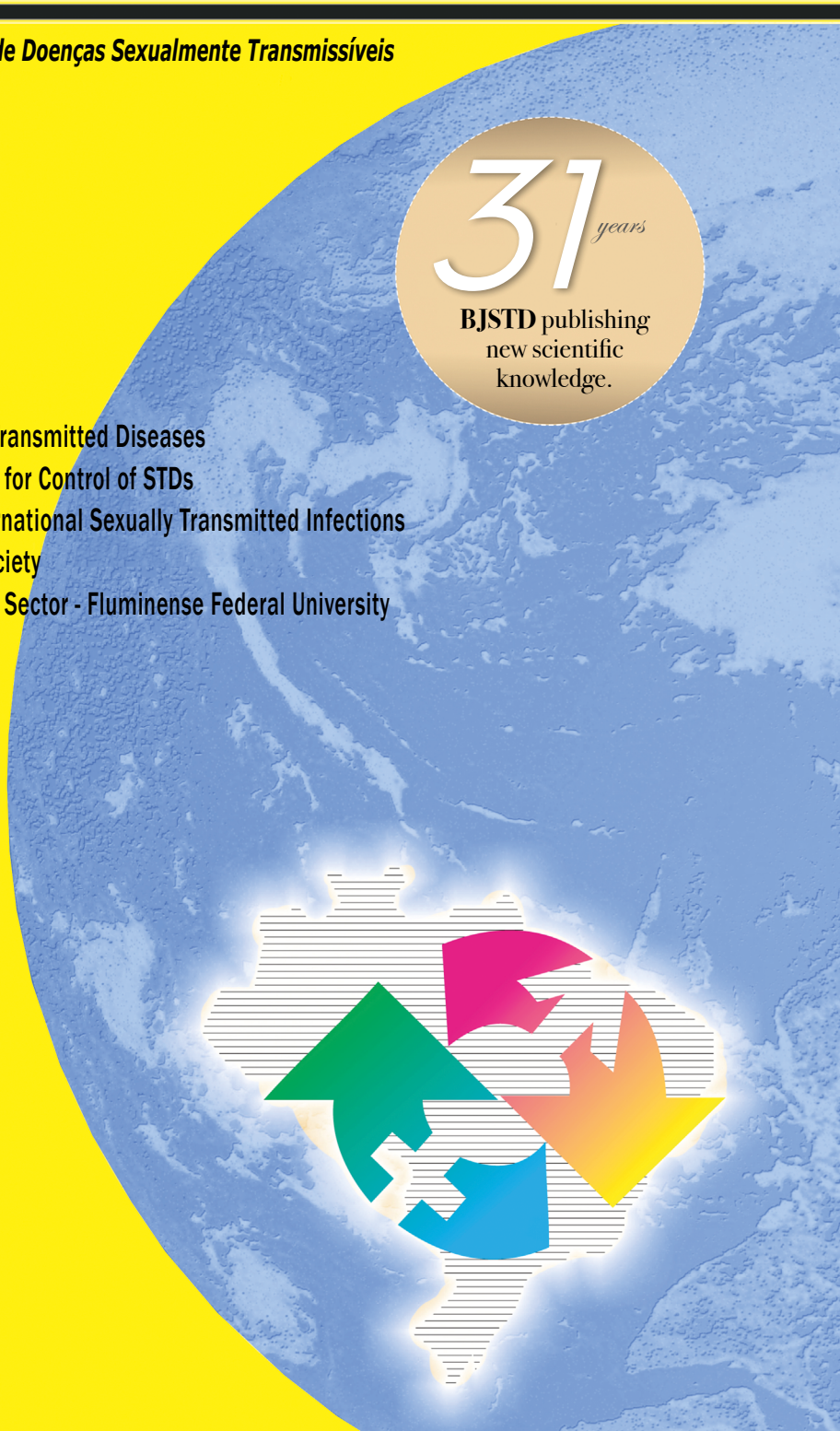
ISSN ON-LINE 2177-8264

DST

Brazilian Journal of Sexually Transmitted Diseases

Volume 31 Nº 4 2019 www.bjstd.org

Jornal Brasileiro de Doenças Sexualmente Transmissíveis



Official Organ of the Brazilian Society for Sexually Transmitted Diseases
Official Organ of the Latin American and Caribbean for Control of STDs
Official Organ for Latin America Union Against International Sexually Transmitted Infections
Official Organ of the Portuguese Papillomavirus Society
Official Organ of the Sexually Transmitted Diseases Sector - Fluminense Federal University

1988·2019 31 anos na vanguarda das DST
SBDST | Sociedade Brasileira de Doenças Sexualmente Transmissíveis

VOLUME 31 Nº 4 2019

CONTENTS

EDITORIAL

CURRENT SCENARIO OF BIOMARKERS IN CERVICAL CANCER AND ONCOGENESIS BY HPV 109
CENÁRIO ATUAL DOS BIOMARCADORES NO CÂNCER CERVICAL E NA ONCOGÊNESE PELO HPV
Luciane Rocha Ernlund Pangracio, Danielle Betina de Oliveira Traesel, Newton Sérgio de Carvalho, Maria da Graça Bicalho

ORIGINAL ARTICLE

GESTATIONAL AND CONGENITAL SYPHILIS IN A MUNICIPALITY IN BRAZIL BETWEEN 2014 AND 2018 112
SÍFILIS GESTACIONAL E CONGÊNITA EM UM MUNICÍPIO DE FRONTEIRA NO BRASIL ENTRE 2014 E 2018
Patricia Simon da Silva, Cassandra Severo Amaral Vieira, Ludmila Mourão Xavier Gomes, Thiago Luis de Andrade Barbosa

ANALYSIS OF HIV/AIDS NOTIFICATIONS IN A MUNICIPALITY OF NATIONAL HEALTH BETWEEN 2007 AND 2017: GENDER, AGE, RACE, SCHOOLING, NEIGHBORHOOD OF ORIGIN, NOTIFYING UNITS AND TREATMENT UNITS 118
ANÁLISE DE NOTIFICAÇÕES DE HIV/AIDS EM UM MUNICÍPIO POLO DE SAÚDE NACIONAL ENTRE 2007 E 2017: SEXO, IDADE, RAÇA, ESCOLARIDADE, BAIRRO DE ORIGEM, UNIDADES NOTIFICADORAS E UNIDADES DE TRATAMENTO
Rodrigo Alberton da Silva, Alexander Acauan de Aquino, Matheus Henrique Benin Lima, Ana Victória Coletto Reichert, Augusto Poloniato Gelain, Julia Belato Teixeira, Luiz Casemiro Krzyzaniak Grando, Louise Pietrobon, Deison Alencar Lucietto

THE REALITY OF 13 YEARS OF PRENATAL CARE TO PREGNANT WOMEN WITH SYPHILIS IN SERGIPE STATE (2007–2019) 123
REALIDADE EM 13 ANOS DA ASSISTÊNCIA PRÉ-NATAL A GESTANTES COM SÍFILIS NO ESTADO DE SERGIPE (2007-2019)
Rute de Oliveira Farias, Izailza Matos Dantas Lopes Letícia Goes Santos Amanda Silveira de Carvalho Dantas

PREVALENCE OF UREAPLASMA UREALYTICUM, MYCOPLASMA HOMINIS AND HUMAN PAPILLOMAVIRUS COINFECTION IN PEOPLE ATTENDING A SEXUALLY TRANSMITTED INFECTIONS (STI)/HIV REFERENCE CENTRE IN SALVADOR, BAHIA, BRAZIL 131
PREVALÊNCIA DA COINFECÇÃO POR UREAPLASMA UREALYTICUM, MYCOPLASMA HOMINIS E PAPILOMAVÍRUS HUMANO EM PESSOAS ATENDIDAS EM CENTRO DE REFERÊNCIA DE DOENÇAS SEXUALMENTE TRANSMISSÍVEIS (DST)/HIV EM SALVADOR, BAHIA
Alyce Lima Amorim, Ana Gabriela Álvares Travassos, Geovane Cruz de Souza, Vitor Cunha Fontes, Maiara Timbó, Eveline Xavier Souza

HPV INFECTION AND ENDOMETRIOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS 138
INFECÇÃO POR HPV E ENDOMETRIOSE: UMA REVISÃO SISTEMÁTICA E METANÁLISE
Geilson Gomes de Oliveira, José Eleutério Júnior, Renata Mírian Nunes Eleutério

LETTER TO THE EDITOR

HIV/AIDS A FORGOTTEN PROBLEM 143
HIV/AIDS, UM PROBLEMA ESQUECIDO
Aliete Cunha-Oliveira

1988·2019 31 anos na vanguarda das DST
SBDST Sociedade Brasileira de Doenças Sexualmente Transmissíveis

Official Organ of the Brazilian Society for Sexually Transmitted Diseases

Av. Roberto Silveira, 123 - Niterói - RJ - Brazil
CEP: 24230-150 - Tel.: + 55 (21) 2710-1549

ALAC DST ITS

Official Organ of the Latin American and Caribbean for Control of STDs

DST - BJDST is the official organ for Latin America Union Against International Sexually Transmitted Infections (IUSTI)
Regioal Representative: Adele Benzaken

Sociedade Portuguesa de Papilomavírus
Presidente: Rui Medeiros
Secretária-Geral: Maria Clara Bicho

Filiado à ABEC BRASIL Associação Brasileira de Editores Científicos

Official Organ of the Sector Sexually Transmitted Diseases

Outeiro de S. João Batista, s/nº
Campus do Valonguinho - Centro
Niterói - RJ - 24210-150 - Brazil
Tel.: +55 (21) 2629-2495 - 2629-2494
Fax: +55 (21) 2629-2507

E-mail: dst@dst.uff.br
http://www.bjstd.org/

Rector of UFF:
Antonio Claudio Lucas da Nóbrega
Vice-Rector:
Fabio Barboza Passos
Provost of Research, Post-Graduate and Innovation:
Andrea Brito Latge
Biomedical Institute:
Otílio Machado Pereira Bastos
Department of Microbiology and Parasitology:
Claudia Maria AU Souto Maior
Chief of STD Sector:
Mauro Romero Leal Passos

CAPES

Órgão de divulgação do Programa de Pós-graduação Mestrado e Doutorado em Microbiologia e Parasitologia Aplicadas, Mestrado profissional em Saúde Matero-Infantil, ambos da UFF e de outros da área médica e Ciências da Saúde.

Editora da UFF
Editora da Universidade Federal Fluminense

ABEU Associação Brasileira das Editoras Universitárias

Targeting and Distribution:

DST - Brazilian Journal of Sexually Transmitted Diseases is directed to members of SBDST, subscribers, libraries, reference centers, gynecologists, urologists, infectious disease specialists, dermatologists, clinicians, family health programs and entities with an agreement.

Exchange requested - Pode-se permuta
On prie l'échange - Se solicita ei caxzje
Mau bitet nu Austausch - Si prega lo escambo

All content of the whole collection since 1989 is available for free on the World Wide Web at www.dst.uff.br

INDEXING:

LILACS EXPRESS Latin American Literature in Health Sciences, The Library of Congress WC – 140, Scholar google

Current scenario of biomarkers in cervical cancer and oncogenesis by HPV

Cenário atual dos biomarcadores no câncer cervical e na oncogênese pelo HPV

Luciane Rocha Ernlund Pangracio[1], *Danielle Betina de Oliveira Traesel*[2], *Newton Sérgio de Carvalho*[2,3], *Maria da Graça Bicalho*[2,4,5]

Cervical cancer (CC) is related to HPV infection and represents the third cause of cancer in women. Annually, more than 500,000 new cases are reported worldwide, with significant death rates. It develops due to genetic and epigenetic alterations that control cell growth and differentiation, and may cause death. These alterations induce uncontrolled cell division and invasion of cervical tissue have severe consequences to women's health[1]. CC incidence and mortality drop considerably since the implementation of screening tests and vaccination strategies. Nevertheless, CC continues to have a high incidence, mainly in low-income countries, where these programs do not cover territorial frontiers and there is lack of resources to implement vaccination or screening tests. Oncogenic HPV types reached 25% of cases in Brazil over the last years[2], and there was no modification on HPV types after four years of the vaccination program, according to Tota et al.[3]. Usually, screening tests in Brazil cover women from 25 to 64 years old. According to Teixeira et al.[4], rates of CC under the age of 25 tend to increase, and women over 64 achieved roughly 20% of CC on research of Brazilian women from two high-income cities.

HPV 16 and 18 are the predominant genotypes linked to progression to invasive cancer. HPV uses evasion mechanisms of the immune system in early and late stages of the infection, causing its persistence in cutaneous and mucosal tissues. Its continuous expression of viral proteins E6 and E7 contribute to disease progression[5]. Starting lesions are well defined and classified into cervical intraepithelial neoplasm 1, 2, and 3, with grade 3 being the highest level of evolution. Factors such as age, smoking, sexually transmitted disease, long-term oral contraceptive use, and parity are associated to a higher risk of cervical cancer development[6,7]. Many CIN 1, 2, and some CIN 3 lesions spontaneously revert. Even though, treatment is still needed, because they have high chances to progress[8]. Treatment just after diagnosis can include from large loop excision of the transformation zone (LLETZ), loop electrosurgical excision procedure (LEEP) to cold-knife conization (CKC), and sometimes other treatment modalities, as laser or cryosurgery. Incidence among young women has expressive rates, and treatment can relate to severe consequences in the reproductive function, such as fetal consequences of low birth weight, premature birth, and miscarriage[9,10].

Molecular markers appear to be of fundamental importance, not only to make the diagnostic, but also to help the treatment establishment, working as a tool to assess the individual patient's risk of having cancer. The best biomarker would be 100% sensibility and specificity, which is not a reality yet[1]. Biomarkers specific to cervical cancer would be of great value, making it possible to identify which CC precursor lesions would progress, influencing clinical decision-making. Scientific research focus on finding biomarkers from:

- identification of wrong protein expression due to oncogenes;
- detection of methylation alterations on cell genes, predicting neoplasm process;
- identification of chromosomal or genetic modifications due to viral integration;
- expression of genic polymorphism in association with a better prognostic[1,10,11].

The present editorial was written to provide readers with the recent scenario regarding molecular markers and its impregnability on diagnosis, treatment, and follow up of cervical precancer and cancer patients. According to current literature, research articles report many possible biomarkers to help with cervical cancer diagnosis, treatment, and prognosis. Immunologic markers are of great interest. Programmed Death 1 (PD-1) and its ligand (PD-L1) can blockade T lymphocytes function and allow tumoral growth[12]. Allelic variations of Human Leukocyte Antigen (HLA) genes are associated to genetic susceptibility in cervical cancer development in the presence of high-risk DNA-HPV11. The overexpression of HLA-E seems to trigger signalization pathways to engage Natural Killer (NK) activating receptors, such as NKG2D, contributing to NK activation against viral infection[5]. The allelic *variants* MICA*008:01/04 and MICA*018:01 are associated to the risk of CC development, and MICA-129 *Val* is related to the risk of tumoral development[7].

Squamous cell carcinoma antigen (SCC-Ag) is related to tumoral size, stromal invasion, and disease relapse[1]; Carcinoma Embryonic Antigen (CEA) is linked to cervical squamous neoplasia when it has higher levels and impact on prognostic on cervical adenocarcinoma[1]. There was no association of Mannose-binding lectin (MBL) with lesions progression or with cervical ongenesis[13]. However, products

[1]Laboratory of Immunogenetics, and Gynecology and Obstetrics and Women Health Post Graduation Program, Hospital de Clínicas, Universidade Federal do Paraná – Curitiba (PR), Brazil.
[2]Gynecology and Obstetrics and Women Health Post Graduation Program, Hospital de Clínicas, Universidade Federal do Paraná – Curitiba (PR), Brazil.
[3]Department of Gynecology and Obstetrics, Universidade Federal do Paraná – Curitiba (PR), Brazil.
[4]Department of Genetics, Universidade Federal do Paraná – Curitiba (PR), Brazil.
[5]Laboratory of Immunogenetics and Hystocompatibility, Universidade Federal do Paraná – Curitiba (PR), Brazil.

of MBL — MASP-1, MASP-2, and MAp-19, showed higher levels related to tumoral progression and a worse prognostic in cervical neoplasia patients[14].

Proteins coded by virus oncogenes E6 and E7 interfere in apoptosis and cell regulation. For that reason, tumor suppressor proteins, such as p53, $p16^{INK4a}$, and Ki-67 were investigated as potential targets. Virus-infected cells express p16 to control irregular cell cycle, which is not present in healthy cervical cells, but is one hundred percent present in high-grade lesions cells[15,16]. Protein 53 (p53) encoded by the gene TP53, seems to be higher in patients with cancer stage II, III and IV, according to the International Federation of Gynecology and Obstetrics (FIGO), older than 48, and with tumor size >= 4 mm and. Absence of p53 is significantly associated with tumors <4 cm, adenocarcinoma and deep invasion.[10]. Histological distribution of Ki-67 is modified, with HPV infection being associated to high-risk HPV infection[16].

Some genes are involved in neoplastic processes. Gene cyclin-dependent kinase inhibitor 3 (CDKN3) is higher in cervical cancer patients, related to it in 31.85% of cases with five years of survival. In those patients that died, survival was of 14 months. *In vitro*, its inactivation showed lower tumoral proliferation, which can be used in the future to develop new strategies to treat neoplasm[17]. The methylation process is of importance in the HPV oncogenic pathway, and Fiano et al.[18] showed that DNA methylation in HPV positive women is associated to high-risk CIN. DNA methylation in host genes and HPV genome is associated to cervical oncogenesis[16,18]. Some molecules, such as GHSR, SST, and ZIC1, from 3q chromosome, *in vitro*, are associated to a higher risk of progression from precursor lesions detected by citology[8]. Gene STK31, after aberrant methylation by E7-HPV16, is considered an oncogenic precursor and risk marker to invasive neoplasia[19].

Genotyping HPV is being incorporated in population screening, and it is used to identify tumoral aggressiveness. Whereas HPV 16 is a marker of high-risk lesion, a better disease-free survival was observed in HPV16 cases, more sensitive to treatment, with a lower rate of growth, and better immune response to virus[9]. Besides genotyping, viral load, viral physical status, and circulating fraction of DNA-HPV are biomarkers that need to be better understood[1,16,20,21].

Genomic and immunologic techniques are the oncology vanguard, whose applications include cervical cancer patients. Limitations to the use of these techniques are costs and population size, which contribute to insufficient scientific evidence to change protocols in use.

From an overall reading of the available literature on biomarkers, we can conclude:

- PD-1/PD-L1 showed promising results in other neoplasms, indicating disease progression and specific immunotherapy;
- the methylation status of target genes, such as STK31, is considered an oncogenic precursor and a risk marker to invasive neoplasia, even if it is not a real value for a biomarker;
- DNA-HPV already incorporated as a secondary screening test, which is a substantial tool to help clinic management for papillomavirus patients.

Risk evaluation is of critical significance to choose a therapeutic strategy for patients that face HPV infection. The aim is to bring the best result to a specific patient, according to each clinical situation. Cervical cancer has a significant impact on women's lives, with many deaths related to this disease even with screening tests. Immunological knowledge must be deepened to bring efficient vigilance, a treatment with less morbidity and better survival.

Participation of each author

Newton Sergio de Carvalho: publication theme, review for sending the paper.

Maria da Graça Bicalho: publication theme, review for sending the paper.

Luciane Rocha Ernlund Pangracio: bibliographic review, writing of the text.

Danielle Betina de Oliviera Traesil: bibliographic review, writing of the text.

Funding

The present paper had no financial support.

Conflict of interests

The authors declare that there is no conflict of interests.

REFERENCES

1. Dasari S, Wudayagiri R, Valluru L. Cervical cancer: Biomarkers for diagnosis and treatment. Clin Chim Acta. 2015;445:7-11. https://doi.org/10.1016/j.cca.2015.03.005
2. Rotelli-Martins CM, Carvalho NS, Naud P, Teixeira J, Borba P, Derchain S, et al. Prevalence of Human Papillomavirus Infection and Associated Risk Factors in Young Women in Brazil, Canada, and the United States: A Multicenter Cross-sectional Study. Int J Gynecol Pathol. 2011;30(2):173-84. https://doi.org/10.1097/pgp.0b013e3181f38dfe
3. Tota JE, Struyf F, Merikukka M, Gonzalez P, Kreimer AR, Bi D, et al. Evaluation of Type Replacement Following HPV16/18 Vaccination: Pooled Analysis of Two Randomized Trials. J Natl Cancer Inst. 2017;109(7):djw300. https://doi.org/10.1093/jnci/djw300
4. Teixeira JC, Maestri CA, Machado HDC, Zeferino LC, De Carvalho NS. Cervical Cancer Registered in Two Developed Regions from Brazil: Upper Limit of Reachable Results from Opportunistic Screening. Rev Bras Ginecol Obstet. 2018;40(6):347-53. https://doi.org/10.1055/s-0038-1660841
5. Franciosi JR, Gelmini GF, Roxo VS, Carvalho NS, Bicalho MDG. Is there a role played by HLA-E, if any, in HPV immune evasion? Scan J Immunol. 2020;91(3):e12850. https://doi.org/10.1111/sji.12850
6. El-Zein M, Ramanakumar AV, Naud P, Roteli-Martins CM, Carvalho NS, Borba PC, et al. Determinants of acquisition and clearance of human papillomavirus infection in previously unexposed young women. Sex Transm Dis. 2019;46(10):663-9. https://dx.doi.org/10.1097%2FOLQ.0000000000001053
7. Von Lisingen R, De França PP, De Carvalho NS, Bicalho MDG. MICA and KLRK1 genes and their impact in cervical intraepithelial neoplasia development in the southern Brazilian population. Human Immunol. 2020;81(5):249-53. https://doi.org/10.1016/j.humimm.2020.02.007
8. Verlaat W, Snijders PJF, Novianti PW, Wilting SM, De Strooper LMA, Trooskens G, et al. Genome-wide DNA Methylation Profiling Reveals Methylation Markers Associated with 3q Gain for Detection of Cervical Precancer and Cancer. Clin Cancer Res. 2017;23(14):3813-22. https://doi.org/10.1158/1078-0432.ccr-16-2641

