The importance of the dentistry professionals' participation in the coping strategies with the human papillomavirus (HPV) infection

Epidemiological studies have shown that infection by the Human Papillomavirus (HPV) is characterized as pandemic. Therefore, it constitutes a serious public health problem[1].

HPV does not observe cultural, social or economic rules, unlike certain infections that affect the economically disadvantaged countries, challenging the best health systems. The HPV oncogenic activity is responsible for 28% of all types of cancer associated with infections in the world. Studies in Brazil indicate that HPV, as a persistent infection, is responsible for almost all cervical cancers and numerous other malignancies in different organic sites as vulva, vagina, anus, penis and oropharynx. In Brazil, the oropharyngeal carcinomas associated with this virus represent 72%. In the United States, in Australia and in Northern Europe, the percentage corresponds to 50% of all cases[2,3].

Then, the perception of relations of HPV infection with carcinogenesis in various areas of the human body significantly demonstrates that the responsibility for preventive measures, diagnosis and treatment of the disease involves medical and dental care, nurses and nursing assistants for the actions they develop with patients, indispensable in the multidisciplinary strategies. It is worth emphasizing what does not always stand out in the literature: the important participation of dentistry, given the significant HPV relationship with premalignant lesions and squamous cell carcinoma of the oral cavity, the most frequent malignant tumor in this location[4]. This verification fully justifies the important inclusion of these professionals in the coping strategies with HPV infection that we discuss in this editorial.

Motivated by the HPV theme, a questionnaire was developed with 52 assertions to be answered by students of various academic training periods while preserving the identity of the participants. The sample, involving 249 dentistry students spread from first to ninth periods, represented five training centers of the state of Rio de Janeiro, Brazil. The questionnaire was applied in the classrooms, with spontaneous adhesion of the participants. The purpose of the research was initially described and followed by information about the epidemiology of HPV infection and its consequences to the population, reinforcing the importance of the dentistry participation in prevention, diagnosis and treatment of the epidemic. The constituent parts of the questionnaire involved assertions about the HPV virus, ways of transmission, infection-related diseases, incidence, prevention, symptoms, treatment and vaccines. The answers were statistically analyzed in percentage terms as to the errors and successes on the elaborated assertions.

Objectively, the study concluded that there are important knowledge gaps in relation to HPV infection, especially concerning the recognition of the oncogenic virus capacity, differential diagnoses, as well as vaccines and vaccination schedules.

This study involving only dentistry students represents a unique work not yet found in the systematic bibliographical review with similar characteristics.

Considering such findings, we suggest that the Ministry of Health, as the main government agency responsible for the health of the Brazilian population, develops national researches with dentistry professionals covering not only the HPV infection, but also many other diseases in which dentists along with doctors, nurses and their assistants can make a task force to achieve prevention, diagnosis and treatment.

Specifically for the construction of a wider strategy joined with the population, the participation of people involved in the social media, such as community leaders, religious in general, influencers on informational pages in social networks, official and unofficial, and especially professional groups of communication media, such as newspapers, magazines, radio and television, is a fundamental element to strengthen health professionals, and to become a popular, great and effective mobilization[5,6].

In addition, it is clear that HPV infection needs the participation of several health professionals, demanding actions informed by multidisciplinary clinical examination of the patient whom anamnesis identifies sexual practices of cunnilingus, fellatio and anilingus, requiring the physical examination of the oral cavity in order to look for changes in the mucosa by HPV infection.

The main changes in the oral mucosa caused by infection with HPV may be benign or malignant caused by various kinds of viral family and express themselves clinically by papilliferous growths (*Oral squamous papilloma*), verrucous (*Verruca vulgaris*), whitish boards (leukoplakias), rounded volume increase, sessile with rosy projections and dull surface (*Condyloma acuminatum*), crateriform ulcers of irregular periphery with high and hardened edges attached to underlying structures (*Squamous cell carcinoma*), or irregular growths with verrucous/papilliferous surface (*Verrucous carcinoma*)[4,7].

All intraoral regions and the lips may virtually show clinical manifestations resulting from HPV infections. HPV lesions in the oral cavity result mostly of oral sex practice and rarely by the virus translocation from one lesion to another area through the habit of putting fingers into the mouth, especially regarding common warts in children[5].

