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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

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Editorial

Sexual transmission of Zika virus

From time to time, the world experiences challenges related to human health. Many of these problems first affect small populations in specific regions of the planet. Depending on the characteristics of the problem, the situation can spread all over the world. This is especially true in the current century with the huge frequency and speed of movement of people and cargo that may carry, unintentionally but effectively, vectors' agents and/or infectious disease originators. It is evident that upon arrival to a new region of the planet, the vectors' agents need favorable conditions to remain viable to new infections. In a new situation, the issue of reducing spread of an emerging infectious disease is aggravated when, in addition to the speed of geographic expansion described earlier, there is a lack of knowledge by the scientific community of aspects of transmission, physiopathology, diagnosis, and treatment.

Therefore, it is fully acceptable and justifiable that the problem of Zika virus (ZIKV) is being addressed as a global public health emergency by the World Health Organization. Although researchers initially characterized the disease as being transmitted by mosquito bite, with benign evolution and remission of symptoms in a few days, a strong association with microcephaly in conceptuses of many pregnant women with Zika manifestation was later noted. The triggering of Guillain-Barré syndrome — an autoimmune disease that can evolve severely in many cases of this arbovirus — was also observed. In addition, new findings with possible associations with Zika continue to arise.

Recent data showed the presence of ZIKV in blood, semen, urine, and saliva, which suggest that the virus could also be transmitted by these corporal fluids[1-5]. As of April 2016, sexual transmission of ZIKV has been documented in several no endemic countries, such as Argentina, Chile, France, Italy, New Zealand, the United States, and Canada, during the 2015 outbreak[5,6]. ZIKV can be spread during sexual intercourse by a man infected with Zika to his partners. In some known case reports of sexual transmission, it is found that men had Zika symptoms. From these case reports, we know that the virus can be spread when the man has symptoms, before symptoms start, and after symptoms end because the virus can stay in semen longer than in blood[3,4,7].

Sexual transmission of ZIKV has been suggested by Foy et al.[8], who described a female patient infected with ZIKV once her husband returned from a trip to southeastern Senegal in 2008, after being infected during his travel. In addition, in December 2013, ZIKV RNA was detected in semen samples for a longer time than in blood and urine samples of a man in Tahiti who sought treatment for hematospermia during a ZIKV outbreak in French Polynesia. The man had experienced symptoms of ZIKV infection two and ten weeks before presentation with hematospermia, and the virus was isolated from semen samples three days after the hematospermia[3]. In 2014, in the United Kingdom, a 68-year-old man had onset of fever, marked lethargy, and an erythematous rash 1 week after returning from the Cook Islands. Serum samples taken 3 days into the febrile illness tested positive for ZIKV by RT-PCR. Semen was indicated positive by RT-PCR analysis, at 27 and 62 days after onset of febrile illness[4]. He had acquired the virus through sexual contact with an individual who returned from a country with the presence of ZKV. Deckard et al. reported a case from Dallas County, Texas. It was a case of ZIKV transmission from an infected man to a sex partner through anal sex – a man with recent travel to an area of active ZIKV transmission and his nontraveling male partner[9]. In February, it was widely reported by the international media that the CDC was investigating the occurrence of 14 new cases of sexual transmission of ZIKV. However, no further details are available in the scientific literature.

STRONG ASSOCIATION OF ZIKV TRANSMISSION BY INTERCOURSE

Therefore, we now have evidence of the strong association between ZIKV transmission and sexual intercourse, since there are already reports of the presence of viral RNA in body fluids, such as semen, urine, and saliva, in addition to blood. It will not be a surprise if in a few weeks we hear about reports of ZIKV found in vaginal fluid, cervical scrapings, and in research by swab of the anal canal. This may particularly be the case if secondary inflammatory/infectious processes are observed. It follows that the professionals who work in the sexually transmitted diseases area must be urgently aware and well informed about these new challenges. Disease transmission via intercourse is not as simple a matter as many people think. In general, multiple anatomical areas and bodily fluids are involved in intercourse and may include mouth, penis, saliva, semen, vagina, vaginal secretion, and anus. In many situations, invisible microtraumas, exfoliations, small fissurae, and discrete bleeding facilitate infections in mucous and semimucous areas.

It is worth noting that the potential for infection by a sexually transmitted disease depends on the number of etiological agents in the infected partner and on the host resistance of the noninfected partner's immune system. Thus, it is logical to think that this equation changes often according to many variables of the carrier of the disease and of the exposed person. The occurrence of infection is especially variable if the exposed person already presents a local favoring situation, such as vulvar/vaginal candidiasis or a general condition such as pregnancy, as examples.

We experienced a similar situation at the beginning of the HIV epidemic in the 1980s. At that time, it was considered a disease of homosexual men. Many sectors of the world press, especially in North America, used to publish reports with the title of "Gay Cancer". Today, we know that there are multiple modes of HIV transmission in addition to sex practiced between men. We must be careful to avoid the same mistakes of the past in our understanding and discussion of disease.

With time, research based on strong evidence will give insight to the true dimensions of the ZIKV situation as it relates to intercourse and assisted reproduction. In case sexual transmission by men is confirmed by additional findings (currently, there are no

studies that indicate sexual transmission by women), prevention should be indicated when men infected with ZIKV have intercourse with people of either sex. Attention should also be given to the testing of donors of semen/ovule for ZIVK.

This must be the vision and the commitment of the professionals working in the area of sexually transmitted diseases. Moreover, the world urgently needs more specialized and involved experts conducting research and in clinical practice in this field to support safe and pleasurable sexual activity.

Before these reports, no arboviruses had been isolated from human semen. There are many unanswered questions and, for now, it is important to be cautious. There is no treatment and no vaccine for ZIKV and the recommendation of condom use and counseling are important to avoid sexual transmission. Even though, in endemic countries, it is not likely that sexual transmission is anywhere close to the frequency of mosquito-borne transmission of ZIKV.

PS: And every day we have access to new scientific knowledge.

In the final review of this editorial we learned of the case reported by Davidson et al[10]: Suspected Female-to-Male Sexual Transmission of Zika Virus - New York City, 2016.

The authors report that: this case represents the first reported occurrence of female-to-male sexual transmission of Zika virus. More, ongoing surveillance is needed to determine the risk for transmission of Zika virus infection from a female to sexual partners her.

MAURO ROMERO LEAL PASSOS
Full Professor, Chief of the Department of Sexually Transmitted Infections of *Universidade Federal Fluminense*
E-mail: mauroromero@id.uff.br

ANGELICA ESPINOSA MIRANDA
Associate Professor, Department of Social Medicine of *Universidade Federal do Espírito Santo*
E-mail: espinosa@ndi.ufes.br

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Anal HPV prevalence in a cohort of individuals infected with HIV-1

Prevalência de HPV anal em uma coorte de indivíduos infectados pelo HIV-1

Nathalia Silva Oliveira[1], David William Provance Jr.[1,2], Beatriz Grinsztejn[3], Ruth K Friedman[3], Valdileia Gonçalves Veloso[3], Jose Ricardo Coutinho[3], Cynthia Braga da Cunha[3], Dennis de Carvalho Ferreira[4], Alcina Frederica Nicol[1]

ABSTRACT

Introduction: Human Papillomavirus (HPV) is the primary etiologic agent of anogenital tract cancer. A higher prevalence and incidence of developing cancer and diseases associated with HPV have been observed in individuals infected with the human immunodeficiency virus (HIV). The natural history of HPV infection has not been completely elucidated, as well as the immune response that occurs as coinfection with HIV/HPV, particularly in the anal mucosa. **Objective**: To analyze the HPV prevalence and clinical, epidemiological, and behavioral data in a cohort of HIV-seropositive individuals from the National Institute of Infectious Diseases, FIOCRUZ, RJ. **Methods**: The study included a total of 114 individuals from the histopathological diagnosis of anal biopsy. PCR and sequencing was performed for HPV DNA identification in anal discharge. Statistical analysis was performed using SPSS 15.0 software. **Results:** Patients Infected with HIV with anal intraepithelial neoplasia (AIN) II/III had nadir CD4 + <50 cells/mm³ compared to normal patients (p=0.01). The most prevalent HPV types in the anal secretion (by Papillocheck) were HPV 16 (29.2%), followed by HPV 52 (23.1%), both high-risk oncogenic, followed by HPV 44 and 55 (21.5%) that are low-risk type. A total of 53.3% HIV-infected individuals analyzed have already been exposed to the four HPV types targeted by the current quadrivalent vaccine (MSDm – HPV types 6, 11, 16, and 18). **Conclusion**: The data suggest that vaccination against HPV could be regarded as a prophylactic measure to reduce the risk of anal intraepithelial lesions in HIV-infected individuals.

Keywords: Papillomaviridae; vaccines; homosexuality; women; anal cancer.

RESUMO

Introdução: O papilomavírus humano (HPV) é o principal agente etiológico do câncer do trato anogenital. A maior prevalência e incidência de desenvolvimento de câncer e doenças associadas ao HPV têm sido observadas em indivíduos infectados pelo vírus da imunodeficiência humana tipo 1 (HIV-1). A história natural da infecção pelo HPV não foi completamente elucidada, assim como a resposta imune que ocorre na coinfecção pelo HIV/HPV, particularmente na mucosa anal. **Objetivo:** Analisar a prevalência de HPV, dados clínicos, epidemiológicos e comportamentais em uma coorte de indivíduos infectados pelo HIV do Instituto Nacional de Infectologia (INI), FIOCRUZ, RJ. **Métodos:** Foi incluído um total de 114 indivíduos com diagnóstico histopatológico de biópsia anal. A tipagem do DNA de HPV foi realizada através da secreção anal. A análise estatística foi realizada utilizando o software SPSS 15.0. **Resultados**: Pacientes HIV positivos com Neoplasia intraepitelial anal de alto grau (NIA II/III) apresentaram CD4+ nadir <50 células/mm³ , comparados a pacientes sem displasia anal (p=0,01). Os tipos de HPV mais prevalentes na secreção anal (pelo *Papillocheck*) foram HPV 16 (29,2%), seguido do HPV 52 (23,1%), ambos de alto risco oncogênico, seguido de HPV 44 e 55 (21,5%), que são baixo risco oncogênico. Um total de 53,3% dos indivíduos infectados pelo HIV já analisados foi exposto aos 4 tipos de HPV, que são alvos da vacina quadrivalente corrente (MSD – HPV 6, 11, 16 e 18). **Conclusão**: Os dados sugerem que a vacinação contra o HPV pode ser considerada como uma medida profilática para reduzir o risco de lesões intraepiteliais anais em indivíduos infectados pelo HIV.

Palavras-chave: Papilomavírus humano; vacinas; homossexualidade; mulheres; câncer anal.

INTRODUCTION

Human Papillomavirus (HPV) is the main causative agent for the development of neoplastic lesions in uterine cervix. In anal tissue, the progression of HPV-positive high-grade lesions to an invasive cancer can require years. This progression can occur more rapidly in young HIV-infected individuals. However, there is a paucity of information on the consequences of HIV/HPV coinfections with regard to neoplastic lesions. Prospective studies can better clarify on the factors that may contribute to the severity and progression of disease surrounding HIV/HPV coinfection. Few studies have reported on the major risk factors associated with HIV/HPV coinfections such as unprotected sex and a high number of sexual partners[1,2]. The aim of this study was to evaluate the HPV prevalence and to cross-analyze clinical, sociodemographic, and behavioral data from HIV-infected subjects diagnosed with anal intraepithelial lesions.

OBJECTIVE

To analyze the HPV prevalence, clinical, epidemiological, and behavioral data in a cohort of HIV-seropositive individuals from the National Institute of Infectious Diseases, FIOCRUZ, RJ.

Work conducted at *Laboratório de Pesquisa Clínica em DST/AIDS* (LapClin DST/AIDS), *Instituto Nacional de Infectologia* (INI), *Fundação Oswaldo Cruz* (Fiocruz) and *Laboratório Interdisciplinar de Pesquisas Médicas* (LIPMED), *Instituto Oswaldo Cruz* (IOC), Fiocruz – Rio de Janeiro (RJ), Brazil.

[1]*Laboratório Interdisciplinar de Pesquisas Médicas* (LIPMED), IOC, Fiocruz – Rio de Janeiro (RJ), Brazil.

[2]*Centro de Desenvolvimento Tecnológico em Saúde* (CDTS), *Instituto Nacional de Ciência e Tecnologia de Inovação em Doenças Negligenciadas* (INCT-IDN), Fiocruz – Rio de Janeiro (RJ), Brazil.

[3]LapClin DST/AIDS, *Instituto Nacional de Infectologia* (INI), Fiocruz – Rio de Janeiro (RJ) Brazil

[4]Department of Endodontics, Postgraduate Program in Dentistry, Universidade Estácio de Sá – Rio de Janeiro (RJ) Brazil.

METHODS

Study Population

The study received approval prior to recruiting participants from the institutional ethical review board at the Evandro Chagas National Institute of Infectious Diseases (INI) of the Oswaldo Cruz Foundation (Fiocruz) in Rio de Janeiro, Brazil (protocol CAE 0044.0.009.000-09). The study enrolled 114 individuals being followed within cohort studies at the INI/Fiocruz-RJ[3]. Participants were either HIV positive (86.8%; 99/114) or negative (13.2%; 15/114). Written informed consent for participation in the study was obtained from all participants in strict compliance with the ethical guidelines involving human subjects in Brazil as required by Resolution No. 466/2012 of the National Health Council.

Anal examination and tissue biopsies

An anal examination through a high-resolution anoscopy was performed by an experienced proctologist, which consisted of a visual inspection of the margin and anal canal using an anoscope. Acetowhite staining was performed to increase the visibility of intraepithelial lesions. Two separate biopsies were obtained for conducting histopathological evaluations and analyses for the presence of HPV. Histopathological findings were categorized as the absence of anal squamous intraepithelial lesions (without dysplasia), atypia, condyloma, AIN I (anal intraepithelial neoplasia I), AIN II/III, and invasive cancer.

Sociodemographic, clinical, and behavioral variables

Sociodemographic, clinical, and behavioral information was extracted from the Audio Computer-Assisted Self-Interview (ACASI) database of the INI/Fiocruz consisting of answers received from each cohort member[3]. The following lifestyle variables were retrieved: smoking status with current exposure to second-hand smoke, illicit drug use, anal sex history, number of sexual partners of the female participants over the last 6 months with distinctions for anal or vaginal sex and number of sexual partners of the male participants over the last 12 months for men. The HPV-associated variables obtained included the history for anal and/or cervical lesions, treatments, and HPV genotyping of anal secretion samples. The variables related to HIV infections recorded were status of HIV serology tests, length of time since a positive HIV diagnosis, $CD4^+$ nadir; $CD4^+$ T lymphocyte levels closest to the anal biopsy date, HIV-1 viral load (detectable at ≥49 copies/IU), use of combination antiretroviral therapy (cART) at the time of performing anal biopsies and the use of two or more analog reverse transcriptase inhibitors and nucleoside reverse transcriptase inhibitor or a non-nucleoside analog and at least one protease inhibitor along with the duration of treatment with highly active antiretroviral therapy (HAART).

Statistical Analysis

Two separate analyses were performed based on HIV status and histopathological diagnosis. The categorical variables that included sex, smoking, illicit drug use, anal sex history, and HPV variables were analyzed by χ^2 test and Fisher's exact test. Continuous variables that included age, number of partners, and HIV variables were analyzed by the non-parametric Kruskal–Wallis test. Statistical analysis was performed with SPSS 15.0 software.

RESULTS

Study population

Age of the patients included in this study ranged from 33.5 to 48.1 years. Average age of the HIV-infected individuals was 42 (±0.9) years and that for the non HIV-infected individuals was 33.6 (±2.5) years. Among the biopsies from HIV-positive patients, 21 presented with normal squamous epithelium, 39 with low-grade neoplasia (AIN I), and 39 samples with high-grade neoplasia (AIN II/III). In the HIV-positive group, the average age of individuals with normal squamous epithelium was 38.5 (±1.8) years; that for low-grade AIN was 41.5 (±1.4) years; and for high-grade AIN, the average was 44.4 (±1.6) years.

In all of the samples collected, high-risk HPV was detected in 78.5% of biopsies while non-high-risk HPV was seen in 44.6% **(Table 1)**. Based on HIV status, more than 80% of the samples from positive individuals showed high-risk HPV compared to 40% for negative patients. Of the individual HPV high-risk genotypes, HPV 16 showed the greatest prevalence with a total of 18 different types identified **(Table 1)**. HIV-1-positive individuals with high-grade AIN had a higher prevalence of high-risk HPV types in the anal secretion specimens compared to individuals without lesions (normal) and low-grade AIN; however there was no statistically significant difference ($p>0.05$).

For non-high-risk HPV, detection was more frequently observed in AIN I or AIN II/III tissue samples than normal tissue (**Table 1**). When examining for infections by multiple HPV genotypes (**Table 2**), it is clear that a large number of samples were positive for two or more HPV genotypes. Surprisingly, we found poor agreement between the two methods analyzed (Papillocheck and PCR), except for the diagnosis of HPV 11, which showed moderate agreement ($k=0.57$; $p=0.000$) and a high specificity for genotypes 31, 43, and 53 (**Table 3**). A graphical representation of the HPV genotype data is shown in **Figure 1**.

DISCUSSION

HPV is the main etiologic agent related to cervical cancer and its association with the development of anal intraepithelial neoplasia is more frequently observed with HIV-1 infections. Over 90% of anal carcinoma in HIV-infected individuals is associated with a persistent HPV infection by at least one HPV genotype with multiple infections being common[4,5].

Some studies have reported age as an important factor in HPV infection[6]. In this study, the average age among HIV-infected individuals was 42 years and 33.6 years for those individuals not infected with HIV, such that this group only provided tissue samples that were diagnosed as being without lesions by histopathology. However, in this study, the average age of participants who were HIV positive and diagnosed with anal lesions showed a slight increase in relation to the lesion severity. The mean age of the subjects with normal samples, AIN I and II/III were 38.5; 41.5, and 44.4 years, respectively, with a statistically significant difference. Our results agree with data reported in our previous study[7].

Table 1 – HPV genotypes found on the anal secretion by Papillocheck according the Histopathology diagnostic (2010–2013).