9. Chong GO, Lee YH, Han HS, Lee HJ, Park JY, Hong DG, et al. Prognostic value of pre-treatment human papilloma virus DNA status in cervical cancer. Gynecol Oncol. 2017;148(1):97-102. https://doi.org/10.1016/j.ygyno.2017.11.003
10. Halle MK, Ojesina AI, Engerud H, Woie K, Tangen IL, Holst F, et al. Clinicopathologic and molecular markers in cervical carcinoma: a prospective cohort study. Am J Obstet Gynecol. 2017;217(4):432.E1-432.E17. https://doi.org/10.1016/j.ajog.2017.05.068
11. Termini L, Villa LL. Biomarcadores na Triagem do Câncer de Colo Uterino. DST – J Bras Doenças Sex Transm. 2008;20(2):125-31.
12. Liu C, Lu J, Tian H, Du W, Zhao L, Feng J, et al. Increased Expression of PD-L1 by Human Papillomavirus 16 E7 Oncoprotein Inhibits Anticancer Immunity. Mol Med Rep. 2017;15(3):1063-70. https://doi.org/10.3892/mmr.2017.6102
13. Maestri CA, Nisihara R, Ramos GP, Mendes HW, Messias-Reason I, De Carvalho NS. Mannose-binding lectin does not act as a biomarker for the progression of preinvasive lesions of invasive cervical cancer. Med Princ Pract. 2018;26(6):530-4. https://doi.org/10.1159/000485037
14. Maestri CA, Nisihara R, Mendes HW, Jensenius J, Thiel S, Messias-Reason I, et al. MASP-1 and MASP-2 serum levels are associated with worse prognostic in cervical cancer progression. Front Immunol. 2018;9:2742. https://doi.org/10.3389/fimmu.2018.02742
15. Fonseca FV, Tomasich FD, Jung JE, Maestri CA, Carvalho NS. The role of P16ink4a and P53 immunostaining in predicting recurrence of HG-CIN after conization treatment. Rev Col Bras Cir. 2016;43(1):35-41. https://dx.doi.org/10.1590/0100-69912016001008
16. Valenti G, Vitale SG, Tropea A, Biondi A, Laganà AS. Tumor markers of uterine cervical cancer: a new scenario to guide surgical practice? Updates Surg. 2017;69:441-9. https://doi.org/10.1007/s13304-017-0491-3
17. Barron EV, Roman-Bassaure E, Sánchez-Sandoval AL, Espinosa AM, Guardado-Estrada M, Medina I, et al. CDKN3 mRNA as a Biomarker for Survival and Therapeutic Target in Cervical Cancer. PLoS One. 2015;10(9):e0137397. https://doi.org/10.1371/journal.pone.0137397
18. Fiano V, Trevisan M, Fasanelli F, Grasso C, Marabese F, Bicalho MDG, et al. Methylation in host and viral genes as marker of aggressiveness in cervical lesions: Analysis in 543 unscreened women. Gynecol Oncol. 2018;151(2):319-26. https://dx.doi.org/10.1016/j.ygyno.2018.08.031
19. Yin F, Wang N, Bi XN, Yu X, Xu X-H, Wang Y-L, et al. Serine/threonine kinases 31(STK31) may be a novel cellular target gene for the HPV16 oncogene E7 with potential as a DNA hypomethylation biomarker in cervical cancer. Virology J. 2016;13:60. https://doi.org/10.1186/s12985-016-0515-5
20. Das P, Thomas A, Kannan S, Deodhar K, Shrivastava SK, Mahantshetty U, et al. Human papillomavirus (HPV) genome status & cervical cancer outcome – A retrospective study. Indian J Med Res. 2015;142(5):525-32. https://doi.org/10.4103/0971-5916.171276
21. Huang Y, He Q, Xu K, Zhou J, Yin J, Li F, et al. A new marker based on risk stratification of human papillomavirus DNA and tumor size to predict survival of locally advanced cervical cancer. Int J Gynecol Cancer. 2019;29:459-65. https://doi.org/10.1136/ijgc-2018-000095

Address for correspondence
LUCIANE ROCHA ERNLUND PANGRACIO
Universidade Federal do Paraná, Hospital de Clínicas,
Laboratório de Imunogenética
Rua Padre Camargo, 280, 1º andar – Alto da Glória
Curitiba (PR), Brazil
CEP: 80060-240
E-mail: luciane.pangracio@hc.ufpr.br

Received on: 12.01.2019
Approved on: 12.30.2019

Gestational and congenital syphilis in a municipality in Brazil between 2014 and 2018

Sífilis gestacional e congênita em um município de fronteira no Brasil entre 2014 e 2018

Patricia Simon da Silva[1], *Cassandra Severo Amaral Vieira*[1,2], *Ludmila Mourão Xavier Gomes*[1], *Thiago Luis de Andrade Barbosa*[1]

ABSTRACT

Introduction: Syphilis is an infectious disease that can cause congenital syphilis when it affects pregnant women, resulting in malformation of the fetus, miscarriage, or fetal death. Unlike many neonatal infections, congenital syphilis is considered a preventable perinatal cause, because it can be diagnosed and treated early during pregnancy. **Objective:** To analyze the reports of cases of gestational syphilis and congenital syphilis registered in Foz do Iguaçu City, Paraná State, between 2014 and 2018. **Methods:** This is a time-series study on the trend of cases recorded in the Notification Diseases Information System. The simple linear regression model was adopted to verify the trend of deaths in the analyzed period. **Results:** A total of 324 reports of gestational syphilis and 137 cases of congenital syphilis were evidenced in the study period. Regarding cases of gestational syphilis, 45.9% were diagnosed during the first trimester of pregnancy, 74.6% were treated with penicillin, and 24.3% were classified as primary syphilis. Roughly 88.3% of cases of congenital syphilis were reported in children under the age of 7 days. A significant increase in the rate of detection of gestational syphilis was observed, representing an increase of 4.0 times (p=0.004) in the years analyzed, and the risk of congenital syphilis increased 5.8 times (p=0.003) in the same period. **Conclusion:** The magnitude of gestational and congenital syphilis is a warning that indicates the need for actions and strategies to reduce cases of gestational syphilis and vertical transmission of syphilis.

Keywords: syphilis; congenital syphilis; sexually transmitted diseases; pregnancy.

RESUMO

Introdução: A sífilis é uma doença infecciosa que, quando acomete gestantes, pode provocar a sífilis congênita, resultante em malformação do feto, abortamento espontâneo e morte fetal. Ao contrário de muitas infecções neonatais, a sífilis congênita é considerada como causa perinatal evitável, desde que diagnosticada e tratada precocemente na gestação. **Objetivo:** Analisar as notificações dos casos de sífilis gestacional e congênita registrados no município de Foz do Iguaçu, Paraná, entre os anos de 2014 a 2018. **Métodos:** Trata-se de um estudo de série temporal sobre a tendência de casos registrados no Sistema de Informação de Agravos de Notificação. Para verificar a tendência dos óbitos no período analisado, adotou-se o modelo de regressão linear simples. **Resultados:** Evidenciaram-se 324 notificações de sífilis gestacional e 137 casos de sífilis congênita no período estudado. Sobre os casos de sífilis gestacional, 45,9% foram diagnosticados durante o 1º trimestre de gestação, 74,6% foram tratados com penicilina e 24,3% dos casos foram classificados como sífilis primária. Cerca de 88,3% dos casos de sífilis congênita foram notificados em crianças com idade inferior a sete dias. Observou-se um aumento significativo na taxa de detecção da sífilis gestacional, representando um aumento de 4,0 vezes (p=0,004) entre os anos analisados, e o risco de sífilis congênita apresentou um aumento de 5,8 vezes (p=0,003) no mesmo período. **Conclusão:** A magnitude da sífilis gestacional e congênita é um alerta que indica a necessidade de ações e estratégias para a redução dos casos de sífilis gestacional e a transmissão vertical da sífilis.

Palavras-chave: sífilis; sífilis congênita; doenças sexualmente transmissíveis; gravidez.

INTRODUCTION

Syphilis is an important public health problem and is characterized by a systemic infection caused by *Treponema pallidum.* When not treated early, it can evolve to a chronic disease with irreversible long-term sequelae[1].

The disease is predominantly transmitted by sexual contact. However, when it affects pregnant women, syphilis can cause congenital syphilis (CS), and the risk of vertical transmission is dependent on the stage of maternal infection and the gestational age in which it occurs. The diagnosis of CS, when compared to syphilis in pregnant women (Gestational Syphilis), is more complex, mainly because approximately half of infected children do not present signs or symptoms at birth. A total of 25% of pregnancies is estimated to end in late abortion or foetal death, 11.0% in neonatal death, 13% in preterm delivery or low birth weight, and 20% in presenting clinical signs of CS[2,3].

Data from the Epidemiological Bulletin of Syphilis indicate that syphilis acquired in Brazil had its detection rate increased from 59.1 cases per 100,000 inhabitants in 2017 to 75.8 cases per 100,000 inhabitants in 2018. Also in 2018, the detection rate of GS was 21.4/1,000 live births, the incidence of CS was 9.0/1,000 live births, and mortality rate due to CS was 8.2/100.000 live births[4].

The increase in notifications of GS and CS in recent years may be related to the strengthening of prenatal services, which provided an increase in coverage of testing of pregnant women and their partners, and follow-up of cases. With the simultaneous treatment of couples, cases of CS can be minimized. However, even if they have high prenatal coverage, the measures adopted are still insufficient to promote the elimination of CS as a public health problem[5,6].

Vertical transmission of syphilis can be avoided, because the appropriate diagnosis and treatment of pregnant women and their partners are performed during the gestational period, with penicillin being the drug of choice in the treatment of syphilis, the only one indicated for pregnant women[7,8].

When notifications are verified, the records of GS and CS are alarming, given that this is a preventable problem, in which an

[1]Universidade Federal da Integração Latino-Americana – Foz do Iguaçu (PR), Brazil.
[2]Family Health Strategy – Foz do Iguaçu (PR), Brazil.

epidemiological picture with high incidence persists throughout the country[9,10].

The Foz do Iguaçu City, located in a border region between Brazil, Paraguay, and Argentina, presents a complex sanitary dynamics, and the existing population mobility influences the daily life of the border, causing negative impacts to health and affecting the care system[11,12]. In this perspective, the epidemiological profile of CS and GS is relevant, so that it can subsidize public health actions.

Considering that CS and GS must be notified in Brazil and information monitoring is of fundamental importance for the elimination of CS, investigation is needed to provide subsidies to plan and define the necessary interventions[7].

OBJECTIVE

To analyze the notifications of CS and GS cases registered in Foz do Iguaçu City, Paraná State, between 2014 and 2018.

METHODS

This is an ecological study of time series on the trend of cases of GS and CS in Foz do Iguaçu City, Paraná State, Southern Brazil, from 2014 to 2018. Data were collected from the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* — SINAN), from compulsory notification forms filled out by health professionals[13].

All cases of GS and CS notified in the city were included in the period analyzed. Variables were studied according to the data presented in the compulsory notification forms of GS and CS, namely: maternal sociodemographic (age group, race/skin color, schooling); obstetric and therapeutic (gestational age, treatment schedule, clinical classification, time of diagnosis of GS); treatment of the partner; age of the child at the time of diagnosis, and deaths from CS in children under one year of age.

Collected data were tabulated using the Microsoft Excel program® 2010 for the construction of graphs and table, and calculation of relative frequencies. Syphilis detection rates in pregnant women were calculated with the number of cases reported by the number of live births, collected in the information base of the Information System on Live Births (*Sistema de Informações sobre Nascidos Vivos* — SINASC), multiplied by 1,000; the incidence rate of congenital syphilis was calculated with the total number of reported cases of congenital syphilis in children under one year of age by the total number of live births of mothers living in the same place, and multiplied by 1,000[14].

In order to verify the trend of deaths in the period analyzed, the simple linear regression model ($y=\beta 0+\beta 1x$) was adopted. Models were constructed based on syphilis detection rates in pregnant women and congenital syphilis (y), according to the variable year (x). Linear trend equations and model adjustment statistics (adjusted R2 value and p-value of the F model adequacy test) were obtained with the statistical software Bioestat 5.0 of Universidade Federal do Pará (UFPA). The significance level adopted was 5%.

RESULTS

Research showed a total of 324 notifications of GS, and 137 of CS in the years analyzed. When cases of GS (**Table 1**) were observed, 48.7% of the reported cases were of women between 20 and 29 years old, 33.0% had education between 0 and 8 years, 36.7% of the records had the schooling field as an ignored item, 58.3% of pregnant women reported having white skin. Regarding prenatal data, 45.9% of cases of GS were diagnosed during the first trimester of pregnancy, 74.6% of cases were treated with penicillin, and 24.3% were classified as primary syphilis.

When analyzing CS data (**Table 2**), 88.3% of reported cases were children under the age of 07 days. All of them received a final diagnosis of recent CS. Among the cases of CS reported, 87.5% of the pregnant women underwent prenatal care, and 74.4% had the diagnosis of GS during the procedure. Regarding treatment performed in pregnant women, 43.0% were reported as inadequate, and in 64.9% of the reported cases the father/partner did not undergo treatment. In the period analyzed, two deaths due to GS were recorded in children under 1 year old.

Figure 1 shows the evolution of syphilis detection in pregnant women as well as the incidence of congenital syphilis in Foz do Iguaçu City in the historical series analyzed. Regarding disease detection, there was a significant increase (R2=0.947; p=0.004) of rates from 6.7 cases/1,000 live births in 2014 to 26.5 cases/1,000 live births in 2018, which represented a 4.0 increase in detection. At the other point of analysis, there was an important increase (R2=0.942;

Table 1 – Characterization of reported cases of syphilis in pregnant women, Foz do Iguaçu City, Paraná State, 2014-2018.

Variable	2014		2015		2016		2017		2018	
	n	%	n	%	n	%	N	%	n	%
Total notifications	30	9.2	39	12.0	59	18.2	79	24.3	117	36.1
Age range										
10 to 14	0	0.0	0	0.0	1	1.7	1	1.3	0	0.0
15 to 19	7	23.3	4	10.3	16	27.1	15	19.0	29	24.8
20 to 29	18	60.0	21	53.8	23	39.0	33	41.8	63	53.8
30 to 39	5	16.7	13	33.3	17	28.8	27	34.2	23	19.7
40 or over	0	0,0	1	2.6	2	3.4	3	3.8	2	1.7
Schooling										
0 to 8 years	11	36.7	13	33.3	25	42.4	23	29.1	35	29.9
9 to 11 years	6	20.0	5	12.8	18	30.5	24	30.4	37	31.6
12 years or more	0	0.0	3	7.7	0	0.0	0	0.0	4	3.4
Ignored	13	43.3	18	46.2	16	27.1	31	39.2	41	35.0

Continue...

Table 1 – Continuation.

Variable	2014		2015		2016		2017		2018	
	n	%	n	%	n	%	N	%	n	%
Skin color										
White	16	53.3	22	56.4	34	57.6	43	54.4	74	63.2
Back	2	6.7	2	5.1	3	5.1	6	7.6	6	5.1
Yellow	0	0,0	0	0.0	0	0.0	0	0.0	0	0.0
Brown	10	33.3	12	30.8	21	35.6	25	31.6	32	27.4
Ignored	2	6.7	3	7.7	1	1.7	5	6.3	5	4.3
Gestational Age (GA)										
1st Quarter	5	16.7	10	25.6	31	52.5	40	50.6	63	53.8
2nd Quarter	9	30.0	10	25.6	15	25.4	20	25.3	27	23.1
3rd Quarter	16	53.3	17	43.6	7	11.9	13	16.5	16	13.7
GA ignored	0	0.0	2	5.1	6	10.2	6	7.6	11	9.4
Ignored	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Treatment plan										
Penicillin	0	0.0	20	51.3	46	78.0	70	88.6	106	90.6
Another treatment	0	0.0	4	10.3	1	1.7	1	1.3	0	0.0
Not accomplished	0	0.0	6	15.4	3	5.1	3	3.8	5	4.3
Ignored	0	0.0	9	23.1	9	15.3	5	6.3	6	5.1
Clinic Classification										
Primary Syphilis	3	10.0	8	20.5	15	25.4	21	26.6	32	27.4
Secondary Syphilis	1	3.3	3	7.7	2	3.4	4	5.1	4	3.4
Tertiary Syphilis	1	3.3	0	0.0	4	6.8	2	2.5	4	3.4
Latent Syphilis	2	6.7	2	5.1	3	5.1	12	15.2	16	13.7
Ignored	23	76.7	26	66.7	35	59.3	40	50.6	61	52.1

Source: Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* — SINAN), 2019[13].

Table 2 – Characterization of reported cases of congenital syphilis, Foz do Iguaçu City, Paraná State, 2014-2018.

Variable	2014		2015		2016		2017		2018	
	n	%	n	%	n	%	n	%	n	%
Total notifications	9	6.5	15	10.9	21	15.3	41	29.9	51	37.2
Children's age										
Less than 07 days	9	100.0	14	93.3	19	90.5	39	95.1	40	78.4
07 to 27 days	0	0.0	1	6.7	2	9.5	2	4.9	0	0.0
28 to 364 days	0	0.0	0	0.0	0	0.0	0	0.0	2	3.9
Final Diagnosis										
Recent congenital syphilis										
Yes	9	100.0	15	100.0	21	100.0	41	100.0	51	100.0
No	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Prenatal care										
Yes	6	66.7	15	100.0	18	85.7	34	82.9	47	92.2
No	3	33.3	0	0.0	3	14.3	6	14.6	3	5.9
Ignored	0	0.0	0	0.0	0	0.0	1	2.4	1	2.0
Time of GS diagnosis										
During prenatal	6	66.7	13	86.7	18	85.7	27	65.9	38	74.5
Childbirth/curettage	2	22.2	1	6.7	2	9.5	8	19.5	10	19.6
After childbirth	1	11.1	1	6.7	1	4.8	4	9.8	1	2.0
Not accomplished	0	0.0	0	0.0	0	0.0	1	2.4	0	0.0
Ignored	0	0.0	0	0.0	0	0.0	1	2.4	2	3.9
GS Treatment										
Adequate	1	11.1	2	13.3	2	9.5	6	14.6	3	5.9
Inadequate	5	55.6	8	53.3	12	57.1	13	31.7	21	41.2
Not accomplished	3	33.3	1	6.7	6	28.6	17	41.5	14	27.5
Ignored	0	0.0	4	26.7	1	4.8	5	12.2	13	25.5
Partner treated										
Yes	1	11.1	2	13.3	4	19.0	9	22.0	4	7.8
No	6	66.7	9	60.0	16	76.2	24	58.5	34	66.7
Ignored	2	22.2	4	26.7	1	4.8	8	19.5	13	25.5
Obits by CS<1 year										
Cases	0	0.0	0	0.,0	0	0,0	1	100.0	1	100.0

Source: Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* — SINAN), 2019[13].

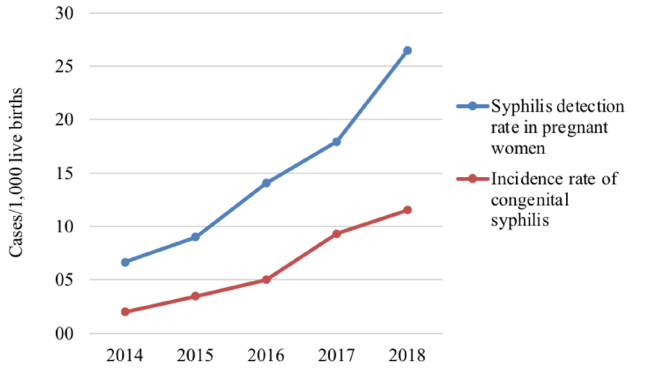
p=0.003) in the risk of congenital syphilis, with its incidence moving from 2.0 cases/1,000 live births to 11.5 cases/1,000 live births for the same period analyzed, representing an increase of 5.8 times.

DISCUSSION

Syphilis is a disease that challenges humanity for centuries. It remains a public health problem, even though it has an effective and low-cost diagnosis and treatment, if diagnosed during pregnancy. Disease should be treated promptly, considering that inadequate clinical management may eventually affect the conceptus transplacentally, and can be transmitted in any gestational phase or stage of maternal disease[5,15].

In this study, most of the registered cases of GS in the city occurred among young adult women, with up to 8 years of study and of white-skin color, which is a similar profile to that of other investigations carried out in the Northeastern (Fortaleza City, Ceará State, and Alagoas State)[3,15] and in the Southern (Maringá City, Paraná State) regions of Brazil[8]. This profile seems to portray the context of social vulnerability in which female patients are inserted, and deserves special attention from health services in prenatal care.

Similarly to other studies[3,16,17], most cases of the present study on GS were classified as primary syphilis, and treatment was performed with penicillin benzathine. The predominance of early diagnosis was evidenced in the first trimester of pregnancy, which is different from another study conducted in Montes Claros City, Minas Gerais State[18], in which detection was performed in advanced periods of pregnancy. Today, there is an epidemic of syphilis devastating the country, and it is essential that health professionals position themselves in the face of this disease in this context, because the disease is totally preventable, provided that there is early uptake and treatment of pregnant women and their partners[19].



Source: Live Birth Information System (*Sistema de Informações sobre Nascidos Vivos* — SINASC), 2019[14].
Syphilis detection rate in pregnant women
Incidence rate of congenital syphilis
Cases/1,000 live births

Figure 1 – Evolution of syphilis detection rates in pregnant women and incidence rate of congenital syphilis in Foz do Iguaçu City, Paraná State, 2014-2018.

As to CS, there was a predominance of cases reported in children under the age of 7 days, all of which had the disease in its recent phase as their final diagnosis, corroborating a study conducted in Almirante Tamandaré City, Paraná State, in which the highest occurrence of CS cases was recorded during the same period[20]. CS is the result of hematogenous dissemination of the pathogen causing the disease by transplacental route from infected pregnant women to their conceptus. Transmission can occur in any gestational phase or clinical stage of the disease. There is also the possibility of direct transmission when the child enters in contact with it in the delivery channel, if there are maternal genital lesions. In 2014, CS was considered if the mother's partner was not treated. However, in 2018, the treatment of the sexual partner no longer enters the definition of criteria to be classified as CS[21].

The present study revealed that the diagnosis of GS occurred during prenatal care, a similar fact found in a study conducted in Palmas City (Tocantins State), in which most mothers had had prenatal care and received the diagnosis of GS during follow-up consultations[6]. The most effective way to control GS is the commitment of Primary Care (PC) to offer all pregnant women quality prenatal care, ensuring early diagnosis and treatment to prevent vertical transmission of the disease[16].

Treatment performed in pregnant women was considered inadequate in most cases, when the father/partner did not adhere to treatment. Appropriate treatment is considered when it is completed 30 days before delivery, with penicillin, and the dose of medication is given according to the stage of the disease. The sexual partner is medicated concomitantly. Inadequate treatment is extremely common, and its main cause is related to the treatment of sexual partners, which can be verified in other realities, which is the main obstacle to the success of treatment[7,15,18].

Penicillin is the drug of choice for treating syphilis so far, it is the main way to fight the disease-causing bacteria and can prevent vertical transmission. Treatment effectiveness is associated to the fact that the partner is tested and treated in addition to the use of condoms during the treatment period[22].

In Brazil, adherence to treatment by partners is low, due to the existing prejudice that pregnancy and the raising of a child are entirely women's responsibility. Paternal involvement, throughout the gestational and postpartum periods, has been studied and has shown many benefits, once the approach of partners increases adherence to breastfeeding, strengthen the marital relationship, decreases domestic violence, postpartum depression, and reduces vertical transmission of infections[5,23].

During the period analyzed, two deaths from CS were registered in children under 1 year old, pointing to the severity of the problem. An evaluative study conducted in the Sobral City (Ceará State) reveals that, between 2007 and 2015, the city recorded a total of two deaths in children under 1 year of age, whose cause was CS[24]. The vertical transmission of syphilis presents different values according to the stage of maternal disease. Nonetheless, appropriate treatment can prevent 97% of cases of vertical transmission[25].

The detection rate of GS and CS is also worrying in the city, which increased in the study period. These indicators reflect the low quality of prenatal care, which, combined with barriers to access services, difficulties in addressing partners, difficulties in performing

active search and concomitant treatment, added to social, political, economic, and individual factors, make it difficult to monitor this population, besides contributing to the occurrence of new cases. Expanding access, improving prenatal care, providing early diagnosis, and timely initiating treatment are important actions to eliminate CS[26].