Another important point to be noted is that sexual practices involving the mouth are not properly mentioned in public health education programs, causing a negligence regarding the use of preventive barriers by practitioners of oral sex. For the practice of fellatio, the male condom use is an effective and necessary preventive[5]. About the

practice of cunnilingus and anilingus, there are no mechanical barriers commercially available. In such situations, polyvinyl chloride (PVC) film cut-outs or rubber sheets used in dentistry are suggested as mechanical barriers to cover the female genitalia and the anus to avoid direct contact of the mouth, especially the tongue, with these regions. The use of these ways of prevention is very small, indeed true anecdotal.

In Brazil, dentistry was historically characterized by an action mostly dissociated from medical and nursing activities, as if the mouth was not an integral and connected part of the human body. This independence of action was largely shaped by market interests, blaming the training centers of dental professionals for not giving priority in their curricular grids to the integration with schools of medicine and nursing. Within this striking Brazilian reality, it is observed there are rare dental schools interconnected with hospitals, making distant the professional integration and consequently causing the weakening of multidisciplinary actions in public health.

To reinforce the main purpose of this editorial about the importance of dentistry professionals' participation in the coping strategies with the HPV infection, we report official numerical data describing the profession in Brazil. The Federal Council of Dentistry of Brazil, in 2018, informed there were 306,789 dentists working, and 220 dentistry schools spread out in every state of the country, including the Federal District[8,9]. Approximately 11,000 new professionals arrive annually at the labor market. According to the Regional Dentistry Council of Rio de Janeiro (CRO-RJ), 31,215 dentists are regularly registered in the municipality, and 19,294 of them are women[10]. This numerical preponderance of female professionals is dominant all over Brazil.

Extending the observation of the strong feminization of dental professionals, it is observed that in other countries of the world this statement is also evident, as follows: women currently represent 40% of the population of dentists in the Netherlands. Based on the participation of educational programs, it is estimated that this number exceeds the 50% in the coming years[11]. In the United States, 42% of students in dentistry are women; in Finland, 75% of dentists are women. Women dentists in Russia are 48% of the workforce. In the United Kingdom, 50% of new freshmen in undergraduate courses in dentistry are women. In India, the same occurs between students, and about 50 to 60% of pupils in all schools of dentistry are female[12]. In Spain, among 26,725 dentists operating in the country, 44.37% are female[13].

We believe that the magnitude of these numbers is strongly appealing, so that the Brazilian public administrators of health prevention and education become alert and add the dental professionals in their health planning strategy.

It is also important to note that most women favor preventive gynecological examinations in their routines of personal care, and medical experts in this area are extremely engaged in coping with HPV infection, especially due to the viral relation with cervical cancer.

Finally, dentistry would for sure interact with other professions and medical specialties and would promptly meet the government call to participate in public health actions on HPV infection.

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Conflict of interests

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Vulnerability of adolescents to sexually transmitted infections

Vulnerabilidade a infecções sexualmente transmissíveis em adolescentes

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ABSTRACT

Introduction: Adolescents are especially susceptible to sexually transmitted infections, with approximately 1/7 of all new cases of human immunodeficiency virus infection in this group. **Objective:** To investigate the vulnerability to sexually transmitted infections among adolescents of the Centers for Testing and Counseling for Sexually Transmitted Diseases / Aids, CTAs, in the city of Juazeiro, state of Bahia, Brazil, from 2006 to 2012. **Methods:** This was an exploratory cross-sectional study that used secondary data from 1,173 adolescents. Data analysis was processed in Stata 9.0 software by descriptive statistics and Pearson's χ^2 test. **Results:** There was predominance of female adolescents (56.86%), brown (22.85%), single (80.22%), with 8–11 years of education (44.76%) and stable partner (56.78%). The prevalence of sexually transmitted infections was of 5.88%, and there was statistically significant association with sex (more prevalent among girls; p=0.014), education (more common among the less educated; p=0.031) and marital status (more frequent among married/common-law; p=0.036). **Conclusion:** Safer sex practices and later start of sexual activity combined with empowering actions, especially girls', are important steps to reduce sexually transmitted diseases among adolescents.