HPV type	HIV serology Histopathology – n (%)				Total
	HIV-negative	HIV-positive			
	No lesion (n=15)	No lesion (n=21)	AIN I (n=39)	AIN II/III (n=39)	
High risk HPV	6 (40.0)	5 (83.3)	19 (86.4)	21 (95.5)	1 (78.5)
Low risk HPV	3 (20.0)	3 (50.0)	12 (54.5)	11 (50.0)	29 (44.6)
High risk					
HPV 16	-	2 (33.3)	6 (27.3)	11 (50.0)	19 (29.2)
HPV 18	-	1 (16.7)	3 (13.6)	3 (13.6)	7 (10.8)
HPV 31	1 (6.7)	1 (16.7)	2 (9.1)	3 (13.6)	7 (10.8)
HPV 33	-	-	2 (9.1)	3 (13.6)	5 (7.7)
HPV 35	1 (6.7)	-	1 (4.5)	2 (9.1)	4 (6.2)
HPV 39	1 (6.7)	-	2 (9.1)	3 (13.6)	6 (9.2)
HPV 45	-	-	5 (22.7)	3 (13.6)	8 (12.3)
HPV 51	1 (6.7)	3 (50.0)	1 (4.5)	1 (4.5)	6 (9.2)
HPV 52	-	3 (50.0)	7 (31.8)	5 (22.7)	15 (23.1)
HPV 56	1 (6.7)	2 (33.3)	6 (27.3)	3 (13.6)	12 (18.5)
HPV 58	-	-	4 (18.2)	6 (27.3)	10 (15.4)
HPV 59	-	1 (16.7)	4 (18.2)	3 (13.6)	8 (12.3)
HPV 68	-	-	6 (27.3)	3 (13.6)	9 (13.8)
HPV 73	-	-	3 (13.6)	-	3 (4.6)
HPV 82	-	1 (16.7)	1 (4.5)	3 (13.6)	5 (7.7)
Probable hr					
HPV 53	1 (6.7)	3 (50.0)	2 (9.1)	5 (22.7)	11 (16.9)
HPV 66	-	1 (16.7)	5 (22.7)	2 (9.1)	8 (12.3)
Low risk					
HPV 6	-	1 (16.7)	3 (13.6)	6 (27.3)	10 (15.4)
HPV 11	-	-	5 (22.7)	2 (9.1)	7 (10.8)
HPV 40	2 (13.3)	-	1 (4.5)	-	3 (4.6)
HPV 42	-	1 (16.7)	4 (18.2)	5 (22.7)	10 (15.4)
HPV 43	-	-	1 (4.5)	2 (9.1)	3 (4.6)
HPV 44, 55	1 (6.7)	2 (33.3)	4 (18.2)	7 (31.8)	14 (21.5)
HPV 70	-	1 (16.7)	3 (13.6)	2 (9.1)	6 (9.2)

HPV: human papillomavirus; HIV: human immunodeficiency virus; AIN: anal intraepitherlial neoplasia; hr: high risk.

In that study conducted in Brazil, it was found that, in cervical cancer cases, women with HIV/HPV coinfection had an average age of 51.1 years. Another study of HIV-infected women in a Brazilian cohort also analyzed samples of AIN and the association with HPV. In this study, women diagnosed with AIN had an average age of 42 years[8]. In a recent study with the same cohort patients, Nicol and colleagues found that HIV-positive women with <30 years of age had a higher prevalence of HPV 6, 11, 16, and 18 with a tendency for HPV seroprevalence of the genotypes 6, 16 in HIV-negative women above 30 years[8].

Some other known risk factors for the development of HPV-associated lesions have been preestablished, such as an early initiation of sexual activity, multiple sexual partners, history of sexually transmitted diseases, teenage pregnancy, and smoking[6]. When analyzing the number of sexual partners of individuals included in the study, we found that the average number of sexual partners for women was 1 over the last 6 months, and that for men was 14.1 in the last 12 months. Even if the analysis time has been different for men and women, the largest number of sexual partners among men compared to women is remarkable; mainly in the number of male sexual partners reported by men. Given that this corroborates the literature, in which studies have shown that men who have sex with men (MSM) are up to 37 times more likely to progress to anal cancer and are considered risk group[9].

Among patients who reported smoking, approximately 38% had pathological diagnosis of high-grade AIN, and all were infected with HIV. As for the report of receptive anal sex, most patients were infected with HIV and were diagnosed with either low- or high-grade AIN. This feature is consistent with previous studies on AIN where men and women are considered to display risk factors for the development of AIN and anal cancer through their receptive anal sex history, high number of sexual partners, and smoking. For women, these same risk factors apply to cervical cancer[4].

Table 2 – Multiple HPV types in anal secretions by Papillocheck according the Histopathology diagnostic (2010-2013).

HPV types	HIV-negative	HIV-positive			Total n (%)
	Nondysplastic (n=15)	Nondysplastic (n=21)	Low-grade AIN (n=39)	High-grade AIN (n=39)	
Multiple infection					
HPV 16, 52	-	4 (66.7)	11 (50.0)	13 (59.1)	28 (43.1)
HPV 39, 66	1 (6.7)	1 (16.7)	7 (31.8)	4 (18.2)	13 (20.0)
HPV 16, 56	1 (6.7)	3 (50.0)	10 (45.5)	13 (59.1)	27 (41.5)
HPV 16, 56	1 (6.7)	3 (50.0)	10 (45.5)	13 (59.1)	27 (41.5)
HPV 11, 45	-	-	9 (40.9)	5 (22.7)	14 (21.5)
HPV 31, 39	2 (13.3)	1 (16.7)	3 (13.6)	5 (22.7)	11 (16.9)
HPV 16, 45	-	2 (33.3)	9 (40.9)	12 (54.5)	23 (35.4)
HPV 68, 70	-	1 (16.7)	6 (27.3)	5 (22.7)	12 (18.5)
HPV 56, 58	1 (6.7)	2 (33.3)	9 (40.9)	7 (31.8)	19 (29.2)
HPV 56, 66	1 (6.7)	2 (33.3)	8 (36.4)	4 (18.2)	15 (23.1)
HPV 16, 53, 58	1 (6.7)	4 (66.7)	9 (40.9)	16 (72.7)	30 (46.2)
HPV 18, 52, 59	-	3 (50.0)	8 (36.4)	6 (27.3)	17 (26.2)
HPV 16, 33, 68	-	2 (33.3)	12 (54.5)	13 (59.1)	27 (41.5)
HPV 16, 44, 55, 52	1 (6.7)	4 (66.7)	12 (54.5)	15 (68.2)	32 (49.2)
HPV 16, 43, 44, 55, 58	1 (6.7)	3 (50.0)	10 (45.5)	15 (68.2)	29 (44.6)
HPV 56, 58, 66, 68	1 (6.7)	2 (33.3)	12 (54.5)	11 (50.0)	26 (40.0)
HPV 44, 55, 51, 52, 59	2 (13.3)	5 (83.3)	10 (45.5)	9 (40.9)	26 (40.0)
HPV 11, 33, 56, 82	1 (6.7)	3 (50.0)	9 (40.9)	10 (45.5)	23 (35.4)
HPV 51, 53, 56, 66	3 (20.0)	4 (66.7)	10 (45.5)	8 (36.4)	25 (38.5)
HPV 16, 44, 55, 52, 53, 58	2 (13.3)	5 (83.3)	14 (63.6)	16 (72.7)	37 (56.9)
HPV 16, 18, 42, 45, 59	-	4 (66.7)	11 (50.0)	15 (68.2)	30 (46.2)
HPV 11, 31, 33, 43, 66	1 (6.7)	2 (33.3)	9 (40.9)	10 (45.5)	22 (33.8)
HPV 16, 18, 52, 58, 59	-	4 (66.7)	12 (54.5)	16 (72.7)	32 (49.2)
HPV 39, 42, 44, 55, 45, 51	3 (20.0)	4 (66.7)	9 (40.9)	12 (54.5)	28 (43.1)
HPV 6, 16, 31, 42, 45	1 (6.7)	3 (50.0)	12 (54.5)	17 (77.3)	33 (50.8)
HPV 33, 39, 42, 44, 55, 45, 58	2 (13.3)	3 (50.0)	12 (54.5)	16 (72.7)	33 (50.8)
HPV 16, 18, 44, 55, 51, 53, 68	3 (20.0)	5 (83.3)	12 (54.5)	15 (68.2)	35 (53.8)
HPV 42, 44, 55, 53, 56, 58, 66	3 (20.0)	4 (66.7)	12 (54.5)	15 (68.2)	34 (52.3)
HPV 6, 42, 45, 52, 58, 66	-	4 (66.7)	16 (72.7)	14 (63.6)	34 (52.3)
HPV 11, 31, 39, 52, 59, 68	2 (13.3)	4 (66.7)	16 (72.7)	12 (54.5)	34 (52.3)
HPV 6, 16, 53, 56, 58, 68	2 (13.3)	4 (66.7)	14 (63.6)	17 (77.3)	37 (56.9)
HPV 16, 31, 44, 55, 51, 53, 56	5 (33.3)	5 (83.3)	13 (59.1)	17 (77.3)	40 (61.5)
HPV 11, 40, 53, 56, 68, 70, 73	4 (26.7)	3 (50.0)	12 (54.5)	9 (40.9)	28 (43.1)
HPV 6, 18, 42, 52, 53, 70, 82	1 (6.7)	5 (83.3)	14 (63.6)	14 (63.6)	34 (52.3)
HPV 16, 42, 44, 55, 56, 66, 68, 70, 73	2 (13.3)	5 (83.3)	15 (68.2)	17 (77.3)	39 (60.0)
HPV 6, 11, 35, 44, 55, 52, 53, 59, 68	3 (20.0)	5 (83.3)	17 (77.3)	15 (68.2)	40 (61.5)
HPV 6, 11, 16, 33, 43, 44, 55, 52, 59, 70	1 (6.7)	4 (66.7)	18 (81.8)	16 (72.7)	39 (60.0)
HPV 6, 16, 18, 35, 44, 55, 52, 58, 59, 68, 73	1 (6.7)	4 (66.7)	16 (72.7)	17 (77.3)	(58.5)

Fisher's exact test, p<0,005; HPV: human papillomavirus; HIV: human immunodeficiency virus; AIN: anal intraepitherlial neoplasia.

Table 3 – Sensitivity and specificity of HPV genotypes found in the biopsies of anal secretion (Papillocheck) (2010–2013).

HPV genotypes	Kappa				
	Sensitivity	Specificity	Coefficient	n	p-value
HPV 6	20.0	92.0	0.14	60	0.248
HPV 11	57.1	96.2	0.57	60	0.000
HPV 16	55.6	73.8	0.28	60	0.029
HPV 18	16.7	96.3	0.17	60	0.167
HPV 31	28.6	100.0	0.41	60	0.000
HPV 33	-	-	-	-	-
HPV 35	25.0	98.2	0.30	60	0.012
HPV 39	0.0	98.2	-0.03	60	0.761
HPV 40	-	-	-	-	-
HPV 42	0.0	98.0	-0.03	60	0.652
HPV 43	33.3	100.0	0.49	60	0.000
HPV 51	-	-	-	-	-
HPV 52	7.1	97.8	0.07	60	0.364
HPV 53	9.1	100.0	0.14	60	0.033
HPV 56	-	-	-	-	-
HPV 58	33.3	98.0	0.41	60	0.001
HPV 59	57.1	84.9	0.32	60	0.009
HPV 66	12.5	96.2	0.12	60	0.296

HPV: human papillomavirus.

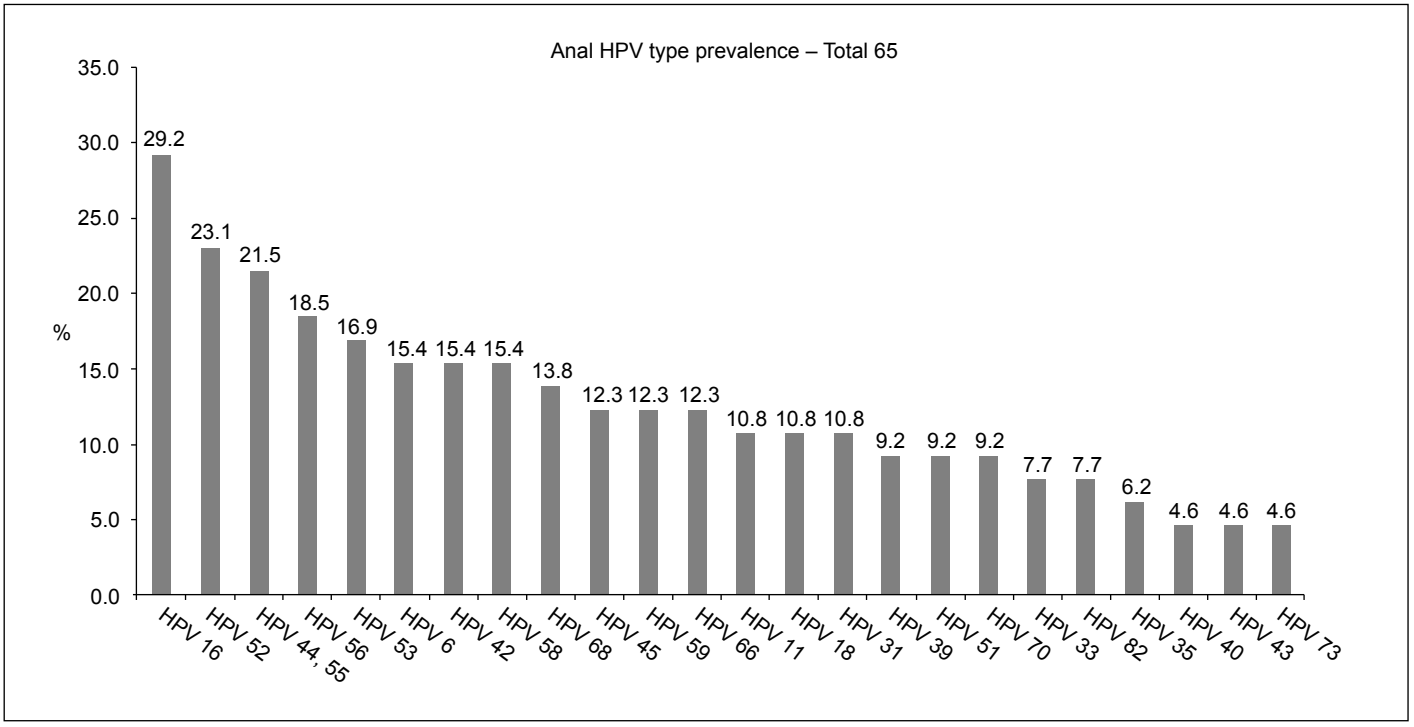

Figure 1 – HPV prevalence found in the anal secretion.

Data from this study showed a high prevalence (94.4%) of patients with $CD4^+$ nadir <50 cells/mm³ who were diagnosed with high-grade AIN. However, the results disagree with one particular study that found that 14.8% of individuals with a high-grade AIN had CD4 nadir below 50 cells/mm³ in a cohort in Brazil of HIV-infected women[10]. In another study, where multivariate analysis was performed, it was observed that a low $CD4^+$ count (≤200 cells/mm³) does not show a strong predictor of high-risk HPV infection[2].

Currently, the increased life span of HIV-infected individuals may be explained due to the impact of treatment with cART. In this study, 81.8% of HIV-1-infected patients were under cART treatment and 42.9% had detectable viral load. No correlation was found between peripheral levels of $CD4^+$ and the use of HAART. In our previous study with cervical samples, this type of correlation was also not observed[11].

HIV/HPV coinfections lead to important biological changes that entail the development of progression of AIN to anal cancer. While most studies that address the immune response against HPV/HIV are directed to cervical cancer, it has been shown that the infection by only HPV displayed no activation of the immune response mediated by Th1 lymphocytes, whereas in the coinfection a profile shift to Th2 occurs[12].

Among the HPV genotypes detected in anal secretion of HIV-infected individuals, HPV 51 showed statistical differences in the samples without lesion. Studies show that infection with high-risk HPV is common in anal samples of HIV-infected individuals, and usually HPV 51 appears moderately associated with anal lesions. In this study, a weak association was found between the HPV types detected in the anal secretion and biopsies, which indicates that HPV detected in secretion is not necessarily of the same type of those underlying the intraepithelial lesion[13].

Of the population analyzed, more than 45% of HIV-negative and 57% of HIV-positive subjects had already been exposed to the four HPV types covered by the current quadrivalent HPV vaccine, suggesting that HPV vaccination should be considered as a prophylactic approach to reduce the risk of anal intraepithelial lesion development on this population. Further studies should be done in a larger population of individuals. The present study has as limitation the nonavailability of some analyzed variables for all patients. However, the data suggest some important clinical approaches.

CONCLUSION

This study showed that there was a strong association in HIV-1-infected individuals between the development of anal intraepithelial lesions to stage AIN II/III with the increasing age and peripheral blood $CD4^+$ nadir <50 cells/mm³. In addition, most HIV-infected individuals analyzed have already been exposed to the four HPV types targeted by the current quadrivalent vaccine (MSD—HPV types 6, 11, 16, and 18) suggesting that vaccination against HPV could be regarded as a prophylactic measure to reduce the risk of anal intraepithelial lesions in HIV-infected individuals.

Conflict of interests

The authors reported no conflict of interests.

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Address for correspondence:
ALCINA F. NICOL
Av. Brasil, 4365 – Manguinhos
Rio de Janeiro (RJ), Brazil
CEP: 21045-900
Phone: +55 (21) 2562-1037
E-mail: nicol@ioc.fiocruz.br; afnnicol@gmail.com

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Potential antiviral activity of *Plexaurella regia* on the replication of Herpes Simplex Virus type 1

Potencial atividade antiviral de Plexaurella regia no ciclo replicativo do vírus Herpes Simples tipo 1

Viveca Giongo[1], Camilly Pestana Pires de Mello[1], Felipe Mateini[1], Juliana Barbosa[2], Jussara Pinheiro Barbosa[3], Beatriz Grosso Fleury[3], Clovis Barreira e Castro[4], Angelo da Cunha Pinto[3], Izabel Christina Nunes de Palmer Paixão[1]

ABSTRACT

Introduction: Latency and resistance of acyclovir-resistant strains of Herpes simplex virus type 1 (HSV-1) have been associated with serious sequelae in immunocompromised individuals, such as AIDS patients. Consequently, the search for new substances with anti-HSV activity is both necessary and urgent. **Objective:** To investigate whether extracts obtained from *Plexaurella spp* can be used in preclinical studies of drugs against herpes simplex virus type 1. **Methods:** Cell viability and inhibitory drug concentrations as screening tests were used to investigate ethyl acetate and dichloromethane extracts from *Plexaurella spp* as antivirals. **Results:** The results of viability assays demonstrated that extracts from *Plexaurella regia* and *Plexaurella grandiflora* showed less cytotoxicity, but only *Plexaurella regia* reached a very expressive CC_{50} value. In antiviral assays, *Plexaurella regia* showed an even more significant result of effective concentration (EC_{50}) and therapeutic index (<2.5 µg/mL and 51.6 µg/mL, respectively) compared with acyclovir (ACV). **Conclusion:** These results demonstrated that extracts from corals have anti-herpetic activities and could contribute towards new strategies to stop the increasing incidence of resistance in herpes-related diseases.