Because it is a city located in a border region, the oscillation migration in Foz do Iguaçu can contribute to the increase in rates of diseases and injuries, including GS. When countries have shared borders, it is natural to occur a displacement of the population in search of health care and, often, there is a preference to cross the border to seek better quality of care, which is the case of the triple frontier of Brazil, Argentina, and Paraguay. One of the most relevant problems in border regions involves organizational issues, when there is a need for active search of patients, and when they reside in another country, increasing the difficulty of contact and, consequently, management of injuries[27].

In the present study, there are limitations that should be observed in the evaluation of results. When using secondary SINAN data, insufficient notifications, and variations in the specificity of information can directly interfere with the quality and quantity of data. In addition, underreporting cases of syphilis and data that were considered ignored may hinder the construction of indicators that better represent the reality of the city to provide better prenatal care. The design adopted is an ecological study of time series that does not allow individual analyses, but aggregates of the population.

The findings show that cases of GS and CS in Foz do Iguaçu City, Paraná State, in the historical series analyzed, show a considerable increase. Results indicate a significant increase in the rate of cases detection, especially when sexual partners do not adhere to the recommended treatment, emphasizing the need for strategies that can contribute to the formulation of effective intervention proposals in family health. Besides that, there was an important increase in the risk of congenital syphilis, which may demonstrate deficiencies in prenatal care for treating syphilis in pregnant women to prevent vertical transmission of the disease to their newborns.

CONCLUSION

Given the growth in the detection rate of GS and the incidence of CS, prevention is a great challenge for professionals who perform prenatal care in the city in question. Carrying out actions that guide strategies to reduce cases of GS and vertical transmission of syphilis is of utmost importance.

ACKNOWLEDGEMENTS

We thank all those who directly or indirectly contributed to the conclusion of this article, as well as Universidade Federal da Integração Latino-Americana (UNILA) and its faculty for the opportunity and support offered.

Participation of each author

The authors declare they were all active participants.

Funding

The authors declare there are no grants or other funding for all authors. The study was funded by the authors.

Conflict of interests

There is no conflict of interest to be reported.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde Departamento de Vigilância, Prevenção e Controle das Doenças Sexualmente Transmissíveis, Aids e Hepatites Virais. Manual Técnico para Diagnóstico da Sífilis. Brasília: Ministério da Saúde; 2016.
2. Nascimento MI, Cunha AA, Guimarães EV, Alvarez FS, Oliveira SRSM, Vilas Boas EL. Gestações complicadas por sífilis materna e óbito fetal. Rev Bras Ginecol Obstet. 2012;34(2):56-62. http://dx.doi.org/10.1590/S0100-72032012000200003
3. Cardoso ARP, Araújo MAL, Cavalcante MS, Frota MA, Melo SP. Análise dos casos de sífilis gestacional e congênita nos anos de 2008 a 2010 em Fortaleza, Ceará, Brasil. Ciênc Saúde Coletiva. 2018;23(2):563-74. http://dx.doi.org/10.1590/1413-81232018232.01772016
4. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. Boletim Epidemiológico Especial Sífilis. Brasília: Ministério da Saúde; 2019.
5. Vasconcelos MIO, Oliveira KMC, Magalhães AHR, Guimarães RX, Linhares MSC, Queiroz MVO, et al. Sífilis na gestação: estratégias e desafios dos enfermeiros da atenção básica para o tratamento simultâneo do casal. Rev Bras Promoç Saúde. 2016;29(Suppl.):85-92. https://doi.org/10.5020/18061230.2016.sup.p85
6. Catunda HLO, Mendes IC, Oliveira ET, Bernardo EBR, Bezerra KC, Sousa DMN, et al. Análise Epidemiológica da Sífilis Congênita no Estado do Ceará, Brasil. DST - J Bras Doenças Sex Transm. 2013;25(1):7-12.
7. Cavalcante PAM, Pereira RBL, Castro JGD. Sífilis gestacional e congênita em Palmas, Tocantins, 2007-2014. Epidemiol Serv Saúde. 2017;26(2):255-64. https://doi.org/10.5123/s1679-49742017000200003
8. Saraceni V, Pereira GFM, Silveira MF, Araujo MAL, Miranda AE. Vigilância epidemiológica da transmissão vertical da sífilis: dados de seis unidades federativas no Brasil. Rev Panam Salud Publica. 2017;41:e44.
9. Favero MLDC, Ribas KAW, Costa MCD, Bonafé SM. Sífilis congênita e gestacional: notificação e assistência pré-natal. Arch Health Sci. 2019;26(1):2-8. https://doi.org/10.17696/2318-3691.26.1.2019.1137
10. Lopes IMD, Lopes AD, Santos RS, Lima SO, Reis FP. Congenital syphilis in a philanthropic maternity of the state of Sergipe: still a challenge. DST - J Bras Doenças Sex Transm. 2018;30(2):41-6. https://doi.org/10.5533/DST-2177-8264-201830202
11. Mello F, Victoria CG, Gonçalves H. Saúde nas fronteiras: análise quantitativa e qualitativa da clientela do Centro Materno Infantil de Foz do Iguaçu, Brasil. Ciênc Saúde Coletiva. 2015;20(7):2135-45. https://doi.org/10.1590/1413-81232015207.09462014
12. Priotto EMTP, Führ AL, Gomes LMX, Barbosa TLA. Iniciação sexual e práticas contraceptivas de adolescentes na tríplice fronteira entre Brasil, Argentina e Paraguai. Rev Panam Salud Pública. 2018;42:e16. https://doi.org/10.26633/RPSP.2018.16
13. Brasil. Ministério da Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis [Internet]. Indicadores e dados básicos da sífilis nos municípios brasileiros [accessed on Nov. 25, 2019]. Available at: http://indicadoressifilis.aids.gov.br/
14. Sistema de Informações de Nascidos Vivos [Internet]. Nascidos vivos Paraná [accessed on Dec. 9, 2019]. Available at: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinasc/cnv/nvpr.def
15. Alves WA, Cavalcanti GR, Nunes FA, Teodoro WR, Carvalho LM, Domingos RS. Sífilis congênita: epidemiologia dos casos notificados em Alagoas. Rev Portal Saúde Soc. 2016;1(1):27-41. https://doi.org/10.28998/rpss.v1i1.2375

16. Mesquita KO, Lima GK, Flôr SMC, Freitas CASL, Linhares MSC. Perfil epidemiológico dos casos de sífilis em gestante no município de Sobral, Ceará, de 2006 a 2010. SANARE. 2012;11(1):13-7.
17. Furtado MFS, Brasil GVS, Aragão FBA, Santos GRB, Pereira SLM, Fontoura CC, et al. Fatores epidemiológicos da sífilis em gestantes no município de São Luís-MA. Rev Uningá. 2017;52(1):51-5.
18. Lafetá KRG, Martelli Júnior H, Silveira MF, Parnaíba LMR. Sífilis materna e congênita, subnotificação e difícil controle. Rev Bras Epidemiol. 2016;19(1):63-74. http://dx.doi.org/10.1590/1980-5497201600010006
19. Santana MVS, Barbosa PNG, Santos JFL. Sífilis gestacional na Atenção Básica. Diversitas J. 2019;4(2):403-19. https://doi.org/10.17648/diversitas-journal-v4i2.783
20. Lima BCF, Mosele TMW, Gavinho B. Incidência de sífilis no município de Almirante Tamandaré, nos anos de 2010 – 2018. Rev Uniandrade. 2018;19(3):133-8. http://dx.doi.org/10.5935/1519-5694.20180017/revuniandrade.v19n3p133-138
21. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde Programa Nacional de DST e Aids. Diretrizes para o controle da sífilis congênita, Brasília: Ministério da Saúde; 2006.
22. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde Departamento de DST, Aids e Hepatites Virais, Protocolo clínico e diretrizes terapêuticas para atenção integral às pessoas com infecções sexualmente transmissíveis. Brasília: Ministério da Saúde; 2015.
23. Horta HHL, Martins MF, Nonato TF, Alves MI. Pré-natal do parceiro na prevenção da sífilis congênita. Rev APS. 2017;20(4):623-7.
24. Ferreira VES, Silva MAM, Araújo Junior DG, Mesquita ALM, Tomaz AL. Avaliação de indicadores da assistência pré-natal com ênfase na prevenção e controle da sífilis congênita. SANARE. 2017;16(Suppl. 1):68-73.
25. Domingues RMSM, Leal MC. Incidência de sífilis congênita e fatores associados à transmissão vertical da sífilis: dados do estudo. Nascer no Brasil. Cad Saúde Pública. 2016;32(6):e00082415. http://dx.doi.org/10.1590/0102-311X00082415
26. Domingues CSB, Kalichman AO, Tayra A, Paula IA, Cervantes V, Souza RA, et al. Sífilis congênita no estado de São Paulo: "o desafio continua". BEPA. 2015;12(142):27-37.
27. Zaslavsky R, Goulart BNG. Migração pendular e atenção à saúde na região de fronteira. Ciênc Saúde Coletiva. 2017;22(12):3981-6. http://dx.doi.org/10.1590/1413-812320172212.03522016

Address for correspondence:
PATRICIA SIMON DA SILVA
Rua Pedro Machado de Souza, 934 – Jardim Ascari
Santa Terezinha de Itaipu (PR), Brazil
CEP: 85875-000
E-mail: patysimon.enf@gmail.com

Received on: 12.23.2019
Approved on: 02.12.2020

Analysis of HIV/Aids notifications in a municipality of national health between 2007 and 2017: gender, age, race, schooling, neighborhood of origin, notifying units and treatment units

Análise de notificações de HIV/Aids em um município polo de saúde nacional entre 2007 e 2017: sexo, idade, raça, escolaridade, bairro de origem, unidades notificadoras e unidades de tratamento

Rodrigo Alberton da Silva[1], *Alexander Acauan de Aquino*[1], *Matheus Henrique Benin Lima*[1], *Ana Victória Coletto Reichert*[1], *Augusto Poloniato Gelain*[1], *Julia Belato Teixeira*[2], *Luiz Casemiro Krzyzaniak Grando*[1], *Louise Pietrobon*[3], *Deison Alencar Lucietto*[4]

ABSTRACT

Introduction: Both human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) are part of the National List of Compulsory Notification of Diseases. Despite the compulsory reporting of HIV infection from 2014, there has been a drop in the detection of new cases in the last five years. **Objective:** Analyze the epidemiological data of HIV/AIDS case reports in the city of Passo Fundo, Rio Grande do Sul, from 2007 to 2017 in relation to gender, neighborhoods, notifying units and treatment units. **Methods:** Retrospective descriptive study, accomplished at the Health Surveillance Sector from the compulsory notifications available in the Information System of Notifiable Diseases (*Sistema de Informação de Agravos de Notificação* – SINAN). A spreadsheet was made in the Microsoft Excel® Program (2016). Data were analyzed using the SPSS® Program, descriptively through measures of prevalence, incidence and distribution. **Results:** There were 1,068 notifications. There was a predominance of males (55.5%) and in the age group from 27 to 43 years. Of the 31 notifying health units, three concentrated 95% of the cases: Specialized Care Service (74.7%); Hospital São Vicente de Paulo (16%); and Hospital das Clínicas of Passo Fundo (4%). The same three units concentrated 98.0% of the treatments: 88, 9 and 1%, respectively. The primary care accounted for 5.0% of the notifications. **Conclusion:** The higher prevalence in young adult men denotes the importance of prevention aimed at this audience. Notifications were mostly from hospitals and a public referral center, with little involvement of primary care in reporting HIV/AIDS.

Keywords: acquired immunodeficiency syndrome; HIV; disease notification.

RESUMO

Introdução: Tanto a infecção pelo vírus da imunodeficiência humana (HIV) quanto a síndrome da imunodeficiência adquirida (AIDS) fazem parte da Lista Nacional de Notificação Compulsória de doenças. Apesar da compulsoriedade da notificação pela infecção pelo HIV a partir de 2014, nota-se uma queda na detecção de novos casos nos últimos cinco anos. **Objetivo:** Analisar os dados epidemiológicos das notificações dos casos de HIV/AIDS no município de Passo Fundo, Rio Grande do Sul, entre os anos de 2007 e 2017 em relação ao sexo, bairros, unidades notificadoras e unidades de tratamento. **Métodos:** Estudo documental, descritivo e retrospectivo, realizado no Setor de Vigilância em Saúde a partir das notificações compulsórias disponibilizadas no Sistema de Informação de Agravos de Notificação (SINAN). Foi construída uma planilha no Programa Microsoft Excel® (2016). Os dados foram analisados no Programa SPSS®, de forma descritiva através de medidas de prevalência, incidência e distribuição. **Resultados:** Foram 1.068 notificações. Houve predomínio de indivíduos do sexo masculino (55,5%) e na faixa etária dos 27 aos 43 anos. Das 31 unidades de saúde notificadoras, três concentraram 95% dos casos: Serviço de Atendimento Especializado (74,7%); Hospital São Vicente de Paulo (16%); e Hospital das Clínicas de Passo Fundo (4,0%). As mesmas três unidades concentravam 98,0% dos tratamentos: 88, 9 e 1%, respectivamente. A atenção primária foi responsável por 5% das notificações. **Conclusão:** A maior prevalência em homens adultos jovens denota a importância de prevenção voltada para esse público. As notificações ocorreram majoritariamente por hospitais e um centro público de referência, com pequena participação da atenção básica na notificação do HIV/AIDS.

Palavras-chave: síndrome de imunodeficiência adquirida; HIV; notificação de doenças.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is an infection caused by the human immunodeficiency virus (HIV). Transmission occurs mostly through intercourse due to fluid exchange between the mucous membranes of the genital or rectal tract. The virus, after transmission, infects host-specific defence cells, CD4 T lymphocytes. From this

[1]Medical School, Universidade de Passo Fundo – Passo Fundo (RS), Brazil.
[2]Medical School, Pontifícia Universidade Católica do Rio Grande do Sul – Porto Alegre (RS), Brazil.
[3]Faculdade Especializada na Área de Saúde do Rio Grande do Sul – Passo Fundo (RS), Brazil.
[4]Institute of Collective Health, Universidade Federal Fluminense – Niterói (RJ), Brazil.

infection, it spreads to the local and systemic lymph nodes, following a cascade of events that, without proper treatment, compromises the immune system of the infected[1].

Since the first cases of AIDS, reported in the 1980s by the Center for Disease Control and Prevention (CDC), no effort has been spared to improve understanding of the disease. Much progress has been made with regard to the implementation of public policies capable of early detection, prevention of transmission, and, consequently, reduction of new cases.

According to the Ministry of Health, in Brazil, in 2018, 43,941 new cases of HIV, and 37,161 cases of AIDS were diagnosed. Despite the compulsory notification of HIV infection from 2014, there is a drop in the detection of new cases in the last five years. This fact is possibly related to the implementation of the "treatment for all" at the end of 2013[2].

Following this trend, the number of AIDS-related deaths worldwide is the lowest this century, with less than 1 million deaths each year from AIDS-related diseases, thanks to continued access to antiretroviral therapy[3].

With regard to Brazilian public health, both HIV infection and AIDS are part of the National List of Compulsory Notification of Diseases, defined by the Ministry of Health. Despite the compulsory notification of HIV infection from 2014, there is a drop in the detection of new cases in the last five years. AIDS has been compulsory in Brazil since 1986, and HIV infection has been known since 2014. Thus, all new cases of infection, symptomatic or not, should be reported to health authorities[2].

The realization of HIV/AIDS notification — mandatory for physicians, other health professionals or those responsible for public or private services — is fundamental for the production of epidemiological data and indicators, which allows the identification of possible priority groups, and subsidizes the adequacy of resources for the adoption of preventive and/or treatment measures.

Despite the health and social relevance of the use of information on the behavior of this disease, especially for the formulation of public loco-regional health policies, there is a lack of publications that address the conduct of the disease in rural municipalities in Brazil.

OBJECTIVE

Considering the above, this study aimed to analyse epidemiological data of HIV/AIDS cases notifications in the municipality of Passo Fundo, Rio Grande do Sul, from 2007 to 2017 in relation to gender, neighbourhood, notifying units, and treatment units.

METHODS

This is a retrospective descriptive documentary study, carried out in the Health Surveillance Sector of the Municipal Health Department of Passo Fundo (SMS/PF).

All HIV/AIDS notifications from 2007 to 2017 made available in the Information System of Notifiable Diseases (*Sistema de Informação de Agravos de Notificação* — SINAN) of the Informatics Department of the Unified Health System (DATASUS) were included.

Based on these notifications, a spreadsheet was constructed in the Microsoft Excel Program® (2016), containing the variables gender, race, age, schooling, notifying health units, health units of treatment, and neighbourhoods of origin.

Subsequently, these data were analysed through descriptive statistics with the help of the Statistical Package for the Social Sciences Program (SPSS)® v. 23, through measures of prevalence, incidence and distribution of notifications according to the type of injury, gender, age and socio-demographic information.

The present study was approved by the Research Ethics Committee of the Universidade de Passo Fundo (Opinion Consubstantiated No. 2,627,373/CAAE No. 83497318.5.0000.5342).

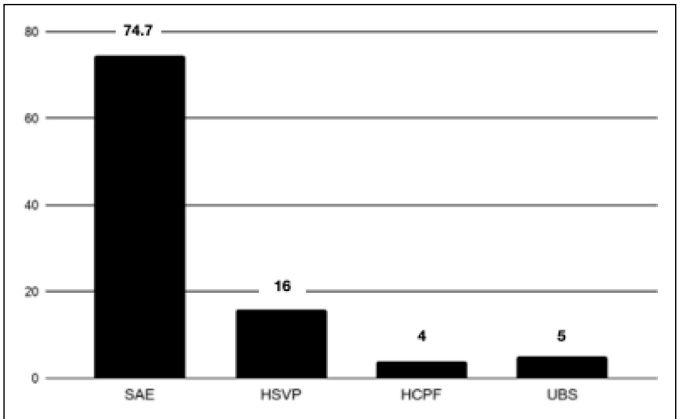
RESULTS

A total of 1,068 HIV/AIDS notifications were recorded in Passo Fundo from 2007 to 2017. A predominance of males was identified (55.5%), and mean age of 35.7 years.

Regarding race, it was found that 81.0% were white (followed by 12.8% browns, 5.4% blacks, 0.2% yellows, 0.2% indigenous people, and 0.4% with ignored race). On the other hand, about education, 40.2% had incomplete elementary school (followed by 18.2% with complete high school, 12.1% with complete elementary school, 7.8% with complete higher education, 6.5% with incomplete high school, 5.4% with incomplete higher education, 0.9% illiterate, and 8.3% with ignored education).

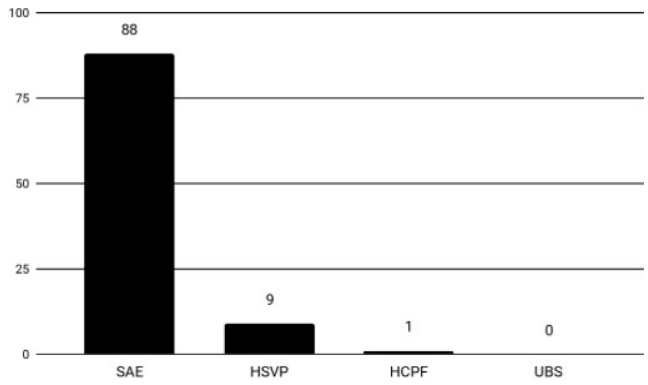
Of the 31 Notifying Health Units of Passo Fundo, three concentrated approximately 95.0% of the cases: Specialized Care Service (SAE); Hospital São Vicente de Paulo (HSVP); and Hospital das Clínicas de Passo Fundo (HCPF) (**Figure 1**). The same three units concentrated 98.0% of the treatments (**Figure 2**).

Basic Health Units (*Unidades Básicas de Saúde* — UBS) accounted for 5% of the notifications. Among the notifying units, the following units registered more than one case in the analysed period: SMS/PF (0.7%); Hospital Municipal de Passo Fundo (HMPF) (0.6%); Hospital Pronto Clínicas (HPC) (0.5%); Epidemiological Surveillance Center (0.3%); Jerônimo Coelho Family Health Strategy (0.2%); Oswaldo Cruz Blood Bank (0.2%); and Hospital Psiquiátrico Bezerra de Menezes (HPBM) (0.2%).



SAE: Specialized Care Service, HSVP: Hospital São Vicente de Paulo, HCPF: Hospital das Clínicas de Passo Fundo, UBS: Basic Health Units; HIV: human immunodeficiency virus.

Figure 1 – Percentage of notifications made by Health Units Notifying HIV cases in Passo Fundo, Rio Grande do Sul, from 2007 to 2017.



SAE: Specialized Care Service, HSVP: Hospital São Vicente de Paulo, HCPF: Hospital das Clínicas de Passo Fundo, UBS: Basic Health Units; HIV: human immunodeficiency virus.

Figure 2 – HIV treatment units in Passo Fundo, Rio Grande do Sul, from 2007 to 2017.

In relation to the neighbourhoods of origin of the reported patients, a relatively homogeneous distribution was observed in the more than 100 neighbourhoods of Passo Fundo, with notifications in up to 90 of them. It was found that 75% of the neighbourhoods had at least one positive case of HIV, with higher concentration in the Centro (14%), Petrópolis (8%) and Vera Cruz (7%).

DISCUSSION

The predominant age group of individuals reported in the present study was from 27 to 43 years, being very similar to that identified in a study conducted in Minas Gerais, which found greater participation between 28 and 45 years, and in a study conducted in Goiás, with a predominance of people between 28.5 and 50.5 years[4,5].

In line with what was expected by HIV/AIDS chronicity, the study in Minas Gerais showed high rates between 40 and 59 years of age, with one third of the cases[4]. These findings may be related to increased longevity and consequent improvement in quality of life. In addition, the influence of technological advances in health, with the use of hormone replacement therapy and the use of drugs for the treatment of sexual impotence, for example, which provided changes in the sexual behavior of the population in this age group without adequate sexual education is emphasized[6]. Moreover, it is known that the phenomenon of aging of the population with HIV is a consequence of the therapeutic advances that have enabled HIV to become a chronic disease.

On the other hand, the study in the Goiás State points to the probable phenomenon of the internalization and pauperization of HIV/AIDS in Brazil, which implies a change in the incidence of transmission from metropolises to the interior of the States, and in a population with a lower educational and socioeconomic level[5].

In the present study, which corresponds to a population in the interior of the State of Rio Grande do Sul, 55.1% of the cases occurred between 20 and 40 years, and only 3.1% of the cases were of men over 60 years of age. This finding corroborates the hypothesis of internalization and pauperization, since there was a significant portion of the notifications (>50%) corresponding to individuals up to 40 years, added a low number of cases in the elderly.

The study conducted in Minas Gerais observed a predominance of males in the notifications (67.8%), with a higher percentage than the present study (55.5%). This higher prevalence of male notifications was also found by the Goiás study, in which 57.9% of the cases occurred in men[4,5].

The predominance of adult men in the notifications of this study corroborates the findings of studies that point to an increase in cases among men who have sex with men (MSM). In a study conducted in a reference center (n=153), it was observed that 31.37% of the male sample were MSM, 56.21% were heterosexual, and in 12.42% there was no available information[7]. Although the majority of the infection occurs among heterosexuals, transmission between MSM has been highlighted as increasing transmission, especially in richer countries. In this sense, it was pointed out that there may be a phenomenon of HIV resurgence in this population[4,5,8].

These aspects illustrate the importance of knowing the geographical distribution and age group of HIV/AIDS in a country of continental dimensions, since it allows health authorities to make the most assertive decisions for planning interventions, optimizing resources and promoting quality of life for individuals affected by the disease.