Keywords: adolescents; sexually transmitted diseases; counseling; aids.

RESUMO

Introdução: Os adolescentes são especialmente susceptíveis às infecções sexualmente transmissíveis, com aproximadamente um sétimo de todos os novos casos de infecção pelo vírus da imunodeficiência humana ocorrendo nesse grupo. **Objetivo:** Investigar a vulnerabilidade a infecções sexualmente transmissíveis em adolescentes usuários do Centro de Testagem e Aconselhamento para Doenças Sexualmente Transmissíveis/Aids, da cidade de Juazeiro, Bahia, de 2006 a 2012. **Métodos:** Tratou-se de um estudo analítico transversal exploratório que utilizou dados secundários de 1.173 adolescentes. A análise dos dados foi realizada pelo *software* Stata 9.0, por estatística descritiva, e teste χ^2 de Pearson. **Resultados:** Houve predomínio de adolescentes do sexo feminino (56,86%), pardos (22,85%), solteiros (80,22%), com 8 a 11 anos de estudo (44,76%) e parceiro estável (56,78%). A prevalência de infecções sexualmente transmissíveis foi de 5,88%, e houve associação estatisticamente significativa com o sexo (mais prevalente entre as meninas; p=0,014), escolaridade (mais frequente entre os de menor escolaridade; p=0,031) e estado civil (mais frequente entre casados/união estável; p=0,036). **Conclusão:** A adoção de práticas sexuais seguras e o início mais tardio da vida sexual, aliados a ações de empoderamento, especialmente das meninas, são medidas importantes para reduzir a propagação das infecções sexualmente transmissíveis entre os jovens.

Palavras-chave: adolescentes; infecções sexualmente transmissíveis; aconselhamento; aids.

INTRODUCTION

Estimates indicate there are more than two million adolescents living with human immunodeficiency virus (HIV) worldwide — about 1/7 of all new cases occur during adolescence —, and in spite of the efforts focused on preventing the infection, teenagers and young people in the age group 20–24 years old are still extremely vulnerable to contamination, especially girls[1].

According to the World Health Organization, access to counseling and testing, as well as the assimilation of information by teenagers, is significantly lesser considering adults, and access and coverage vary in different countries and regions[2]. The consequence can be observed in the mortality rates related to HIV, which increased 50% in this group from 2005 to 2012, although the overall number of deaths showed reduction of 30%[1], emphasizing the need of prioritizing actions for this population.

Adolescence involves the period between 10 and 19 years of age, characterized by numerous biological, psychological, social, and behavioral transformations[3]. Adolescents make up a group particularly susceptible to sexually transmitted infections (STI), due to new experiences and experiments that often occur in this age group, early start of sexual activity, difficulty to distinguish self-care attitudes, such as condom use, and involvement with alcohol and other drugs[3]. Those ones who live in economic and social vulnerability situations are more exposed to the risk of being infected with STIs[2].

When the situation of adolescents is compared with other age groups, they are considered the most vulnerable to STIs[4]. They are also a heterogeneous group (with some being particularly vulnerable to HIV and other infections) composed of orphans, migrants and refugees, prisoners, girls who have sex with older men and with multiple or simultaneous sexual partners, the sexually abused and exploited, who live on the streets and are socially marginalized and discriminated[2].

This study was developed in the STD/Aids Reference Unit of the city of Juazeiro, Bahia State, by the Center of Epidemiology and Health of the Universidade Federal do Vale do São Francisco.

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We can also characterize a higher or a lesser adolescents' vulnerability according to sex, as it is observed that girls are at greater risk, due to biological, social and economic motives[5]. Unequal gender relations and non-recognition of women's rights, including the sexuality legitimacy, are some of the reasons that make girls especially vulnerable to STIs[4]. This heterogeneity of adolescents needs to be recognized, from infection modes, age, sex, sexual orientation up to their roles and responsibility for the family and community[2], since such differences may influence the ability to make decisions and to access health services.