Keywords: natural products; antivirals; drug resistance; HSV-1.

RESUMO

Introdução: Latência e resistência de cepas de Herpes simples tipo 1 (HSV-1) ao aciclovir têm sido associados a sequelas graves em pacientes imunocomprometidos, como pacientes com AIDS. Por essa razão, a pesquisa por novas substâncias com atividade anti-HSV-1 é uma necessidade urgente. Objetivo: Investigar se os extratos obtidos de *Plexaurella spp* poderiam ser usados em estudos pré-clínicos de drogas contra o vírus herpes simples tipo 1. **Métodos:** A viabilidade celular e concentrações inibitórias das drogas foram utilizados como testes de triagem para investigar os extratos etil acetato e diclorometano de *Plexaurella spp* como antivirais. **Resultados:** Os resultados de viabilidade demonstraram que os extratos de *Plexaurella regia* e *Plexaurella grandflora* não foram citotóxicas, mas somente *Plexaurella regia* alcançou um valor de CC_{50} expressivo. Nos ensaios antivirais, *Plexaurella regia* mostraram um resultado ainda mais significante de concentração efetiva (EC_{50}) e índice terapêutico (<2.5 µg/mL e 51.6 µg/mL, respectivamente) comparado com aciclovir (ACV). **Conclusão:** Estes resultados mostram que os extratos de corais têm atividade anti-herpética e podem contribuir para novas estratégias de redução da incidência de resistência de doenças relacionadas aos herpes vírus.

Palavras-chave: produtos naturais; antiviral; resistência a medicamentos; HSV-1.

INTRODUCTION

Marine organisms comprise over half a million species. Due to their unusual living environment in comparison with terrestrial organisms, marine organisms produce a variety of substances, which quite often have various unprecedented chemical structures. Issues such as competition for space and predation have originated new biochemical pathways for these organisms, providing essential metabolites for their adaptation[1]. Over 40 novel natural product compounds are now commercially available, including antiviral products isolated from various marine organisms, which provide alternative therapeutic drugs[2,3].

A literature survey revealed that Gorgonian corals have proven to be a prolific source of a variety of biologically active compounds with cytotoxic effects on human leukaemia[4], such as being inhibitors of acetylcholine receptors[5-7]. The species of corals in tropical or temperate waters of the western North Atlantic are relatively well known, but those found at the south of the Amazon River are not, despite having common elements with the fauna of the Caribbean octocorals[8]. Silva & Pérez[7], in 2002, reported 59 species of octocorals on the Brazilian coast based on the biosynthetic origin of bioactive terpenes. This classification could provide a system to produce *ex situ* compounds[9].

Almost 90% of people worldwide have one or both HSV-1 and HSV-2 viruses. In developed countries, the acquisition of HSV-1 is delayed from early childhood to adolescence or young adulthood[10]. Herpes simplex virus (HSV) belongs to *Herpesviridae*, subfamily *Alphaherpesvirinae*, and contamination occurs through direct contact with infected secretions, mostly during infancy, with clinical manifestations varying from labial lesions to gingivostomatitis, keratoconjunctivitis, and genital infections[11]. The virus persists for life in local sensory ganglia and reactivation depends on the status of the patient's immune system. The primary infection or virus reactivation

[1]Department of Cell and Molecular Biology, Institute of Biology, *Universidade Federal Fluminense* (UFF) – Niterói (RJ), Brazil
[2]Department of Marine Biology, Institute of Biology, UFF – Niterói (RJ), Brazil.
[3] Department of Chemistry, Institute of Chemistry, *Universidade Federal do Rio de Janeiro* – Rio de Janeiro (RJ), Brazil.
[4]Department of Invertebrates, National Museum, UFRJ – Rio de Janeiro (RJ), Brazil.

is the cause of herpes encephalitis (HSE), and both demonstrated the need for new drugs due to the increasing resistance to acyclovir, penciclovir, ganciclovir, foscarnet, and cidofovir[12]. Resistant viral isolates can be observed especially in immunocompromised patients, in patients with HIV, and in recipients of solid organ or bone marrow transplants who are treated with antivirals for long intervals. Presently, the main focus is to circumvent this problem through the development of broad-spectrum antivirals, in particular those targeting common cellular pathways[13]. For HSV-1, the growing resistance makes the search for innovative antivirals both necessary and urgent[14,15].

This study involved an evaluation of the fractions obtained from *Plexaurella regia, Plexaurella grandiflora* and *Muriceopsis sulphurea,* all endemic on the Brazilian coast, as antivirals against HSV-1.

METHODS

Collection and preparation of crude extracts

The octocorals were collected by scuba divers in Parque Municipal Marinho de Recife de Fora, Porto Seguro, Bahia, and stored in ethanol to obtain the crude extracts.

The extracts were fixed in organic solvents of different polarities (hexane, dichloromethane, and ethyl acetate) and evaporated separately under reduced pressure.

Analysis by Gas Chromatography coupled to mass spectrometry (GCMS)

The mass spectra of low resolution (70 ev) was obtained on a Hewlett Packard 5987A. The fragments were described by the ratio mass/charge (m/z) and their intensities expressed as a percentage of base peak (100%). The chromatographic column used was a fused silica capillary column with stationary phase HP-5 MS (5% phenyl methyl siloxane) measuring 30 m long with an internal diameter of 0.25 mm and a thickness of 0.25 µm. The samples were injected using 1 µl of the fractions, previously diluted in CH_2Cl_2. The chromatographic conditions were: initial column temperature: 50°C (4 min), gradient: 100C/min, final temperature of the column: 290°C (20 min), injector temperature: 270°C, detector temperature: 290°C, carrier gas: hydrogen, injection mode: flow division split 1:20.

Cells and viruses

Vero cells (African green monkey *Cercopithecus aethiops* kidney cells; ATCC, Manassas, VA, USA) were cultured in Dulbecco's modified medium, supplemented with 5% of fetal bovine serum (FBS; HyClone, Logan, UT, USA), 0.1 µM HEPES, and 2.5 µg/mL gentamycin, at 37°C in 5% CO_2. Vero cells were subconfluent in all assays and were used prior to passage 20. Stock of HSV-1 was obtained with HSV-1 (AR- 29)[16], KOS[17] strain at a multiplicity of infection (MOI) equal to 0.1 for 1 h at 37°C. Briefly after the incubation, the monolayer was washed out with phosphate-buffered saline (PBS) and cells were cultured for an additional 48 h. After this period, cells were lysed through three cycles of freezing and thawing, centrifuged at 1500×*g* at 4°C for 20 min to remove cellular debris, and the supernatants were collected, titered by plaque assay, and stored at -70°C for further studies.

Cytotoxicity assays

The MTT cytotoxic assay was performed in Vero cells in 96-multiwell plates (10^5/well) treated with different concentrations of the crude extracts from *Plexaurella regia*, *Plexaurella grandiflora,* and *Muriceopsis sulphurea* at 37ºC with atmosphere of 5% CO_2 for 72 h. Afterwards, 50 µL of MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (MTT; Sigma) and 1mg/mL of stock, were added to each well for 3 h. After incubation and discard, each well received 50 µL of acid-isopropanol (0.04N HCl in isopropanol). The concentration was determined by an automatic plate reader with a 570 nm test wavelength and a 690 nm reference wavelength[18,19]. The 50% cytotoxic concentration (CC_{50}) was calculated by linear regression analysis of the dose-response curves generated from the data.

Plaque assay

Monolayers of Vero cells in six-well plates were exposed to different dilutions of the supernatant from yield-reduction assays for 1 h at 37°C. Next, cells were washed with PBS and DMEM medium containing 5% FBS and then 1% methylcellulose (Fluka) (overlay medium) was added to cells. After 72 h at 37°C, the monolayers were fixed with 10% formaldehyde in PBS and stained with a 0.1% solution of crystal violet in 70% methanol, and the virus titers were calculated by scoring the plaque-forming units (PFU). Additionally, other experiments were performed in the format of a plaque-reduction assay. In those particular cases, various concentrations of the compounds were added in the overlay medium and after 72 h, cells were fixed and plaques counted.

Plaque reduction assay

Monolayers of Vero cells (10^5) in 24-well plates were infected with HSV-1 (AR-29 or KOS strain) at an MOI equal to 1 for 1 h at 37°C. Cells were washed with PBS to remove residual viruses and various concentrations of the extract in Medium 199 with 2,5% FBS were added. After 20 h, cells were lysed, cellular debris were cleared by centrifugation, and virus titers in the supernatant were determined by the plaque-forming assay using Vero cells, as described in the previous item. For comparison, linear regression of the dose response curves for ACV was also performed to calculate EC_{50} values.

RESULTS

The octocorals were collected by scuba divers in the Marine Park of Recife de Fora, Porto Seguro, Bahia, and stored in ethanol to obtain the crude extracts. Specimens were identified at Museu Nacional, UFRJ[20,21]. The extracts were separately prepared in organic solvents of different polarities (hexane, dichloromethane

(DCM), and ethyl acetate (EtOAc)), and evaporated under reduced pressure except *P. grandiflora*, which was extracted with DCM and EtOAc (**Table 1**).

Analysis by thin layer chromatography (TLC) of crude extracts of each coral revealed that hexane and DCM extracts of *P. regia* and *M. sulphurea* showed the same chromatographic profile while *P. grandiflora* corresponded to that observed in other species, i.e., DCM extract provided a separate chromatogram of the EtOAc extract.

For a detailed analysis, each crude extract (15 mg) was filtered on a column by adsorption on silica gel 60–70 to 230 mesh, using DCM (30 mL). After evaporation of solvents, an aliquot of each sample (1 mg/mL) was analyzed by gas chromatography-mass spectrometry (GC-MS), showing that *P. regia* and *M. sulphurea* crude extracts have a similar chemical composition with predominance of sterols, fatty acids, and fatty acid esters. While *P. grandiflora* produces a variety of sesquiterpenes, *P. region* produces valencene and sesquiterpene. However, for *M. sulphurea,* such metabolite was not detected in the fractions analyzed by GC-MS (**Tables 2**, **3** and **4**).

Viability and antiviral activities of the octocorals fractions were identified according to the species and the solvent used for purification. Thus, P-1 corresponds to *Plexaurella regia*, P-2 to *Plexaurella grandiflora,* M-1 to *Muriceopsis sulphurea* and each one adds 1 for hexane, 2 for dichloromethane and 3 for ethyl acetate.

Table 1 – Crude extracts of *P. grandiflora, P. regia,* and *M. sulphurea*, extracted successively with hexane, dichloromethane (DCM), and ethyl acetate (EtOAc).

Octocoral	Hexane	DCM	AcOEt
Plexaurella grandiflora	—	14.3 g	0.38 g
Plexaurella regia	4.5 g	0.3 g	0.06 g
Muriceops sulphurea	4.6 g	0.4 g	0.13 g

Table 2 – Secondary metabolites from *Plexaurella grandiflora*, analysed by gas chromatography coupled with mass spectrometry (GC-MS).

Fraction	Molecular formula	M+*	%	Substance
1	$C_{15}H_{24}$	204	3	β-cubebene
2	$C_{15}H_{24}$	204	2	β-cariofilene
3	$C_{15}H_{24}$	204	14	γ-muurolene
4	$C_{15}H_{24}$	204	28	α-amorfene
5	$C_{15}H_{24}$	204	4	α-muurolene
6	$C_{18}H_{36}O_2$	284	6	Ethyl palmitate
7	$C_{20}H_{38}O_2$	310	3	Ethyl oleate
8	$C_{20}H_{40}O_2$	312	2	Ethyl stearate
9	$C_{30}H_{60}O_2$	452	6	Cetyl myristate
10	$C_{32}H_{64}O_2$	480	35	Cetyl palmitate
11	$C_{34}H_{66}O_2$	506	20	Stearate octadecenyl
12	$C_{27}H_{46}O$	386	15	Cholest-5-en-3-ol (cholesterol)
13	$C_{28}H_{36}O$	398	16	Ergost -5,22-dien-3-ol
14	$C_{28}H_{48}O$	400	33	23*S*-methyl cholesterol

*Molecular ion.

Tests of cell viability performed in Vero cells from kidneys of African green monkeys (*Cercopithecus aethiops*) showed that all extracts from *Muriceopsis sulphurea* provided very low CC_{50} values and consequently have not been investigated in antiviral assays (**Figure 1**). The same was observed for hexane and dichloromethane extracts from *P. grandiflora*. Moreover, the results obtained with the ethyl acetate were the most promising, reaching a CC_{50} value similar to the reference, the LCA[22], reaching 132 µg/ mL (**Figure 1**). From analyzing the results separately for each fraction, we identified the fractions P-1.3, P-2.2 and P-2.3 as a dose dependent toxicity ensuring that the toxicity of the substance is in accordance to the administered dose.

The antiviral assay was performed with the fractions that showed the highest values of CC50. It has been also identified the fraction P-1.3

Table 3 – Secondary metabolites obtained from *Plexaurella regia*, analysed by gas chromatography coupled with mass spectrometry (GC-MS).

Fraction	Molecular formula	M+	%	Substance
1	$C_{15}H_{24}$	204	50	Valencene
2	$C_{30}H_{60}O_2$	452	6	Cetyl myristate
3	$C_{32}H_{64}O2$	480	46	Cetyl palmitate
4	$C_{32}H_{66}O_2$	482	10	Palmitate octadecenyl
5	$C_{34}H_{68}O_2$	508	7	Cetyl stearate
6	$C_{27}H_{46}O$	386	11	Cholest-5-en-3-ol (cholesterol)
7	$C_{28}H_{36}O$	398	16	(22E,24S)crinosterol
8	$C_{28}H_{48}O$	400	31	Ergost -5- en-3-ol
9	$C_{29}H_{48}O$	412	36	Stigmast -5-en-3-ol
10	$C_{32}H_{64}O_2$	256	50	Palmitic acid
11	$C_{20}H_{42}$	282	17	n-Eicoseno
12	$C_{24}H_{50}$	338	6	Tetracosane
13	$C_{25}H_{52}$	352	12	Pentacosane
14	$C_{26}H_{54}$	366	13	Hexacosane
15	$C_{27}H_{56}$	380	13	Heptacosane
16	$C_{28}H_{58}$	394	11	Octacosane
17	$C_{29}H_{60}$	408	9	Nonacosane

Table 4 – Secondary metabolites obtained from *Muriceops sulphurea*, analysed by gas chromatography coupled with mass spectrometry (GC-MS).

Fraction	Molecular formula	M+	%	Substance
1	$C_{18}H_{36}O_2$	284	7	Ethyl palmitate
2	$C_{20}H_{32}O_2$	304	4	Arachidonic acid
3	$C_{30}H_{60}O_2$	452	5	Cetyl myristate
4	$C_{32}H_{64}O_2$	480	23	Cetyl palmitate
5	$C_{34}H_{66}O_2$	506	12	Cetyl oleate
6	$C_{34}H_{68}O_2$	508	5	Cetyl stearate
7	$C_{17}H_{34}$	238	41	1-Heptadecene
8	$C_{31}H_{54}O$	442	15	4 α-methylgorgostanol
9	$C_{27}H_{46}O$	386	25	Cholest-5-en-3-ol (cholesterol)
10	$C_{28}H_{36}O$	398	14	Ergost -5,22-dien-3-ol
11	$C_{28}H_{48}O$	400	19	23*S*-methyl cholesterol
12	$C_{30}H_{50}O$	426	22	Gorgosterol

as the compound with antiviral activity (**Figure 2**). Concentrations were 100% effective in inhibiting viral production, even at a concentration of 2.5 µg /mL (**Figure 2**). These data were used for the determination of TI (Therapeutic Index), which indicates the safety of the substance as an antiviral drug. TI is determined by the ratio CC_{50}/ EC_{50} (**Table 5**).

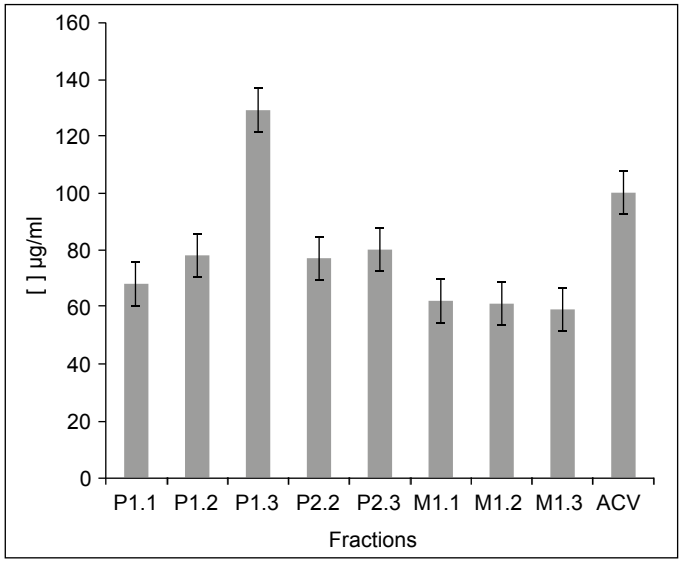

Figure 1 – Effect of coral extracts on Vero cell viability. The cytotoxic concentration that causes 50% lysis and cell death (CC_{50}) were obtained by linear regression of measurements obtained from the average of triplicates of four different concentrations (25, 50, 75, and 100 µg/ml). P-1 refers to *Plexaurella regia*, P-2 to *Plexaurella grandiflora,* and M-1 to *Muriceopsis sulphurea.* According to the solvent used for purification, 1 - hexane, 2 - dichloromethane and 3 - ethyl acetate.

