

CORRELATION BETWEEN RECURRENT VULVOVAGINITIS AND SEXUALLY TRANSMITTED INFECTIONS

CORRELAÇÃO ENTRE VULVOVAGINITES RECORRENTES E INFECÇÕES SEXUALMENTE TRANSMISSÍVEIS

CORRELACIÓN ENTRE VULVOVAGINITIS RECURRENTE E INFECCIONES DE TRANSMISIÓN SEXUAL

✉ Eclair Aymée Morais Kirniew Ximenes¹, ✉ Mariana Aroucha Carneiro², ✉ Talita dos Santos Nascimento³ e ✉ Felipe Bezerra Frota⁴

ABSTRACT

The objective of this study was to correlate recurrent vulvovaginitis and Sexually Transmitted Infections (STIs) and analyze the importance of adding the Polymerase Chain Reaction (PCR) test for STIs to the diagnostic work-up of recurrent vulvovaginitis. The descriptive, cross-sectional, observational and retrospective research method was adopted. The medical records of 115 patients treated at a gynecological office were evaluated, who had positive PCR tests for STIs with some microorganism from August 2021 to October 2023. A large number of these patients, corresponding to 26%, had repeated discharges and at least 50% of them were proven to be cured of these discharges after STI treatment. It appears that there may be a relationship between recurrent vulvovaginitis and STIs, however, it is important to expand this research topic, as the study has limitations.

Keywords: *Sexually Transmitted Infections; Bacterial Vaginosis; Vulvovaginal Candidiasis; Multiplex Polymerase Chain Reaction.*

RESUMO

O objetivo desse estudo foi correlacionar Vulvovaginites Recorrentes e Infecções Sexualmente Transmissíveis (IST's) e analisar a importância de acrescentar, na propedêutica diagnóstica das vulvovaginites de repetição, a realização do exame de Reação em Cadeia de Polimerase (PCR) para IST's. Foi adotado o modo de pesquisa descritiva, de corte transversal, observacional e retrospectivo. Foram avaliados prontuários de 115 pacientes atendidas em consultório ginecológico, que tiveram exames de PCR positivo para IST's com algum microorganismo, de agosto de 2021 a outubro de 2023. Um número alto dessas pacientes, que corresponde a 26%, apresentaram corrimentos de repetição e pelo menos 50% delas foram comprovadamente curadas desses corrimentos após tratamento da IST. Consta-se que pode haver uma relação entre vulvovaginites recorrentes e IST's. No entanto, é importante a expansão dessa temática de pesquisa, visto que o estudo possui limitações.

Descritores: *Infecções Sexualmente Transmissíveis; Vaginose Bacteriana; Candidíase Vulvovaginal; Reação em Cadeia da Polimerase Multiplex.*

RESUMEN

El objetivo de este estudio fue correlacionar la vulvovaginitis recurrente y las Infecciones de Transmisión Sexual (ITS) y analizar la importancia de agregar la prueba de Reacción en Cadena de la Polimerasa (PCR) para ITS al estudio diagnóstico de la vulvovaginitis recurrente. Se adoptó el método de investigación descriptivo, transversal, observacional y retrospectivo. Se evaluaron las historias clínicas de 115 pacientes atendidas en un consultorio ginecológico, quienes tuvieron pruebas PCR positivas para ITS con algún microorganismo desde agosto de 2021 hasta octubre de 2023. Un gran número de estas pacientes, correspondiente al 26%, tuvieron secreciones vaginales recurrentes y Se demostró que al menos el 50% de ellas se curaron de estas secreciones después del tratamiento de las ITS. Parece que puede haber una relación entre la vulvovaginitis recurrente y las ITS, sin embargo, es importante ampliar este tema de investigación, ya que el estudio tiene limitaciones.

Descriptores: *Infecciones de Transmisión Sexual; Vaginosis Bacteriana; Candidiasis Vulvovaginal; Reacción en Cadena de la Polimerasa Multiplex.*

¹ Escola de Saúde Pública do Ceará, Fortaleza/CE - Brasil.