In Brazil, skin color, sex, place of residence, having or not some type of disability can determine opportunities and access to the right to health[4]. Adolescents in the northeastern region of the country, more specifically in the northeastern semi-arid region, are in a situation of inequality when compared to other Brazilian regions, and, consequently, have their vulnerabilities amplified and their rights daily violated[4] and therefore they are more exposed to STIs.

Many adolescents living with some STI, especially HIV, are unaware of their status, and effective strategies are necessary to promote greater access to counseling and HIV testing, which are essential for early diagnosis, reduction of transmission and improvement of life quality[3]. The Testing and Counseling Centers (CTA) are among the services that provide assistance to STIs cases and are gateways to the application of prevention strategies. These services, in addition to prevention activities of HIV infection and other STIs, such as hepatitis B, C, and syphilis, also perform confidential and anonymous diagnostic tests, distribute supplies to prevent transmission, as male and female condoms, refer users with positive testing to services and offer monitoring after diagnosis, including counseling for HIV-positive and serodiscordant couples[6].

In general, adolescents have more access to information about STIs and self-care, which does not necessarily mean adopting protective attitudes.

OBJECTIVE

To investigate the vulnerability of STIs amongst adolescents of the CTA to STD / Acquired Immune Deficiency Syndrome (Aids) in the city of Juazeiro, state of Bahia, Brazil, in the period from 2006 to 2012.

METHODS

Observational cross-sectional analytical study of exploratory character based on secondary data from health services. The study was developed in the CTA Reference Unit for STD / Aids of Juazeiro, where also operates the Specialized Assistance Service (SAE) in STD / HIV / Aids.

The data were extracted from the Entry Forms of the CTA Information System (FE-SI-CTA), of the clinical records of the SAE and the Care Description Form in which the complementary sociodemographic data are registered. The study population consisted of adolescents enrolled in the aforementioned CTA, between 2006 and 2012, excluded blank forms and repeated forms (when the individual had more than one FE-SI-CTA registered, it was considered the most recent one, observed the date of the interview).

The sample calculation took as groundwork 40,245 adolescents (considering the population estimate of this age group of the city in 2012)[7], adopting the outcome prevalence of 50%, and the estimated error of 4% was defined as the sample size corresponded to 1,040 subjects. As the total of adolescents with valid forms slightly exceeded the sample size, all of them were included, totaling 1,173 participants.

The data collection took place in the service during the working period through the evaluation of the documents mentioned above, with direct typing in a specific database for research, since a digital information system is not available in the CTA of Juazeiro yet. Prior to the start of the data collection, the staff was trained for the standardization of procedures.

Sociodemographic variables were analyzed (sex, age, color, marital status, schooling, professional situation and clientele origin), as well as variables related to individual vulnerability (type of exposure, STD in the former year, steady partner, sexual preference, number of sexual partners in the previous year, condom use with steady and nonsteady partners, motive for not using a condom with a steady and nonsteady partner, age of the first sexual experience, condom use in the first sexual experience and serology results for HIV, hepatitis B, hepatitis C, and syphilis). The categories adopted for the variables were the same presented in the FE-SI-CTA and in the Care Description Form, except age group and age of first sexual experience, which were categorized based on the frequency observed in the sample.

The conclusive variable (STI) was categorized as "no" when the result of all serologies was negative, and "yes" for the positive result. For the analysis of the association, all observations that did not present the results of the test (ignored information) were excluded, and the adolescents who had more than one infection were computed only one time.

The data were typed in Microsoft Office Excel 2007, sent to Stata 9.0 software, and processed for quality control and analysis of coherence and consistency through the generation of frequency tables. Whenever failures were identified, the collection tools were consulted again. The statistical analysis was performed by the distribution of variables by sex, in absolute and relative values. Pearson's χ^2 test was used for association analysis, and it was adopted the confidence interval of 95% (significance level of 5%).

This study is part of the Epidemiological Survey on Testing and Counseling Center Reference Unit for STD / Aids of Juazeiro-BA, which was adopted by the Committee of Ethics in Human and Animal Studies of Universidade Federal do Vale do São Francisco (Univasf), following the recommendations of the current legislation. As secondary data, secrecy and confidentiality was assured by the responsible researcher.