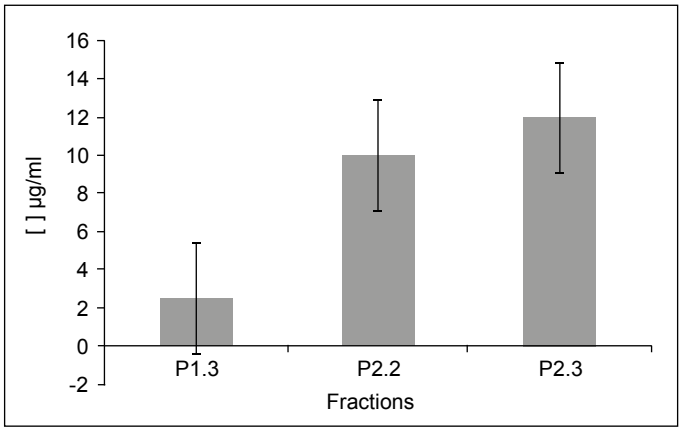

Figure 2 – Concentrations of coral fractions that inhibit 50 % of viral production. The antiviral effect that causes 50 % of inhibition (EC_{50}) was obtained by plaque assay with 2,5, 5, 10, 12, 15 and 20 µg/ml of hexane fraction from *Plexaurella regia* (P1.3), dichloromethane (P 2.2), and ethyl acetate (P 2.3) from *Plexaurella grandiflora* in Vero cells infected with HSV-1 (MOI 1).

Table 5 – Antiviral activities of extracts from *Plexaurella regia*, *Plexaurella grandiflora,* and *Muriceopsis sulphurea* on HSV-1 replication.

Fraction	CC50[a]	EC50[b]	TI[c]
P-1.1	68		
P-1.2	78	-	-
P-1.3	129	<2.5	51.6
P-2.2	77	12	6,4
P-2.3	80	10	8
M-1.1	62	-	-
M-1.2	61	-	-
M-1.3	59	-	-
ACV*	>100**	0.91**	110***

*Acyclovir; **data obtained by Castro[17]; ***CC50=100mg/mL; a: In this assay, Vero cells were cultured in the presence of the extracts for 72 hours at 37°C; b: Antiviral assay that determined the concentration of the extract that reduces the titer of HSV-1 by 50% in Vero cell culture; c: Selectivity Index means how safe some fractions could be as antivirals as reference EC_{50} = 2.5 µg/mL.

DISCUSSION

Recently, the great challenge for HSV infections lies in the search for drugs that could control the development of resistance and latency, especially in AIDS patients and individuals after hematopoietic stem cell transplantation (HSCT)[23]. Resistance to ACV is mediated in 95% of the cases by mutations in the TK gene and in 5% of the cases by mutations in the DNA pol gene, resulting in the alteration of enzyme activity[15,24].

Genotyping findings confirmed that the UL23 TK gene of HSV-1 has an uncommonly high polymorphism[15,25]. The recently discovered inhibitors of the HSV helicase-primase are the most potent development candidates today, but they depend on long-term studies[26].

Marine sponges are considered notable sources of bioactive compounds found in the marine environment. The most important antiviral reported so far is the nucleoside Ara-A (vidarabine), isolated from the sponge Tethya crypta. It inhibits viral DNA polymerase and DNA synthesis of herpes, vaccinia, and varicella zoster viruses[27]. In our study we analysed crude extracts, believing that natural products have great relevance in pharmacology due to their high chemical diversity. The purification of P. regia and P. grandiflora extracts revealed fatty acid esters as common substances for both algae. Additionally, it is consistent with previous antiviral studies that showed that fatty acid esters, specially C14 and C15 isoforms, are able to inactivate enveloped viruses like herpes[28]. These bioactive molecules are often secondary metabolites, whose main function is to enable and/or modulate cellular communication and defence.

CONCLUSION

The highest antiviral activity for HSV-1 was obtained by *P. regia* extract isolated by ethyl acetate. The majority compound is valencene and its molecular formula is C15H24. In conclusion, we suggest Plexaurella spp as a source for anti-HSV compounds.

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Address for correspondence:
IZABEL CHRISTINA NUNES DE PALMER PAIXÃO
Universidade Federal Fluminense, Instituto de Biologia
Rua Outeiro de São João s/n – Campus do Valonguinho, Centro
Niterói (RJ), Brazil
CEP: 24020-141
E-mail: izabeluff@gmail.com

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Sexual and domestic violence among women attending a STI/AIDS clinic in Vitória, Brazil

Violência sexual e doméstica em mulheres atendidas em uma clínica de DST/AIDS em Vitória, Brasil

Raquel Barbosa Miranda[1], Maria Alix Leite Araújo[2], Bettina Moulin Coelho Lima[3], Roumayne Fernandes Andrade[2], Nathalia Lima[1], Angélica Espinosa Miranda[4]

ABSTRACT

Introduction: Violence against women can take several forms; ranging from sexual harassment, discrimination, and discounting to even more serious forms such as those physical and sexual in nature. **Objective:** To describe the frequency of domestic and sexual violence reported by women attending a sexually transmitted infections (STI) clinic in Vitória, Brazil. **Methods:** Women attending the STI/AIDS clinic during the period of study were invited to participate and were interviewed after signing a written consent form. The assessment questionnaire included information on socio-demographic characteristics such as risk behaviors for STI and clinical, domestic, and sexual violence reports. **Results:** A total of 276 (96.8%) women agreed to participate, of which 109 (39.5%) were HIV-positive and 167 (60.5%) were HIV-negative. History of domestic violence was reported by 52.6% of women, mainly related to alcohol abuse (41.6%), use of illicit drugs (27.2%), and psychiatric problems (25.3%). Previous sexual violence was reported by 28.6%, and 31.6% of these cases occurred when the participants were younger than 14 years old. A total of 69.2% of women were between 18 and 34 years old; 11.2% reported frequent use of alcohol; 21% use of illicit drugs and 2.2% reported injectable drugs. Regarding the use of condoms, HIV-positive women were less afraid to ask the partner to use condoms compared with HIV-negative women (31.2% *versus* 41.9%, p=0.022). **Conclusion:** History of domestic and sexual violence was frequently reported in this study. The effects of violence to women's physical and mental health are widely known as a serious public health problem. In addition to its importance, violence is an invisible problem in our society and we need to learn how to approach it during clinical consultation.
Keywords: sexual violence; domestic violence; sexually transmitted diseases; AIDS; women.

RESUMO

Introdução: A violência contra as mulheres pode assumir várias formas, desde assédio sexual, discriminação e desrespeito até formas mais graves tais como violência física e sexual. **Objetivo:** Descrever a frequência de violência doméstica e sexual relatadas por mulheres atendidas em um clínica de doenças sexualmente transmissíveis (DST) em Vitória, Brasil. **Métodos:** As mulheres que buscaram atendimento clínico na clínica de DST/AIDS, durante o período de estudo, foram convidadas a participar e responderam a uma entrevista após assinar um termo de consentimento informado. O questionário utilizado incluiu dados sobre as características sócio-demográficas e clínicas, os comportamentos de risco para DST e a história de violências domésticas e sexuais. **Resultados:** Um total de 276 (96,8%) mulheres concordaram em participar do estudo, das quais 109 (39,5%) eram HIV-positivas e 167 (60,5%) eram HIV-negativas. História de violência doméstica foi relatada por 52,6% das mulheres, principalmente relacionada ao abuso de álcool (41,6%), uso de drogas ilícitas (27,2%), e problemas psiquiátricos (25,3%). Violência sexual prévia foi relatada por 28,6% das mulheres, e 31,6% desses casos ocorreu quando as participantes tinham menos de 14 anos de idade. Um total de 69,2% das mulheres tinham entre 18 e 34 anos; 11,2% relataram o uso frequente de álcool; 21% o uso de drogas ilícitas e 2,2% relataram o uso de drogas injetáveis. Em relação ao uso de preservativos, as mulheres HIV-positivas tinham menos receio de pedir ao parceiro para usar preservativos em comparação com mulheres HIV-negativas (31,2 *versus* 41,9%, p=0,022). **Conclusão:** História de violência doméstica e sexual foi frequentemente relatada neste estudo. Os efeitos da violência sobre a saúde física e mental das mulheres são amplamente conhecidos como um grave problema de saúde pública. Para além dessa importância, a violência é um problema invisível em nossa sociedade e precisamos aprender como abordá-lo na prática clínica.
Palavras-chave: violência sexual; violência doméstica; doenças sexualmente transmissíveis; AIDS; mulheres.

INTRODUCTION

The impact of HIV/AIDS on women's health can be associated with women's autonomy in several ways. The prevalence of HIV is lower in more egalitarian societies where women's rights are protected[1]. Most women are infected with HIV through high-risk heterosexual contact, possibly due to a lack of HIV knowledge, lower perception of risk, drug or alcohol abuse, or different interpretations of safe sex[2]. Relationship dynamics also play a role, in which some women may not insist on condom use because they fear physical abuse or abandonment[3]. They may have less knowledge about infections and hold negative attitudes towards people living with the disease. They are also less likely to negotiate safe sex practices with their partners[4,5].

Domestic and sexual violence occurs globally, in various cultures, and affects people of all economic status[6,7]. The proportions of women who have reported being physically abused by an intimate partner vary from 15% to 71% depending on the country[8]. Laws on domestic violence vary by country. While it is generally outlawed in the Western World, this is not the case in many developing countries[6]. Victims of domestic violence may be trapped in violent domestic relationships through isolation, power and control, insufficient financial resources, fear, shame, or to protect children[9,10].

Domestic violence may be committed in or outside the home and consist of, in most cases, physical, psychological, sexual violence, and neglection[11,12]. The victims are predominantly women,

Work conducted at *Centro de Referência em DST/AIDS* – Vitória (ES), Brazil
[1]*Universidade Brasileira Multivix* – Vitória (ES), Brazil.
[2]Postgraduate Program in Public Health, *Universidade de Fortaleza (UNIFOR)* – Fortaleza (CE), Brazil.
[3]*Centro de Referência em DST/AIDS* – Vitória (ES), Brazil.
[4]Postgraduate Program in Infectious Diseases, *Universidade Federal do Espírito Santo (UFES)* – Vitória (ES), Brazil.

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children, the elderly, and people with disabilities — people who are vulnerable and physically disadvantaged. Sexual violence is defined as the sexual act performed without the desire of one party or the marketing of sexuality and the use of sexual exploitation through intimidation, threat, and use of force[13]. HIV-positive women report an increase in gender-based violence with partners and also in families, communities, and healthcare settings after their HIV diagnosis and throughout the life-cycle[10].

Brazilian Law No. 11,340/2006, known as the Maria da Penha Law, defines sexual violence as any act that constrains the individual to witness, maintain, or participate in any unwanted sexual activity. It also can be the annulment of sexual and reproductive rights, whether it is through prohibiting the use of contraception, prostitution, or inducing abortion[14]. This type of violence is considered a violation of sexual and reproductive rights and one of the most egregious forms of violence[15].

Violence against women is an important issue in Brazil.

OBJECTIVE

To describe the frequency of domestic and sexual violence reported by women attending a sexually transmitted infections (STI) clinic in Vitória, Brazil.

METHODS

Women aged 18 to 49 years attending a STI/AIDS clinic in Vitória, Brazil, between March and December 2008 were invited to participate in this descriptive study. Patient interviews included demographic, behavioral, and clinical data using a questionnaire validated during a pilot study. Participants were interviewed after providing informed consent. The Ethical Committee on Research of the *Universidade Federal do Espírito Santo* approved this study.

History of domestic violence was measured by the reported frequency of physical violence (at least once a week) involving the woman's sexual partner and/or other members of the family residing in the same home. The history of sexual violence was measured as any previous episode of sexual assault. The interview script that was used had been tested previously and was validated in a pilot study prior to the initiation of data collection for the present study. The interviewers were trained on how to approach questions about violence, and the data obtained during the interview was compared to the data on the patient's prenatal registration card, when available.

Standard descriptive statistical analyses were performed, including frequency distributions for categorical data and calculation of medians and interquartile ranges (IRQs) for continuous variables. The frequency of domestic and sexual violence was calculated to reflect the cumulative frequency of this outcome, with corresponding 95% confidence intervals (CI) in the 2 primary groups (HIV-infected and HIV-non-infected). Associations among demographic and behavioral variables with HIV infection were tested using the χ^2 test, with Yates correction or Fisher's exact test, when appropriate. Odds ratios and 95%CI were calculated in bivariate analyses to estimate the strength of the associations between violence and each covariate.

RESULTS

A total of 276 (96.8%) women agreed to participate in this study and answered the questionnaire, of which 109 (39.5%) were HIV-positive and 167 (60.5%) HIV-negative. The median age among all patients was 30 years (interquartile range [IQR]: 23–36) and the median years of schooling was 8 years (IQR: 5–11). There was no statistical difference between HIV-positive and HIV-negative groups regarding age and education.

Table 1 describes demographic and behavioral factors. A total of 69.2% of women were aged between 18 and 34 years; 11.2% of women reported frequent use of alcohol, 21% of illicit drug use in general, and 2.2% injection drug use. Regarding the use of condoms, HIV-positive women were less afraid to ask their partner to use condoms compared with HIV-negative women (31.2% *versus* 41.9%, p=0.022)

Women reported history of domestic violence in 52.6% of cases; the most common were related to alcohol abuse (41.6%), use of illicit drugs (27.2%) and psychiatric problems (25.3%). History of sexual violence was reported by 28.6%, and 31.6% of these incidences occurred when the participants were younger than 14 years old (**Table 2**).

DISCUSSION

This study showed a high rate of domestic and sexual violence among women attending a STI/AIDS clinic in Vitória. In São Paulo, the prevalence of violence among women attending health care facilities was 59.8% and recurrent violence was associated with HIV infection[16]. The notification of violence against women is compulsory in Brazil, however it is an underreported problem[17]. Many of these women do not report the violence to health care professionals or to the police and consequently, these issues stay invisible. This point highlights the importance of evaluating our approach towards the victims of violence when they seek health care facilities to treat the injuries. Health professionals should consider the situation as an opportunity to also offer emotional support, counseling, and treatment. Victims of violence, and those living in fear

Table 1 – Demographic and behavioral characteristics among women attending an STD/AIDS clinic in Vitória, Brazil (n=276).

Variables	n	%
Marital status		
Married/Living together	127	46.0
Single/Divorced/Widow	149	54.0
Age (years)		
18–34	191	69.2
35–49	85	30.8
Schooling (years)		
Up to 8	159	57.6
More than 8	117	42.4
Tobacco use	64	23.2
Regular use of alcohol (several times a week)	31	11.2
Illicit drugs abuse (no injectable)	58	21.0
Injectable drug abuse	6	2.2
Condom use (Always/almost Always)	189	68.5

of violence, require assistance and their needs must be considered in health care. Additionally, the effects of violence on the physical and mental health of women have been described in other studies conducted in Brazil and in other countries[18-21].

Domestic abuse often escalates from threats and verbal abuse to physical violence. Although physical injury may be the most obvious danger, the emotional and psychological consequences of domestic abuse are also severe. Emotionally abusive relationships can destroy one's self-worth, lead to anxiety and depression, and make one feel helpless and alone[22]. No one should be subjected to this kind of pain — and the first step to leaving is recognizing that the situation is abusive.

Brazilian law prohibits domestic violence, and the government has taken steps that specifically address violence against women and spousal abuse. In 2006, the Brazilian President signed the Law of Domestic and Family Violence. The law triples previous punishments for those convicted of such crimes, and also creates a special court system in all states to preside over these cases. It is also the first official codification of domestic violence crimes[23].

The "Maria da Penha" Law was introduced to punish men who attack their partners, or ex-partners, and forced the Brazilian government to establish public services to protect victims of domestic violence, including a special police force and court system. This law also helped to establish that the crimes are not just sexual assaults, but there are also cultural, psychological, and moral issues underlying these attacks. It is these secondary issues that can often lead to beatings and even murder[14].

Women, who are married or are in long-term cohabiting relationships, are particularly vulnerable to the diseases as a result of gender-inequalities[5,24]. The socioeconomic dependency on men results in low autonomy for women[9].

Table 2 – History of domestic and sexual violence among women attending an STD/AIDS clinic in Vitória, Brazil (n=276).

Violence	n (%)	HIV status	
		Positive	Negative
History of domestic violence related to:			
Alcohol	115 (41.6)	43 (39.4)	72 (43.1)
Illicit drugs	75 (27.2)	29 (26.6)	46 (27.5)
Psychiatric problems	70 (25.3)	26 (23.8)	44 (26.3)
Physical violence – partners	48 (17.4)	17(15.6)	31(18.5)
Physical violence – children	10 (3.6)	4 (3.6)	6 (3.6)
History of sexual violence	79 (28.6)	41(37.6)	38 (22.7)
Age of suffered sexual assault			
≤14 years	25 (31.6)	17(41.4)	8 (21.0)
15–19 years	21(26.5)	9 (21.9)	12(31.5)
20–24 years	14(17.7)	5 (12.1)	9 (23.6)
≥25 years	19 (24.0)	10 (24.3)	9 (23.6)
Sexual assault - more than once	32 (40.5)	17(41.4)	15 (39.5)
Who was the one that raped			
Adult in the family	10 (12.6)	4 (9.7)	6 (15.7)
Young men in the family	2 (2.5)	1 (2.4)	1 (2.6)
Neighbor	42 (53.1)	20 (48,8)	22 (57.9)
Unknown person	22 (27.8)	13 (31.7)	9 (23.7)
Several people	3 (3.8)	3 (7.3)	0 (0.0)

The data obtained in the present study, although relevant, does have limitations and cannot be extrapolated with respect to epidemiology and social risk factors in women because all patients interviewed in were specifically STI/AIDS clinic patients. The data excludes all consultations made in the participating family health or private clinics and the cross-sectional design of the study is not ideal for evaluating risk factors. The possibility that there may have been a response bias cannot be dismissed due to the tendency of an individual to give socially acceptable responses. Moreover, lack of accuracy in the women's responses with respect to age at first sexual intercourse, number of sexual partners, drug use, and condom use, among others, cannot be overlooked. However, despite these limitations, the high rate of participation demonstrates that programs focused on violence against women could successfully deliver acceptable, confidential, and private services for women attending a STI/AIDS clinic.

