380A are more likely to cause more growth of pathogenic organism since LNG-IUS contain hormones that inhibit bacterial growth, as earlier reported by Lessard in 2007.³¹ The LNG-IUS is an underused method in Nigeria.²³ A relatively recent

market survey in Kenya found that if a more affordable version of LNG-IUS were available, it may increase demand and uptake of the method.³³

Limitations

Some of the limitations of this study include participants lost to follow up and refusal to continue to be part of the study for various reasons after recruitment at 3 months and 6 months follow up appointments, refusal to undertake swab test in the examination room after consenting, and language barrier/communication issues between participants and research assistant/primary investigator. These we overcame by use of interpreters, re-counseling and ensuring voluntary uptake of method of contraception. Those who refuse were excluded from the study.

CONCLUSION

This study revealed that the use of copper T380A intra-uterine contraceptive device could drastically alter the normal bacterial flora in the vagina of women and encourage the growth of a variety of pathogenic organisms. More organisms persisted in the genital tract of women who used copper T380A compared to previous studies that revealed fewer organisms. A variety of organisms were also isolated in this study. The most common organism from this study was coagulase negative staphylococcus which was different from most other studies. It is a less virulent type of staphylococcus and usually seen with presence of foreign body such as an IUD in the human body. Levonorgestrel intra-uterine system may be responsible for the tendency for the growth of lesser number of organisms and lower risk of cervico-vaginal infection in the study. Fewer number of organisms remained in the genital tract of women using LNG-IUS after prolonged use which may be due to the hormonal component of the device inhibiting bacterial growth. This may constitute an advantage of LNG-IUS over the copper-bearing IUD.

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Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