RESULTS

The sociodemographic characteristics of participants according to sex are detailed in **Table 1**. Of the total of 1,173 adolescents investigated, 56.86% were women. The frequency of assistance increased with age, and the age group with the highest concentration of care was 19 years old, for both females and males. Sixteen-year-old girls sought more the service. However, from 17 years of age, this search was more observed among boys. The age group up to 12 years old distinguishes, as the percentage of girls attended

was more than twice of the boys. As for the civil state, about 20% of young people were married or living in a common-law status, a situation more frequent in females.

Although more than 2/3 of the adolescents had no record of skin color, among those who had, most of them were defined as brown.

Table 1 – Sociodemographic characteristics of adolescents attended at the Testing and Counseling Centers (CTA) in Juazeiro, Bahia, Brazil, from 2006 to 2012, according to sex (N=1,173).

Variables			Male		Female	
	n	%	n	%	n	%
	1,173	100	506	43.14	667	56.86
Age group (years old)						
≤12	33	2.81	8	1.58	25	3.75
13	50	4.26	16	3.16	34	5.10
14	69	5.88	20	3.95	49	7.35
15	123	10.49	51	10.08	72	10.79
16	156	13.30	60	11.86	96	14.39
17	194	16.54	85	16.80	109	16.34
18	250	21.32	115	22.73	135	20.24
19	298	25.40	151	29.84	147	22.04
Color						
Brown	268	22.85	110	21.74	158	23.69
Black	62	5.29	31	6.13	31	4.64
White	54	4.60	24	4.74	30	4.50
Not informed	789	67.26	341	67.39	448	67.17
Marital status						
Married/ Common-law	225	19.18	59	11.66	166	24.89
Single	941	80.22	444	87.75	497	74.51
Not informed	7	0.60	3	0.59	4	0.60
Education (years)						
None	7	0.60	1	0.20	6	0.90
1–3	69	5.88	30	5.93	39	5.85
4–7	420	35.81	172	33.99	248	37.18
8–11	525	44.76	227	44.86	298	44.68
12 or more	148	12.61	75	14.82	73	10.94
Not informed	4	0.34	1	0.20	3	0.45
Occupation						
Freelance	64	5.46	45	8.89	19	2.85
Unemployed	110	9.38	61	12.05	49	7.35
Employed	222	18.92	137	27.08	85	12.74
Student	619	52.77	246	48.62	373	55.92
Housework	148	12.62	12	2.37	136	20.39
Not informed	10	0.85	5	0.99	5	0.75
Clients origin						
Dissemination material	185	15.77	91	17.98	94	14.09
Friends/users	489	41.69	223	44.07	266	39.88
Newspaper/ radio/TV	9	0.77	4	0.79	5	0.75
Blood bank	4	0.34	3	0.60	1	0.15
Service/health professional	418	35.63	154	30.43	264	39.58
Call centers	29	2.47	14	2.77	15	2.25
Others	27	2.30	11	2.17	16	2.40
Not informed	12	1.03	6	1.19	6	0.90

The most prevalent schooling was 8 to 11 years of education, with similar percentage between the sexes, although, in general, women showed less years of education. The predominant occupation was student. The percentage of participants with formal employment was higher among boys and, housework among girls. In relation to the origin of the clientele, friends/users was predominant in both sexes, with higher percentage of males, followed by health service/ professional, with higher percentage of females, and dissemination material more frequent among males.

Table 2 presents the variables related to situations of vulnerability to STIs, according to sex. The kind of exposure most prevalent was sexual intercourse, with similar distribution between sexes,

Table 2 – Vulnerability situations according to sex of adolescents attended at Testing and Counseling Centers (CTA) of Juazeiro, Bahia, Brazil, from 2006 to 2012 (N=1,173).