² Escola de Saúde Pública do Ceará, Fortaleza/CE - Brasil.

³ Escola de Saúde Pública do Ceará, Fortaleza/CE - Brasil.

⁴ Escola de Saúde Pública do Ceará, Fortaleza/CE - Brasil.

INTRODUCTION

Vulvovaginitis and vaginosis are infections of the female reproductive tract in which the physiological vaginal environment is altered, allowing the proliferation of other microorganisms, in addition to the natural flora, where *Lactobacillus*¹ predominates.

Vulvovaginitis and vaginosis represent one of the most frequent complaints of pathological vaginal discharge, accounting for the majority of gynecological consultations². *Gardnerella Vaginalis* and *Candida Albicans* are the causative agents of the most common vaginitis. Its main symptoms include odor, pruritus, dyspareunia, burning, which impairs the quality of life of affected women, in addition to being associated with pelvic and urinary infections, and endometritis^{3,4}.

Bacterial Vaginosis (BV) affects women of childbearing age, pre-menopausal women, and pregnant women, with an incidence rate ranging from 30% to 50%.⁵ It is characterized by an alteration in the vaginal microbiota of aerobic *Lactobacillos*, leading to the proliferation of anaerobic bacteria, including *Gardnerella vaginalis*, *Atopobium vaginae*, *Mobiluncus spp.*, *Bacteroides spp.* and *Prevotella spp*⁶. The diagnosis is made by the presence of three of the four Amsel Criteria, which are: homogeneous vaginal discharge, similar to milk; foul odor released by the addition of potassium hydroxide (KOH) at 10%; Vaginal pH above 4.5; presence of *clue cells* on fresh examination^{5,6}. In ideal situations, the Nugent score is used for diagnosis, which considers the Gram result of vaginal secretion and cytopathology, visualizing clue cells⁷.

Despite the variability of treatments, more than half of women experience recurrence of symptoms in less than a year. Although there is no universally accepted definition of recurrent bacterial vaginosis, studies have defined it as three or more confirmed episodes within twelve months⁶.

On the other hand, Vulvovaginal Candidiasis (CVV) is a fungal infection caused mainly by *Candida Albicans*. After anaerobic BV, it is considered the most common vaginal infection. Studies indicate that it can affect up to 75% of women of reproductive age at least once in their lives, and up to 9% of women have more than three episodes per year, which is defined as recurrent vulvovaginal candidiasis (CVVR)⁸.

The vaginal mucosa is the gateway to different pathogenic microorganisms⁵. The bacteria that colonize the vagina, especially lactobacilli, are considered the first line of defense against infections⁹. When there is no vaginal microflora due to lactobacilli, there is an alteration of the microbiota, making the environment susceptible to urogenital infections¹⁰. Changes in the vaginal microbiome, especially those that cause bacterial vaginosis, are associated with increased risk of sexually transmitted infections, such as human papillomavirus (HPV), human immunodeficiency virus (HIV), and pelvic inflammatory diseases, related to pathogens such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*. Delay in treatment can have long-term consequences, such as infertility and chronic pelvic pain^{9, 11}.

Genital mycoplasmas, such as *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Ureaplasma parvum*, can be found in the normal microbiota of the vagina, but are associated with adverse outcomes during pregnancy (such as premature labor and premature rupture of membranes), urethritis, and infections

after surgical procedures^{1, 12}. Such species have been detected in cervical samples from patients with salpingitis and acute endometritis and have been associated with cervicitis¹.

In recent years, through techniques based on the analysis of the *polymerase chain reaction* (PCR), it has been possible to detect genes involved in the pathogenicity of several bacterial isolates, allowing the identification, in a single sample, of microorganisms found within the vaginal ecosystem, in healthy and pathological conditions^{5,12}. Called Multiplex Polymerase Chain Reaction, these tests represent the first line of diagnosis of STIs in developed countries and, through them, it is possible to identify up to six etiological agents in a single test: *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum/parvum* and *Trichomonas vaginalis*¹³.