Health professionals should be trained to identify and counsel cases of domestic violence. It is important to consider violence when a women goes to a heath care facility to report STI/AIDS[16,25].

Analyzing violence against HIV women, from a public health perspective, offers a method of capturing the many dimensions of the phenomenon in order to develop multi-sector responses; it is important to develop and implement new approaches to guide program planners and policymakers[10]. Often the healthcare system is the first point of contact with women who are victims of violence. Data provided by this study will contribute to raising awareness among healthcare policymakers and care providers of the seriousness of the problem and how it affects women's health. Ideally, the findings will inform a more effective government response, including from the health, justice, and social service sectors, as a step towards fulfilling the state's obligation to eliminate violence against women under international human rights laws.

Violence against women has a far deeper impact than the immediate harm caused. It has devastating consequences for the women who experience it and a traumatic effect on those who witness it, particularly children. It is shameful for states that fail to prevent it and societies that tolerate it. Violence against women is a violation of basic human rights that must be eliminated through political will and by legal and civil action in all sectors of society.

It is important to highlight that the health sector alone has little impact in the fight against domestic and sexual violence. In order to achieve suitable and comprehensive care, it is essential to strengthen intersectional coordination, specifically by integrating all sectors of society involved and for them to work collaboratively. In this context, social service providers and healthcare professionals have prominent responsibilities. Beyond the clinical approach, they should understand their role as articulators of care and actors that share responsibilities for ensuring comprehensive care for women's health.

CONCLUSION

History of domestic and sexual violence was frequently reported in this study. The effects of violence on women's physical and mental health are widely known as a serious public health problem. In addition to its importance, violence is an invisible problem in our society and we need to learn how to approach it during clinical consultations.

Conflict of interests

The authors report no conflict of interests.

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Address for correspondence:
ANGELICA ESPINOSA MIRANDA
Departamento de Medicina Social, Universidade Federal do Espírito Santo
Avenida Marechal Campos, 1468 – Maruípe
Vitória (ES), Brasil
CEP: 29040-091
E-mail: espinosa@ndi.ufes.br

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Seroprevalence of toxoplasmosis, syphilis, hepatitis B, hepatitis C, rubella, cytomegalovirosis and human immunodeficiency virus infection among pregnant patients followed up from 2008 to 2012 at hospital universitário Antônio Pedro, Niterói (RJ)

Soroprevalência para toxoplasmose, sífilis, hepatite B, hepatite C, rubéola, citomegalovírus e vírus da imunodeficiência humana em gestantes atendidas no hospital universitário Antônio Pedro, Niterói (RJ) entre 2008 e 2012

Remberto Mauricio de la Cruz Vargas Vilte[1], Kátia Martins Lopes de Azevedo[2], Sérgio Setúbal[2], Solange Artimos de Oliveira[2]

ABSTRACT

Introduction: Screening and treatment of infectious diseases in pregnant women have great importance in planning preventive actions and development of maternal and child health policies. **Objective:** To evaluate the seroprevalence of toxoplasmosis, syphilis, hepatitis B, hepatitis C, rubella, cytomegalovirosis and human immunodeficiency virus (HIV) infection among pregnant women followed up at a University Hospital of Niterói, RJ. **Methods:** A cross-sectional study was done by reviewing serological tests recorded in the medical records of pregnant women attending the antenatal service of the Hospital Antônio Pedro, Universidade Federal Fluminense, from 2008 to 2012. **Results:** The seroprevalences found were 61.4 (IgG) and 2.4% (IgM) for toxoplasmosis; 95.1 (IgG) and 0.5% (IgM) for rubella; 95.1 (IgG) and 1.2% (IgM) for cytomegaloviruosis; 0.9% for hepatitis B surface antigen; 1.6% for hepatitis C virus; 1.5% for syphilis and 5.8% for HIV infection. There were no statistically significant differences between seroprevalences of patients with or without HIV infection. The rates of congenital transmission were 4.2% (2/48) for HIV, 33.3% (5/15) for toxoplasmosis, and 22.2% (2/9) for syphilis. There were congenital abnormalities in 1/5 newborn whose mother was seropositive for rubella IgG and/or IgM in the prenatal routine. Coinfection HIV/toxoplasmosis was found in one newborn. **Conclusion:** The large proportion of pregnant women susceptible to toxoplasmosis (38.8%) and hepatitis B (66.3%) shows the necessity of diagnostic and preventive measures for toxoplasmosis and HBV vaccination to reduce the risk of vertical transmission of these infections, thus improving the health of mother and newborn.

Keywords: seroepidemiologic studies; pregnant women; infectious disease transmission, vertical.

RESUMO

Introdução: A triagem e o tratamento das doenças infecciosas em gestantes são de grande importância para o planejamento de ações preventivas e a elaboração de políticas de saúde materno-infantil. **Objetivo:** Determinar a soroprevalência de toxoplasmose, sífilis, hepatite B, hepatite C, rubéola, citomegalovírus (CMV) e infecção pelo vírus da imunodeficiência humana (HIV) em gestantes acompanhadas no Hospital Universitário Antônio Pedro, Niterói (RJ). **Métodos:** Foi feito um estudo transversal por meio de revisão de testes sorológicos registrados nos prontuários médicos de gestantes atendidas, de 2008 a 2012, no Ambulatório de Pré-Natal. **Resultados:** As prevalências encontradas foram: 61,4 (IgG) e 2,4% (IgM) para toxoplasmose; 95,1 (IgG) e 0,5% (IgM) para rubéola; 95,1 (IgG) e 1,2% (IgM) para CMV; 0,9% para hepatite B (HBsAg); 1,6% para hepatite C; 1,5% para sífilis; e 5,8% para infecção pelo HIV. Não houve, entre gestantes infectadas e não infectadas pelo HIV, diferenças estatisticamente significativas nas frequências das infecções estudadas. As taxas de transmissão vertical foram de 4,2% (2/48) para o HIV; 33,3% (5/15) para toxoplasmose; e 22,2% (2/9) para sífilis. Foram detectadas alterações compatíveis com rubéola congênita em 1/5 crianças cuja mãe apresentava IgM e IgG positivas para tal infecção durante a gestação. A coinfecção HIV/toxoplasmose ocorreu em uma criança. **Conclusão:** O número de gestantes susceptíveis à toxoplasmose (38,8%) e ao vírus da hepatite B (VHB) (66,3%) revela a necessidade de medidas diagnósticas e preventivas da toxoplasmose durante a gestação e vacinação para o VHB, visando diminuir o risco dessas infecções durante a gravidez, melhorando, assim, a saúde materno-infantil.

Palavras-chave: soroprevalência; gestante; transmissão vertical.

INTRODUCTION

Toxoplasmosis, rubella, hepatitis B, hepatitis C, syphilis, cytomegaloviruses, and human immunodeficiency virus (HIV) are infections that can affect pregnant women and be vertically transmitted to the newborn. These infections are often asymptomatic among adults, and can result in severe consequences when contracted by the child during the pregnant-puerperal period, both throughout pregnancy and at the time of labor or while breast-feeding. The conduction of serological tests in the prenatal period allows the diagnosis of these infections and the adoption of measures which would enable the reduction of the harms they could cause to neonatal health[1].

In this context, it is important to monitor the susceptibility of women at reproductive age to these infections. Population serological surveys allow obtaining precise estimations of the seroprevalence, according to age group. However, these activities take a while, are

Study carried out at *Hospital Universitário Antônio Pedro* (HUAP), *Universidade Federal Fluminense* (UFF) – Niterói (RJ), Brazil.
[1]Postgraduate Program in Medical Sciences, UFF – Niterói (RJ), Brazil.
[2]Discipline of Infectious and Parasitic Diseases, School of Medicine, UFF – Niterói (RJ), Brazil.

expensive, and have momentary results, considering that the proportion of seropositive people may change with the improved socioeconomic and sanitary conditions, or with the adoption of national prevention and vaccination programs.

Some of the alternatives capable of providing useful approximations of population seroprevalence, for purposes of monitoring the susceptibility to these diseases include the use of serum samples collected for other population surveys, and the aliquots of serum obtained for other ends. These samples are suitable for the detection of groups of susceptible people and suggest adjustment in vaccinations. An alternative would be to use the routine tests carried out by pregnant women during the prenatal period, in order to favor an approximate awareness of the epidemiological status of the infections in the study population.

Considering the importance of knowledge on the main infectious diseases that can be transmitted from the pregnant woman to the fetus, the change in their epidemiological profile in the last years, and the lack of national publications, studies that aim at determining their prevalence are very relevant to plan for preventive actions and to elaborate on maternal and child health policies.

OBJECTIVE

This paper aimed at determining the prevalence of antibodies for toxoplasmosis, syphilis, hepatitis B and C, rubella, cytomegaloviruses, and HIV, as well as the frequency of transmission of these infections among pregnant women who were present at the Pre-Natal Outpatient ward of Hospital Universitário Antônio Pedro (HUAP), Niterói (RJ), from January 2008 to December 2012.

METHODS

This is a cross-sectional study conducted through the revision of clinical and epidemiological data and laboratory tests obtained from the medical records of pregnant women assisted from January 2008 to December 2012, in the High Risk Prenatal Outpatient Ward of HUAP. In cases of clinical and/or laboratorial suspicion of vertical transmission of the analyzed infections, a descriptive study was carried out by revising the medical records of the newborns.

Exclusion criteria

The following cases were excluded:

1. when the medical records of pregnant women and newborns were unavailable in the Medical Files of HUAP;
2. the pregnant woman did not attend the prenatal appointments, be it for abortion or changes in health service;
3. the results of the HIV serology were not in the medical records;
4. pregnancy was embryonic and/or resulted in hydatidiform mole;
5. there was no continuity in the follow-up of newborns in the medical appointments at HUAP.

Analyzed variables

The variables studied were age, schooling, city of residence, number of previous pregnancies, number of previous abortions, comorbidities and qualitative results of serological tests to detect antibodies for toxoplasmosis, syphilis, hepatitis B and C, rubella, CMV, HIV, and detection of the hepatitis B surface antigen (HBV) (HBsAg).

Laboratory tests

Serological examinations were carried out in HUAP's laboratory, according to the recommendations of the manufacturers, and the results were classified as "positive," "negative," or "undetermined." The following tests were conducted:

1. toxoplasmosis: detection of IgM (LIASON – Toxo IgM, DiaSorin S.p.A, Italy) and IgG (LIASON – Toxo IgG, DiaSorin S.p.A, Italy);
2. rubella: detection of IgM (LIASON – Rubella IgM, DiaSorin S.p.A, Italy) and IgG (LIASON – Rubella IgG, DiaSorin S.p.A, Italy);
3. hepatitis B: detection of the surface antigen (HBsAg) (ADVIA Centaur CP Anti-HBs, Siemens Healthcare Diagnostics Inc., USA) and of antibodies for the hepatitis B surface antigen – anti-HBs (ADVIA Centaur CP Anti-HBs, Siemens Healthcare Diagnostics Inc., USA) through chemiluminescent immunoassay;
4. hepatitis C: detection of hepatitis C antibodies (anti-HCV) (ADVIA Centaur CP HCV, Siemens Healthcare Diagnostics Inc., USA);
5. syphilis: VDRL (WAMA Diagnóstica, Brazil);
6. CMV: detection of IgG (LIASON – CMV IgG II, DiaSorin S.p.A, Italy) and IgM (LIASON – CMV IgM II, DiaSorin S.p.A, Italy);
7. HIV: detection of antibodies for HIV-1/HIV-2 (ADVIA Centaur HIV 1/0/2 Enhanced Healthcare Diagnostics Inc., USA).

Statistical analysis

The data of interest were recorded, stored, and analyzed with the Statistical Package for the Social Sciences (SPSS), version 17. The categorical and continuous variables were calculated by frequencies, means, and medians. The difference between the proportions of categorical variables was carried out with Pearson's χ^2 test, with statistical significance of 5%.

The study was approved by the Research Ethics Committee of HUAP (CEP/HUAP n. 140/2011).

RESULTS

General characteristics of the population

In the book of the First Care Prenatal Outpatient at HUAP, from January 2008 to December 2012, a total of 1,112 patients were registered. Seventy-four (6.7%) patients were excluded according to the following situations: absence of medical record (36 cases); in case of pregnant women, discontinuity in attending the prenatal appointments (24 cases); absence of the results of the serologic tests for HIV (6 cases); abortion (4 cases); hydatidiform mole (2 cases); and pseudocyesis (2 cases). Therefore, the study universe was composed of 1,038 patients with properly documented serological results.

The age of the pregnant women ranged from 13 to 46 years old (mean: 26.86 years; median: 27 years), the most common being the age group of 21–30 years old (507 cases – 48.8%), followed by

31–40 years old (279 cases – 26.9%). Two-hundred and seventeen (20.9%) patients were younger than 20, and 35 (3.4%) were older than 41 years old (**Table 1**).

As to the origin, 479 (46.1%) pregnant women came from the city of Niterói; 395 (38.1%) came from São Gonçalo; and 115 (11.1%) came from other cities in the State of Rio de Janeiro.

Regarding schooling, it was observed that 391 (37.7%) pregnant women had completed elementary school, and 293 among them (28.2%) had completed high school. For 354 patients (34.1%), it was not possible to assess this item in the analyzed records (**Table 1**).

Pregnant women were assessed according to the positive or negative results of the HIV serologic tests, and considered in each one of the two groups according to the following variables: age group, schooling, and origin. The different frequencies observed between these two groups were not significant (**Table 1**).

The mean of pregnancies was 2.4 (variation of 1 to 13), and 344 (33.1%) patients were primigravida. It was observed that 279 of 1,038 (26.9%) patients had a previous history of abortion. The mean gestational age at the time of the first prenatal appointment was 20.9 weeks: 487 (47%) were in the second trimester, 266 (25.6%) were in the first trimester, and 285 (27.4%) were in the last trimester of pregnancy.

Seroprevalence study

IgG anti-*Toxoplasma gondii* antibodies were detected in 624 (61.4%) of the 1,017 pregnant women whose results were known (**Table 2**). In 24 (2.4%) patients, IgM antibodies were detected. Susceptibility to toxoplasmosis, that is, the absence of IgG, was observed in 395 (38.8%) pregnant women. There was no statistically significant association between the frequency of IgG anti-*Toxoplasma gondiii* and sociodemographic variables (data not shown). An association was observed between the older age and the values of frequencies of the antibodies against *Toxoplasma gondii,* and this result was statistically significant (p<0.0001) (**Table 3**).

IgG antibodies against rubella were detected in 951 (95.1%) of the 1,000 pregnant women whose results were known. There were IgM antibodies in five (0.5%) cases. Of the 943 pregnant women tested for IgG and IgM antibodies against CMV, 897 (95.1%) and 11 (1.2%) were positive, respectively.

Nine pregnant women carried the HBsAg antigen (prevalence of 0.9%) (**Table 2**).The positive aspect of this marker was distributed in all age groups studied, and was found only in the group of pregnant women not infected with HIV. The anti-HBs antibodies were present in 296 (33.7%) of the 879 pregnant women tested. The frequency of these antibodies reduced with age, and this association was statistically significant (p<0.0001) (**Table 4**). Fifteen patients were anti-HCV positive, which represents prevalence of 1.6%. Out of these 15 HCV-positive pregnant women, 2 belonged to the HIV-positive group.

Regarding syphilis, 15 (1.4%) of the 1,034 blood samples tested by VDRL were positive, but in none of the cases the FTA-ABS test was carried out to confirm the infection.

HIV was positive in 58 (5.6%) pregnant women. Among these, two (3.4%) presented the HIV/HCV coinfection, and two others (3.4%), the HIV/syphilis coinfection. One pregnant woman (1.7%) had the HIV/toxoplasmosis/rubella/herpes/HPV coinfection. Eight (13.8%) were primigravida. Of the total, 37 (63.8%) pregnant women had prior knowledge of their condition of being infected with HIV, and 21 (36.2%) among them were diagnosed with it because of the prenatal routine. Of the 58 HIV-positive pregnant women, 10 (17.2%) had already acquired immune deficiency syndrome (AIDS), and 48 (82.8%) were asymptomatic. The use of antiretroviral therapy (ART) was observed in 56 (96.6%) pregnant women, and the therapeutic scheme zidovudine, lamivudine, lopinavir, and ritonavir (AZT/3TC/LPVr) was used for most patients (39 cases – 67.2%).

Even though there were differences in the seroprevalence analyzed in HIV-positive and HIV-negative pregnant women, these changes were not statistically significant (**Table 2**).

Comorbidities

Comorbidities most commonly presented by the 1,038 pregnant women analyzed were: arterial hypertension (187

Table 1 – Sociodemographic characteristics of the population according to the result of the serological test for the human immunodeficiency virus

Characteristics	HIV			P-value
	Positive n=58 (%)	Negative n=980 (%)	Total n=1,038 (%)	
Age group (in years)				
<20	11 (19.0)	206 (21)	217 (21)	0.3662
21–30	33 (56.9)	474 (48.4)	507 (48.8)	
31–40	14 (24.1)	265 (27.0)	279 (26.9)	
≥41	0 (0)	35 (3.6)	35 (3.3)	
Schooling				
Elementary school	31 (53.4)	360 (36.7)	391 (37.7)	0.0921
High school and higher education	13 (22.4)	280 (28.6)	293 (28.2)	
Not informed	14 (24.1)	340 (34.7)	354 (34.1)	
Origin				
Niterói	23 (39.7)	456 (46.5)	479 (46.1)	0.1129
São Gonçalo	30 (51.7)	365 (37.2)	395 (38.1)	
Others	4 (6.9)	111 (11.3)	115 (11.1)	
Not informed	1 (1.7)	48 (4.9)	49 (4.7)	

HIV: human immunodeficiency virus.

cases – 18%), obstetric and gynecologic as well as fetal changes (151 cases – 14.5%), type II and/or gestational diabetes (126 cases – 12.1%), obesity (50 cases – 4.8%), and thyroid dysfunction (29 cases – 2.8%).