The findings of this research showed a concentration of seropositive care in a medium-sized municipality in the interior of the country — an aspect that deserves to be investigated in other locations with the same geographic and population profile.

First, it was found important centralization of notifications in three health services in the city. The SAE, a public care unit focused on HIV and sexually transmitted infections, had 75% of the notifications. The two largest hospitals in the city were also important, presenting, respectively, 16 and 4% of communications. Only 5% of the notifications occurred in the UBS.

It can be inferred that primary health care services and professionals are having little participation in HIV notifications. This is a fact that contrasts the prerogatives of primary care as a privileged space for the accomplishment of most prevention, screening and syndromic diagnoses.

It is also assumed that primary care services have low rates of diagnosis of the disease and/or that they are referring users to specialized centres without having previously completed the compulsory notification. This, in turn, may be related to the centralization of the management and treatment of patients in the SAE, which would induce the basic units to delegate the task of notification.

This logic is especially harmful for the adoption of preventive public health measures, which could be planned based on information on the geographical distribution of the disease in the city. It is known that underreporting may compromise the correct distribution of antiretroviral drugs and the focus of public policies to vulnerable populations[4].

Secondly, when analysing the sites of treatment of the disease, an even greater centralization was identified. Most cases are managed by the SAE (88%). In this scenario, the finding is positive, and meets the expectation that the organization of care of these patients in specialized centres is the objective of public policies, with an experienced health team, a local pharmacy for the distribution of medications, and control of adherence to treatment and transmission of the virus.

However, it is assumed that the number of patients treated in the HSVP is still high (9%), despite this being a hospital of regional coverage, which points both to centralization and to the excessive referral of patients. However, if these individuals are correctly redirected to SAE after hospital treatment, it is suspected that the notifications remain outdated.

Another important point observed in this study was the distribution of HIV cases in neighbourhoods, since 75% of them had at least one reported case, demonstrating wide and relatively homogeneous dissemination of the disease in the city.

Three neighbourhoods had a higher percentage of notifications, including the Centro (14%), Petrópolis (8%) and Vera Cruz (7%). It is believed that these higher numbers are related to the number of residents in these localities (which are among the largest neighbourhoods in the municipality).

The decentralization of HIV screening tests to UBS seems to be a good public health strategy, especially since many testing centres are stigmatized as sites of HIV-positive patients — driving a portion of the population away from these procedures. Even so, there is still a need for greater adherence of the UBS with regard to the completion of compulsory notifications.

It is worth mentioning that in 2014 the Minister of Health included HIV infection as compulsory notification, a fact that brought changes in the epidemiological profile of notifications and may have affected the final results of this study. AIDS notifications and criteria, for example, have lost space in the general overview of notifications in favor of the growth of HIV infection notifications[4].

In the meantime, it is emphasized that the strategy of reporting HIV cases identified by screening, mandatory since then, has shown good adherence, indicating success of the government measure in this segment of patients[4].

This study has as strengths the expressive number of notifications analysed (1,068 cases) and the description of data in a locality in the interior of the State of Rio Grande do Sul. The lack of data from non-metropolitan cities on the profile of HIV in Brazil has been described in the literature[5].

It is also noteworthy that the findings of this research point to the high incidence of the disease in young men and adults, in addition to the problem of low rates of notification by primary care. This diagnosis can support the proposition of health interventions and the organization of the health care network in the municipality.

This study has as main limitation the fact that the notifications analysed are restricted to those of the Epidemiological Surveillance Service of the municipality of Passo Fundo, making it impossible to extrapolate the findings. Another aspect to be mentioned is that the data of the compulsory notification form, which appears as an official source of information for health authorities and researchers, is susceptible to errors in filling and low adherence of the professionals themselves.

Future challenges in combating the HIV epidemic include broad access to diagnostic testing and elimination of discrimination. It is known that prejudice towards HIV-positive users still remains an important obstacle to access diagnosis and treatment in the Unified Health System (*Sistema Único de Saúde* — SUS). In a study conducted in the city of Araçatuba, 23% of users of the public system stated they would not accept to be seen after an HIV-positive patient, and 42% stated they preferred to be seen before an HIV-positive patient. This reaffirms the rooting of discrimination in society[4,9].

As pointed out in this study, although the incidence of HIV infection in the elderly population is lower than in other age groups, it is important to emphasize that, often, the possibility of infection is not considered by health professionals, both because of the lack of information on AIDS in the elderly and because of the non-prioritization of this focus of approach in the health system. Considering that these aspects are related to professional training and updating[10], it is essential that changes in health education are implemented.

Finally, in view of the results of this study, permanent education measures are suggested for primary health professionals, in order to promote greater adherence to this level of care in notifications; strengthening HIV/AIDS prevention actions, especially in the young and adult male population; and the realization of strategic planning processes in the face of possible phenomena of aging and chronicity of HIV, as well as the internalization and pauperization of the disease in municipalities of different sizes in Brazil.

CONCLUSION

The higher prevalence in adult-young men denotes the importance of prevention aimed at this public. The notifications occurred mainly by hospitals and a public reference centre, with little participation of primary care in the notification of HIV/AIDS.

ACKNOWLEDGMENT

To the Health Surveillance Sector of the Municipal Health Department of Passo Fundo, Rio Grande do Sul, for providing the data supply, and to Prof. Daniela Bertol Graeff of the Research and Statistics Department of the Faculty of Medicine of the Universidade de Passo Fundo for helping with the statistical analysis of the data.

Participation of each author

Research conception and design: RAS, AAA, MHBL, AVCR, APG, LCKG, LP, DAL. Interpretation of data and elaboration of the article: RAS, AAA, MHBL, AVCR, APG, JBT, LCKG. Critical revision of the preliminary version: RAS, LP, DAL. Final approval of the version to be published: RAS, AAA, MHBL, AVCR, APG, JBT, LCKG, LP, DAL. Agreement to be accountable for all aspects of work: RAS, AAA, MHBL, AVCR, APG, JBT, LCKG, LP, DAL.

Funding

The authors report that no funding, equipment or drug supplies were received. All the materials used in the study were funded by the researchers themselves.

Conflict of interests

The authors report no conflict of interests.

REFERENCES

1. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, Aids e Hepatites Virais. Manual técnico para o diagnóstico da infecção pelo HIV em adultos e crianças. Brasília: Ministério da Saúde; 2018.
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de DST, Aids e Hepatites Virais. Boletim Epidemiológico: aids e DST. Brasília: Ministério da Saúde; 2019.
3. Joint United Nations Programme on HIV/AIDS. Miles-to-go: closing the gaps, breaking barriers, righting injustices: Global AIDS update 2018. Geneva: Joint United Nations Programme on HIV/AIDS; 2018.
4. Castro SS, Scatena LM, Miranzi A, Miranzi Neto A, Camargo FC, Nunes AA. HIV/AIDS case definition criteria and association between sociodemographic and clinical aspects of the disease reported in the State of Minas Gerais from 2007 to 2016. Rev Soc Bras Med Trop. 2018;51(4):427-35. https://doi.org/10.1590/0037-8682-0117-2018
5. Dias RFG, Bento LO, Tavares C, Ranes Filho H, Silva MAC, Moraes LC, et al. Epidemiological and clinical profile of HIV-infected patients from Southwestern Goias State, Brazil. Rev Inst Med Trop São Paulo. 2018;60:e34. https://doi.org/10.1590/s1678-9946201860034
6. Saggiorato AKS, Schuelter-Trevisol F. Perceptions about AIDS and sexual behavior among elderly people in the city of Tubarão, state of Santa Catarina, Brazil. DST - J Bras Doenças Sex Transm. 2015;27(1-2):29-34. https://doi.org/10.5533/DST-2177-8264-2015271-206
7. Orlandi V, Fronza D, Horvath JAD, Yonegura WHT, Gomes DS. Clinical and epidemiological profile of patients who seek post-exposure prophylaxis after sexual exposure to HIV and their adherence to the medication regimen in a specialized center in Cascavel, Paraná, Brazil. DST - J bras Doenças Sex Transm. 2019;31(1):14-8. https://doi.org/10.5533/DST-2177-8264-201931103
8. Lucas S, Nelson AM. HIV and the spectrum of human disease. J Pathol. 2015;235(2):229-41. https://doi.org/10.1002/path.4449
9. Garbin CAS, Martins RJ, Belila NM, Garbin AJI. The stigma of HIV positive users of the public health system. DST - J bras Doenças Sex Transm. 2017;29(1):12-6.
10. Lima PAB, Rezende CHA, Hattori WT, Pinto RMC. Perception of health professionals from a city in the interior of Brazil on the vulnerability of older adults to HIV infection. DST - J bras Doenças Sex Transm. 2018;30(4):129-32. https://doi.org/10.5533/DST-2177-8264-201830404

Address for correspondence:
RODRIGO ALBERTON DA SILVA
Rua Teixeira Soares, 817 – Centro
Passo Fundo (RS), Brazil
CEP: 99010-080
E-mail: rodrigoalbertondasilva@gmail.com

Received on: 12.12.2019
Approved on: 01.19.2020

The reality of 13 years of prenatal care to pregnant women with syphilis in Sergipe state (2007–2019)

Realidade em 13 anos da assistência pré-natal a gestantes com sífilis no estado de Sergipe (2007-2019)

Rute de Oliveira Farias[1], *Izailza Matos Dantas Lopes*[1], *Letícia Goes Santos*[1], *Amanda Silveira de Carvalho Dantas*[1]

ABSTRACT

Introduction: Syphilis is an infectious disease caused by *Treponema pallidum*, its two main routes of transmission are sexual and transplacental (vertical). The latter is of particular worrisome, since it can generate congenital syphilis and can be avoided by early maternal serological screening. **Objective:** To analyze the conditions of prenatal care for syphilitic pregnant women in Sergipe State between 2007 and 2019. **Methods:** A cross-sectional, retrospective, and descriptive study was carried out, with the collection of notified cases of gestational and congenital syphilis in the Brazilian Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificação* - SINAN). **Results:** There was a considerable increase in the number of reported cases of gestational syphilis in the last 13 years. About 36% of pregnant women were identified in the 3rd trimester of pregnancy, 68.1% were brown, 56.8% had studied for up to 8 years, and 50.1% were between 20 and 29 years old. The clinical phase latent to the diagnosis was responsible for 70.3% of the cases, followed by the primary (11%) and tertiary (7.3%) phases. Of the total number of pregnant women, 20.2% did not perform the non-treponemal test, and 97.2% were treated with penicillin. Regarding the numbers of congenital syphilis, although 75% of the mothers performed prenatal care, 37.8% received the diagnosis at the time of delivery/curettage, resulting in 72.9% of infant deaths from the disease. Moreover, there was a predominance of untreated partners (77.7%) in relation to those treated (10.8%). **Conclusion:** Although most of them performed prenatal care, there was a predominance of diagnoses performed only in the 3rd trimester of pregnancy, mainly at the time of delivery or curettage, not respecting the minimum therapeutic interval of 30 days before delivery. Thus, in Sergipe State, the most important factor in the high prevalence of vertical transmission of syphilis is the ineffectiveness of prenatal care provided to infected pregnant women, which remains.

Keywords: Syphilis. Pregnant Woman. Public Health.

RESUMO

Introdução: a sífilis é uma doença infecciosa causada pelo *Treponema pallidum*, suas duas principais vias de transmissão são a sexual e a transplacentária (vertical). Este último é particularmente preocupante, pois pode gerar sífilis congênita e pode ser evitado por meio de triagem sorológica materna precoce. **Objetivo:** Analisar as condições da assistência pré-natal para gestantes sifilíticas no estado de Sergipe entre 2007 e 2019.**Métodos:** Foi realizado um estudo transversal, retrospectivo e descritivo, com coleta de casos notificados de sífilis gestacional e congênita no Sistema de Informação de Agravos de Notificações (SINAN). **Resultados:** Houve um aumento considerável no número de casos notificados de sífilis gestacional nos últimos 13 anos. Cerca de 36% das gestantes foram diagnosticadas no 3º trimestre da gestação, 68,1% eram pardas, 56,8% haviam estudado até 8 anos e 50,1% tinham entre 20 e 29 anos. A fase clínica latente ao diagnóstico foi responsável por 70,3% dos casos, seguida das fases primária (11%) e terciária (7,3%). Do total de gestantes, 20,2% não realizaram o teste não treponêmico e 97,2% foram tratadas com penicilina. Em relação aos números de sífilis congênita, embora 75% das mães realizassem o pré-natal, 37,8% receberam o diagnóstico no momento do parto/curetagem, resultando em 72,9% dos óbitos infantis pela doença. Além disso, houve predomínio de parceiros não tratados (77,7%) em relação aos tratados (10,8%).**Conclusão:** Apesar de a maioria das gestantes realizar o pré-natal, houve predomínio de diagnósticos realizados apenas no 3º trimestre da gestação, principalmente no momento do parto ou curetagem, não respeitando o intervalo terapêutico mínimo de 30 dias antes do parto. Assim, no estado de Sergipe, o fator mais importante na alta prevalência da transmissão vertical da sífilis é a ineficácia da assistência pré-natal prestada às gestantes infectadas, que permanece.

Palavras-chave: sífilis; gestantes; saúde pública.

INTRODUCTION

Syphilis is a sexually transmitted infection (STI) of a systemic character, curable, and exclusive to humans. It is identified by *Treponema pallidum*, a Gram-negative bacterium from the spirochete group, whose only natural host is people.[1]

Vertical transmission occurs in cases of untreated or inadequately treated syphilitic pregnant women, which can be transmitted at any stage of pregnancy and any stage of the disease, with direct transmission through the vaginal canal being possible in case of an active lesion in the region.[2]

Thus, it occurs when there is fetal contamination by a maternal spirochete. The disease is part of the group of infections acquired in the uterus or during the birth process: Toxoplasmosis, Others (syphilis), Rubella, Cytomegalovirus (CMV), and Herpes Simplex Virus (HSV), forming the term TORCH.[3]

The probability of congenital syphilis occurrence is influenced by the clinical stage in which the mother is and the duration of fetal exposure, reaching from 70 to 100% when a pregnant woman has primary or secondary syphilis. Therefore, the possibility of transplacental transmission is proportional to maternal bacteremia, and is greater the closer the infection is onset.[4]

Syphilis in pregnancy can result in adverse outcomes at birth due to half of the untreated cases, which includes: prematurity, low birth weight, fetal deformities (neurological, medical and organ damage), fetal death, and neonatal death.[5]

Due to this morbidity, great emphasis was placed on routine screening for syphilis in all pregnant women, since the incidence of congenital syphilis reflects the disease rate in women of childbearing age.

[1]Universidade Tiradentes – Aracaju (SE), Brazil.

Thus, many fetal cases develop because the mother did not receive prenatal care, treatment with penicillin, or received it inappropriately before or during pregnancy.[3]

Thus, early maternal diagnosis is crucial to ensure that appropriate and timely therapy is initiated, in addition to allowing family counseling on the prognosis for the implementation of an appropriate care plan.[3] The Brazilian Ministry of Health recommends screening for gestational syphilis in the first prenatal consultation, in addition to the third trimester (between 28 and 32 weeks) and the time of delivery.[4]

The World Health Organization (WHO) estimates a worldwide incidence of 12 million new cases of syphilis per year, with one million of them affecting pregnant women. Despite this, there is a national tendency for failures in prenatal care, with the loss of several opportunities in preventing infection and the illness of children with congenital syphilis.[6,7]

In Sergipe State, according to the latest Epidemiological Bulletin of Syphilis, 645 cases of gestational syphilis were reported in 2018, with a detection rate of 19 cases in pregnant women per thousand live births. There is no vaccine against syphilis, and a previous infection does not confer protective immunity, allowing the reinfection of pregnant women every time they are exposed to the pathogen.[8]

Regarding access to prenatal care, national data for 2018 show that most mothers of children with congenital syphilis received prenatal care (81.8%), whereas 13.3% did not, and 4.9% presented ignored information. Despite that, most of them had their diagnosis at the time of delivery/curettage (31.8%), 5.6% after delivery, and 0.8% did not even receive it, in addition to 4.3% ignored.[8]

In view of the above, the objective was to conduct a survey with data from SINAN to assess how the conditions under which prenatal care is provided to pregnant women with syphilis in Sergipe State, from 2007 to 2019. The analysis of the quality of prenatal care provided over these years may allow the identification of potential deficiencies in the care of pregnant women with syphilis in the state. This can serve as a subsidy for developing preventive measures and structuring quality services, as well as enabling the planning of government health strategies and policies in this regard.

OBJECTIVE

To analyze the reality of prenatal care in syphilitic pregnant women using statistical data from SINAN on gestational and congenital syphilis in Sergipe State, from 2007 to 2019.

METHODS

This is a cross-sectional, observational, retrospective, and descriptive study, using the SINAN database, inserted in the item "Epidemiological and Morbidity" of the Tabnet program, with the Department of Informatics of the Unified Health System (DATASUS). The considered inclusion criteria were all those reported and confirmed cases of the gestational and working groups, and congenital people, from 2007 to June 2019. The total cases of gestational syphilis was 4,028; of congenital syphilis, it was 3,814. The exclusion criteria used were the cases of syphilitic women who did not receive prenatal care in Sergipe State or other regions of Brazil.

The variables used were taken from the SINAN research forms of Syphilis in Pregnant Women and Congenital Syphilis. Among them are data referring to the mother a result of serological tests, clinical classification, time of diagnosis, whether prenatal care was performed, socioeconomic data and infected child as a final classification and evolution to death.

After evaluating the data cited in SINAN, they were inserted in Excel tables and spreadsheets, in which analytical descriptions were made. The statistical analysis used was descriptive and inferential. The categoric variables were displayed with absolute and relative frequencies, which characterize the descriptive analysis.

On the inferential part, Pearson's Chi-square Test with Monte-Carlo simulations and association between variables was used. The level of statistical significance adopted was 5% ($p \leq 0.05$), and all tests were two-tailed. The software used for analysis was the Statistical Package for the Social Sciences (IBM SPSS 25.0).

The present paper was not submitted to the Research Ethics Committee (Comitê de Ética em Pesquisa — CEP), as according to instance No. 3 of the single paragraph from the 1st article of Resolution No. 510, of April 7, 2016. The data were extracted from the public domain platform, which does not identify the research participants.

RESULTS

From 2007 to June 2019, 4,028 cases of pregnant women with syphilis in Sergipe State were quantified in SINAN. Of the total number of notified pregnant women, 22.9% were identified in the 1st trimester of pregnancy, 35.7% in the 2nd trimester, 36% in the 3rd trimester, and 5.4% had their gestational age ignored. There is a maximum number of cases of gestational diagnosis diagnosed in the 1st trimester, which had the highest peak in 2016, with a value of 36.4%, and the lowest peak in 2009, with 6.2%.

On the other hand, there was a significant increase in the number of cases diagnosed in the 3rd quarter of 2016, maintaining slight fluctuations in previous years, with a maximum value of 57.5% in 2009, and a minimum of 22.7% between 2007 and 2008 (**Figure 1**).

The socioeconomic profile of these women shows a prevalence of mixed skin-color, representing 68.1% of reported cases, followed by black people (11.8%), and, finally, white people (11.7%). Regarding education, most of them had a study time of up to 8 years (56.8%), whereas 19.3% had more than 8 years, considering up to high school. As for the age group, more than half of the cases (50.1%) occurred in women aged between 20 and 29; 25.7% between 30 and 39; and 20.2% between 15 and 19 (**Table 1**).

When analyzing a clinical classification of syphilis in pregnant women, the statistics revealed that the highest proportion of women were in a latent stage (70.3%), which shows three rates of increase in their values: the first, abrupt and significant of 60.4%, between 2010 and 2012; and the remaining two, more discreet of 9.6%, between 2013 and 2015, and 14.9%, between 2016 and 2018.

Primary syphilis was the second highest prevalence in the state (11%), displaying fluctuations in the study period with maximum and minimum values of 30.1 and 4.5%, respectively. Since 2009, it showed an approximate reduction of 22.4% until 2012, when it remained stable until 2016. As for secondary syphilis, there were almost no changes so low from 2011 to 2019, with a prevalence of 2.2%.

Finally, the relevance of the tertiary stage (7.3%) was noted with its values increasing more intensively (15.7%) between 2009 and 2010. From then on, the change on behavior of the evolution, with an intense but progressive reduction, returning in 2012 (6.1%) to values similar to those of 2009 (6.2%) (**Figure 2**).

The analysis of the prescribed treatment regimen showed that most pregnant women were treated with penicillin (97.2%). However, a significant number of cases (4.6%) of congenital individuals were associated to an appropriate method of maternal treatment.

As to the moment in which the mother was diagnosed with syphilis, 38.7% received it during prenatal care, 37.8% at the time of delivery/curettage, 10.1% after delivery, and 0.5% had no diagnosis. **Table 2** shows the relation between the late diagnosis of syphilis in pregnant women (at the time of delivery) and the occurrence of congenital syphilis (36.5%), in addition to most stillborn/abortion cases resulting from the disease (88.5%).

Concerning access to prenatal care, 75% of mothers of children with congenital syphilis performed it, whereas 19.7% did not, and 5.4% presented ignored information. Despite the fact that performing prenatal care in the syphilitic mother was related to most cases of congenital diseases (79.4%) and to most cases in which the detection of syphilis in pregnancy was done late, 48.7 % at delivery, 75.4% after delivery/curettage, and 60% did not receive the diagnosis (**Table 3**).

In the period between 2007 and 2019, there were some variations in the number of unapproved partners, with a maximum value of 90.7% in 2016, and a minimum of 59% between 2007 and 2008. In general, there is a tendency for these cases to occur (77.7%) to

Table 1 – The number and percentage distribution of cases of pregnant women with syphilis by age, education, and ethnicity in Sergipe State, 2007–2019.