At the level of the Unified Health System (SUS), the diagnosis of STIs is usually based only on anamnesis and clinical examination data, and sometimes some simpler tests are performed, such as vaginal pH measurement, amine test, bacterioscopy, Gram and culture, when available¹. PCR tests are carried out by several laboratories, but only at the supplementary health level.

In a study carried out with 175 patients treated by gynecologists at the School of Primary Care (CEAP) of the Christus University Center, in the city of Fortaleza, Ceará, 23% of women were diagnosed with vaginitis, vulvitis or vulvovaginitis; 7% with Bacterial Vaginosis; 6% with Candidiasis; 1% with Inflammatory Disease no specific; 1% with perineal pelvic pain; 1% with trichomoniasis. These diagnoses would be better clarified if PCR for STIs were available¹⁴.

In view of the above, it is noted that changes in the vaginal microbiota are associated with an increase in genital tract infections, with the increased risk of acquiring sexually transmitted infections, which generate negative consequences in the long term, gaining greater relevance. For this reason, this study aimed to correlate recurrent vulvovaginitis and STIs and to analyze the importance of adding PCR testing for STIs to the diagnostic workup of recurrent vulvovaginitis.

METHODS

To carry out this study, the descriptive, cross-sectional, observational, and retrospective research method was adopted.

The research was carried out by gynecologists and obstetricians from the School of Public Health of Ceará – ESP/CE and by a resident student of Gynecology and Obstetrics at the same institution. The period chosen was from August 2021 to October 2023, and the study location was the researchers' doctor's office.

The population consisted of patients assisted during general gynecology outpatient consultations of the complementary health system, who had microorganisms found in the PCR test for STIs. A total of 282 PCR reports for STIs were analyzed, accessed through the electronic database of the physician who requested the test, and separate reports with the presence of at least one microorganism.

Data from patients with abnormal PCR tests were obtained from electronic medical records. The collection instrument was developed using the Google forms collection tool and consisted of a questionnaire in the form of a checklist. The questions

in the questionnaire included: obstetric gynecology history (age, marital status, parity, and contraceptive method), diagnostic criteria for recurrent vulvovaginitis, medications used, and treatment performed.

All patients diagnosed with recurrent vulvovaginitis by clinical examination or PCR for candidiasis or bacterial vaginosis (3 or more episodes in one year) were included in the study. Patients who did not meet the criteria for recurrent vulvovaginitis or who had already received tests were excluded from the sample PCR samples collected in another service. Patients with immunosuppression and immunodeficiencies already diagnosed prior to the consultation were also excluded.

Patients were considered cured if, after treatment of the microorganism found in PCR for STI and treatment of vulvovaginitis, they no longer complained of recurrent vaginal discharge in subsequent consultations.

Google Colab was used for the descriptive analysis of data in the construction of a script, which generated graphs and tables using the Python language.

The project was carried out after approval by the Ethics Committee for Research involving human beings of the School of Public Health of Ceará (ESP-CE), under opinion No. 6,119,122. In addition, it is noteworthy that the research complied with Resolution No. 466/2012, which comprises scientific research with human beings.