Vertical transmission

Of the 24 children exposed to toxoplasmosis during pregnancy, 15 were followed-up at HUAP. In 10 children, the infection was ruled out due to the quantitative reduction in IgG values and the absence of IgM antibodies in serial serological examinations carried out after birth. Congenital toxoplasmosis was confirmed in five children, and one of them was coinfected with HIV. One child died a few hours after labor due to severe brain, cardiac, and hepatic changes, and the other four were treated with sulfadiazine, pyrimethamine, and folinic acid. Among these children, the one infected with HIV was simultaneously treated with zidovudine, lamivudine, and nevirapine. It was not possible to establish the outcome in nine children due to the lack of data in medical records (**Table 5**).

Out of the five newborns exposed to rubella, the infection was ruled out for two of them as their serological tests for IgG and IgM antibodies against rubella were negative. During the follow-up in the Neuropediatric Service of HUAP, there was one case of macrocephaly and retardation in psychomotor development. Even though the serologic tests had been negative for IgM

Table 3 – Frequency of the studied infections (rubella, cytomegalovirus, toxoplasmosis, syphilis) according to the result and the age group of the pregnant women.

Age group	[a]anti-rubella IgG+	anti-rubella IgG-	P-value
<20	155 (93.4%)	11 (6.6%)	
20–29	471 (95.2%)	24 (4.8%)	
30–39	278 (95.5%)	13 (4.5%)	0.573*
≥40	47 (97.9%)	1 (2.1%)	
	[b]anti-CMV IgG+	anti-CMV IgG-	
<20	148 (96.7%)	5 (3.3%)	
20–29	445 (94.7%)	25 (5.3%)	0.609*
30–39	262 (94.6%)	15 (5.4%)	
≥40	42 (97.7%)	1 (2.3%)	
	[c]anti-toxoplasma IgG +	anti-toxoplasma IgG-	
<20	90 (53.6%)	78 (46.4%)*	
20–29	294 (55.9%)	213 (46.6%)	<0.0001*
30–39	205 (69.7%)	89 (30.3%)	
≥40	35 (72.9%)	13 (27.1%)	
	[d]VDRL+	VDRL-	
>20	6 (3.5%)	164 (96.5%)	
20–29	8 (1.5%)	507 (98.5%)	0.0455**
30–39	1 (0.3%)	299 (99.7%)	
≥40	0 (0.0)	49 (100%)	

*Pearson χ^2; **Fisher test; CMV: cytomegalovirus; [a]in 38 cases the result of anti-rubella IgG was ignored; [b]in 95 cases the result of anti-CMV IgG was ignored; [c]in 21 cases the result of anti-toxoplasma IgG was ignored; [d]in 4 cases the result of VDRL was ignored.

Table 2 – Frequency of the infections studied as per the results of the serologic tests for the human immunodeficiency virus.

Serology	HIV			P-value
	Positive n=58 (%)	Negative n=980 (%)	Total n=1,038 (%)	
Toxoplasmosis (IgG)				
Positive	34 (58.6)	590 (60.2)	624 (60.1)	
Negative	22 (37.9)	371 (37.9)	393 (37.9)	0.9684*
Not informed	2 (3.5)	19 (1.9)	21 (2)	
Rubella (IgG)				
Positive	49 (84.5)	902 (92.0)	951 (91.6)	
Negative	5 (8.6)	44 (4.5)	49 (4.7)	0.1184**
Not informed	4 (6.9)	34 (3.5)	38 (3.7)	
CMV (IgG)				
Positive	48 (82.8)	849 (86.6)	897 (86.4)	
Negative	2 (3.4)	44 (4.5)	46 (4.4)	0.5538**
Not informed	8 (13.8)	87 (8.9)	95 (9.2)	
Syphilis (VDRL)				
Positive	2 (3.4)	13 (1.3)	15 (1.4)	
Negative	55 (94.9)	964 (98.4)	1.019 (98.2)	0.1983**
Not informed	1 (1.7)	3 (0.3)	4 (0.4)	
Hepatitis B (HBsAg)				
Positive	0 (0.0)	9 (0.9)	9 (0.9)	
Negative	57 (98.3)	938 (95.7)	995 (95.9)	0.5896**
Not informed	1 (1.7)	33 (3.4)	34 (3.2)	
Anti-HBs				
Positive	24 (41.4)	272 (27.8)	296 (28.5)	
Negative	30 (51.7)	553 (56.4)	583 (56.2)	0.1141*
Not informed	4 (6.9)	155 (15.8)	159 (15.3)	
Hepatitis C (anti-HCV)				
Positive	2 (3.4)	13 (1.3)	15 (1.4)	
Negative	53 (91.4)	854 (87.7)	907 (87.4)	0.2237**
Not informed	3 (5.2)	113 (11.5)	116 (11.2)	

*Pearson χ^2; **Fisher test; HIV: human immunodeficiency virus; CMV: cytomegalovirus; HCV: hepatitis C virus.

antibodies and positive for IgG antibodies against rubella, this child was confirmed as a case of congenital rubella syndrome by the clinical-epidemiological criterion. In two cases, it was not possible to evaluate the follow-up of children because of the lack of data in medical records (**Table 5**).

In 6 out of the 11 children exposed to CMV, congenital infection was ruled out during clinical and laboratory follow-up. In the five others, it was not possible to rule out the infection due to the lack of data in medical records (**Table 5**).

Of the 15 (1.5%) newborns exposed to syphilis, congenital infection was registered in two newborns, who were then treated with crystalline penicillin. The infection was ruled out in seven newborns after clinical and laboratory follow-up (long bone x-ray, transfontanelar ultrasound, fundoscopy, VDRL, and analysis of liquor). In six children, it was not possible to assess the occurrence of vertical transmission due to the lack of data in medical records (**Table 5**).

Of the nine children exposed to HBV, seven were vaccinated against hepatitis B and received anti-hepatitis B immunoglobulin in the first 12 hours of life. However, it was not possible to rule out infection in the nine newborns due to the lack of data in medical records (**Table 5**).

Table 4 – Frequency of infections caused by the viruses of hepatitis B and C according to the age group of the pregnant women.

Age group	[a] anti-HBs IgG+	anti-HBs IgG-	P-value
<20	75 (54.0%)	64 (46.0%)	
20–29	172 (38.6%)	273 (61.4%)	<0.0001*
30–39	45 (17.8%)	208 (82.2%)	
≥40	4 (9.5%)	38 (90.5%)	
	[b]HBsAg+	HBsAg-	
<20	1 (0.6%)	165 (99.4%)	
20–29	2 (0.4%)	498 (99.6%)	0.0538**
30–39	4 (1.4%)	287 (98.6%)	
≥40	2 (4.4%)	45 (95.7%)	
	[c] anti-HCV IgG+	anti-HCV IgG-	
>20	0 (0.0%)	151 (100%)	
20–29	7 (1.5%)	453 (98.5%)	0.1638**
30–39	7 (2.6%)	259 (97.4%)	
≥40	1 (2.2%)	44 (97.8%)	

*Pearson χ^2; **Fisher test; HCV: hepatitis C virus; [a]in 159 cases, the result of anti-Hbs IgG was ignored; [b]in 34 cases, the result of HBsAg was ignored; [c]in 21 cases the result of anti-HCV IgG was ignored.

It was not possible to assess the occurrence of infection in the 15 children born from anti-HCV positive mothers due to the lack of data in medical records.

Forty-nine children, born from the 58 HIV-positive pregnant women, were followed-up at the Pediatric Infectology Service of HUAP. For 46 of them, HIV infection was ruled out with anti-HIV serological tests and viral load quantification. At the end of this study, one child was still being followed-up to complete the laboratory examinations. HIV vertical transmission was observed in two children, and one of them also had congenital toxoplasmosis. Because of the lack of medical records, it was not possible to establish the outcome for nine children followed-up at another service (**Table 5**).

DISCUSSION

The results of our study demonstrate that even though there national programs addressed to controlling these diseases (including sexually transmitted diseases – STDs), women at fertile age are still prone to the infections analyzed here, with the risk of transmitting them to their children, leading to fetal loss, congenital malformations, and neonatal death. National and international studies have been showing the importance of the early screening of infectious, vertically transmitted diseases during the prenatal period, enabling treatment, and the introduction of preventive measures to control congenital infections[1].

The seroprevalence of IgG anti-toxoplasma antibodies in our study was 61.4%. The values described for pregnant women in national studies ranged from 31%, in Caxias do Sul (RS)[2], to higher percentages, like 74.4%, in Recife (PE)[3], and 91% in Mato Grosso do Sul[1]. According to Detanico et al.[2], seroprevalence is higher among pregnant women aged more than 30 years old, and when there is handling of raw meats, consumption of raw vegetables or meat, raw unpasteurized milk, direct contact with the ground[4], contact with cats and/or dogs, low socioeconomic and schooling levels, and little knowledge about the disease[5].

In international studies, seroprevalence values of IgG anti-toxoplasma antibodies among pregnant women are also variable: 18.8% in Spain[6], 50.6% in Morocco[7], and 80.3% in Congo[8]. The factors associated with higher prevalence are similar to those described by national authors.

In our study, IgM antibodies were detected in 2.4% (24) of pregnant women, suggesting current or recent infection caused by this protozoan, with possibility of transmission to the fetuses. Vertical transmission took place in 5 (33.3%) of the 15 followed-up

Table 5 – Outcome of children exposed to toxoplasmosis, rubella, hepatitis B, hepatitis C, syphilis, cytomegalovirus and human immunodeficiency virus.

Infection	Children exposed	Infection ruled out	Vertical transmission	Ignored
Toxoplasmosis	24	10 (41.7%)	5 (20.8%)	9 (37.5%)
Rubella	5	2 (40%)	1 (20%)*	2 (40%)
Hepatitis B	9	**	–	9 (100%)
Hepatitis C	15	–	–	15 (100%)
Syphilis	15	7 (46.7%)	2 (13.3%)	6 (40%)
CMV	11	6 (54.5%)	–	5 (45.5%)
HIV	58	46 (79.3%)	2 (3.4%)	10 (17.3%)

*Clinical diagnosis; **prophylaxis in 7 children; HIV: human immunodeficiency virus; CMV: cytomegalovirus.

cases, confirming the possibility of transmission to the fetus when the infection occurs during the gestational period, and this event may have severe consequences. In the national papers, the positive result for IgM anti-toxoplasma antibodies ranged from 0.4 to 3.4%[9,10].

Our results demonstrated there is still a large proportion (38.8%) of pregnant women prone to toxoplasmosis (negative IgG), who are, therefore, exposed to the risk of a prime infection during the gestational period, which indicates the need to implement measures to prevent and control toxoplasmosis during pregnancy.

The seroprevalence of IgG antibodies against rubella among the pregnant women assessed in this study was 95.1%. This result is higher to the percentages found in other national analyses: 89% in Paraná[11], 93.1% in São José do Rio Preto (SP)[10], and 92.5% in Niterói (RJ)[12]. The high values for seroprevalence may be associated with the implantation of the National Plan for the Control of Rubella and Congenital Rubella Syndrome in Brazil, in 1998[13], which contemplates, among other strategies, the vaccination of women at a fertile age. The maintenance of high rates of immunization coverage is essential to control the congenital rubella syndrome. Even if not expected, the congenital rubella syndrome may occur in locations with low rates of susceptibility, as demonstrated by Désinor et al.[14] in a region of Haiti, where only 4% of the pregnant women were susceptible.

Seroprevalence for CMV observed in our study was 95.1%, higher to the value (76.6%) found by Inagaki et al.[9] among pregnant women in Sergipe, and lower to that (97.5%) found by Spano et al.[15] in Vitória (ES). In the state of Mato Grosso do Sul, Figueiró-Filho et al.[1] detected the seroprevalence of 82%, is lower to that observed in this study. However, unlike what we observed here, chronic infection by CMV was statistically associated with older age among pregnant women.

Even though some studies have demonstrated lower percentages of seroprevalence for CMV in pregnant women than those we found – 46.8% in France[16] and 68.3% in Italy[17] – similar or higher values were found in the international literature in general: 92.6% in Havana, Cuba[18]; 87.3% in Nagasaki, Japan[19]; and 95% in Santiago, Chile[20]. According to Yamamoto et al.[20], the high seroprevalence for CMV suggests that maternal reinfection would be the main form of congenital infection, which would lead to the search of the virus directly in the fetuses or in the newborns, using detection in the blood, urine, and saliva through viral culture or polymerase chain reaction.

The seropositivity for syphilis detected in our study was 1.4%, similar to that found in a study conducted with pregnant women in Paraná: 1.6%[11]. The difference is that, in this study, it was possible to observe a statistically significant association between the increasing seroprevalence and the age of the women. Other studies with pregnant women, conducted in South America, also showed similar frequencies: 4.5% in Cochabamba, Bolivia[21] and 0.6% in Lima, Peru[22]. In both studies, the frequency of syphilis was significantly higher among pregnant women with previous history of STD.

Unlike the observations in this study, an analysis carried out in Malawi, Zambia, and Tanzania[23] showed 6.6% seroprevalence of syphilis. Potter et al.[23] observed that the positivity for syphilis was higher among HIV-positive pregnant women (7.3%) than among HIV-negative pregnant women (2.5%). In the study by Potter et al.[23], seven independent and statistically significant factors were correlated with the prevalence of syphilis and HIV:

1. different cities in the studied countries;
2. HIV infection;
3. age between 20 and 24 years old;
4. being a widow, separated or divorced;
5. having been treated for genital ulcer in the past year;
6. history of stillbirth;
7. history of preterm birth.

In our study, HBsAg was detected in 0.9% of the cases, which is within the positive range (0.3–1.8%) found in national studies conducted with pregnant women[1,10,11,24-26]. Values that are similar to those observed in Brazil are also described in the global literature: 0.2% in Cordoba, Argentina[27]; 0.6% in Granada, Spain[28]; 0.9% in India[29]; and 1.5% in Tripoli, Libya[7]. Studies carried out with pregnant women from African countries and China detected higher frequencies, like 8.2% in Nigeria[30] and 6.7% in Jiangsu, east of China[31]. The differences found are related mainly to the regional differences and to the age when the infection occurred[32].

Considering the high risk of HBV vertical transmission, prophylaxis with vaccine and hyperimmune immunoglobulin in the first 12 hours of life was performed in seven of the nine children exposed in this study. However, it was not possible to rule out the occurrence of vertical transmission, since newborns were not properly followed-up after birth. Results that are similar to ours were described by Perim et al.[33] in a study about the prevalence of HbsAg conducted with pregnant women from Ribeirão Preto (SP): out of the 26 newborns of women who were HBsAG positive, only in 18 prophylaxis for hepatitis B was conducted properly.

An unexpected finding of this study was the lower frequency of anti-HB antibodies in older age groups. These antibodies were present in 296 (33.7%) of the 879 pregnant women tested. The frequency of these antibodies decreased with age, and this association was statistically significant ($p<0.0001$). It is possible that this prevalence among pregnant women aged less than 30 years old is related to the immunization program against hepatitis B instituted by the government.

The frequency of antibodies against the hepatitis C vírus (anti-HCV) in our study was 1.6% higher than the values found in other national studies carried out with pregnant women, as follows: 0.3 in Mato Grosso do Sul[25], 0.6% in Espírito Santo[26], and 0.7% in São Paulo[10]. Higher frequencies of anti-HCV in pregnant women are described in the international literature: 2.1% in Gabon, Central Africa[34], and 15.8% in Egypt[35]. These frequencies reflect the higher HCV seroprevalence in the general population of these countries.

HCV transmission from mother to child is not a common incidence. The estimations of the percentage of vertical transmission range from 3 to 10%[36]. In large studies, the risk seems do not exceed 4%[37,38]. Some of the risk factors would be HIV coinfection, high maternal viral load, previous or current intravenous use of illicit drugs, vaginal labor, breastfeeding, and the female gender of the child[37]. Many of these risk factors were never confirmed. The risk of transmission is maximum in mothers coinfected with HIV[36]. The high viral load at the

time of birth is also a risk factor, especially when the virus is associated with mononuclear cells in peripheral blood. Female infants have twice as much the chance of acquiring the infection from their mothers, when compared to male infants[37]. The time when the transmission occurs is uncertain, but evidence points to intrauterine transmission[39]. HCV is present in maternal milk, but the incidence of infection among the infants who are breast-fed is similar to those who are bottle-fed[36,38]. However, a recent systematic study was incapable of identifying any measure (types of childbirth, type of feeding) capable of reducing the transmission from mother to child[36].

Even though this study has observed higher frequency of anti-HCV in HIV-positive pregnant women (3.4%), in comparison that observed among non-infected pregnant women (1.3%), this result was not statistically significant. Higher frequencies in HIV-positive pregnant women were also observed by other authors. Jamieson et al.[40], in Bangkok, Thailand, observed that the frequency of HCV was 3.8% in pregnant women infected by HIV, and 0.3% in HIV-negative pregnant women. The risk factors identified for the HCV infection were use of injectable drugs, a partner with a history of use of injectable drugs and a previous history of blood transfusion.

The frequency of seropositivity for HIV in our study was 5.8%, 14 times higher than the national estimated value (0.4%)[41]. However, one must consider the fact that HUAP is a reference center for the prenatal follow-up of prenatal women infected with HIV; for this reason, there is a concentration of a large number of pregnant women referred from other health units, in this hospital. In a study with similar characteristics, Gonçalves et al.[10] found seroprevalence of 2.1% for HIV in 574 pregnant women who were present at the High Risk Pregnancy Unit from the Base Hospital of São José do Rio Preto (SP), from January 2006 to December 2007.

Other national studies have reported different prevalence rates among pregnant women, depending on the location and the characteristics of the study population. In the Metropolitan Region of Vitória (ES), Lima et al.[26] assessed 332 parturients and 202 pregnant women from February to October 1999, and obtained prevalence rates of HIV infection in both groups, and in total the percentage of women (534) was 0.9, 0 and 0.6%, respectively. The risk factors associated with HIV infection were the report of STD and the fact of having a partner with history of blood transfusion, drug usage, or seropositive for HIV. In another study, also conducted in Vitória, from January to December 1999, Miranda et al.[24] found prevalence of 0.8% for HIV among the 1,068 pregnant women studied. The associated risk factors were a previous history of STD, negligence regarding the use of condoms, prostitution, blood transfusions, and use of injectable drugs. One case of coinfection by HIV and HBV was identified in one of the women, by HIV and syphilis, in another one, and HBV and syphilis, in five of them[24].