Variables	nº	%
Age range		
10 to 14	39	1.0
15 to 19	812	20.2
20 to 29	2,019	50.1
30 to 39	1,034	25.7
40 or more	122	3.0
Ignored	0	0.0
Total	4,026	100
Education		
Up to 8 years	2,185	56.8
Over 8 years	742	19.3
Incomplete High School	34	0.9
Higher Education	30	0.8
Not Applicable	2	0.1
Ignored	857	22.3
Total	3,850	100
Race/skin color		
White	470	11.7
Black	475	11.8
Yellow	26	0.6
Brown	2,744	68.1
Indigenous	10	0.2
Ignored	303	7.5
Total	4,028	100

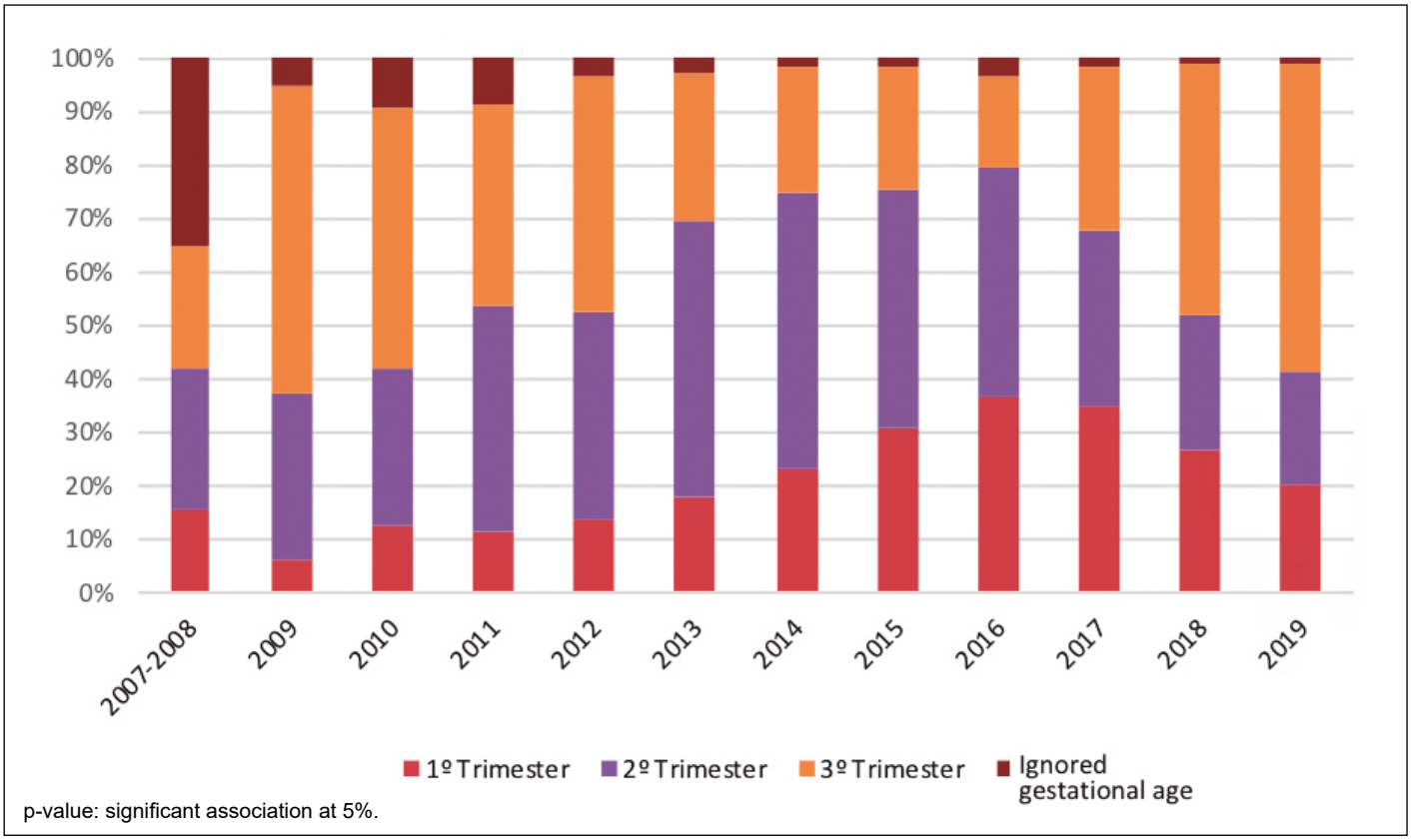


Figure 1 – Percentage distribution of pregnant women according to gestational age per year in Sergipe State, 2007–2019.

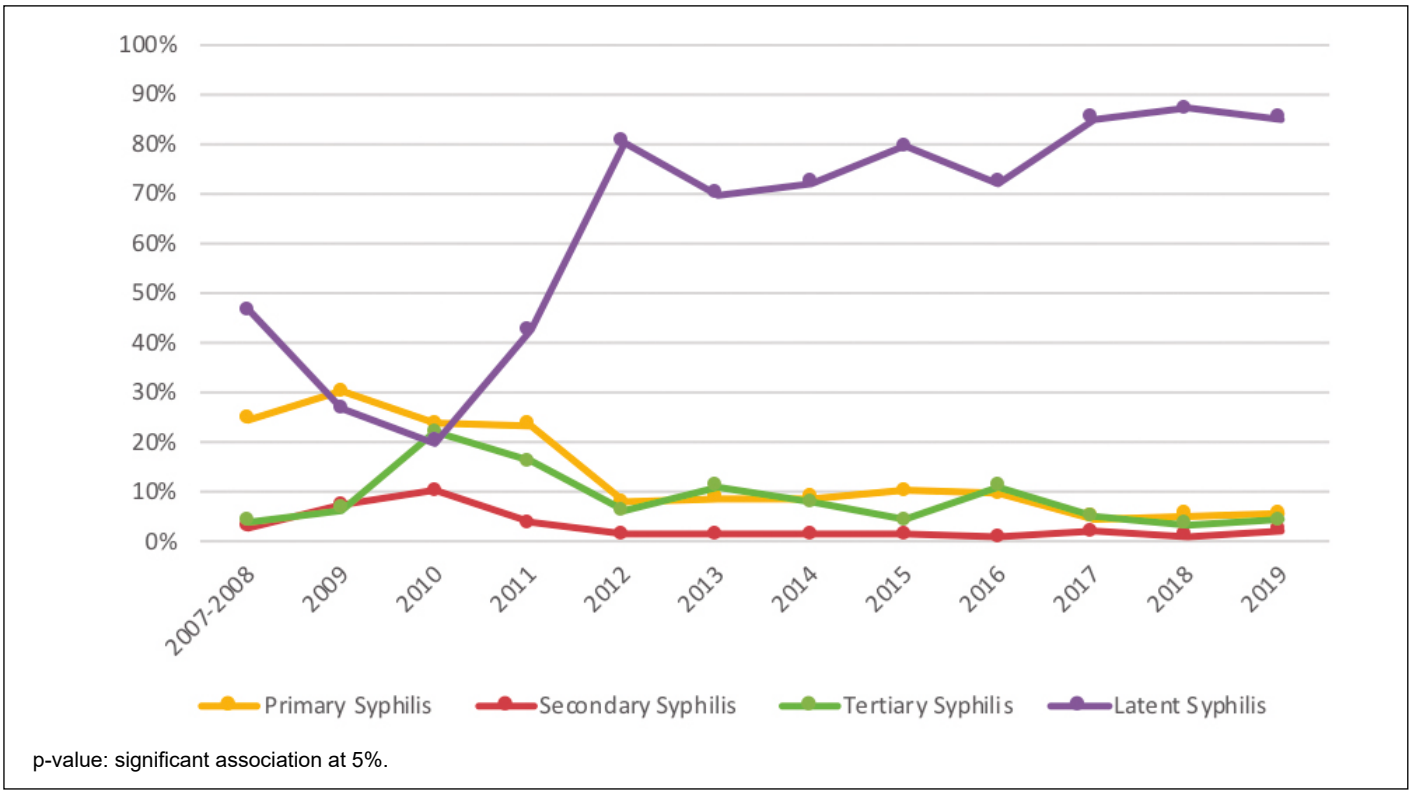


Figure 2 – Percentage distribution of cases of pregnant women with syphilis according to clinical classification by year of diagnosis in Sergipe State, 2007–2019.

Table 2 – Number of congenital syphilis cases according to the child's final classification at the time of maternal syphilis diagnosis in Sergipe State, 2007–2019.

Variables	Child's Final Classification				
	CS	Stillborn / Abortion	Discarded	Ignored	p-value
Moment of Maternal Diagnosis					<0.001
During prenatal care	1,296 (47.3%)	15 (8.2%)	42 (25.1%)	58	
At delivery	1,000 (36.5%)	161 (88.5%)	93 (55.7%)	10	
After delivery	363 (13.2%)	6 (3.3%)	22 (13.2%)	12	
Not performed	14 (0.5%)	0	0	1	
Ignored	68 (2.5%)	0	10 (5.9%)	5	
Total	2,741	182	167	86	

CS: congenital syphilis; p-value: significant association at 5%.

Table 3 – Number and percentage distribution of consequent cases of congenital syphilis according to the performance of maternal prenatal care related to the child's final classification and at the time of maternal diagnosis in Sergipe State, 2007–2019.

Variables	Performed Prenatal Care				
	Yes	No	Ignored	Total	p-value
Child's Final Classification					<0.001
Congenital Syphilis	2,177 (79.4%)	476 (17.4%)	88 (3.3%)	2,741	
Stillbirth/Abortion	31 (17%)	137 (75.3%)	14 (7.7%)	182	
Discarded	95 (56.9%)	55 (32.9%)	17 (10.2%)	167	
Ignored	80	1	5	86	
Moment of Maternal Diagnosis					<0.001
During prenatal care	1,402 (99.4)	0	9 (0.6%)	1,411	
During delivery/curettage	616 (48.7%)	572 (45.2%)	76 (6.1%)	1,264	
After delivery	304 (75.4%)	85 (21%)	14 (3.5%)	403	
Not performed	9 (60%)	4 (26.7%)	2 (13.3%)	15	
Ignored	52	8	23	83	

p-value: significant association at 5%.

the detriment of the treated ones (10.8%), even with a decrease of approximately 18.2% observed from 2016 to 2018. Lack of treatment by partners was associated to most cases of congenital syphilis (78.6%), stillborn (85.2%), and deaths (81.7%) due to congenital syphilis.

DISCUSSION

Sergipe State follows the Brazilian and the Northeast tendency of increasing the number of quantified cases in pregnant women, with a total of 4,028 cases reported in SINAN from 2007 to 2019. Data agree with the latest Epidemiological Bulletin of Syphilis (2019), which shows the same evolution in the number of cases in this period, with emphasis on the 111.5% increase observed between 2016 and 2018.[8, 9, 10]

Such increase can be partly attributed to the change on defined criteria, which started to consider notification during prenatal care, childbirth, and puerperium, since October 2017. Consequently, between 2017 and 2018, the northeastern region showed the largest increase in the number of notifications (59.6%). However, detection rates of pregnant women in Sergipe State (19.0/1,000 live births) remain below the national average (21.4/1,000 live births), despite the increase observed in the last year.[4]

An analysis of the evolution of the gestational age for syphilis detection in pregnant women in Sergipe State from 2007 to 2019, shows a reduction of about 16.3% in the number of cases diagnosed in the first trimester over the last four years. Such data is provided with the profile observed in the Epidemiological Bulletin of Syphilis (2019), which refers to the diagnosis in this gestational phase that occurs with the lowest incidence proportion in the Northeast (25.9%) and North (28.3%).[8]

On the other hand, there was an increase in the number of cases diagnosed in the third trimester over the last four years. Furthermore, in general terms, the majority of notified pregnant women (36%) were diagnosed in the third trimester of pregnancy, to the detriment of the first trimester (22.9%). It can be inferred that there were gaps in the early screening system for these women, revealing the delay in the diagnosis of maternal patients who persist in this state.[11]

Furthermore, these data can be related to the opening of new beds at Hospital Santa Isabel, in 2003, and Maternidade Nossa Senhora de Lourdes, in 2008, which contributed to the diagnosis of some pregnant women with a test from the Research Laboratory for Venereal Diseases (*Laboratório de Pesquisa para Doenças Venéreas* - VDRL) late, only at the moment of birth or curettage (third trimester). On the other hand, weaknesses in the prenatal care of these pregnant women in their basic health units in the previous trimesters and the information systems of the municipalities are highlighted, resulting in lost opportunities for early diagnosis and treatment.[11,12]

Regarding the epidemiological profile of the studied pregnant women, the results demonstrate a predominance of the age group of 20 to 29 years (50.1%) aligned with data from the Epidemiological Bulletin of Syphilis (2019), which states that, in this period, 52.5% of syphilitic pregnant women were in this age group.[8]

In contrast, the age group between 30 and 39 years old was the second most prevalent in the state (25.7%), a profile observed since 2005 showed that the proportion of this age group was greater than 15 to 19 years, with an inversion of this relation since 2011.[4] This change agrees with the inversion of the Brazilian age pyramid, which has been occurring due to the aging population, which influences the number of syphilis in pregnant women.[13]

As for the education of these pregnant women, the largest proportion of them had up to 8 years of study (56.8%), whereas those who had more than 8 years corresponded to 19.3% of them, disregarding those who had higher education.

According to Lopes et al.,[14] maternal education is considered a marker of socioeconomic status, related to being of cultural and behavioral profiles. This, in turn, is related to the health care of the mother/child binomial. Literacy can be considered a protective factor in this sense, because it facilitates the search for information and a better understanding of written medical advice.

Thus, women with low education, mainly below 8 years, and of low age, are associated to lower socio-cultural groups. The contributing factor to the restriction and limitation of adequate care, both in prenatal care and after delivery, is considered a risk factor for fetal exposure to pathogens. In contrast, mothers with a higher school level understand the health-disease process better, in addition to having more access to health services.[14, 15]

When it comes to high school, health information becomes even more specified, with details on pathogenic organisms and how to intervene in the environment and interpersonal relationships to prevent the spread of diseases, or acting on prophylaxis which increases protection against congenital infections.[14, 15]

The most prevalent race/color was brown (68.1%), following the national pattern of miscegenated population, linked to the ethnic backgrounds of Brazil.[17, 18]. Thus, the study of the epidemiological profile of syphilis cases in pregnant women in SE is an important way to assess the difficulties of accessing prenatal care of quality and even allows correlating with existing social inequalities.[19, 20]

It became evident that, among the clinical classification of gestational syphilis, the most recent latent stage is the most prevalent in 13 years in the state (70.3%), except between 2009 and 2010. Such a stage displayed a significant and abrupt increase in only two years (2010 to 2012), followed by two other peaks in 2015 and 2018.

Such data agree with the removal of category "syphilis of unknown duration" in 2014, by the Centers for Disease Control and Prevention, categorizing latent syphilis as: early period (up to one year of infection) and late period (after one year of infection or when that time is unknown). In the last protocol of the Ministry of Health of STIs (2019), this period was extended to two years of infection, which is an asymptomatic period in which most pregnant women do not know exactly when they were infected. Diagnosis is based only on the reactivity of serological tests, justifying the majority of syphilis diagnoses performed at this stage.[4]

Primary syphilis, the second most prevalent in the state (11%), fell by about 19.2%, and has been prominent since 2009. The lower incidence of this phase can be justified by the thatits characteristic lesion, the "hard cancro", lasts for only three to eight weeks and is often not noticed or valued by the patient.[9, 21]

As to secondary syphilis, there were practically no significant changes from 2011 to 2019. The non-specific symptoms of this phase, such as low fever, malaise, headache, and adynamia, which disappear in a few weeks, bring a false impression of cure that contributes to

patients not seeking health services or not reporting these symptoms on pre-natal consultations.[22, 23]. These early stages have a greater chance of fetal infection, seen there is a greater spirochetemia.[9,22]

Finally, tertiary syphilis, the third most prevalent in the state (7.3%), maintains a pattern of rising and decreasing values, with peak numbers in 2010, 2013, and 2016. Such stage occurs in 15 to 25% of untreated infections, after a variable latency period, and can appear between two and 40 years after infection with systemic manifestations.[4]

In general, among untreated pregnant women, one third remains in a latent stage for life; one third heals spontaneously, and the remaining one third develops late manifestations.[9]

Whatever the clinical stage of the gestational syphilis is, it is considered a systemic infection, generating several possibilities of exposure of the placenta to Tp, which can cross the layer of Langerhans cells and infect the fetus. Thus, several histological changes are observed, which impair placental function and its exchange with the conceptual product.[24]

Macroscopy is the increase in weight and size, paleness of the tissue and the thinning of the sinciciotrophoblast with the evolution of pregnancy, facilitating the transfer of Tp to the fetus, whereas micro is affected by inflammatory reactions and delayed maturation of the villus. In addition, there is an increase in chorionic villus and stroma densification by the increase in collagen.[7]

The high incidence of this phase reflects delays in the medical diagnosis of gestational syphilis, which agrees with studies by Barros et al.[25] and Lopes et al.[26], and suggests that, despite having a wide coverage of the Family Health Strategy (FHS), there is still an involvement in the functioning of prenatal care performed in Sergipe State.

Primary Health Care in the state has 100% territorial coverage, with at least one BHU per municipality. However, even with primary assistance coverage considered satisfactory, Sergipe follows a worldwide recrudescence tendency of syphilis, especially in pregnant women and of congenital type[11, 14, 25].

Adequate prenatal care should consist of at least six consultations and start in the first trimester, with one consultation, in addition to two in the second, and three in the third trimester. Besides that, treatment for syphilis should already have started in the first trimester to reduce the prevalence of congenital syphilis, which is a marker of a country's development. This criterion is justified by the fact that this disease is preventable with early treatment with penicillin by the mother[4, 15, 27].

The high number of cases of pregnancy problems is mainly related to the weakness of routine prenatal actions in the early identification and treatment of this condition. In many cases, the number of consultations performed, or the assistance provided is not of high quality, causing failures in the blocking of preventable diseases, such as congenital syphilis, in this case[28].

Prenatal care is one of the most important public health measures, consisting of a set of clinical and educational procedures guided by clinical protocols that have the function of providing guidance and resolving doubts and anxieties of the pregnant woman, providing the highest quality assistance to the mother/child binomial. It also aims at preventing, early detecting, and treating the most frequent intercurrences in that period. However, due to the socioeconomic status, women often do not have access to health services, laboratory and imaging tests or even a multi-professional team that is prepared to provide the appropriate assistance and guidance.[27, 28, 29]

Once the pregnant woman is diagnosed with syphilis, she must start treatment. Literature states that, in 2018, 81.1% of cases had treatment prescribed according to the clinical disease classification, with Sergipe State being the one with the highest prevalence in this case (90.4%). Nonetheless, there are restrictions to such information, because there is no guarantee that the data on the clinical classification of the reported disease is consistent with its real phase.[4, 30]

As for the reasons for a high incidence of inappropriate treatments, reduction in the use of non-penicillin regimen and incomplete treatment are highlighted for being incompatible with the clinical stage or if used in less than 30 days before delivery, which ends up facilitating a congenital infection.[7, 31]

As for the moment of maternal diagnosis, the values still show a tendency for delay, with 37.8% of cases detected at the time of delivery/curettage. This incidence is very close to the cases detected during prenatal care (38.7%); 10.1% after delivery, and 0.5% did not even receive diagnosis.

These values are above the national average, which shows a much higher prevalence of cases diagnosed during prenatal care (57.6%), in addition to the lower detection values at the time of delivery/curettage (31.8%), and after delivery (5.6%).[4]

When relating such information with data from congenital syphilis, the identification of pregnant women as syphilitic only at the time of delivery/curettage resulted in the majority of infant deaths from this condition (72.9%), and 36.5% of cases of consequent congenital syphilis.

This reveals the existence of gaps in the interruption of vertical transmission, and at the timely and adequate treatment of these concepts, targets planned since 2012, with emphasis on Nascer Project, which instituted the control of congenital syphilis, throughearly diagnosis and treatment.[32, 33, 34]

Although most of the analyzed pregnant women had performed prenatal care (75%), such information does not guarantee that care was adequate. This is reflected by the results, which show that, even with prenatal care, 48.7% of pregnant women received the syphilis diagnosis during delivery, 75.4% after birth/curettage, and 60% did not even receive it. Consequently, most of these mothers had their therapeutic regimen classified as inadequate (59.5%), that is, performed less than 30 days before the birth or not performed (28.6%).

This means that most of congenital syphilis cases (79.4%) were associated to maternal prenatal delivery. This reinforces the importance of the quality of prenatal care, with effective strategies to reduce fetal infection with syphilis, following the perspective of identifying maternal diseases still during pregnancy. Unwanted practices, such as "prenatal discharge", should be strictly inhibited, favoring the continued provision of care to pregnant women until delivery.[26, 27, 31]

According to the Brazilian Federation of Gynecology and Obstetrics Associations (*Federação Braliseira das Associações de Ginecologia e Obstetrícia* - FEBRASGO), treating the partner is considered imperative on the prevention of congenital syphilis. Results show that when partners do not treat it, there will be a series of damage caused by the fetus, reflecting the majority of cases of congenital syphilis (78.6%), stillborn (85.2%), and deaths (81.7%) for grievance. Thus, strategic measures of joint treatment of partners must be developed, given the persistence of the predominance of untreated cases (77.7%) to the detriment of those treated (10.8%).[35]

The statistics present that the public is not sufficiently included in the prenatal strategy target. Thus, projects to include these items should be encouraged so that the effective control of the risk of infection in women of childbearing age is possible. Lack of joint treatment or performance of inappropriate treatment, and not registering its therapeutic regimen performed on the prenatal card are important reasons for classifying the treatment as inadequate.[1, 7, 36]

However, many cases of syphilis in pregnant women and congenital syphilis are underreported or poorly reported, fact which can be considered one of the restrictions of the present study, as well as the data available in DATASUS. The cases ignored/left blank and those discarded are also included.

This is worrying because notification of cases of syphilis during pregnancy is part of the strategy for preventing congenital syphilis. Therefore, it must be ideally done in prenatal services, when an intervention is still possible, that is, when no transmission to the fetus has happened yet.[37] In late cases, notification is also possible in delivery/postpartum care settings since October 2017.[4]

Furthermore, epidemiological and socio-demographic studies on the topic can be carried out based on these notifications, directing the Brazilian Ministry of Health to plan health actions and create intervention measures in this regard.[37, 38] Thus, health professionals should be encouraged and sensitized to the correct filling of documents that feed the DATASUS database.

Nevertheless, the epidemiological analysis made it possible to observe important characteristics of these populationsegments and demonstrate the magnitude that the disease represents in the state. The present study is expected to contribute to the development of health strategies to monitor the quality of prenatal care provided to pregnant women with syphilis.

Strategies must be developed to promote the permanent education of health professionals involved in each sphere of care, so that they are well trained and qualified to identify risk conditions for congenital infection.

CONCLUSION

IIn Sergipe State, there was a significant increase in the number of syphilis cases notified in pregnant women over the last 13 years, which occurred, in part, due to changes in the definition criteria of cases, which started to be considered not only during pre-birth, but also on delivery and puerperium, as of October 2017.

Among the epidemiological characteristics most frequently found in these pregnant women are in their brown ethnicity, education time of up to 8 years, and an age range from 20 to 29 years old. As for the quality of the prenatal care offered, if there was a predominance of diagnoses only in the third trimester of pregnancy, with a latent clinical phase being the most found, followed by the primary and tertiary phases, most of them were performed in the prenatal period.

Moreover, a large amount of them have not even been tested. Although most of them were treated with penicillin, there is a prevalence of inadequate regimens due to high rates of diagnosis performed only at the time of delivery or curettage, because neither the minimum therapeutic interval of 30 days before delivery was respected, nor the predominance of unidentified partners, which predisposes to the reinfection of the pregnant women.

In this way, Sergipe State remains the most important factor in the high vertical transmission of syphilis due to the ineffectiveness of prenatal care provided to pregnant women with syphilis.

Participation of each author

Rute de Oliveira Farias: lead author of research.
Izailza Matos Dantas Lopes: research advisor.
Letícia Goes Santos: auxiliary research editor.
Amanda Silveira de Carvalho Dantas: auxiliary research editor.

Funding

The authors declare that there is no external source of funding for the study.

Conflict of interests

The authors declare no conflict of interests.