RESULTS

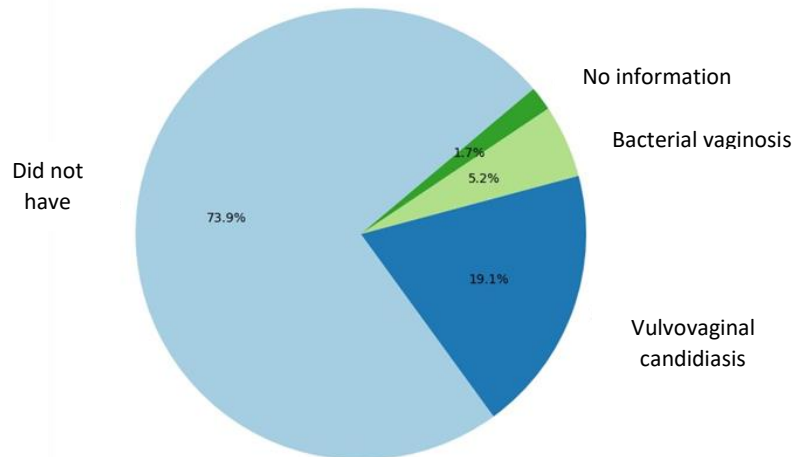
A total of 282 PCR results for STIs were analyzed. Of these, 115 tested positive for one or more microorganisms, corresponding to 40% of all patients. Of the patients with PCR-positive microorganisms for STIs, the predominant age group was 24 to 40 years, corresponding to 74.8%; being under 24 years old, 11.3%; between 40 and 55 years old 11,3%; and between 55 and 65 years old, 2.6%.

When analyzing contraceptive methods, it was found that most patients did not use any contraceptive method or used an intrauterine device (IUD) and only 13 patients (11%) used condom as individual or combined contraception.

Of the total number of patients studied and with a positive test, 77 returned to treat the microorganism and 38 did not return. Of the patients treated, the vast majority used Doxycycline 100mg, every 12 hours, for 7 days.

Of the total number of patients, 30 (26%) had recurrent vaginal discharge, and several treatments had already been performed, 22 cases of Vulvovaginal Candidiasis (19.1%), six cases of Bacterial Vaginosis (5.2%) and two cases of indeterminate Vulvovaginitis (1.7%) (Graph 1).

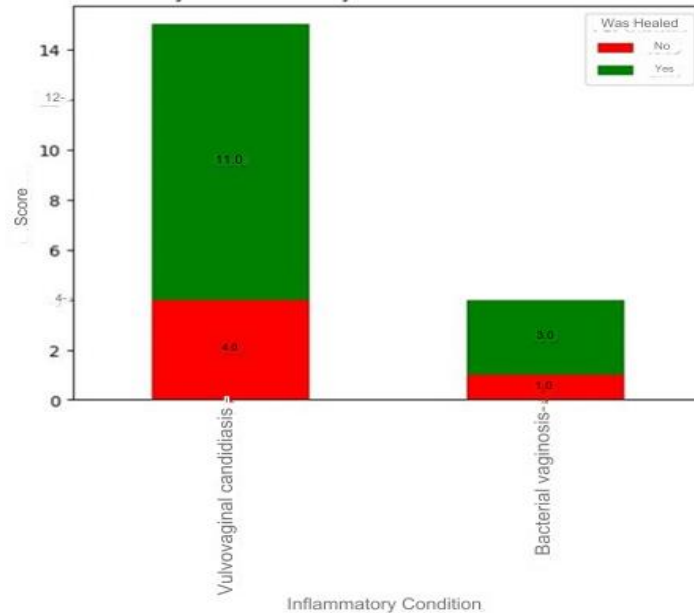
Graph 1: Percentage of patients who had recurrent vaginal discharge and the type of inflammatory condition found.



Source: Produced by the authors.

Of the 22 patients with recurrent Vulvovaginal Candidiasis, only 19 underwent specific treatment for the microorganism found in PCR examination, leaving 11 cured, seven without information after treatment and four not cured. Of the six patients with recurrent bacterial vaginosis, three patients were cured, two patients had no information, and one was not cured (Graph 2).

Graph 2: Number of patients cured of vaginal discharge according to the inflammatory condition found.



Source: Produced by the authors.

In cases of recurrent Bacterial Vaginosis, the microorganisms found were *Mycoplasma Hominis*, *Ureaplasma Parvum* and *Ureaplasma Urealyticum*; and in cases of Recurrent Candidiasis, *Mycoplasma hominis*, *Ureaplasma Parvum* and *Ureaplasma Urealyticum*. No cases of recurrent vulvovaginitis were found in patients with *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis* (Table 1).