A study about the estimated prevalence of HIV, conducted by the spatial analysis of pregnant women in Porto Alegre (RS), assessed all of the live births registered in the data base of the National System of Live Births (SINASC), and all of the newborns exposed to HIV during pregnancy registered in the data base of the National System of Disease Notification (SINAN) in 2003. These were geo-referenced data, and the estimations of HIV seroprevalence obtained among pregnant women ranged from 0 to 8%. The areas with high prevalence of HIV-positive pregnant women were those close to slums, where the income and the schooling is lower, but fertility rates are high[42].

Considering the specificity of our study, the HIV seroprevalence observed here is also high, when compared to values observed in other countries, as follows: 0.5% of seroprevalence for HIV among pregnant women in Lima, Peru[22] and 0.54% in Cordoba, Argentina[27]. Other studies presented even lower frequencies, like 0%, in Spain, in a study conducted by Ramos et al.[43]. Also in Spain, seroprevalence rates of 0.15 and 0.16% were described by Gutierrez-Zufiaurre et al.[6] and Sampedro et al.[28], respectively.

This study had the limitations of any retrospective analysis, especially regarding the identification of vertical transmission. A study involving the revision of medical records may be affected by the difficulty to locate the records, the quality of medical records, the possible loss of test results, and especially by the lack of response from those in charge of the children at the health service, thereby confirming or ruling out the vertical transmission of the infections assessed.

However, our study was capable of detecting important rates of vertical transmission of HIV, toxoplasmosis, and syphilis. One child presented changes compatible with congenital rubella, and five presented congenital toxoplasmosis; one of these had congenital coinfection with HIV and toxoplasma. The large number of pregnant women prone to toxoplasmosis reinforces the need for diagnostic and preventive measures against this infection during pregnancy.

Therefore, the results of this study demonstrate the importance of early prenatal serological screening for the described infections, with the goal of reducing the incidence of congenital transmission. Besides, it is important to increase the publication of information about how to prevent these infections and the necessary hygiene habits, as well as to encourage and improve the immunization coverage against rubella and hepatitis B, aiming to reduce the risk of these infections during pregnancy, thus contributing toward a better mother–child health.

Conflict of interest

The authors declare there is no conflict of interest.

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Address for correspondence:
SOLANGE ARTIMOS DE OLIVEIRA
Disciplina de Doenças Infecciosas e Parasitárias, Faculdade de Medicina, Hospital Universitário Antônio Pedro
Marquês do Paraná, 303 – Centro
Niterói (RJ), Brasil
CEP: 24030-210
E-mail: artimos@vm.uff.br

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Epidemiological profile and maternal-fetal transmission of syphilis in pregnant women of Cascavel (PR)

Perfil epidemiológico e transmissão materno-fetal da sífilis em gestantes de Cascavel (PR)

Ana Carolina de Oliveira Lago[1], Douglas Soltau Gomes[2]

ABSTRACT

Introduction: Gestational syphilis is a serious public health problem. Diagnosis and treatment failures determine high risk of vertical transmission and may result in adverse perinatal outcomes in a large number of cases. **Objective:** To analyze the epidemiology of gestational syphilis and its maternal–fetal transmission in Cascavel (PR) to contribute to the improvement of control actions of this disease. **Methods:** This cross-sectional descriptive study was carried out at the Municipal Department of Health of Cascavel. Socio-demographic information and variables related to the diagnosis and treatment of 135 pregnant women were collected from the database of the Notifiable Diseases Information Systems (SINAN). These women resided in Cascavel and were diagnosed with syphilis, and these were notified from 2008 to 2013. Information on the clinical course of the cases came from notification records of congenital syphilis in the same period. The analysis of the adequacy of treatment received by those pregnant women was based on the recommendations of the Ministry of Health. **Results:** The incidence of syphilis in pregnant women had risen in the study period and had contributed to a vertical transmission of 23.3% and to the maintenance of the incidence rates of congenital syphilis above the targets set by the Ministry of Health. Although 95.6% of pregnant women have received prenatal care and 99.3% have undergone nontreponemal serology, the treatment prescribed for them was inappropriate in 47.9% of cases. The main reason (82.5%) for this inadequacy was the absence of treatment for the partner. A considerable percentage of missing data in the records of gestational syphilis, and the lack of notification of the mothers of 11 children with congenital syphilis recorded in SINAN in this period were found. **Conclusion:** An increase in efforts for the notification and improvements in the quality of prenatal care provided to pregnant women, especially to those related to the treatment prescribed for them and their partners, are still needed to ensure control of syphilis among pregnant women and its transmission.
Keywords: syphilis; pregnant women; epidemiology; prenatal care.

RESUMO

Introdução: A sífilis gestacional constitui um sério problema de saúde pública. A falha em seu diagnóstico e tratamento determina alto risco de transmissão vertical, podendo acarretar, em boa parte dos casos, desfechos perinatais desfavoráveis. **Objetivo:** Analisar a epidemiologia da sífilis gestacional e sua transmissão materno-fetal em Cascavel (PR), visando contribuir para a melhoria das ações de controle desse agravo. **Métodos:** Trata-se de estudo transversal e descritivo realizado na Secretaria Municipal de Saúde de Cascavel. Foram coletadas, a partir do Sistema de Informação de Agravos de Notificação (SINAN), informações sociodemográficas e variáveis relacionadas ao diagnóstico e tratamento de 135 gestantes com sífilis residentes em Cascavel, notificadas entre 2008 e 2013. Informações relativas à evolução clínica dos casos vieram de fichas de notificação de sífilis congênita do mesmo período. A análise da adequação do tratamento recebido pelas gestantes baseou-se nas recomendações do Ministério da Saúde. **Resultados:** A incidência de sífilis em gestantes esteve em ascensão no período em estudo, tendo contribuído para uma transmissão vertical de 23,3% e para a manutenção das taxas de incidência de sífilis congênita acima das metas estabelecidas pelo Ministério da Saúde. Embora 95,6% das gestantes tenham realizado pré-natal e 99,3% tenham realizado sorologia não treponêmica, o tratamento prescrito a elas foi inadequado em 47,9% dos casos, sendo o não tratamento do parceiro o principal motivo (82,5%) dessa inadequação. Constatou-se um considerável percentual de variáveis com o campo ignorado nas fichas de notificação de sífilis gestacional, além da falta de notificação das mães de 11 crianças com sífilis congênita registradas no SINAN nesse período. **Conclusão:** A ampliação dos esforços de notificação, além de melhorias na qualidade do pré-natal fornecido às gestantes, principalmente no que diz respeito ao tratamento prescrito a elas e a seus parceiros, ainda é necessária para garantir o controle da sífilis entre gestantes e de sua transmissão vertical.
Palavras-chave: sífilis; gestantes; epidemiologia; cuidado pré-natal.

INTRODUCTION

Sexually transmitted diseases (STD) represent a serious public health problem worldwide, causing social, economic, and health damages to the population[1]. According to the estimates of the World Health Organization (WHO), approximately 340 million new cases of STD occur annually in the adult population worldwide, of which 12 million are cases of syphilis[2]. In Latin America and the Caribbean, a total of 3 million cases per year in the adult population, and in Brazil, an average prevalence of syphilis among pregnant women ranging from 1.4 to 2.8%, with a vertical transmission rate of 25%, are estimated[3,4].

Gestational syphilis is universally considered one of the leading causes of maternal, fetal, and newborn morbidities[5]. Although syphilis is an ancient disease with a well-defined etiological agent and with an effective treatment at a low cost, the number of infected pregnant women who are not treated properly is still high. This condition may lead to adverse perinatal outcomes in at least 50% of cases, possibly causing neonatal death (9%), stillbirths and late fetal death (21%), premature birth and low birth weight (6%), and children showing clinical evidence of syphilis (16%)[6,7].

As a consequence of the high prevalence of syphilis among pregnant women, congenital syphilis numbers have been alarming. In Brazil, an average of 15,000 new cases of congenital syphilis are estimated to occur per year, with 2.7 deaths per 100,000 live births among children aged under 1 year[3]. Although the Ministry of Health

Work conducted at the *Faculdade Assis Gurgacz* (FAG) – Cascavel (PR), Brazil.
[1]Doctor at FAG – Cascavel (PR), Brazil.
[2]Doctor, Gynecologist and Obstetrician at *Universidade Federal de Santa Maria* (UFSM). Mastologist, PhD, and MSc in Medical Pathology at the *Universidade Federal de Minas Gerais* (UFMG). Professor of Obstetrics and Gynecology at FAG – Cascavel (PR), Brazil.

has launched the elimination of congenital syphilis project, which determined a target for reducing syphilis incidence to less than or equal to one case per thousand live births, the average incidence was still 1.9 cases per thousand live births in 2005, varying according to the place of residence[6].

Despite this dimension, it is believed that such numbers are underestimated, as underreporting frequently occurs in many countries. Underreporting in Latin America is estimated in 34% in Peru, 32.2% in Argentina, 26% in Chile, and 22.2% in Venezuela[4]. In Brazil, although congenital syphilis and syphilis in pregnancy are notifiable diseases since 1986 and 2005, respectively, only 32% of cases of gestational syphilis and 17.4% of congenital syphilis are reported[8].

Syphilis epidemiological surveillance has proven to be a fundamental strategy for the elimination of the congenital form of the disease. A simple count of cases of congenital syphilis does not help to prevent this disease, as the resources are allocated only to prevent complications of the disease after the end of pregnancy. As syphilis is a vertically transmitted disease, it deserves surveillance during pregnancy, when timely interventions can still be performed.

Recent research has shown high levels of incidence of gestational syphilis in the country, especially in cities of the Northeast and Southeast regions. However, few studies are based on epidemiological surveillance data or analyze changes on syphilis incidence for a considerable period of time, especially in Southern Brazil. In this context, the present study aimed at describing the epidemiological characteristics of syphilis in pregnant women and their influence on vertical transmission rates in Cascavel (PR). Therefore, it is expected that the results could be used as tools for planning, evaluating, and improving ongoing control measures, so that it would soon be possible to reduce the maternal–fetal transmission, as it has occurred with other diseases such as human immunodeficiency virus (HIV).

METHODS

This is a cross-sectional, descriptive, and retrospective surveillance study carried out in the city of Cascavel (PR). The study sample comprised all cases of gestational syphilis in women living in the city of Cascavel which were reported in the Notifiable Diseases Information System (SINAN) from 2008 to 2013, according to the case definition from the Ministry of Health. During this period, 138 cases of gestational syphilis have been identified, 3 of which were related to cases of syphilis in nonresidents of Cascavel. These three cases were excluded from the sample; therefore, the final sample consisted of a total of 135 pregnant women.

Secondary data from the congenital syphilis notification forms for residents in Cascavel in the same period were used. The data included the total number of cases and the clinical course of the disease (recent congenital syphilis, late congenital syphilis, stillbirth, and fetal death from syphilis). Additional information was also obtained from the Brazilian Institute of Geography and Statistics (IBGE) on both total and pregnant women population, and from the Live Births Information System (SINASC) on the number of live births in the same city. The data was collected in May 2014 from the database of the Epidemiological Surveillance Department of the Municipal Health Department of the city of Cascavel, which contained the information compiled from the SINAN forms in addition to the data from SINASC.

For the characterization of the cases based on data from SINAN notification/investigation forms, the following variables were used: age, education, ethnicity, occupation, prenatal care provided, gestational age, clinical classification of the disease at diagnosis, syphilis serology, treatment prescribed to the pregnant women, concomitant treatment to the partner, reasons for the absence of treatment for the partner, occurrence of vertical transmission, and perinatal outcome on those cases of vertical transmission.

As information concerning the date of cessation of treatment and confirmation on whether the pregnant woman followed the treatment were not available on the notification forms, it was not possible to establish whether the treatment was carried out as prescribed. However, it could be determined whether the treatment was prescribed adequately or not, according to the recommendations from the Ministry of Health. Therefore, treatments that were considered prescribed adequately were those with Penicillin G Benzathine, in a dosage compatible with the clinical classification of the disease, and with concomitant treatment for the partner.

With regard to the variables on the concomitant treatment for the partner as regards the regimen prescribed, and the reasons for the absence of treatment, only the period from 2010 to 2013 was considered. Prior to its amendment in April 2010, the form for the notification of syphilis in pregnancy did not contain this information, thereby preventing the analysis of the cases which occurred in 2008 and 2009. Thus, of the 135 women with gestational syphilis, 119 were eligible for analysis of the characteristics related to the partner's treatment for the period from 2010 to 2013.

The data was collected in Excel 2013 and analyzed by means of the Statistical Package for the Social Sciences (IBM SPSS), version 20. Mean and standard deviation were calculated for continuous variables, and absolute and relative frequencies were calculated for the nominal and ordinal variables. To investigate the association between categorical variables, χ^2 test or Fisher's exact test were used, considering a level of statistical significance below 0.05. The research project was approved by the Research Ethics Committee of the *Universidade Estadual do Oeste do Paraná* (UNIOESTE), under opinion No. 640,889.

RESULTS

The age of women with gestational syphilis ranged from 15 to 42 years, with mean age of 25.17 years (±6.78 years), and higher frequencies in the age group between 15 and 23 years (46.7% – 63/135). With regard to the sociodemographic characteristics, most pregnant women had only incomplete primary education (43% – 58/135), were white (60% – 81/135) and housewives (68.9% – 93/135) (**Table 1**).

Gestational syphilis showed a progressive increase in its incidence rate from 2010. A reduction on its incidence was observed only from 2009 to 2010, which occurred concomitantly with the reduction of

the number of inhabitants in the city. Among all the years for which the analysis was carried out, 2013 showed the highest incidence of gestational syphilis with 6.41 cases per 1,000 pregnancies, which corresponded to an increase of approximately six times as compared to the same indicators in 2008.

An increased incidence of congenital syphilis from 2010 to 2012 was also observed, and the year 2012 showed the highest numbers of the period, with 2.27 cases per 1,000 live births. Moreover, it was noticed that congenital syphilis incidence remained above one case per 1,000 live births from 2011 to the end of the studied period (**Table 2**).

Table 1 – Distribution of cases of gestational syphilis, according to the sociodemographic characteristics of pregnant women – Cascavel, Paraná, 2008 to 2013 (n=135).

	Frequency	
	Absolute (n)	**Relative (%)**
Age		
15–23	63	46.7
24–33	49	36.3
34–42	23	17.0
Educational level		
PE incomplete	58	43.0
PE complete	37	27.4
High school	28	20.7
Higher education	2	1.5
Ignored	10	7.4
Ethnicity		
White	81	60.0
Black	9	6.7
Yellow	1	0.7
Brown	41	30.4
Ignored	3	2.2
Occupation		
Housewife	93	68.9
Maid	10	7.4
Other	30	22.2
Ignored	2	1.5

Source: Notifiable Diseases Information System (SINAN).
PE: Primary education.

Between 2008 and 2013, 34 cases of congenital syphilis were reported, among which only 23 had the disease notified when the mother was pregnant. The vertical transmission rate obtained was 17% (23/135), considering 23 children and 135 mothers among those reported. This same rate was 23.3% when calculated considering 34 children reported with 146 mothers (135 mothers reported + 11 mothers not reported). Vertical transmission showed increasing incidence pattern in the period, with evolution to early syphilis in 19 (82.6% – 19/23) cases, death owing to congenital syphilis in 1 (4.3% – 1/23) case and stillbirth in 3 (13% – 3/23) cases.

Most of the women held the prenatal care (95.6% – 129/135); only 3% (4/135) of them did not obtain such care, and in two cases this information was not available. However, among those who held the prenatal care, 16.3% (21/129) ended up transmitting the disease to the fetus. Of the 135 pregnant women reported, 134 (99.26% – 134/135) underwent nontreponemal serologic test (VDRL [Venereal Disease Research Laboratory]) during the prenatal care. The pregnant woman who did not undergo this examination was diagnosed by means of treponemal test. VDLR titration was equal to or above 1:8 in 54.5% (73/134) of cases, being higher in cases of progression to congenital syphilis (89.5% – 17/19) compared to those women who gave birth to healthy children (60.4% – 67/111) ($p<0.05$). Titration was also high in the only case of evolution to fetal death, with a value of 1:64.

Confirmatory treponemal test was performed in 97% (131/135) of the pregnant women. In four cases (3% – 4/135) this test was not performed, and the diagnosis was based only on the VDRL. With regard to the clinical classification of gestational syphilis, 51.1% (69/135) of the women were in the latent stage of the disease at diagnosis, 27.4% (37/135) in the primary stage, 5.2% (7/135) in the secondary stage, and 7.4% (10/135) in the tertiary stage, and this information was ignored in 12 (8.9% – 12/135) cases.

Syphilis diagnosis was carried out in the first two trimesters of pregnancy in most cases, in the following manner: in the first quarter in 37% (50/135) of women, in the second quarter in 38.5% (52/135) of them, and in the third quarter in 23% (31/135) of cases. In the subgroup of pregnant women in which the vertical transmission occurred, the diagnosis was carried out in the third trimester of pregnancy in most cases (60.9% – 14/23), whereas among those

Table 2 – Distribution of cases of gestational syphilis and congenital syphilis – Cascavel, Paraná, 2008 to 2013.

Year	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	
Inhabitants/year	**291,747**	**296,241**	**286,205**	**289,340**	**292,372**	**305,615**	**Total**
Live births/year	**4,169**	**4,114**	**4,406**	**4,358**	**4,447**	**4,638**	
Gestational syphilis							
Frequency	7	9	7	26	37	49	135
Incidence coefficient[1]	0.96	1.21	0.98	3.59	5.06	6.41	
Congenital syphilis							
Frequency	4	2	2	6	11	9	34
Incidence coefficient[2]	0.96	0.48	0.45	1.38	2.47	1.94	

Source: Notifiable Diseases Information System (SINAN), Live Births Information System (SINASC), and Department of the Unified Health System (DATASUS).
[1]Incidence rate calculated from the number of cases of gestational syphilis/1,000 pregnant women (the estimated number of pregnant women is 2.5% of the total population); [2]incidence rate calculated from the number of cases of congenital syphilis/1,000 live births.

who did not vertically transmit the disease, diagnosis of syphilis was made mostly in the first trimester (43.6% – 48/110).

Treatment was prescribed for the pregnant women in 131 (97% – 131/135) cases and in all of them the prescription was Penicillin G Benzathine. However, in 27 (20.6% – 27/131) cases the prescribed dose of this drug was not consistent with the clinical classification of the disease. For 12 pregnant women with primary syphilis and 2 with secondary syphilis, penicillin dosage was above the recommendation for each of these classifications, and for 13 pregnant women with syphilis in the latent stage, the prescribed dose was below the recommended. As for those who were classified as tertiary syphilis, the dosage of the drug was appropriate for the clinical stage of the disease in all these cases (**Table 3**).