REFERENCES

1. Norwitz ER, Hicks CB. Syphilis in pregnancy. UpToDate [Internet]; 2020 [accessed on July 30, 2019]. Available at: https://www.uptodate.com/contents/syphilis-in-pregnancy
2. Nonato SM, Melo APS, Guimarães MDC. Sífilis na gestação e fatores associados à sífilis congênita em Belo Horizonte - MG, 2010-2013. Epidemiol Serv Saúde [Internet]. 2015 [acessed on Apr. 2, 2019];24(4):681-94. Available at: http://dx.doi.org/10.5123/S1679-49742015000400010
3. Johnson KE. Overview of TORCH infections. UpToDate [Internet]; 2020 [accessed on July 30, 2019]. Available at: https://www.uptodate.com/contents/overview-of-torch-infections
4. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Doenças de Condições Crônicas e Infecções Sexualmente Transmissíveis. Protocolo clínico e diretrizes terapêuticas para atenção integral às pessoas com infecções sexualmente transmissíveis. Brasília: Ministério da Saúde; 2019.
5. Taylor MM, Nurse-Findlay S, Zhang X, Hedman L, Kamb ML, Broutet N, et al. Estimating benzathine penicillin need for the treatment of pregnant women diagnosed with syphilis during antenatal care in highmorbidity countries. PLoS One. 2016;1(7):e0159483. https://doi.org/10.1371/journal.pone.0159483
6. Andrade ALMB, Magalhães PVVS, Moraes MM, Tresoldi AT, Pereira RM. Late diagnosis of congenital syphilis: a recurring reality in women and children health care in Brazil. Rev Paul Pediatr. 2018;36(3):376-81. https://doi.org/10.1590/1984-0462/;2018;36;3;00011
7. Sergipe. Secretaria de Estado da Saúde de Sergipe. Plano Estadual de Saúde. Vigência 2016 a 2019. Sergipe: Secretaria de Estado da Saúde; 2016.
8. Camarano AA. Novo Regime Demográfico uma nova relação entre população e desenvolvimento. Rio de Janeiro: Instituto de Pesquisa Econômica Aplicada (Ipea); 2014.
9. Lopes Filho JR, Silva Neto LS. Relação entre mortalidade infantil e escolaridade materna no estado do tocantins de 2010 a 2015. Rev Patol Tocantins. 2018;5(4):5-11. https://doi.org/10.20873/uft.2446-6492.2018v5n4p5
10. Moreira KFA, Oliveira DM, Alencar LN, Cavalcante DFB, Pinheiro AS, Orfão NH. Perfil dos casos notificados de sífilis congênita. Cogitare Enferm. 2017;22(2):e48949. http://dx.doi.org/10.5380/ce.v22i2.48949
11. Santiago AT, Silva AC, Martins DS, Araújo PX. Sífilis gestacional: Análise de casos da cidade de Marabá – Pará. In: Anais Eletrônicos; 2019; Marabá, Brazil. Marabá: Universidade do Estado do Pará; 2019.
12. Hicks CB, Clement M. Epidemiology, pathophysiology and clinical manifestations in patients not infected with HIV. UpToDate [Internet]; 2020 [accessed on July 30, 2019]. Available at: https://www.uptodate.com/contents/syphilis-epidemiology-pathophysiology-and-clinical-manifestations-in-hiv-uninfected-patients

13. Rezende JF, Montenegro CAB. Rezende: obstetrícia fundamental. 14ª ed. Rio de Janeiro: Guanabara Koogan; 2019.
14. Barros LB. Prevalência de casos notificados de sífilis em gestante e sífilis congênita no estado de sergipe entre 2007 e junho de 2013 [monography]. Sergipe: Universidade Federal de Sergipe; 2013.
15. Lopes IMD, Lopes AD, Santos RS, Lima SO, Reis FP. Congenital syphilis in a philanthropic maternity of the state of Sergipe: still a challenge. DST - J Bras Doenças Sex Transm. 2018;30(2):41-6. http://dx.doi.org/10.5533/DST-2177-8264-201830202
16. Lockwood CJ, Magriples U. Prenatal care: initial assessment. UpToDate [Internet]; 2020 [accessed on July 30, 2019]. Available at: https://www.uptodate.com/contents/prenatal-care-initial-assessment
17. Figueiredo PP, Lunardi Filho WD, Lunardi VL, Pimpão FD. Infant mortality and prenatal care: contributions of the clinic in the light of Canguilhem and Foucault. Rev Latino-Am Enfermagem. 2012;20(1):201-10. https://doi.org/10.1590/S0104-11692012000100026
18. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância, Prevenção e Controle das Infecções Sexualmente Transmissíveis, do HIV/Aids e das Hepatites Virais. Boletim Epidemiológico Sífilis. 2018;49(45).
19. Brasil.Ministério da Saúde. Portaria no. 33, de 14 de julho de 2005 [Internet]. 2007 [accessed on July 14, 2019]. Available at: http://bvsms.saude.gov.br/bvs/saudelegis/svs/2005/prt0033

Address for correspondence:
RUTE DE OLIVEIRA FARIAS
Rua Albino Rufino de Santana, 100, casa 5 – Farolândia
Aracaju (SE), Brazil
CEP: 49030-040
E-mail: rutxinhafarias@gmail.com

Received on: 03.23.2020
Approved on: 04.16.2020

Prevalence of ureaplasma urealyticum, mycoplasma hominis and human papillomavirus coinfection in people attending a sexually transmitted infections (STI)/HIV reference centre in Salvador, Bahia, Brazil

Prevalência da coinfecção por ureaplasma urealyticum, mycoplasma hominis e papilomavírus humano em pessoas atendidas em centro de referência de doenças sexualmente transmissíveis (DST)/HIV em Salvador, Bahia

Alyce Lima Amorim[1], Ana Gabriela Álvares Travassos[1], Geovane Cruz de Souza[1], Vitor Cunha Fontes[1], Maiara Timbó[2], Eveline Xavier Souza[2]

ABSTRACT

Introduction: *Ureaplasma urealyticum* and *Mycoplasma hominis* are frequently found at many women's and men's urogenital tract, and have been associated with non-gonococcal urethritis, cervicitis, infertility, chorioaminionitis and adverse pregnancy outcomes. Some studies show high prevalence of *human papillomavirus* (HPV) in patients with non-gonococcal urethritis, while also presenting high frequency of *Ureaplasma urealyticum* infection in women with cervicalcytology abnormalities and men with genital warts. **Objectives:** To evaluate the prevalence of *Ureaplasma urealyticum*, *Mycoplasma hominis* and HPV coinfection in people attending a sexually transmitted infections (STI)/HIV reference centre and to identify the risk factors associated. **Methods:** A cross-sectional study with patients aged >18 years, carried out for *Ureaplasma urealyticum* and *Mycoplasma hominis* from July 1st to December 31, 2015, in a STI/HIV reference centre from the State of Bahia, Brazil. Sociodemographic and clinical data were obtained from secondary data from patients' charts and laboratory findings, and analyzed using SPSS 20.0. Pearson's χ^2 test or Fisher's exact test was used to evaluate categorical variables. HPV clinical diagnosis was considered positive as the presence of genital warts. **Results:** In this study, 849 patients were included — 196 men and 653 women. Of the sample, 51.4% was diagnosed with at least one of the two bacteria. The prevalence of *Mycoplasma hominis* infection was higher in coinfection (16.7%) than in isolated infection (2.2%). The prevalence of *Ureaplasma urealyticum* isolated infection was 32.4%. A strong association was found between the presence of genital warts and *Ureaplasma urealyticum* infection, with an estimated risk of 1.230 (p=0.014). **Conclusion:** Our findings suggest the need for further investigation for *Ureaplasma urealyticum* infection in patients presenting genital warts on physical examination. In addition, in this context, greater attention should be given to women and pregnant women.

Keywords: *Ureaplasma urealyticum*; *Mycoplasma hominis*; *Human papilloma virus*; reproductive tract infections.

RESUMO

Introdução: *Ureaplasma urealyticum* e *Mycoplasma hominis* são frequentemente encontrados no trato urogenital de homens e mulheres, e têm sido associados à ocorrência de uretrites não gonocócicas, cervicites, infertilidade, corioamnionite e outras patologias obstétricas. Alguns estudos mostraram alta prevalência de papilomavírus humano (HPV) em pacientes com uretrites não gonocócicas, bem como alta frequência de infecção por *Ureaplasma urealyticum* em mulheres com anormalidades na citologia cervical e homens apresentando verruga genital. **Objetivos:** Avaliar a prevalência da coinfecção por *Ureaplasma urealyticum*, *Mycoplasma hominis* e HPV em pessoas atendidas em um centro de referência de DST/HIV e identificar os fatores de risco associados. **Métodos:** Estudo transversal com pacientes maiores de 18 anos, testados para *Ureaplasma urealyticum* e *Mycoplasma hominis* entre 1º de julho e 31 de dezembro de 2015, em um centro de referência de DST/HIV da Bahia, Brasil. Os dados clínicos e sociodemográficos foram obtidos por coleta de dados secundários a partir dos prontuários e achados laboratoriais dos pacientes e analisados usando SPSS 20.0. O teste de χ^2 Pearson ou teste exato de Fisher foram usados para avaliar as variáveis categóricas. O diagnóstico clínico do HPV foi considerado positivo quando houve presença de verruga genital. **Resultados:** Foram incluídos neste estudo, 849 pacientes, sendo 196 homens e 653 mulheres. Da amostra, 51,4% foi diagnosticada com infecção por pelo menos uma das duas bactérias. A prevalência de infecção por *Mycoplasma hominis* foi maior na coinfecção (16,7%) do que isoladamente (2,2%). A prevalência da infecção isolada por *Ureaplasma urealyticum* foi de 32,4%. Houve forte associação entre a presença de verruga genital e infecção por *Ureaplasma urealyticum*, com estimativa de risco de 1,230 (p=0,014). **Conclusão:** Nossos achados sugerem a necessidade de investigação adicional para a infecção por *Ureaplasma urealyticum* nos pacientes apresentando verruga genital ao exame físico. Além disso, nesse contexto, maior atenção deve ser dada a mulheres e gestantes.

Palavras-chave: *Ureaplasma urealyticum*; *Mycoplasma hominis*; *Human papilloma virus*; infecções genitais.

INTRODUCTON

Ureaplasma urealyticum (UU) and *Mycoplasma hominis* (MH), commonly known as mycoplasma and ureaplasma, are often isolated in the urogenital tract of men and women[1]. Simultaneous colonization by the two pathogens is very common and may be associated with factors such as young age, low socioeconomic status, sexual relations with multiple partners, non-use of condoms and being afrodescendant[2].

UU and MH have been associated with non-gonococcal urethritis, pelvic inflammatory disease, salpingitis, bacterial vaginosis, infertility, obstetric pathologies (premature delivery, abortion, postpartum and post-abortion fever, and chorioamnionitis) and pyelonephritis[2,3]. However, one of the main difficulties in identifying these organisms as causing these diseases is their occurrence in apparently healthy individuals[3].

[1]Medical Course, Department of Life Sciences, Universidade Estadual da Bahia – Salvador (BA), Brazil.
[2]Medical Course, Universidade Federal da Bahia – Salvador (BA), Brazil.

Human papillomavirus (HPV) infection is a determining element in the development of most cases of cervical cancer in women, and has also been identified as a risk factor for the development of cancers of the penis, anus and oropharynx[4]. Genital HPV infection is usually transmitted during intercourse, and its prevalence in sexually active women worldwide can range from 20 to 60%, which allows us to conclude that this is one of the most common sexually transmitted infections (STIs) in women[5].

The diagnosis of HPV may be clinical, determined by the presence of condyloma acuminatum or warts in the anogenital region; subclinical through examination of the affected region; pathological, by performing biopsy of the lesion; and, finally, diagnosis of latent (asymptomatic) form, obtained by molecular biology methods (polymerase chain reaction (PCR), hybrid capture)[6].

Studies have shown a high prevalence of HPV in patients with gonococcal and non-gonococcal urethritis[7-10]. This may be associated with the fact that patients with urethritis represent a group of high-risk behaviors for STIs, including HPV infection[11]. In addition, the inflammation of the urinary tract shown in uncontrolled urethritis can induce cell exfoliation, which contributes to the detection of asymptomatic HPV infection in men[12].

A study conducted in 2011 showed that women with abnormalities in the cytopathological examination of the cervix have a high frequency of UU and MH infections[7]. In this study, it was found that patients infected with these species have a risk of evolution of HPV infection increased by 4.7 times. In addition, a study conducted in Poland showed that 88.9% of women diagnosed with HPV in cytopathology had UU coinfection[13].

A study evaluating the presence of STIs in male patients with condyloma acuminatum deserves attention, because it identified a prevalence of asymptomatic infection by UU in 67.5% of men who presented condyloma acuminatum[14].

In view of the importance of diagnosing and treating symptomatic and asymptomatic infections by these microorganisms to ensure the interruption of the transmission cycle among the population, it was necessary to study the prevalence of these infections and the associated risk factors, with the intention of tracing a current epidemiological profile that may guide an update in the screening and management strategies of patients.

OBJECTIVE

The main objective of this study was to evaluate the prevalence of UU, MH and HPV, coinfection and the presence of condyloma acuminatum in people treated at an STIs/HIV referral center in Salvador, Bahia. The secondary objective of the study was the determination of risk factors associated with the higher prevalence of these coinfections.

METHODS

A cross-sectional study was performed with patients tested for UU and MH, between July 1st and December 31, 2015, through a retrospective analysis with secondary data from medical records and laboratory data. The data surveyed were recorded in a previously established form containing clinical and sociodemographic information.

All patients admitted and tested at the unit for UU and MH in the mentioned period were included. Exclusion criteria were age below 18 years and incomplete data regarding the study objective. Clinical and epidemiological data associated with the presence of UU and MH infection were evaluated in the medical records of patients seen at the Specialized Center for Diagnosis, Care and Research (*Centro Estadual Especializado em Diagnóstico, Assistência e Pesquisa* — CEDAP), in Salvador, Bahia.

The acquisition of biological material for the culture of MH and UU is done by collecting a sterile vial containing the first urinary jet in men and endocervical/vaginal material with brush or cytology brush in women. Screening, quantification and detection of antibiotic sensitivity were determined with the MYCOFAST Screening Evolution 3 kit, which presents sensitivity of 92.3% and specificity of 98.25% for UU, and sensitivity of 93.25% and specificity of 95.3% for MH. Infection by UU and/or MH was considered positive by positive culture result for one or both pathogens.

For the population studied, continuous quantitative variables (age) and nominal qualitative variables (gender, marital status, current pregnancy, contraceptive use, use of current condom, symptomatology, and presence of other STIs, including HPV) were adopted. The clinical and physical examination data of the patient were collected from the anamnesis performed on the day of collection of biological material for culture. HPV infection was considered positive when there was the presence of condyloma acuminatum (genital wart), recorded in medical records by the attending physician.

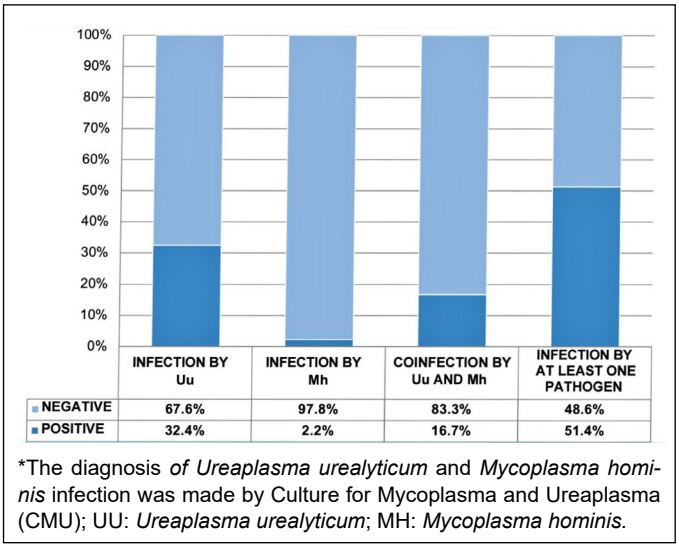
Subsequently, the data were entered in EPIDATA version 3.1 and compiled into a database with the Microsoft Excel 2017 program®. The analysis was performed with the program SPSS for Windows version 20.0®. Pearson χ^2 test or Fisher's exact test was used to evaluate categorical variables. The continuous variables were evaluated using Student's *t*-test. For all tests used, statistical significance is considered when the $p<0.05$ and 95% confidence interval (95%CI).

As this is a retrospective study, through a review of secondary data recorded in medical records and laboratory protocol book, with no interview, procedures or interventions, the study brings few risks to patients. The study was approved by the research ethics committee (CEP) of the Health Department of the State of Bahia (*Secretaria da Saúde do Estado da Bahia* — SESAB), through opinion number 1,792,012. Confidentiality will be maintained regarding the name and personal data obtained in the review of medical records as provided for in Resolution no. 466/2012.

RESULTS

A total of 893 patients performed culture for MH and UU (CMU) between July and December 2015 at the studied STI/HIV reference center. Of this total, 44 patients were excluded from the sample, resulting in 849 patients included in the following analysis, among them 196 men and 653 women. The mean age among women was 35.17 years and, among men, 32.18 years, both with standard deviation of 11.38 years.

Figure 1 shows the prevalence of UU and MH infection alone or together in the population studied. It is noted that more than half



*The diagnosis *of Ureaplasma urealyticum* and *Mycoplasma hominis* infection was made by Culture for Mycoplasma and Ureaplasma (CMU); UU: *Ureaplasma urealyticum*; MH: *Mycoplasma hominis.*

Figure 1 – Prevalence of Ureaplasma urealyticum and Mycoplasma hominis infections in patients treated at the sexually transmitted infections (STI)/human immunodeficiency virus (HIV) referral center, Salvador, Bahia, in 2015 (n=849).

of the population that underwent the ureaplasma and mycoplasma culture (UMC) was diagnosed with infection by at least one of the two bacteria (51.4%). The prevalence of MH infection was higher in coinfection (16.7%) than isolation (2.2%), reinforcing the synergism between simultaneous infection by the two bacteria. The prevalence of UU isolation infection (32.4%) exceeded more 30% of the prevalence of MH-isolated infection (2.2%).

Table 1 shows that 89.7% of patients diagnosed with infection by at least one of the two bacteria were women. In addition, females had a 1,414 (95%CI 1.305–1.531) higher risk of UU and/or MH infection compared to males, which was statistically significant (p<0.001). Having a fixed partner was identified as a protective factor for UU and/or MH infection, with a 0.656 (95%CI 0.490–0.878) lower risk of having infection by at least one of the bacteria compared to patients without a fixed partner. This finding was statistically significant (p=0.004).

Also in **Table 1**, it is verified that 38.3% of patients diagnosed with infection by at least one of the bacteria have HIV, but this condition did not have a statistically significant association with the presence of UU and/or MH infection. The same occurred with the use of condoms; although there is no statistically significant association with the presence of infection by bacteria, a high prevalence of irregular use or no condom use was observed in the population diagnosed with UU and/or MH infection (51.8%).

Analyzing only the group of women who underwent UMC in the period studied, it was found that being pregnant presented a 3.159 (95%CI 1.419–7.033) higher risk of UU and/or MH infection, an alarming risk estimate that was statistically significant (p=0.003).

Starting from **Table 2**, the same phenomenon was verified within the group of patients who were diagnosed with condyloma acuminatum in the genital region on physical examination: the vast majority

Table 1 – Prevalence of *Ureaplasma urealyticum* and/or *Mycoplasma hominis* infections according to sex, steady partner, human immunodeficiency virus (HIV) serological status, and condom use in patients treated at the sexually transmitted infections (STI)/HIV reference center, Salvador, Bahia (2015).

Categories	Infection by UU and MH				P-value (χ^2)	OR (95%CI)
	Positive		Negative			
	Total=436		Total=413			
	n	%	n	%		
Gerder						
Male	45	10.3	151	36.6	<0.001	0.282 (0.208–0.383)
Female	391	89.7	262	63.4		1.414 (1.305–1.531)
Steady partner						
Yes	63	14.4	91	22	0.004	0.656 (0.490–0.878)
No	373	85.6	322	78		1.097 (1.029–1.70)
Serological status						
HIV+	167	38.3	137	33.2	0.119	1.155 (0.963–1.384)
HIV-	269	61.7	276	66.8		0.923 (0.835–1.021)
Use of condom						
Regular	91	20.9	69	1.7	0.393	1.123 (0.860–1.468)
Irregular/ None	226	51.8	201	48.7		0.958 (0.868–1.057)
Pregnant*		n=391		n=262		
Yes	33	8.4	7	2.7	0.003	3.159 (1.419–7.033)
No	358	91.6	255	97.3		0.941 (0.907–0.975)

*Male patients were excluded for analysis of this variable; OR: *odds ratio*; 95%CI: 95% confidence interval; Pearson χ^2 test and Fisher's exact test were used for variable analysis; The diagnosis of *Ureaplasma urealyticum* and *Mycoplasma hominis* infection was made by Culture for Mycoplasma and Ureaplasma (CMU); UU: *Ureaplasma urealyticum*; MH: *Mycoplasma hominis.*

were female, representing 91.7% of patients with genital wart in the sample studied. Additionally, the female gender was identified with a higher risk 1.247 (95%CI 1.169–1.330) of presenting genital wart compared to males, a finding that was statistically significant (p<0.001).

Although most patients with genital wart did not have a fixed partner (86%), this factor did not present any statistically significant association with the presence of genital wart.

Also in **Table 2**, HIV+ serological status showed a lower association, with a risk of 0.344 (95%CI 0.231–0.512) lower than having genital wart when compared to the non-HIV-infected group; a finding that was statistically significant (p<0.001).

Table 2 – Prevalence of condyloma acuminated according to sex, steady partner, serological status for human immunodeficiency virus (HIV), condom use and pregnancy in patients treated at the sexually transmitted infections (STI)/HIV referral center, Salvador, Bahia (2015).

Categories	Condyloma acuminatum				P-value (χ^2)	OR (95%CI)
	Positive		Negative			
	Total=157		Total=692			
	n	%	n	%		
Gender						
Male	13	8.3	183	26.4	<0.001	0.313 (0.183–0.535)
Female	144	91.7	509	73.6		1.247 (1.169–1.330)
Steady Partner						
Yes	22	14	132	19.1	0.137	0.735 (0.484–1.114)
No	135	86	560	80.9		1.063 (0.988–1.143)
Serological Status						
HIV+	22	14	282	40.8	<0.001	0.344 (0.231–0.512)
HIV-	135	86	410	59.2		1.451 (1.329–1.585)
Use of condom						
Regular	22	14	138	19.9	0.022	0.640 (0.429–0.957)
Irregular/ None	95	60.5	332	48		1.149 (1.035–1.277)
Pregnant*		n=144		n=509		
Yes	14	9.7	26	5.1	0.041	1.903 (1.021–3.548)
No	130	90.3	483	94.9		0.951 (0.898–0.995)

*Male patients were excluded for analysis of this variable; Pearson χ^2 test and Fisher's exact test were used to analyze the variables; OR: *odds ratio*; 95%CI: 95% confidence interval.

The prevalence of irregular use or no condom use was high within the group of patients diagnosed with genital wart, representing 60.5% of these patients. Similarly, this behavior was identified as a risk factor for presenting genital wart, with an estimated risk 1.149 (95%CI 1.035–1.277) times higher than the group in regular condom use. This result was statistically significant (p=0.022) to the χ^2 test.

Finally, **Table 2** also exposes another statistically significant finding (p=0.041) that deserves attention: being pregnant was also identified as a risk factor for genital wart, with a risk of 1.903 (95%CI 1.021–3.548) higher than pregnant women presenting condyloma acuminated in relation to the group of non-pregnant women.