Variables			Male		Female	
	n	%	n	%	n	%
	1,173	100	506	43.14	667	56.86
Type of exposiure						
Sexual intercourse	938	79.97	409	80.83	529	79.31
Vertical transmission	27	2.30	5	0.99	22	3.30
No risk	30	2.56	14	2.77	16	2.40
Others	123	10.48	50	9.88	73	10.94
Not informed	55	4.69	28	5.53	27	4.05
STD in former year						
Yes	480	40.92	170	33.60	310	46.48
No	459	39.13	225	44.47	234	35.08
Not informed	234	19.95	111	21.93	123	18.44
Steady partner						
Yes	666	56.78	218	43.08	448	67.17
No	469	39.98	271	53.56	198	29.68
Not informed	38	3.24	17	3.36	21	3.15
Sexual preference						
Heterosexual	1,027	87.55	426	84.19	601	90.10
Homosexual	25	2.13	21	4.15	4	0.60
Bisexual	26	2.22	20	3.95	6	0.90
No sexual life	41	3.50	13	2.57	28	4.20
Not informed	54	4.6	26	5.14	28	4.20
Number of sexual partners in the previous year (partners)						
None	151	12.87	60	11.86	91	13.64
1	474	40.41	121	23.91	353	52.92
2–4	353	30.09	188	37.15	165	24.74
5–10	121	10.31	82	16.20	39	5.85
11–50	55	4.69	42	8.30	13	1.95
51–100	2	0.17	2	0.40	0	0.00
>100	3	0.26	2	0.40	1	0.15
Not informed	14	1.2	9	1.78	5	0.75
Use of condom with steady partner						
Always	207	17.65	94	18.58	113	16.94
Never	258	21.99	69	13.64	189	28.34
Sometimes	370	31.54	145	28.65	225	33.73
Does not apply	318	27.11	185	36.56	133	19.94
Not informed	20	1.71	13	2.57	7	1.05

Continue...

Table 2 – Continuation.

Variables			Male		Female	
	n	%	n	%	n	%
	1,173	**100**	**506**	**43.14**	**667**	**56.86**
Motive for not using condom with steady partner*						
Do not like	202	31.17	62	27.31	140	33.25
Partner not acceptance	55	8.49	10	4.41	45	10.69
No condom at the moment	98	15.12	55	24.23	43	10.21
Trust partner	168	25.93	62	27.31	106	25.18
Others	80	12.35	18	7.93	62	14.73
Not informed	45	6.94	20	8.81	25	5.94
Use of condom with nonsteady partner						
Always	193	16.45	132	26.09	61	9.15
Never	121	10.31	53	10.47	68	10.19
Sometimes	211	17.99	132	26.09	79	11.84
Does not apply	628	53.54	176	34.78	452	67.77
Not informed	20	1.71	13	2.57	7	1.05
Motive for not using condom with nonsteady partner**						
Does not like	91	25.85	47	23.74	44	28.57
Partner not acceptance	19	5.40	3	1.51	16	10.39
Not available at the moment	78	22.16	64	32.32	14	9.09
Trust partner	38	10.79	18	9.09	20	12.99
Others	70	19.89	37	18.69	33	21.43
Not informed	56	15.91	29	14.65	27	17.53
Age of first sexual intercourse (years old)						
≤12	96	8.18	54	10.67	42	6.30
13	124	10.57	60	11.86	64	9.59
14	169	14.41	71	14.03	98	14.69
15 y	163	13.90	70	13.83	93	13.94
>15	246	20.97	100	19.76	146	21.89
Does not know/ does not remember	11	0.94	7	1.38	4	0.60
Not applied	91	7.76	39	7.71	52	7.80
Not informed	273	23.27	105	20.76	168	25.19
Use of condom in the first sexual intercourse						
Yes	145	12.36	60	11.86	85	12.74
No	116	9.89	55	10.87	61	9.15
Does not remember	4	0.34	1	0.20	3	0.45
Not applied (did not start sexual life)	92	7.84	41	8.10	51	7.65
Not informed	816	69.57	349	68.97	467	70.01

STD: sexually transmitted diseases; *excluded participants who in the variable use of condom with steady partner reported using condom always and those who did not have a fixed partner (N=648); **excluded participants who in the variable use of condom with nonsteady partner reported using condom always and those who did not have a nonsteady partner (N = 352).

followed by vertical transmission, often about three times higher among women. The occurrence of STIs in the previous year was increased and more common in females. Most women had a regular partner, unlike men. Heterosexual preference was observed, but the proportion of homosexuals and bisexuals was approximately five times higher among men. Most women had only one partner in the previous year; among men, the majority had two to four partners. High percentage of adolescents mentioned more than four sexual partners in the former year (15.44%), and among men, this percentage was of 25.31% compared to women, who showed the percentage of 7.95%.