Table 1: Distribution of microorganisms found in Multiplex PCR tests by inflammatory condition.
(The sum exceeds the sample number, as the microorganisms were counted individually)

Microorganism	Total number of exams N= 282	Recurrent Vulvovaginal Candidiasis	Recurrent Bacterial Vaginosis
<i>Chlamydia trachomatis</i>	6	0	0
<i>Neisseria gonorrhoeae</i>	1	0	0
<i>Trichomonas vaginalis</i>	2	0	0
<i>Mycoplasma genitalium</i>	1	0	0
<i>Mycoplasma hominis</i>	45	13	4
<i>Ureaplasma urealyticum</i>	24	3	2
<i>Ureaplasma parvum</i>	88	19	4
Negative Results	167	-	-
Positive Results	115	22	6
Only 1 microorganism detected	72	11	2
Multiple organisms detected	43	11	4

Source: Produced by the authors.

The patients who did not have their vulvovaginitis cured had the following microorganisms: *Mycoplasma Hominis* and *Ureaplasma Parvum* (Table 2).

Table 2: Number of patients cured according to the microorganism found in Multiplex PCR examination.

Microorganism	Cured	Unhealed
<i>Chlamydia trachomatis</i>	0	0
<i>Neisseria gonorrhoeae</i>	0	0
<i>Trichomonas vaginalis</i>	0	0
<i>Mycoplasma genitalium</i>	0	0
<i>Mycoplasma hominis</i>	9	3
<i>Ureaplasma urealyticum</i>	2	0
<i>Ureaplasma parvum</i>	11	5
Only 1 microorganism detected	7	2
Multiple organisms detected Number of patients	7	3
	14	5

Source: Produced by the authors.

DISCUSSION

In recent years, much has been studied about the vaginal microbiota, its relationship with women's reproductive health, and the risk of acquiring sexually transmitted infections. Today, it is known that the composition of the vaginal microbiota is the first line of defense against pathogenic microorganisms, and the breaking down of this barrier, mainly due to behavioral and environmental issues, can cause harm^{15, 16}.

Ravel *et al*, in 2011, analyzed the bacterial vaginal community of 396 North American women of diverse ethnicities and concluded that, for the human vagina, there is no single central microbiome, but several central microbiomes defined by I-V community groups. Community groups I, II, III and V are dominated by *Lactobacillus spp.*, while community group IV is characterized by a scarcity of *Lactobacillus spp.* and a diversity of strict and facultative anaerobes¹⁶.

In the Brazilian study published by Marconi *et al.*, in 2020, in which vaginal flora from 609 women of reproductive age were studied and divided into five bacterial

communities, according to Ravel et al, bacterial community IV prevailed in 27.4%, reflecting the bacterial vaginosis rate of 28.6%. The prevalence of vaginosis is relevant, considering the association between abnormal vaginal microbiota, adverse pregnancy outcomes, and increased risk of acquiring STIs. In addition, almost half of the women who tested positive for at least one of the three STIs investigated in this study (*Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis*) had bacterial community IV¹⁵.

There is already a consensus in several studies on the relationship between bacterial flora *imbalance* with the prevalence of non-lactobacilli and the acquisition of STIs. However, in this study, we sought to answer whether the treatment of STIs would be able to help balance the vaginal flora and cure recurrent vulvovaginitis. To this end, we started by analyzing PCR results for STIs, as they are currently the most sensitive tests for screening sexually transmitted infections, approximately 20-30% more than other tests¹⁷.

Of the microorganisms found, *Neisseria gonorrhoea* and *Chlamydia trachomatis* may be asymptomatic, but should be treated for the risk of pelvic inflammatory disease (PID), ectopic pregnancy, and tubal infertility. *Chlamydia trachomatis* infection is also associated with adverse pregnancy outcomes, such as chorioamnionitis, preterm birth and low birth weight. *Mycoplasma genitalium* is an emerging STI and is believed to be associated with urethritis, cervicitis, PID, and tubal infertility¹⁹. Such microorganisms were found in 8.6% of the sample and were associated with dysbiosis, but none of them were associated with cases of recurrent vulvovaginitis in our study.