Table 3 shows the prevalence of symptoms within the population studied. In the group of patients diagnosed with infection by at least one bacteria (UU and/or MH), almost half (42.7%) did not show symptoms at the time of diagnosis. Among the symptoms

Table 3 – Presence or not of symptoms according to positive or negative result for *Ureaplasma urealyticum* and/or *Mycoplasma hominis* infection in patients treated at the sexually transmitted infections (STI)/human immunodeficiency virus (HIV) reference center, Salvador, Bahia (2015).

Symptoms	Infection by UU and/or MH				P-value (χ^2)	OR (95%CI)
	Positive		Negative			
	Total=436		Total=413			
	n	%	n	%		
Asymptomatic						
Yes	186	42.7	147	35.6	0.035	1.199 (1.012–1.420)
No	250	57.3	266	64.4		0.890 (0.799–0.992)
Genital pruritus						
Yes	34	7.8	23	5.6	0.195	1.400 (0.839–2.336)
No	402	92.2	390	94.4		0.976 (0.942–1.012)
Urethral discharge						
Yes	21	4.8	79	19.1	<0.001	0.252 (0.159–0.400)
No	415	95.2	334	80.9		1.177 (1.118–1.239)
Pelvic pain						
Yes	43	9.9	31	7.5	0.224	1.314 (0.845–2.044)
No	393	90.1	382	92.5		0.975 (0.935–1.016)
Dysuria						
Yes	30	6.9	96	23.2	<0.001	0.296 (0.201–0.436)
No	406	93.1	317	76.8		1.213 (1.144–1.287)
Hematuria						
Yes	0	0	2	0.5	0.236	
No	436	100	411	99.5		1.005 (0.998–1.012)
Pain in intercourse						
Yes	13	3	11	2.7	0.780	1.119 (0.507–2.471)
No	423	97	402	97.3		0.997 (0.974–1.020)
Vaginal discharge*	n=391		n=262			
Yes	96	24.6%	65	24.8%	0.941	0.990 (0.753–1.301)
No	295	75.4%	197	75.2%		1.003 (0917–1.098)

*Male patients were excluded for analysis of this variable; Pearson χ^2 test and Fisher's exact test were used for variable analysis; the diagnosis of *Ureaplasma urealyticum and Mycoplasma hominis* infection was made by Culture for Mycoplasma and Ureaplasma (CMU); UU: *Ureaplasma urealyticum*; MH: *Mycoplasma hominis*; OR: *odds ratio*; 95%CI: 95% confidence interval.

contemplated by the study questionnaire, the most prevalent among patients with positive UMC results were: pelvic pain (9.9%), genital pruritus (7.8%), dysuria (6.9%) and urethral discharge (4.8%). Excluding male patients from the analysis, a high prevalence of vaginal discharge was found in female patients diagnosed with infection by at least one bacterium (24.6%).

The percentage of patients with urethral discharge and dysuria was higher in the group that was not diagnosed with either bacterium, representing 19.1 and 23.2% of the patients in this group, respectively. Thus, the presence of these two symptoms may be more associated with urogenital tract infections by other pathogens, which not UU and MH. This possibility is reinforced by the finding that the presence of urethral discharge and dysuria are protective factors for UU and/or MH infection, with a statistically significant p ($p<0.001$), speaking more in favor of other infections that need to be further investigated.

Finally, **Table 4** presents the statistical analysis of coinfection with UU, MH and HPV, the central objective of the present study. Of the total number of patients who had a clinical diagnosis of HPV (n=157), 91 patients were identified with simultaneous UU infection, which represents more than half of the patients with genital wart (58%). In addition, UU infection was identified as a factor associated with the presence of genital wart, with an estimated risk of 1.230 (95%CI 1.054–1.436). This result presents statistical significance (p=0.014). It is also observed in **Table 4** that, although almost a quarter of patients with condyloma acuminatum present MH infection simultaneously (22.9%), no statistically significant association was found between the presence of MH infection and the higher risk of developing genital wart.

Table 4 – Prevalence of *Ureaplasma urealyticum* and *Mycoplasma hominis* infections in patients diagnosed with condyloma acuminatum at the time of collection of material for culture for mycoplasma and ureaplasma at the sexually transmitted infections (STI)/human immunodeficiency virus (HIV) reference center, Salvador, Bahia (2015).

RESULT CMU	Condyloma acuminatum				P-value (χ^2)	OR (95%CI)
	Positive		Negative			
	Total=157		Total=692			
	n	%	n	%		
Infection by UU						
Yes	91	58.0	326	47.1	0.014	1.230 (1.054–1.436)
No	66	42.0	366	52.9		0.795 (0.653–0.968)
Infection by MH						
Yes	36	22.9	125	18.10	0.160	1.269 (0.915–1.762)
No	121	77.1	567	81.90		0.941 (0.858–1.031)

Pearson χ^2 test and Fisher's exact test were used for variable analysis; the diagnosis of *Ureaplasma urealyticum and Mycoplasma hominis* infection was made by Culture for Mycoplasma and Ureaplasma (CMU); UU: *Ureaplasma urealyticum*; MH: *Mycoplasma hominis*; OR: *odds ratio*; 95%CI: 95% confidence interval.

DISCUSSION

In our study, the female gender was more associated with both UU and/or MH infection ($p<0.001$), and with the presence of condyloma acuminatum ($p<0.001$), indicating that being a woman in our sample was a risk factor for the presence of the STIS evaluated. Several factors may be associated with this finding. The position of the individual in society results from the interaction between different categories, often resulting from biological attributes that express a condition of inequality in the social space and determine the "social place" of each individual. Gender corresponds to one of these categories and, historically, gender inequality has determined a greater vulnerability of women in the social space, where the rights of access to services, including the health service, took a long time to achieve and still shows weaknesses[15]. The inequity of access of the female population, as well as the inferior role of women in sexual and reproductive decisions, typical of a patriarchal society that still characterizes contemporary Brazil[16,17], have a direct impact on the greater vulnerability of women in the acquisition of STIs.

A finding deserves to be highlighted in the study: more than half of the participants (51.4%) was diagnosed with at least one of the two bacteria analyzed, and, of the total number of patients diagnosed with UU and/or MH, almost half (42.7%) presented no symptoms at the time of the consultation. This result is not unexpected. Many studies show the large number of asymptomatic patients who are diagnosed with infection by these bacteria, with the prevalence of ureaplasmas infection ranging from 40 to 80%, and mycoplasmas from 10 to 20% in women of asymptomatic reproductive age[9,18,19]. Mycoplasmas may be normal in inhabitants of the urogenital tract of man and woman in certain circumstances, but titration greater than or equal to 10^3 colony forming units (CFU)/mL already demonstrates imbalance of the microbiota and favors proliferation of other pathogens[20,21]. This leads to an important reflection about the strategies that need to be developed in order to identify the asymptomatic population with the infection through an expanded screening, so that they are treated properly, thus interrupting the transmission cycle.

Infection by MH leads to an increase in pH in the vaginal microenvironment, resulting from the production of ammonia from the breakdown of arginine, the largest source of mycoplasmas energy. Similarly, urease released by ureaplasmas hydrolyzes urea into ammonia and alkalizes the vaginal pH. This increase in pH is responsible for facilitating the development of aerobic vaginitis and bacterial vaginosis[20,21]. The combination of all these disorders to the vaginal microbiota increases the risks of complications during pregnancy, such as preterm delivery, abortion, corioamnionitis and even fetal funitis[19,22]. In our study, pregnancy was identified as a risk factor for the presence of UU and MH infection, as well as for the presence of genital wart. It is worth noting the risk of the presence of UU and/or MH infection in the group of pregnant women, which was 3.159 (p=0.003) higher in relation to the group of non-pregnant women, indicating the need for greater commitment to clinical suspicion and diagnostic investigation of these infections during pregnancy in order to protect the pregnancy from possible complications.

As expected, the positive association between the presence of genital wart and UU infection was identified through this study, with

an estimated risk of 1,230 higher than patients not diagnosed with infection by the bacterium. In our study, the percentage of patients who presented condyloma acuminatum on physical examination, and simultaneously, were diagnosed with UU was of 58%; an alarming rate. A previous study, conducted with men at a Dermatological Institute in Israel, identified a high frequency of UU infection in patients with condyloma acuminatum identified on physical examination: more than half of patients with genital wart (67.5%) was diagnosed with UU infection, even without signs and symptoms of urethritis[14]. Another study, conducted with non-pregnant women in the Department of Gynecology of the University of Rome, determined that 53% of patients diagnosed with HPV infection by means of PCR also had UU infection detected through culture, with an estimated risk of 2.95 ($p<0.001$)[23].

Although the association between HPV infection and UU has been identified in some studies, it is not known exactly whether there is a synergism mechanism between these two pathogens. A mitogenic potential was attributed to UU antigens in a previous study conducted with patients with Reiter syndrome[24]. This knowledge allows us to possibly infer that UU has some role in stimulating cell proliferation evidenced in the form of condyloma acuminatum as a result of HPV infection.

However, the possibility that the association between the two pathogens is behavioral cannot be ruled out, since both are transmitted during intercourse, thus involving the same risk factors related to sexual habits[11,14].

Despite the fact we did not find a statistically significant association between the presence of condyloma and MH infection, it was possible to identify a positive association between the presence of condyloma and UU infection, an alarming prevalence of at least one of the two bacteria investigated (51.4%) and high prevalence of UU and MH coinfection (16.7%) in the population studied. Attention should be paid to the fact that this research was conducted with a convenience sample and, therefore, the information cannot be extrapolated precisely to the general population. In a reference center for STIs, patients seeking care are expected to have coinfections.

CONCLUSION

The identification of women and pregnant women as a group of greater vulnerability in the present study is an important factor that signals the need for actions that aim at expanding access to health information and care by this group, as well as encouraging female self-care by the health professional.

In health services, the research of mycoplasma and ureaplasma through the realization of culture is often neglected, even in the presence of symptoms of urethritis. The high prevalence found in this study, however, shows the need for change in this approach, so that the presence of genital wart may be another sign that these infections may be present.

As stated, this study was conducted with a convenience sample from a reference center specialized in the management of STIs, which determines some limitations. Therefore, it is essential to conduct research from diverse populations with broader characteristics, such as people assisted in primary care in Basic Health Units and Family Health Program.

ACKNOWLEDGEMENTS

We addressed sincere thanks to Lúcia Tachard Netto, Magali Mendes de Andrade, Carlos Lima and Monaliza Rebouças, dedicated professionals whose participations enabled the elaboration of this work.

Participation of each author

Ana Gabriela: definition of the methodology, statistical analysis of the data, and continuous guidance during writing of the work. Alyce Lima: data collection, database typing, statistical data analysis, table and chart construction, and job writing. Geovane Souza: data collection and database typing. Vitor Cunha: data collection and database typing. Maiara Timbó: definition of methodology, data collection, and statistical analysis of data. Eveline Xavier: definition of methodology, data collection, and statistical analysis of data.

Funding

There was funding of the research through a grant provided by the Fundação de Amparo à Pesquisa do Estado da Bahia (FAPESB), due to participation in the Institutional Program of Scientific Initiation Scholarships (PIBIC).

Conflict of interests

There is no conflict of interest to be reported.

REFERENCE

1. Taylor-Robinson D, McCormack WM. The genital mycoplasmas (first of two parts). N Engl J Med. 1980;302(18):1003-10. https://doi.org/10.1056/nejm198005013021805
2. Leli C, Meucci M, Vento S, D'Alò F, Farinelli S, Perito S, et al. Microbial and vaginal determinants influencing Mycoplasma hominis and Ureaplasma urealyticum genital colonization in a population of female patients. Infez Med. 2013;21(3):201-6.
3. Furr PM, Taylor-Robinson D. Prevalence and significance of Mycoplasma hominis and Ureaplasma urealyticum in the urines of a non-venereal disease population. Epidemiol Infect. 1987;98(3):353-9. https://dx.doi.org/10.1017%2Fs0950268800062117
4. zur Hausen H. Papillomavirus infections--a major cause of human cancers. Biochim Biophys Acta. 1996;1288(2):F55-78. https://doi.org/10.1016/0304-419x(96)00020-0
5. Smith JS, Gilbert PA, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of human papillomavirus infection in males: a global review. J Adolesc Health. 2011;48(6):540-52. https://doi.org/10.1016/j.jadohealth.2011.03.010
6. Silveira GPG. Ginecologia Baseada em Evidências. 2ª ed. São Paulo: Atheneu; 2008. 650 p.
7. Biernat-Sudolska M, Szostek S, Rojek-Zakrzewska D, Klimek M, Kosz-Vnenchak M. Concomitant infections with human papillomavirus and various mycoplasma and ureaplasma species in women with abnormal cervical cytology. Adv Med Sci. 2011;56(2):299-303. https://doi.org/10.2478/v10039-011-0028-9
8. Kawaguchi S, Shigehara K, Sasagawa T, Shimamura M, Nakashima T, Sugimoto K, et al. Liquid-based urine cytology as a tool for detection of human papillomavirus, Mycoplasma spp., and Ureaplasma spp. in men. J Clin Microbiol. 2012;50(2):401-6. https://doi.org/10.1128/JCM.05219-11

9. Magaña-Contreras M, Contreras-Paredes A, Chavez-Blanco A, Lizano M, De la Cruz-Hernandez Y, De la Cruz-Hernandez E. Prevalence of sexually transmitted pathogens associated with HPV infection in cervical samples in a Mexican population. J Med Virol. 2015;87(12):2098-105. https://doi.org/10.1002/jmv.24278
10. Lukic A, Canzio C, Patella A, Giovagnoli M, Cipriani P, Frega A, et al. Determination of cervicovaginal microorganisms in women with abnormal cervical cytology: the role of Ureaplasma urealyticum. Anticancer Res. 2006;26(6C):4843-9.
11. Goldstone S, Palefsky JM, Giuliano AR, Moreira Jr. ED, Aranda C, Jessen H, et al. Prevalence of and risk factors for human papillomavirus (HPV) infection among HIV-seronegative men who have sex with men. J Infect Dis. 2011;203(1):66-74. https://dx.doi.org/10.1093%2Finfdis%2Fjiq016
12. Hillman RJ, Botcherby M, Ryait BK, Hanna N, Taylor-Robinson D. Detection of human papillomavirus DNA in the urogenital tracts of men with anogenital warts. Sex Transm Dis. 1993;20(1):21-7. https://doi.org/10.1097/00007435-199301000-00005
13. Ekiel AM, Friedek DA, Romanik MK, Jóźwiak J, Martirosian G. Occurrence of Ureaplasma parvum and Ureaplasma urealyticum in women with cervical dysplasia in Katowice, Poland. J Korean Med Sci. 2009;24(6):1177-81. https://doi.org/10.3346/jkms.2009.24.6.1177
14. Zvulunov A, Medvedovsky E, Biton A, Horowitz S, Vardy D. Association of Ureaplasma urealyticum colonization in male urethra and Condyloma acuminatum. Isr Med Assoc J. 2000;2(8):580-2.
15. Fonseca RMGS. Eqüidade de gênero e saúde das mulheres. Rev Esc Enferm USP. 2005;39(4):450-9. https://doi.org/10.1590/S0080-62342005000400012
16. Nascimento AMG, Barbosa CS, Medrado B. Mulheres de Camaragibe: representação social sobre a vulnerabilidade feminina em tempos de AIDS. Rev Bras Saúde Mater Infant. 2005;5(1):77-86. https://doi.org/10.1590/S1519-38292005000100010
17. Silva CM, Vargens OMC. A percepção de mulheres quanto à vulnerabilidade feminina para contrair DST/HIV. Rev Esc Enferm USP. 2009;43(2):401-6. https://doi.org/10.1590/S0080-62342009000200020
18. Rodrigues MM, Fernandes P, Haddad JP, Paiva MC, Souza MOC, Andrade TC, et al. Frequency of Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium, Mycoplasma hominis and Ureaplasma species in cervical samples. J Obstet Gynaecol. 2011;31(3):237-41. https://doi.org/10.3109/01443615.2010.548880
19. Donders GGG, Ruban K, Bellen G, Petricevic L. Mycoplasma/Ureaplasma infection in pregnancy: to screen or not to screen. J Perinat Med. 2017;45(5):505-15. https://doi.org/10.1515/jpm-2016-0111
20. Harada K, Tanaka H, Komori S, Tsuji Y, Nagata K, Tsutsui H, et al. Vaginal infection with Ureaplasma urealyticum accounts for preterm delivery via induction of inflammatory responses. Microbiol Immunol. 2008;52(6):297-304. https://doi.org/10.1111/j.1348-0421.2008.00039.x
21. Passos Eea. Rotinas em Ginecologia. 7ª ed. Porto Alegre: Artmed; 2017. 1074 p.
22. Donders GG, Van Calsteren K, Bellen G, Reybrouck R, Van den Bosch T, Riphagen I, et al. Predictive value for preterm birth of abnormal vaginal flora, bacterial vaginosis and aerobic vaginitis during the first trimester of pregnancy. BJOG. 2009;116(10):1315-24. https://doi.org/10.1111/j.1471-0528.2009.02237.x
23. Verteramo R, Pierangeli A, Mancini E, Calzolari E, Bucci M, Osborn J, et al. Human Papillomaviruses and genital co-infections in gynaecological outpatients. BMC Infect Dis. 2009;9:16. https://doi.org/10.1186/1471-2334-9-16
24. Horowitz S, Horowitz J, Taylor-Robinson D, Sukenik S, Apte RN, Bar-David J, et al. Ureaplasma urealyticum in Reiter's syndrome. J Rheumatol. 1994;21(5):877-82.

Address for correspondence:
ALYCE LIMA AMORIM
Rua Silveira Martins, 552, bloco 25, casa 4 – Cabula
Salvador (BA), Brazil
CEP: 41150-000
E-mail: alyce_amorim@hotmail.com

Received on: 07.17.2019
Approved on: 12.30.2019

HPV INFECTION AND ENDOMETRIOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

INFECÇÃO POR HPV E ENDOMETRIOSE: UMA REVISÃO SISTEMÁTICA E METANÁLISE

Geilson Gomes de Oliveira[1], *José Eleutério Júnior*[1,2], *Renata Mírian Nunes Eleutério*[3]

ABSTRACT

Introduction: Recent research has focused on the role of persistent ascending bacterial infections and sexually transmitted infections (STI) as a factor associated to endometriosis. Indeed, some studies investigated the possible role of HPV in endometriosis, but this topic remains inconclusive. **Objective:** The present study aims to meta-analyze research that assessed the presence of HPV infection in patients with endometriosis. **Methods:** MEDLINE, Embase, Scopus, LILACS, Cochrane Library, and OpenGrey were searched until February 10th, 2020. Search terms included "endometriosis" and "HPV" without language restrictions. The combined relative risks and 95% confidence interval (95%CI) were calculated, and heterogeneity was assessed with I-square (I^2). **Results:** Meta-analysis with low heterogeneity found a relative risk of twice as much in women exposed to HPV in relation to the unexposed control. **Conclusion:** Results indicate that HPV could be a risk factor for developing endometriosis.

Keywords: papillomaviridae; endometriosis, papillomavirus infections; sexually transmitted diseases; PCR; DNA probes, HPV.

RESUMO

Introdução: A pesquisa recente enfocou o papel de infecções por bactéria ascendente persistente e infecções sexualmente transmissíveis (IST) como um dos fatores associados à endometriose. Na verdade, alguns estudos investigaram o possível papel do HPV na endometriose, mas esse tópico permanece inconclusivo. **Objetivo:** O presente estudo tem como objetivo fazer uma metanálise de pesquisas que avaliaram a presença de infecção por HPV em pacientes com endometriose. **Métodos:** As bases de dados MEDLINE, Embase, Scopus, LILACS, Biblioteca Cochrane e OpenGrey foram pesquisadas até 10 de fevereiro de 2020. Os termos de pesquisa incluíram "endometriose" e "HPV" sem restrições de idioma. Os riscos relativos combinados e intervalo de confiança de 95% (IC95%) foram calculados, e a heterogeneidade foi avaliada usando o I-quadrado (I^2). **Resultados:** A metanálise com baixa heterogeneidade encontrou um risco relativo duas vezes maior em mulheres expostas ao HPV em relação ao controle não exposto. **Conclusão:** Os resultados indicam que o HPV pode ser um fator de risco para o desenvolvimento de endometriose.

Palavras-chave: papillomaviridae; endometriose; infecções por papillomavírus; doenças sexualmente transmissíveis; reação em cadeia da polimerase; sondas de DNA de HPV.

INTRODUCTION

The pathogenesis of endometriosis remains a challenging task for science[1]. Established theories cannot explain all the phenotypes known of the disease, leading to understanding endometriosis as a disease of multiple causes and manifestations[2].

Reflux of menstrual tissue into the abdominal cavity is an event that occurs in 90% of women of childbearing age. Under normal conditions, the peritoneal immune system eliminates the refluxed tissue, and dysregulation of this clearance mechanism could implicate in the predisposition to implantation and growth of ectopic lesions[3]. Both macrophage M2 polarization, and dysfunction of Natural Killer cells and T lymphocytes occur in patients with endometriosis[4].

Female upper genital tract is not aseptic, like it was previously supposed[5]. Proliferative changes in the uterine microbiota favor diseases such as endometriosis, due to immune desensitization, escape from apoptosis, and oxidative stress[6]. Contamination by *Escherichia coli* in refluxed menstrual blood could promote ectopic endometrial growth mediated by toll-like receptors (TLRs)[7]. The microbiota and ascending infections of female genital tract play a critical role in favoring the immunological and inflammatory changes of endometriosis[8]. Human papillomavirus (HPV), which also uses escape mechanisms from innate and adaptive immune responses, is present in endometriotic lesions[9].

OBJECTIVE

The objective of this systematic review and meta-analysis was to study and to describe the presence of HPV in endometriosis tissues in comparison with controls, bringing evidence that can support or deny the association between HPV and endometriosis.

METHODS

Search strategy

This systematic review followed the guidelines for meta-analysis of observational studies in epidemiology (MOOSE)[10], intending to review literature on HPV and endometriosis. For this, we used the following databases: MEDLINE, Embase, Scopus, LILACS, and Cochrane Central Register of Controlled Trials. Besides that, additional relevant references were searched using the OpenGrey databases (http://www.opengrey.eu/) for non-indexed trials. The research strategy was carried out using the following keywords without field restrictions: "Human Papillomavirus" OR "HPV" AND "endometriosis"

[1]Department of Pathology, Universidade Federal do Ceará – Fortaleza (CE), Brazil.
[2]Department of Women, Children, and Adolescents, Universidade Federal do Ceará – Fortaleza (CE), Brazil.
[3]Biomedicine Course, Centro Universitário Unichristus – Fortaleza (CE), Brazil.

OR "ectopic endometrium." The search was limited to studies in humans but without geographical or language restrictions. Electronic literature was searched until February 10th, 2020.

Study selection

Duplicate articles were excluded. Each article was examined based on its title and summary by all researchers. Those with irrelevant titles or abstracts were excluded. A complete copy of references considered for analysis, by at least one of the researchers, was obtained and read by the reviewers. Any disagreements during review were resolved by consensus. Inclusion criteria were observational studies that detected HPV by any method of detection in tissues of patients with endometriosis and compared to the control patients, without the disease. Exclusion criteria were:

- case reports and systematic reviews;
- studies conducted with the same patients;
- HPV detection by cytology;
- studies in which the control tissue was from the same patient of the case group. A flow chart of the selection process is available in **Figure 1**.