Of the 119 cases notified between 2010 and 2013, the partner's treatment which was concomitant to the patient's was carried out in 66 (55.5% – 66/119) cases. In 50 (42% – 50/119) cases, the partner was not treated together with the pregnant woman, thus reaching 48.6% (18/37) of the cases in 2012. The main reason for the absence of partner's treatment was the lack of contact of the pregnant woman with her partner after the diagnosis of syphilis, occurring in 36% (18/50) of cases. Other frequent reasons were not undergoing the syphilis serology as requested by the doctor in 9 (18% – 9/50) cases, and not having attended the health unit (US), although it was requested in 7 (14% – 7/50) cases (**Table 4**).

The treatment was prescribed appropriately in 52 (43.7% – 52/119) cases; however, the prescription was improper for 57 (47.9% – 57/119) pregnant women, and in 10 (8.4% – 10/119) cases this information is unknown. In the analysis of each studied year, the percentage of inappropriately prescribed treatment remained above 14.3%. In 2012, this percentage reached its peak, accounting for 51.4% (19/37) of cases. Although not statistically significant, it was observed that maternal–fetal transmission of syphilis occurred in 11.5% (6/52) of pregnant women with correctly prescribed treatment, whereas among those whose treatment was prescribed inappropriately, a larger number of patients eventually transmitted this disease to the fetus, corresponding to 22.8% (13/57) of them. The absence of the treatment of the concomitant partner stood out as the main reason for this inadequacy, occurring in 47 (82.5% – 47/57) of these cases (**Table 5**).

DISCUSSION

The results showed syphilis as a disease which is still present among pregnant women in Cascavel, and they also show its

Table 4 – Distribution of cases of gestational syphilis, according to the reasons for the absence of partner's treatment – Cascavel, Paraná, 2010 to 2013 (n=50)[a].

Reason for the absence of partner's treatment	Frequency	
	Absolute (n)	Relative (%)
Partner had no more contact with the pregnant women	18	36
Partner was not summoned to the HU for treatment	4	8
Partner was summoned to the HU for treatment but did not attend	7	14
Partner was referred/summoned to the HU but refused treatment	2	4
Partner with nonreactive serology	4	8
Serology requested for the partner, but with results ignored	9	18
Patient had no fixed partner	4	8
Ignored	2	4

Source: Information System for Notifiable diseases (SINAN).
[a]Considering the partners who were not treated concomitantly to pregnant women; HU: health unit.

Table 5 – Distribution of cases of gestational syphilis, according to the reasons for the inadequacy of treatment prescribed to pregnant women – Cascavel, Paraná, 2010 to 2013 (n=57)[a].

Reason for inadequate treatment to pregnant women	Frequency	
	Absolute (n)	Relative (%)
Pregnant women treatment not performed	3	5.3
Dosage not consistent with clinical classification	23	40.4
Partner not concomitantly treated	47	82.5

Source: Notifiable Diseases Information System (SINAN).
[a]There were 16 pregnant women with more than one reason for inadequacy of the prescribed treatment.

Table 3 – Adequacy of dosage of the treatment prescribed to pregnant women, according to the clinical diagnosis – Cascavel, Paraná, 2008 to 2013 (n=135).

	Dosage adequacy								p-value[a]
	Adequate		Inadequate		Ignored		Not performed		
	n	%	n	%	n	%	n	%	
Clinical Classification									
Primary	25	27.2	12	44.4	0	0	0	0	
Secondary	5	5.4	2	7.4	0	0	0	0	
Tertiary	10	10.9	0	0	0	0	0	0	
Latent	52	56.5	13	48.1	1	7.7	3	100	0.005
Ignored	0	0	0	0	12	92.3	0	0	
Total	92		27		13		3		

Source: Notifiable Diseases Information System (SINAN).
[a]Statistical χ^2 test.

progressive increase from 2010. Although the number of pregnant women in the city has been estimated based on a fixed percentage of the total population each year (2.5%), the increased number of cases of gestational syphilis during the study period was higher than the increase of the pregnant women in this city in the same period. Therefore, it is possible that this increase in disease incidence is related not only to its higher transmission but also to the increase in disease's diagnosis and reporting owing to the strategies that have been offered by the health system. On the other hand, failures in diagnosis and reporting of cases are probably still occurring. For 11 mothers of children with congenital syphilis, no syphilis records during pregnancy were found in the SINAN database. Thus, the total number of cases may be even higher than the one found in this study, which already shows disturbing numbers of such disease.

In our study, vertical transmission of syphilis was equivalent to 23.3%. Although this number is lower than the Brazilian estimate, such transmission rate showed a progressive increase between 2009 and 2012. Moreover, the congenital form of the disease has not only increased but also achieved numbers increasingly distant from the target set by the Ministry of Health to eliminate its occurrence. This situation reflects a possible failure in the health care of infected pregnant women with regard to the control and prevention of maternal–fetal transmission of syphilis.

If the treatment is not carried out or is conducted improperly, pregnancies can result in miscarriage, stillbirth, or fetal death in approximately 40% of cases and may also lead to birth of child with congenital syphilis in another 40% of cases[9]. In our study, 82.6% of the children of these women identified with congenital syphilis showed favorable outcomes with good survival conditions. All cases were classified with the recent type of the disease. However, adverse outcomes were also observed, such as three cases of stillbirth and fetal death related to congenital syphilis, which corresponded to 2.9% of the pregnancies with the infection.

The sociodemographic profile of the analyzed pregnant women indicates that syphilis is mainly occurring among young women (mean age equivalent to 25 years), with a high percentage among adolescents, in addition to revealing a poor educational level. Similar results were found by other authors[10-14]. Rodrigues *et al*. [15], in a national multicenter study that researched the vulnerability characteristics for syphilis in 3,047 puerperae, indicated that the risk of positivity for this disease is three times higher in patients with low educational level, and also high in cases of early pregnancy. Moreover, our study revealed that the majority of the pregnant women are housewives, followed by maids, which probably is in alignment to the profile of pregnant women of the city. The same can be inferred to the fact that the majority of the participants had white or brown skin color.

The prenatal care is fundamental in ensuring maternal and fetal health. It aims at following up women during pregnancy, promoting health and identifying risk factors to prevent complications for both the mother and the child. Official figures show a high coverage of this service, reaching more than 85% of pregnant women[16]. However, studies show that prenatal care has not accomplished a good control of the diseases that may occur during pregnancy[17]. Similar to other studies[13,18], we observed that the majority of the women (95.6%) received the prenatal care. However, this number is still lower than the guidelines from the Ministry of Health, which recommends that such service should cover 100% of the pregnant women[19]. Receiving prenatal care is not the only determining factor to prevent vertical transmission of syphilis; the quality of this service in terms of diagnosis and treatment provided is also of utmost importance. According to our study, prenatal care was incapable of ensuring the occurrence of favorable outcomes, as 16.3% of those women who received prenatal care vertically transmitted syphilis to their children. These results corroborate the quality deficiency of prenatal care, which has been associated with the alarming occurrence of this disease among pregnant women and its transmission to the fetus[20,21].

The diagnosis of syphilis during pregnancy is based on the screening of pregnant women with nontreponemal test (VDRL) in the first and third quarters, in addition to its conduction in childbirth or curettage. Laboratory confirmation by means of treponemal tests is recommended during pregnancy, but it is not mandatory; thus, it should not lead to delays in the treatment[3]. The timing and quantity of serological tests performed could not be determined based on the data from the notifications. However, in accordance with these recommendations, most of the pregnant women studied underwent treponemal confirmatory test. For the four cases in which this test was not performed, the diagnosis was based only on VDRL, without delay in treatment. The easy access to laboratory tests facilitates the identification and coverage of those cases requiring treatment, thus contributing to the control of syphilis transmission.

Another issue highlighted in this study concerns the association of high titers of VDRL with the occurrence of adverse outcomes during pregnancy. According to the literature, high titers are associated with syphilis recent acquisition, which has been linked to higher chances of vertical transmission and consequent unfavorable situations[3,22]. Given the potential seriousness of these cases, the need to devote special attention to pregnant women with syphilis is clear, specifically to those with evidence of recent infection.

With regard to the gestational period when diagnosis was carried out, it was noted that, in general, diagnosis was performed early. The majority of pregnant women were diagnosed in the first two quarters. Although less frequent, the diagnosis performed in the third trimester of pregnancy was associated with the vertical transmission of the disease. This association is probably due to the fact that when the diagnosis is carried out late in pregnancy, less time is available for the treatment of the disease, which needs to be carried out fully and timely to be able to prevent the vertical transmission. This finding reinforces the importance of the quality of the prenatal care, with early diagnosis, treatment, and prevention practices, such as counseling on condom use and partner's serological screening, which may reduce the need for treatment in the last trimester of the pregnancy, during which the actions may be limited.

Among the pregnant women with a prescribed treatment, the chosen antibiotic was Penicillin G Benzathine in its entirety. Although this drug has been prescribed for most pregnant women in a dosage which is appropriate for the particular stage of infection, the dosage was inadequate for a considerable portion of the women.

The overdose occurred in pregnant women with primary and secondary syphilis, possibly owing to the need of restarting the treatment, which would require an increased dose, or to the secular assumption that, in case of doubt, a higher dose schedule should be prescribed. We also observed a probable misclassification of syphilis in 10 pregnant women reported with tertiary syphilis, considering that its manifestation is rare and takes a long time. These pregnant women probably had latent syphilis; however, the prescribed dose may be considered appropriate, as the treatment is similar for both stages, except for the neurosyphilis.

The Penicillin G Benzathine was prescribed in a lower than recommended dose only for a portion of women with the latent form of the disease. It is recommended that a treatment of latent syphilis be carried out with two doses in the early syphilis and three doses in the late latent syphilis[3]. As the notification information system did not allow differentiating between these sub-classifications, the prescription elaborated with three doses of penicillin was considered appropriate for the latent form of the disease. Classified as below the recommended levels, prescriptions with two doses may have been appropriate, if the pregnant woman had been diagnosed with latent recent classification. Prescriptions equivalent to one dose in some cases may be due to the positive serology in a short period of time, which were therefore considered as primary syphilis and mislabeled as latent. Although information for the determination of the causes of inadequate dosages were missing, the fragility of health care for pregnant women was evident, considering the failures on the provisions for medication in the required dosage, which are essential to prevent the occurrence of transmission of syphilis to the fetus.

Given the potential for disastrous effects of syphilis on pregnancy, failures in its treatment should not be tolerated, considering its easy application, its low cost and its high efficacy[7,9]. Compared to the criteria of adequacy used in this study, a considerable percentage of pregnant women (47.9%) were treated inappropriately, and the absence of concomitant treatment for the partner appeared as the main reason (82.5%) of this inadequacy. These findings are similar to those of other national studies that analyzed this issue[11,12,23,24]. Thus, although pregnant women receive prenatal care and are administered the treatment correctly, they remained susceptible to reinfection from their untreated partners, resulting in greater chance of fetus contamination.

The absence of contact with the pregnant women, which is the main factor associated to the lack of treatment for the partners, reveals an even worse situation. Although pregnant women are exempt from the risk of reinfection in these cases, these men remain unaware of the possibility of having the disease, which makes them potent disseminators of the disease. Also relevant is the lack of partner treatment because of the nonperformance of serological tests ordered by the doctor. In such cases, the request for an examination represents a lost opportunity to prescribe a treatment for these men. The Ministry of Health recommends the treatment of the partner as essential and not dependent on the realization of laboratory diagnostics[3]. Therefore, actions related to care for the partner in prenatal care represent an important strategy to handle this disease during pregnancy, as it is a decisive factor for the pregnant women's cure and for the epidemiological control of the disease.

It is worth mentioning that, in addition to the probable underreporting of cases, a large part of the records had variables that are important for the diagnosis and monitoring of pregnant women and children with blank or ignored fields. Underreporting of characteristics such as educational level of the pregnant women and the clinical classification of the disease in the reporting forms – tools for precisely that purpose – reinforces the prenatal care deficiency, since a public health resource that is important for the planning of actions for pregnant women and their children is underutilized.

CONCLUSION

This study showed that despite being a disease of easy diagnosis, treatment, and control, syphilis remains a serious public health problem, presenting a high occurrence among pregnant women in our midst, with consequent and worrying incidence of vertical transmission. Maternal characteristics, such as low educational level and age ranging from adolescence to early adulthood were associated with gestational syphilis and indicated the most vulnerable groups for which strategies to combat this disease should be directed.

Results showed that provision of prenatal care for pregnant women is not enough to ensure disease control. Elimination of gestational syphilis and its disadvantageous consequences will only be possible when the monitoring of women during pregnancy is broad and carried out with quality. Therefore, early identification of pregnant women, examinations in accordance with the recommendations and, most importantly, the proper and timely treatment to pregnant women and their partners are necessary for preventing maternal–fetal transmission.

Considering the importance of surveillance of syphilis in pregnancy, an increase in the reporting of cases and an improvement in the quality of information related to them are necessary to the actions aimed at eliminating congenital syphilis.

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Conflict of interest

The authors report no conflict of interests.

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Address for correspondence:
ANA CAROLINA DE OLIVEIRA LAGO
Rua Conselheiro Carrão, 1451 – Hugo Lange
Curitiba (PR), Brasil
CEP: 80040-130
E-mail: analago_30@hotmail.com

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TEMARIO PRELIMINAR

Primer Módulo — La vigencia de un problema de salud publica

9,00-9,10	Bienvenida. Reflexiones sobre ITS
9,10 – 9,30	Situación de ITS en América Latina y el Caribe
9,30 – 9,50	¿Que se conoce de las ITS en Argentina?
9,50 – 10,15	Implicancias biopsicosociales de las ITS
10,15 – 10,30	Preguntas y Respuestas
10,30 – 11	Intervalo

Segundo Módulo — Sífilis: una enfermedad re-emergente

11,00 – 11,20	Patogénesis de la Sífilis
11,20 – 11,40	Manifestaciones dermatológicas
11,40 – 12,00	Sífilis congénita
12,00 - 12,20	Tratamiento y seguimiento - situaciones especiales
12,20 – 12,40	Preguntas y Respuestas
12,40 – 14,00	Receso de mediodía

Tercer Módulo — ITS Emergentes

14,00 – 14,20	Transmisión sexual del Virus del Zika. Impacto en el embarazo.
14,20 – 14,40	*M. genitalium*, un patógeno poco conocido
14,40 – 15,00	¿El cambio de paradigmas de como, cuando y a quien tamizar *Chlamydia trachomatis*?
15,00 – 15,15	Preguntas y Respuestas
15,15 – 15,45	Intervalo

Cuarto Módulo — La ITS mas prevalente… el Papiloma Virus Humano

15,45 – 16-10	Aspectos inmunológicos, Patogenia y Oncogenesis de la infección
16,10 – 16,30	Infección de VPH en el varón- Manejo actual de los condilomas acuminados-
16,30 – 16,50	Manejo de las lesiones intraepiteliales de bajo y alto grado
16,50 – 17,10	Actualización en vacunas
17,10 – 17,30	Preguntas y Respuestas
17,30 – 18,00	Resolución casos clínicos.

Quinto Módulo — Diagnóstico de ITS desde un caso clínico.

9 – 9,15	Caso clínico clave
9,15 – 9,30	El lugar de la microscopia
9,30 – 9,45	El lugar de los cultivos
9,45 – 10,00	El valor de la serología
10,00 – 10,15	Rol de la biología molecular
10,15 – 10.30	Uso de pruebas rápidas
15,15 – 15,45	Intervalo

Sexto Módulo — Abordaje actual de la secreción genital

11,00 – 11,20	Infecciones endógenas
11,20 – 11,40	Cervicitis
11,40 – 12,00	Secreción uretral en el varón
12,00 - 12,20	Complicaciones y secuelas de las ITS.
12,20 – 12,40	Preguntas y Respuestas
12,40 – 14,00	Receso de mediodía

Séptimo Módulo — Enfoque terapéutico

14,00 – 14,30	Enfoque adecuado del tratamiento antimicrobiano de las ITS
14,30 – 15,00	El problema de la resistencia antimicrobiana
15,00 -15,30	Estado actual de la Vigilancia de la Susceptibilidad Antimicrobiana de Gonococo en Argentina – PROVSAG-
15,30 – 16,00 hs	Intervalo

Octavo Módulo — ITS Virales

16,00 – 16,20	VIH e ITS- PREP- Nuevas Propuestas
16,20– 16,40	Avances en transmisión vertical del VIH
16,40 – 17,00	Hepatitis Virales , desde la prevención a la cura
17,00 – 17,20	Herpes genital con enfoque bio-psico-social.
17,20 – 18,00	Preguntas y Respuestas
18,00 – 19,30	Simposio CDC: Técnicas comportamentales en la prevención de ITS

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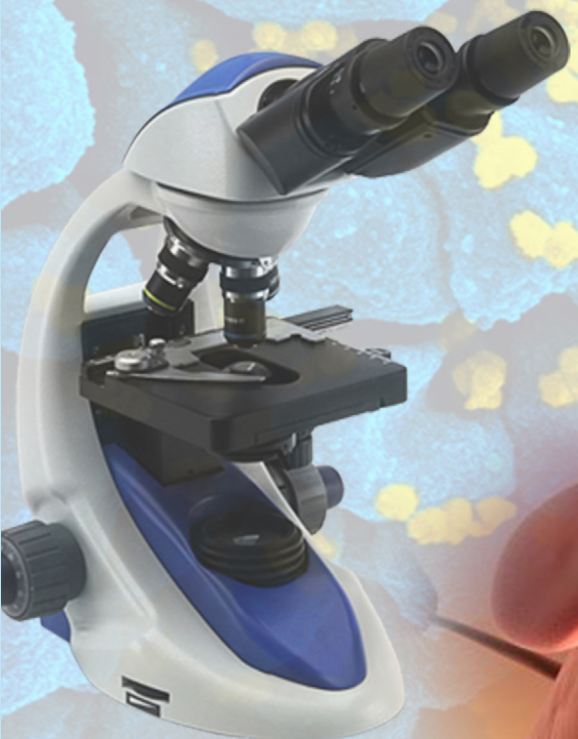

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