On the other hand, the microorganisms *Mycoplasma hominis*, *Ureaplasma parvum* and *Ureaplasma urealyticum* were the main microorganisms found in the samples of patients with recurrent vulvovaginitis. Called genital mycoplasmas, they are commonly found colonizing the genital tract of asymptomatic women. They are pointed out as innocent in non-pregnant women. However, there is an association with obstetric events, such as premature labor, low birth weight, premature rupture of membranes, spontaneous abortion, and neonatal death^{19, 20}.

However, there are inconsistencies between studies and uncertainty about the interaction of these specific organisms and the vaginal microbiota in general, generating divergences in recommendations for testing and treatment¹⁹. It is not yet known whether these microorganisms corroborate the acquisition of recurrent vulvovaginitis and whether treating them would bring benefit, as well as in the treatment of *Neisseria gonorrhoea*, *Chlamydia trachomatis* and *Mycoplasma genitalium*, microorganisms known to be pathogenic.

CONCLUSION

The study demonstrated the existence of a high rate of women who have some pathogenic microorganism in vaginal secretion. Of these women, the vast majority are young people who do not use condoms, paying attention to the behavioral exposure that predisposes them to the acquisition of STIs.

A high number of these patients, which corresponds to 26%, had recurrent discharge and at least 50% of them were proven to be cured of these discharges after STI treatment.

There is, therefore, a relationship between recurrent vulvovaginitis and STIs, and it is possible to achieve a cure of the discharge condition, based on the research and treatment of the microorganism found.

It is important, however, to expand this research theme, since it has limitations that involve the number of patients, the fragile diagnostic and treatment criteria, and the difficulty with incomplete data in the medical records. In addition a long-term follow-up of such patients would be necessary to really prove the cure of recurrent vulvovaginitis.

REFERENCES

1. Linhares IM, Amaral RL, Robial R, Eleutério Junior J. Vaginites e vaginoses. São Paulo: Federação Brasileira das Associações de Ginecologia e Obstetrícia (Febrasgo), 2018. (Pro-tocolo Febrasgo – Ginecologia, nº 24/ Comissão Nacional Especializada em Doenças In-fectocontagiosas).
2. Ministério da Saúde (BR). Protocolo Clínico e Diretrizes Terapêuticas para Atenção Integral às Pessoas com Infecções Sexualmente Transmissíveis – IST [recurso eletrônico]/Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. Brasília: Ministério da Saúde, 2022.
3. Yuk YS, Choi JE, Kim JK. Age and sex trends of Gardnerella vaginalis infection in patients with sexually transmitted infections in Korea. *Iran J Microb.* 2021 Dez. 22.
4. Baek J-C, Jo H-C, Lee S-M, Park J-E, Cho I-A, Sung J-H. Prevalence of Pathogens and Other Microorganisms in Premenopausal and Postmenopausal Women with Vulvovaginal Symptoms: A Retrospective Study in a Single Institute in South Korea. *Medicina.* 2021 Jun. 4;57(6):577.
5. Nardis C, Mosca L, Mastromarino P. Vaginal microbiota and viral sexually transmitted diseases. *Ann Ig.* 2013 Sep-Oct;25(5):443-56.
6. Faught BM, Reyes S. Characterization and Treatment of Recurrent Bacterial Vaginosis. *J Women's Heal.* 2019 Set. 1;28(9):1218–26.
7. Freitas F, Menke CH, Rivoire WA, Passos EP, Al E. Rotinas em Ginecologia. Porto Alegre: Artmed Editora; 2011.
8. Rosati D, Bruno M, Jaeger M, Ten Oever J, Netea MG. Recurrent Vulvovaginal Candidiasis: An Immunological Perspective. *Microorganisms.* 2020 Jan. 21;8(2):144.
9. Lewis FMT, Bernstein KT, Aral SO. Vaginal Microbiome and Its Relationship to Behavior, Sexual Health, and Sexually Transmitted Diseases. *Obst Gynecol* [Internet]. 2017 Abr.;129(4):643–54.
10. Van Houdt R, Ma B, Bruisten SM, Speksnijder AGCL, Ravel J, de Vries HJC. Lacto-bacillus iners-dominated vaginal microbiota is associated with increased susceptibility to Chlamydia trachomatis infection in Dutch women: a case-control study. *Sexual Transm Infect.* 2017 Set. 25;94(2):117–23.
11. Bardin MG, Giraldo PC, Benetti-Pinto CL, Sanches JM, Araujo CC de, Amaral RLG do. Habits of Genital Hygiene and Sexual Activity among Women with Bacterial Vaginosis and/or Vulvovaginal Candidiasis. *Rev Bras Ginecol Obstet* [Internet]. 2022 Abr. 8;44:169–77