The consistent or routine use of condoms (uses always) with regular partner was low, with similar percentages in both sexes, but the proportion of women who never used it was the double of men (**Table 2**). The main reasons reported for not using condoms were as follows: "do not like it", with higher percentage among women; "trust partner", with similar percentage between the sexes; and "not available at the moment," with twice as often among men. It stands out that the percentage of women who declared "partner does not accept" as the reason for not using condoms was two times higher than that of men (**Table 2**).

Concerning the consistent use of condoms with no steady partner, only 26% of men and 9.15% of women adopted this behavior; the percentage of those who never used it was similar between sexes. The more reported reasons to not use condom were "do not like" among women and "not available at the moment," between men. The proportion of women who said "partner not acceptance" was seven times higher than that of men (**Table 2**).

Most adolescents reported having initiated the sexual life early, less than 15 years of age. It was observed the percentage reporting sexual initiation before 12 and 13 years old, respectively 8.18 and 10.57%; in both cases, the frequency was higher among men. The use of condom in first sexual experience was low, with prevalence of a slightly higher use among women, although almost 70% had no record of this information (**Table 2**).

The prevalence of STIs in this population was of 5.88% (**Table 3**). **Table 3** shows the frequency of each quarter (HIV, hepatitis B and C, and syphilis) according to sex. Syphilis registered the highest STI occurrence, and in women it was almost twice that of men; the HIV seropositivity was five times higher among women. Considering the results of the serology for hepatitis B and C, the prevalence of infection was low, but it stands out the percentage of young people who did not carry out the tests besides ignoring information.

Table 4 presents the results of analysis of the association between the outcome (STI) and the sociodemographic variables, showing statistically significant association with sex (almost twice the frequency among girls), education (more common among adolescents with lower education) and marital status (more common among married/common-law). The presence of STI did not show statistically significant association with age and skin color.

DISCUSSION

The female predominance in the study was similar to the observed by the CTA in the southern region of Brazil[8] and in the northeast region (Feira de Santana, BA, Brazil)[9], evidencing women's greater concern regarding health care and, consequently, the greater demand for services. However, this may also mean that women are more exposed to situations of risk of STIs and wish to know their serological status.

The prevalence of STIs in this group of adolescent was high, but it might be underestimated because many adolescents did not perform some of the serologies offered, especially hepatitis B and C, or had no record of the test results. Adolescents are more susceptible to STIs due to the inherent age characteristics and often deficiency in information and practical knowledge, therefore they need actions and specific health interventions[5]. Adolescence is one of the richest stages of human life, full of possibilities for learning, experimentation, and innovation that needs to be lived fully and healthy. Facing the inequalities and reducing the vulnerabilities of that group are urgent tasks and can be done through universal public policies and specific policies for different living conditions of adolescents[4], empowerment and individual and collective responsibility.

The STI frequency difference observed between sexes can be related to the fact that the consistent use of condoms has been lower among adolescents, especially with nonsteady partners, showing gender-related inequalities regarding sexuality, and also to the fact that women are more susceptible to contamination by biological[5] issues, and therefore more exposed and vulnerable. In addition, women are often shy to discuss issues about sexuality and STD/Aids, demonstrating greater ignorance about these themes when compared with men[10].

Table 3 – Results of serology for human immunodeficiency virus (HIV), hepatitis and syphilis, according to sex, of adolescents attended at the Testing and Counseling Centers (CTA) of Juazeiro, Bahia, Brazil, from 2006 to 2012 (N=1,173).