- Kroon SJ, Ravel J, Huston WD. Cervico-vaginal microbiota, women's health and reproductive outcomes. *Fertility Sterility.* 2018;110(3):45-9.
- Srinivasan S, Liu C, Mitchel CM, Fiedler TL, Thomas KK, Agnew KT, et al. Temporary variability of human vaginal bacteria and relationship with bacterial vaginosis. *PLoS One.* 2010;5:e10197.
- Tachedjian G, O'Hanlon DE, Ravel J. The implausible "in vivo" role of hydrogen peroxide as an antimicrobial factor produced by vaginal microbiota. *Microbiome.* 2018;6:29.
- Aldunate M, Srbinovski D, Hearps AC, Latham CF, Ramsland PA, Gugasyan R, et al. Antimicrobial and immune modulatory effects of lactic acid and short chain fatty acids produced by vaginal microbiota associated with eubiosis and bacterial vaginosis. *Front Physiol.* 2015;6:164.
- Breshears LM, Edwards VL, Ravel J, Peterson ML. *Lactobacillus crispatus* inhibits growth of *Gardnerella vaginalis* and *Neisseria gonorrhoeae* on a porcine vaginal mucosa model. *BMC Microbiol.* 2015;15:276.
- Srinivasan S, Liu CC, Mitchell CM, Fiedler TL, Thomas KK, Agnew KJ, et al. Temporal variability of human vaginal bacteria and relationship with bacterial vaginosis. *PLoS One.* 2012;5:e10197.
- Ronnquist PD, Forsgren-Brusk UB, Grahn-Håkansson EE. *Lactobacilli* in the female genital tract in relation to other genital microbes and vaginal pH. *Acta Obstet Gynecol Scand.* 2006;85:726-35.
- Achilles SL, Austin MN, Meyn LA, Mhlanga F, Chirenje ZM and Hillier SL. Impact of contraceptive initiation on vaginal microbiota. *Am J Obs Gyn.* 2018;218(6):622.
- Bassis CM, Allsworth JE, Wahi DE, Young VB, Bell JD. Effects of intrauterine contraception on the vaginal microbiota. *Contraception.* 2017;96:189-95.
- Jacobson JC, Turok DK, Dermish AI, Nygaard ML, Settles ML. Vaginal microbiome changes with levonorgestrel intrauterine system placement. *Contraception.* 2014;90:130-5.
- Auler ME, Morreira D, Rodrigues FFO, Margarideo PFR, Matsumoto FE, Silva EG, et al. Biofilm formation on intrauterine devices in patients with recurrent vulvovaginal candidiasis. *Med Mycol.* 2014;48(1):211-6.
- El-Hamid ANA, Sayyed TM, Salem EH, Hassan AN. Screening for bacterial vaginosis before and after intrauterine device insertion. *Menofia Med J.* 2019; 32:1411-6.
- Yen S, Shaffer MA, Moncada J, Campbell CJ. Bacterial vaginosis in sexually experienced and non-sexually experienced young women entering the military. *Obstet Gynaecol.* 2003;102:972-3.
- Fortney JA, Feldblum PJ, Raymond EG. Intrauterine devices. The optimal long-term contraceptive method?. *J Reprod Med.* 1999;44(3):269-74.
- Grimes DA. Intrauterine device and upper genital tract infection. *Lancet.* 2000;356(9234):1013-9.
- Donders GGG, Bellen G, Ruban K, Ruban K, Van Buick B. Short and long-term influence of the levonorgestrel-releasing intrauterine system (Mirena[®]) on vaginal microbiota and *Candida*. *J Med Microbiol.* 2018;67:308-13.
- Donders GGG, Viera-Baptista P. Bacterial vaginosis and inflammatory response showed association with severity of cervical neoplasm in HPV-positive women. *Diagn Cytopathol.* 2017;45:472-3.
- Caixeta RC, Ribeira AA, Segatti KD, Saddi VA, Figueredo Alves RR, et al. Association between the human papillomavirus, bacterial vaginosis and cervicitis and the detection of abnormalities in cervical smears from teenage girls and young women. *Diagn Cytopathol.* 2015;43:780-5.
- Ferraz do Lago R, Simoes JA, Bahamondes L, Camargo RPS, Perrotti M, Monterio I. Follow-up of users of intrauterine device with or without bacterial vaginosis and other cervicovaginal infections. *Contracept J.* 2003;68:105-9.
- Hubacher D. The levonorgestrel intrauterine system: Reasons to expand access to the public sector of Africa. *Global Health Sci Practice.* 2015;3(4):532-7.
- Daniel WM. *Biostatistics: a foundation for analysis in health sciences.* 7th ed. New York: Wiley; 1999.
- Tille PM. In: *Bailey and Scott's diagnostic microbiology.* 14th ed. Missouri: Elsevier; 2014: 9780.
- Brunie A, Rademacher KH, Nwala AA, Danna K, Saleh M, Afolabi K. Provision of the levonorgestrel intrauterine system in Nigeria: Provider perspectives and service delivery cost. *Gates Open Res.* 2020;4: 119.
- Rademacher KH, Sripipatana T, Pfitzer A, Mackay A, Thurston S, Jackson A, Menotti E, Traeger H. A global learning agenda for the levonorgestrel intrauterine system (LNG IUS): addressing challenges and opportunities to increase access. *Glob Health Sci Pract.* 2018;6(4):635-43.
- Sabah Abd Al, Kareem Al, Daniz TB, Shafaq, TB, Kareem Al, et al. Biofilm Formation on Intrauterine Device and Associated Infections. *Iraqi Postgrad Med J.* 2013;12(4):562-7.
- Haukkama M, Strandén P, Jousimies-Somer H, Siitonen A. Bacterial flora of the cervix in women using different methods of contraception. *Am J Obstet Gynecol.* 1986;154(3):520-4
- Kaliterna V, Kučičec-Tepeš N, Pejković L, Zavorović S, Petrović S, Barišić Z. An intrauterine device as a possible cause of change in the microbial flora of the female genital system. *J Obstet Gynaecol Res.* 2011; 37(8):1035-40.
- Wahab SA, Altaieb S, Saleh A, Sakr E, Hamly AK, Hegab M, et al. Effect of Copper T intrauterine device on cervico-vaginal flora. *Int J Gynaecol Obstet.* 1985; 23(2):153-6.
- Baris H, Arman-Karakaya Y. Effects of contraception on cervical cytology: data from Mardin City. *Türk Patoloji Derg.* 2013;29(2):117-21.

30. Kanat-Pektas M, Ozat M, Gungor T. The effects of TCu-380A on cervicovaginal flora. *Arch Gynecol Obstet.* 2008;277(5):429-32.
31. Lessard T, Simões JA, Discacciati MG, Hidalgo M, Bahamondes L. Cytological evaluation and investigation of the vaginal flora of long-term users of the levonorgestrel-releasing intrauterine system (LNG-IUS). *Contraception.* 2008;77(1):30-3.
32. Enrol O, Simavlı S, Derbent AU, Ayrim A, Kafalı H. The impact of copper-containing and levonorgestrel-releasing intrauterine contraceptives on cervicovaginal cytology and microbiological flora: a prospective study. *Eur J Contracept Reprod Health Care.* 2014;19(3):187-93.
33. Nander G, Rademarcher K, Solomon M, Mercer S, Wawire J, Ngahu R. Experience with the levogestrel releasing intrauterine system in Kenya: Qualitative interviews with users and their partners. *Eur J Contracept.* 2018;28(4):303-8.

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