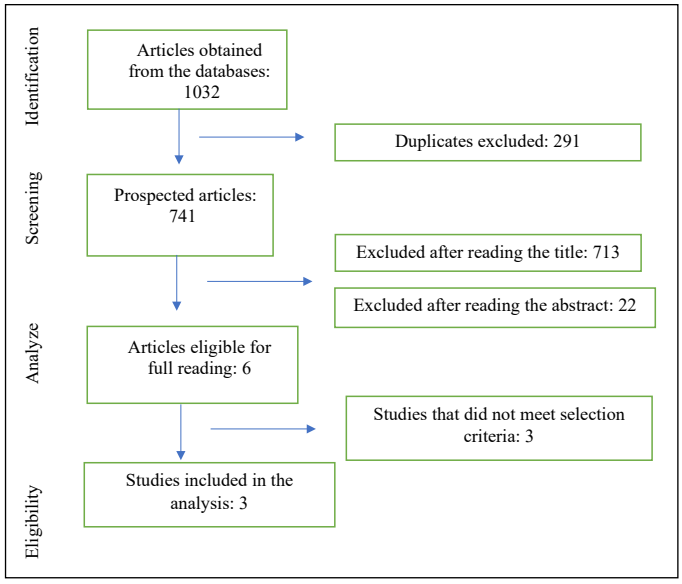


Figure 1 – Flow chart of the selection process of studies on the association of HPV and endometriosis.

Data extraction

The authors examined full-text articles assessed for eligibility, and evaluated the content of texts, according to the data extraction protocol. Any disagreement was resolved by consensus. Data of interest extracted from the eligible references formed the following analysis subgroups: authors; year of publication; country; study design; diagnostic method; type of tissue studied in the case; type of control; HPV positivity for case group; HPV positivity for the control group.

The risk of a bias assessment tool for non-randomized studies of Cochrane interventions (ROBINS-I)[11] was used to assess the methodological quality of studies, and the two authors analyzed risk of bias. The domains evaluated were:

- bias due to confusion;
- bias when selecting participants for the study;
- bias in the classification of interventions;
- bias due to deviations from intended interventions;
- bias due to missing data;
- bias in measuring results;
- bias in the selection of the reported result.

The categories for analyzing risk of bias are "Low risk", "Moderate risk", "Serious risk", "Critical risk", and "No information on which to base a judgment about risk of bias". The result of analysis is available in **Table 1**.

Statistical analysis

Statistical analysis and graph generation were performed using the software R-3.6.1 (R Foundation for Statistical Computing, 2019). *Odds ratio* (RR) and 95% confidence interval (95%CI) were calculated for each article. The presence of heterogeneity in the meta-analysis was assessed with the value of the percentage I square (I^2%) and Cochran's Q test. Low heterogeneity was considered when I^2 reached 25%, moderate when I^2 was close to 50%, and high when I^2 was close to 75%, according to the Higgins and Thompson classification[15]. Fixed effects models were used for low and moderate heterogeneity, whereas random effect model was used for high heterogeneity. The result of meta-analysis was reproduced graphically in a forest plot. Egger's linear regression test[16]; funnel plot was also used to check possible publication bias. In case Egger's test returned with a significant result, Duval and Tweedie's trim-and-fill method was used. There were no analyzes of pre-planned subgroups. The Mantel-Haenszel method was used to analyze combined data,

Table 1 – Studies to assess quality and risk of bias with ROBINS-I tool in studies on the association between HPV and endometriosis.

First author	Bias due to confusion	Bias when selecting participants for the study	Bias in the classification of interventions	Bias due to deviations from the intended interventions	Bias due to lack of data	Bias in measuring results	Bias in the selection of the reported result	Medium-Risk
Vestergaard et al.[12]	Moderate	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Heidarpour et al.[13]	Low	Moderate	Low	Low	Low	Low	Low	Low
Rocha et al.[14]	Moderate	Low	Moderate	Moderate	Low	Low	Low	Low

HPV: human papillomavirus.

extracted from the studies selected in this meta-analysis. The estimator described by DerSimonian-Laird was used to calculate the variance between studies (tau^2). A value of $p<0.05$ was considered statistically significant.

RESULTS

Database searching generated 1,032 entries, of which 291 were duplicated, leaving 741 titles for choosing by title, and only 28, by summary. Six studies were considered for complete reading, and only three met all the eligibility criteria (**Table 2**).

After applying all the selection criteria, studies were subjected to risk analysis of critical bias, as described in the methodology (**Table 2**), in which a low risk of accumulated bias was observed. The selected studies evaluated a total of 211 samples, 111 cases, and 100 controls. The overall HPV positivity in the case group was 34.2% (n=38), whereas 17% (n=17) of controls were positive.

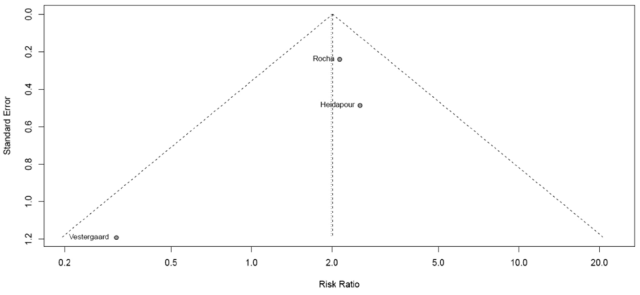
Meta-analysis obtained a relative risk of 2.0112 (1.3126 to 3.0815) with a p=0.0013, considering a fixed effect. Heterogeneity of meta-analysis was 27.1%, with tau ^ 2=0.0938, indicating low heterogeneity, and a p=0.2536 for the heterogeneity test (**Figure 2**).

Funnel graph (**Figure 3**) showed an apparent asymmetric distribution. After applying Egger's test, a p=0.473 and a residual standard error of 2.11 in one degree of freedom were obtained, suggesting the absence of publication bias. Because of this, an adjustment analysis with the trim-and-fill method was not needed. Due to the low number of existing studies that met the selection criteria, no meta-regression was performed.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis on the association between HPV and endometriosis. Data show that there is a relative risk of twice as much for HPV detection in tissues of patients with endometriosis than in patients who do not have the disease. It may mean that a genital HPV infection would play a role in the disease's genesis. However, the mechanism of this participation remains speculative.

Ascending bacterial and viral infections promote a series of changes in the peritoneal microenvironment, which favor the formation of endometriosis[17,18]. Interestingly, the DNA of endometriotic lesions



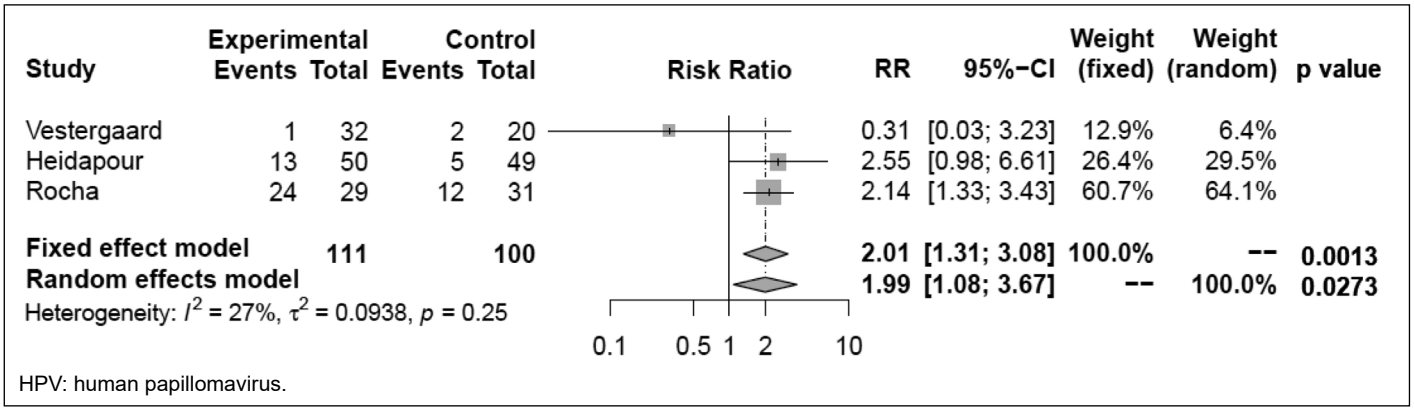
HPV: human papillomavirus.

Figure 3 – Funnel plot of observational studies on the association between HPV and endometriosis eligible for meta-analysis (Egger's test with p=0.473).

Table 2 – Synthesis of observational studies on the association between HPV and endometriosis eligible for meta-analysis.

Study	Country	Year	N	Method	Tissue	Result
Vestergaard et al.[12]	Denmark	2010	52	PCR	Case: Endometriosis Control: Endometrium	No association
Heidarpour et al.[13]	Iran	2017	99	PCR	Case: Ovarian Endometriosis Control: Ovaries without endometriosis	p=0.041
Rocha et al.[14]	Brazil	2019	60	PCR	Case: Tissues of the genital tract and peritoneum of patients with endometriosis Control: The same tissues in patients without endometriosis	p=0.001

HPV: human papillomavirus; PCR: polymerase chain reaction.



HPV: human papillomavirus.

Figure 2 – Forest plot of observational studies on the association between HPV and endometriosis eligible for meta-analysis.

has 96% homology with Shigella's DNA[19]. Various etiologies that affect the female lower genital tract have been reported as potentially involved, such as *Ureaplasma Urealyticum*[20], *Mycoplasma sp*.[21], and *Chlamydia trachomatis*[22]. Medium- and high-risk HPVs were not only detected colonizing peritoneal fluid in patients with endometriosis, but also representing the second largest population in ectopic endometrial lesions[9].

A few studies sought to investigate the association of HPV in the development of endometriosis. Vestergaard et al.[12], when studying the relation of endometriosis with several viruses, obtained a low prevalence of detection, and did not observe an association between HPV and endometriosis. These authors worked only with a few cases, and selected only endometrial tissue as the control, whereas cases of endometriosis brought together different tissues. As an ascending infection, the viral load and HPV detection are overestimated in the endometrium, concerning peritoneal cavitary tissues[14]; therefore, the groups were not homogeneous.

Pioneering work by Oppelt et al.[23], studied HPV, herpes virus, and *Chlamydia trachomatis* in several endometriosis sites. Even though there was no statistical significance, HPV could be associated to endometriosis lesions. Nonetheless, the study was excluded for two reasons: the control group had healthy tissues from patients with endometriosis, and the control group had patients diagnosed with cancer. We understand that there was an overlap of group selection and selection bias, which would compromise the study result.

Two studies, both using the PCR technique, performed only on endometriotic tissue, found an association between HPV and endometriosis. Heidarpour et al.[13] studying only ovarian endometriosis and high-risk HPV, and Rocha et al.[14], later, reached the same result, suggesting a role for HPV in the disease's genesis or maintenance. However, these are still studies with few cases. Heidarpour et al.[13] studied only ovarian endometriosis, whereas Rocha et al.[14] studied several sites intending to demonstrate ascending infection, and not explore the association between HPV and endometriosis.

Interestingly, some studies found a significant lesser association between cervix cancer, mouth, and pharynx in patients with endometriosis, pathologies in which HPV is highly associated[24,25]. We believe that these conditions manifest themselves in different age groups than those in which pelvic endometriosis occurs. Endometriosis and malignancy, however, could result from an infection with an oncovirus, such as HPV, which deserves to be the subject of future studies[23].

A strength of this meta-analysis was to obtain significant relative risk and low heterogeneity between studies, despite including studies with different methodologies. Moreover, there was no significant publication bias. However, it was only possible to include three studies, which weakened the reach of our meta-analysis. Further studies, preferably with designs in which only endometriotic tissues are compared to similar healthy tissues, are required.

CONCLUSION

The meta-analysis of three selected studies, which investigated the detection of HPV in tissues of patients with endometriosis and compared them with controls, supports the hypothesis that infection with this virus may be an independent risk factor for the development of endometriosis.

Participation of each author

The authors declare that all authors were active participants.

Funding

The authors declare no grants or other funding for all authors were received.

Conflict of interests

Nothing to declare.

REFERENCES

1. Mehedintu C, Plotogea Mn, Ionescu S, Antonovici M. Endometriosis still a challenge. J Med Life. 2014;7(3):349-57.
2. Gordts S, Koninckx P, Brosens I. Deep endometriosis: Pathogenesis. Fertil Steril. 2017;108(6):872-885.e1. https://doi.org/10.1016/j.fertnstert.2017.08.036
3. Burney R, Giudice L. Pathogenesis and Pathophysiology of Endometriosis. Fertil Steril. 2012;98(3):511-9. https://doi.org/10.1016/j.fertnstert.2012.06.029
4. Symons LK, Miller JE, Kay VR, Marks RM, Liblik K, Koti M, et al. The Immunopathophysiology of Endometriosis. Trends Mol Med. 2018;24(9):748-62. https://doi.org/10.1016/j.molmed.2018.07.004
5. Chen C, Song X, Wei W, Zhong H, Dai J, Lan Z, et al. The microbiota continuum along the female reproductive tract and its relation to uterine-related diseases. Nat Commun. 2017;8(1):875. https://doi.org/10.1038/s41467-017-00901-0
6. Agostinis C, Mangogna A, Bossi F, Ricci G, Kishore U, Bulla R. Uterine Immunity and Microbiota: A Shifting Paradigm. Front Immunol. 2019;10:2387. https://doi.org/10.3389/fimmu.2019.02387
7. Khan KN, Kitajima M, Hiraki K, Yamaguchi N, Katamine S, Matsuyama T, et al. Escherichia coli contamination of menstrual blood and effect of bacterial endotoxin on endometriosis. Fertil Steril. 2010;94(7):2860-3.E3. https://doi.org/10.1016/j.fertnstert.2010.04.053
8. Lin WC, Chang CY, Hsu YA, Chiang JH, Wan L. Increased Risk of Endometriosis in Patients With Lower Genital Tract Infection: A Nationwide Cohort Study. Medicine (Baltimore). 2016;95(10):e2773. https://doi.org/10.1097/MD.0000000000002773
9. Koninckx PR, Ussia A, Tahlak M, Adamyan L, Wattiez A, Martin DC, et al. Infection as a potential cofactor in the genetic-epigenetic pathophysiology of endometriosis: a systematic review. Facts Views Vis Obgyn. 2019;11(3):209-16.
10. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12. https://doi.org/10.1001/jama.283.15.2008
11. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919
12. Vestergaard AL, Knudsen UB, Munk T, Rosbach H, Bialasiewicz S, Sloots TP, et al. Low prevalence of DNA viruses in the human endometrium and endometriosis. Arch Virol. 2010;155(5):695-703. https://doi.org/10.1007/s00705-010-0643-y
13. Heidarpour M, Derakhshan M, Derakhshan-Horeh M, Kheirollahi M, Dashti S. Prevalence of high-risk human papillomavirus infection in women with ovarian endometriosis. J Obstet Gynaecol Res. 2017;43(1):135-9. https://doi.org/10.1111/jog.13188
14. Rocha RM, Souza RP, Gimenes F, Consolaro MEL. The high-risk human papillomavirus continuum along the female reproductive tract and its relationship to infertility and endometriosis. Reprod Biomed Online. 2019;38(6):926-37. https://doi.org/10.1016/j.rbmo.2018.11.032

15. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58. https://doi.org/10.1002/sim.1186
16. Egger M, Smith GD, Altman DG. Systematic reviews in Health Care: Meta-analysis in context. London: BMJ; 2001.
17. Khan KN, Fujishita A, Hiraki K, Kitajima M, Nakashima M, Fushiki S, et al. Bacterial contamination hypothesis: a new concept in endometriosis. Reprod Med Biol. 2018;17(2):125-33. https://doi.org/10.1002/rmb2.12083
18. Leonardi M, Hicks C, El-Assaad F, El-Omar E, Condous G. Endometriosis and the microbiome: a systematic review. BJOG. 2020;127(2):239-49. https://doi.org/10.1111/1471-0528.15916
19. Kodati VL, Govindan S, Movva S, Ponnala S, Hasan Q. Role of Shigella infection in endometriosis: a novel hypothesis. Med Hypotheses. 2008;70(2):239-43. https://doi.org/10.1016/j.mehy.2007.06.012
20. Noh EJ, Kim DJ, Lee JY, Park JH, Kim JS, Han JW, et al. Ureaplasma Urealyticum Infection Contributes to the Development of Pelvic Endometriosis Through Toll-Like Receptor 2. Front Immunol. 2019;10:2373. https://doi.org/10.3389/fimmu.2019.02373
21. Campos GB, Marques LM, Rezende IS, Barbosa MS, Abrão MS, Timenetsky J. Mycoplasma genitalium can modulate the local immune response in patients with endometriosis. Fertil Steril. 2018;109(3):549-60.e4. https://doi.org/10.1016/j.fertnstert.2017.11.009
22. Dragic M, Posteraro P, Marani C, Natale M, Vecchioni A, Sanguinetti M, et al. Assessment of Chlamydia trachomatis, Neisseria gonorrhoeae, and Mycobacterium tuberculosis infections in women undergoing laparoscopy: the role of peritoneal fluid sampling. Microbiol Med. 2016;31(4):6038. http://dx.doi.org/10.4081/mm.2016.6038
23. Oppelt P, Renner SP, Strick R, Valletta D, Mehlhorn G, Fasching PA, et al. Correlation of high-risk human papilloma viruses but not of herpes viruses or Chlamydia trachomatis with endometriosis lesions. Fertil Steril. 2010;93(6):1778-86. https://doi.org/10.1016/j.fertnstert.2008.12.061
24. Saavalainen L, Lassus H, But A, Tiitinen A, Härkki P, Gissler M, et al. Risk of gynecologic cancer according to the type of endometriosis. Obstet Gynecol. 2018;131(6):1095-102. https://doi.org/10.1097/AOG.0000000000002624
25. Gandini S, Lazzeroni M, Peccatori FA, Bendinelli B, Saieva C, Palli D, et al. The risk of extra-ovarian malignancies among women with endometriosis: A systematic literature review and meta-analysis. Crit Rev Oncol Hematol. 2019;134:72-81. https://doi.org/10.1016/j.critrevonc.2018.12.009

Address for correspondence:
GEILSON GOMES DE OLIVEIRA
Rua Aluisio Borba, 132, casa 4 – Engenheiro Luciano Cavalcante
Fortaleza (CE), Brazil
CEP: 60813-730
E-mail: geilson.ce@gmail.com

Received on: 11.13.2019
Approved on: 12.28.2019

HIV/AIDS A FORGOTTEN PROBLEM

HIV/AIDS, UM PROBLEMA ESQUECIDO

Aliete Cunha-Oliveira[1]

In the early 1980s, a new disease identified as related to sexual activity appears in the USA. It spread rapidly to the dimension of a deadly pandemic. Once detected, it was soon associated with sexuality, first with male homosexuality, but soon it also reached heterosexuals, crossing the frontiers of the initial risk groups (commercial sex practitioners, male homosexuals, hemophiliacs, and injecting drug users), turning into a cross-cutting and global threat. But the discovery and clinical use of antiretroviral drugs have blurred the threatening and deadly image of the disease. If people would restraint and protected themselves when the disease was acute, fast, and visibly deadly, they soon let themselves be deceived by easy optimism. The false imminence of a vaccine would only further increase this unjustified optimism[1].

The disease has lost its visibility and threatening power, without ceasing to be a very serious public health problem, responsible for the loss of an increasing number of lives and resources. It became insidious, invisible, slower to evolve, but just as deadly as before. The gain obtained in survival has created a new reality. Opinion and pressure groups in the area of sexuality became concerned with the quality of life of infected people, with their right to sexuality, with the weight of myths and ghosts created in the early days of the disease, seeking to eradicate the danger of marginalization and exclusion of HIV-positive people.

The initial myths associated with the disease were replaced by new ones associated with the perspectives of treatment and the epidemiological evolution. They are: "heterosexuals are the ones at risk", "AIDS no longer kills", "having sex does not entail more risk than not having it", "there already is a vaccine", "infected people are very sick", "oral sex is not dangerous". The idea that the risk lies with heterosexuals deserves special attention. Although the heterosexuals group is today the hardest hit in absolute numbers, a reflection is in place here, considering that just as heterosexuals are today the most affected group, they are also, in the long run, the group most represented one in sociodemographic terms. According to Frieden[2], men who have sex with men constitute 2% of the population but account for more than half of new infections in the USA. In 2018, in the European Union/European Economic Area, 39.8% of new infections occurred in men who have sex with men[3].

Another myth that deserves our greatest attention is the idea that you do not die of AIDS. In fact, despite the 690,000 annual deaths worldwide[4], the idea persists, calling attention to the imperative need for individual preventive measures. This myth is based on the fact that many of the deaths do not result directly from AIDS itself, but rather due to diseases or conditions that result from immunosuppression or the person's poor general condition. Which, in any case, would not be present without the underlying disease.

The fact that infected people are thought to be characterized by being very ill seems to be due to campaigns and the media. When testimonies from infected people are presented, they are in the AIDS phase and not in the HIV-positive phase. And when HIV-positive people make an appearance, which is rare, they tend to be full of optimism and with a great quality of life. Campaigns are focused almost exclusively on AIDS and rarely on seropositivity, which allows the asymptomatic carrier as an HIV transmitter to be neglected, which, after all, is, or should be, the main reason for prevention campaigns. The emergence of new antiretroviral therapies has also blunted the patient's HIV-positive appearance.

As Massano-Cardoso[5] says, in a world characterized by so much and diversified information, there have been no major changes in behavior. Both young and older people continue to be exposed to highly publicized risks. How to explain these discrepancies and paradoxes on a growing excess of information and a profound lack of knowledge? It is a mistake to regard information as synonymous with knowledge. In this way, it may be possible to reverse, or at least minimize, such blatant ignorance in matters of behavioral risk and lifestyles.

Funding

The author declares there are no grants or other funding.

Conflict of interests

There is no conflict of interests to be reported.

REFERENCES

1. Cunha-Oliveira A. Para uma História do VIH/Sida em Portugal e os 30 Anos da Epidemia (1983-2013). Coimbra: Imprensa da Universidade de Coimbra; 2018. v. 23. 122 p. http://doi.org/10.14195/978-989-26-1510-3
2. Frieden T. Commemorating 30 years of HIV/AIDS. U.S. Department of Health and Human Services / Centers for Disease Control and Prevention; 2011 [cited on Jan 2, 2020]. Accessed on: https://www.cdc.gov/media/releases/2011/s0602_hivaids30years.html
3. European Centre for Disease Prevention and Control/WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2019 – 2018 data. Stockholm: ECDC; 2019.
4. UNAIDS. UNAIDS data 2020. Geneva: Joint United Nations Programme on HIV/AIDS; 2020.
5. Massano-Cardoso S. Crónicas Paraepidemiológicas. Coimbra: Instituto de Higiene e Medicina Social / Faculdade de Medicina da Universidade de Coimbra; 2005. n. 2.

Address for correspondence:
ALIETE CUNHA-OLIVEIRA
Escola Superior de Enfermagem de Coimbra, Centro de Estudos Interdisciplinares do Século XX, Universidade de Coimbra
Health Sciences Research Unit: Nursing, Sociedade de História Interdisciplinar da Saúde
Avenida Bissaya Barreto, s/n
Coimbra, Portugal
CEP: 3004-011
E-mail: alietecunha@esenfc.pt

Received on: 03.01.2020
Approved on: 04.09.2020

[1]School of Nursing of Coimbra, Center of Interdisciplinary Studies of the 20th century, Universidade de Coimbra – Coimbra, Portugal.