12. Kebbi-Beghdadi C, Aeby S, Baud D, Greub G. Evaluation of a Multiplex Real-Time PCR Assay for Detecting Chlamydia trachomatis in Vaginal Samples. *Diagnostics*. 2022 Mai. 4;12(5):1141.
13. Lima L de Miranda, Hoelzle CR, Simões RT, Lima MI de M, Fradico JRB, Mateo ECC, et al. Sexually Transmitted Infections Detected by Multiplex Real Time PCR in Asymptomatic Women and Association with Cervical Intraepithelial Neoplasia. *Rev Bras Gineco Obste* [Internet]. 2018 Sep 1 [citado 2022-11-17];40:540-6.
14. Lins dos Santos R, Tonin Beneli Fontanezi C, da Silva Negreiros FD, Maria Correia Pequeno A. PERFIL CLÍNICO-EPIDEMIOLÓGICO DE PACIENTES ATENDIDOS EM UMA CLÍNICA ESCOLA DE UM CENTRO UNIVERSITÁRIO DE FORTALEZA. *Cadernos ESP* [Internet]. 2020 Jun. 29;14(1):30-7.
15. Marconi C, El-Zein M, Ravel J, Ma B, Lima MD, Carvalho NS, et al. Characterization of the vaginal microbiome in women of reproductive age from five regions in Brazil. *Sex-ual Transm Dis*. 2020 Jun. 8;Publish Ahead of Print.
16. Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SSK, McCulle SL, et al. Vaginal microbiome of reproductive-age women. *Proceed Nat Academy Sci*[Internet]. 2010 Jun. 3;108(Supplement 1):4680–7.
17. Choe HS, Lee DS, Lee SJ, Hong SH, Park DC, Lee MK, et al. Performance of Any-plex™ II multiplex real-time PCR for the diagnosis of seven sexually transmitted infections: comparison with currently available methods. *Intern J Infec Dis*. 2013 Dez.;17(12):e1134-40.
18. Tamarelle J, Thiébaud ACM, de Barbeyrac B, Bébéar C, Ravel J, Delarocque-Astagneau E. The vaginal microbiota and its association with human papillomavirus, Chlamydia trachomatis, Neisseria gonorrhoeae and Mycoplasma genitalium infections: a systematic review and meta-analysis. *Clin Microb Infec*. 2019 Jan.;25(1):35-47.
19. Jonduo ME, Valley LM, Wand H, Sweeney EL, Egli-Gany D, Kaldor J, et al. Adverse pregnancy and birth outcomes associated with *Chlamydia trachomatis*, *Ureaplasma urealyticum* and *Ureaplasma parvum*: a systematic review and meta-analysis. *BMJ Open*. 2022 Ago.;12(8):e062990.
20. Xu Y, Hu J, Huang Y, Shi L. Maternal *Ureaplasma* exposure during pregnancy and the risk of preterm birth and BPD: a meta-analysis. *Archi Gynecol Obstet*. 2022 Mar. 12;306(6):1863–72.