Variables			Male		Female*	
	n	%	n	%	n	%
	1,173	**100**	**506**	**43.14**	**667**	**56.86**
HIV serology testing						
Non-reagent	1,007	85.85	436	86.16	571	85.61
Reagent	16	1.36	2	0.40	14	2.10
Not carried out	10	0.85	2	0.40	8	1.20
Not informed	140	11.94	66	13.04	74	11.09
Hepatitis B serology						
Non-reagent	397	33.84	166	32.81	231	34.63
Reagent	9	0.77	3	0.59	6	0.90
Not carried out	200	17.05	85	16.80	115	17.24
Not informed	567	48.34	252	49.80	315	47.23
Hepatitis C serology						
Non-reagent	203	17.31	79	15.61	124	18.59
Reagent	3	0.25	1	0.20	2	0.30
Not carried out	339	28.90	146	28.85	193	28.93
Not informed	628	53.54	280	55.34	348	52.18
VDRL serology						
Non-reagent	939	80.05	409	80.83	530	79.46
Reagent	49	4.18	15	2.96	34	5.10
Not carried out	14	1.19	4	0.79	10	1.50
Not informed	171	14.58	78	15.42	93	13.94

VDRL: Venereal Disease Research Laboratory; *eight adolescents had two sexually transmitted infections (STIs) simultaneously (six had syphilis and HIV; two had syphilis e hepatitis B).

Syphilis was the most prevalent STI, with frequency almost twice higher in females, evidencing the risk of vertical transmission and occurrence of congenital syphilis. Syphilis is a disease that could be controlled with relative easiness, since there are effective means of diagnosis and treatment available. The vertical transmission is preventable through the early supply of serology for pregnant women during prenatal care and the appropriate treatment of the infected, including the treatment of the partners, which is indispensable to break the disease transmission chain[11]. There are frequent associations between the different STDs, with an important relationship between syphilis and the increased risk of contracting HIV, especially with the presence of genital ulcers[12].

The prevalence of HIV seropositivity was similar to that found in another CTA in Bahia, in young people aged 13 to 19 years old (1.26%)[9]. As well as syphilis, there were more cases of HIV infection in females, a situation also observed in other studies[8,9]. This result reveals the tendency to increase the incidence of HIV infection

Table 4 – Results of the analysis of association between sociodemographic variables and sexually transmitted infection (STI) in adolescents attended at the Testing and Counseling Centers (CTA) of Juazeiro, Bahia, Brazil, from 2006 to 2012 (N=1,173).

Variables	Yes		No		Total		p[b]
	n	%	n	%	n	%	
	69[a]	**5.88**	**1,104**	**94.12**	**1,173**	**100**	
Sex							
Male	20	3.95	486	96.05	506	100	0.014
Female	49	7.35	618	92.65	667	100	
Education[c4]							
None	1	14.29	6	85.71	7	100	
1–3	6	8.70	63	91.30	69	100	
4–7	35	8.33	385	91.67	420	100	0.031
8–11	21	4.00	504	96.00	525	100	
12 or more	6	4.05	142	95.95	148	100	
Age (years old)							
≤12	2	6.06	31	93.94	33	100	
13	1	2.00	49	98.00	50	100	
14	4	5.80	65	94.20	69	100	
15	8	6.50	115	93.50	123	100	0.966
16	9	5.77	147	94.23	156	100	
17	11	5.67	183	94.33	194	100	
18	14	5.60	236	94.40	250	100	
19	20	6.71	278	93.29	298	100	
Marital status[c7]							
Married/ Common-law	20	8.89	205	91.11	225	100	0.036
Single	49	5.21	892	94.79	941	100	
Color[c789]							
Brown	22	8.21	246	91.79	268	100	
Black	5	8.06	57	91.94	62	100	0.776
White	6	11.11	48	88.89	54	100	

[a]Adolescents with coinfections (8) were considered only one time (n=69); [b]level of statistical significance; [c]number of observations lost in variable.

among women, a process known as the feminization of Aids, which has been occurring in practically all countries[5].

According to data from the Ministry of Health, the gender ratio (which expresses the number of cases in men divided by the number of cases in women) in 1989 was of six cases in men per one case in women (6:1) and in 2011 it grew to 1.7:1. However, since 1998, in the age group from 13 to 19 years old, the number of Aids cases was higher among women, an inversion observed only in this age group[13]. In 2013, the ratio of sexes in the age group from 13 to 19 years old was 1.3:1, but, as age increases, the sex ratio decreases, with greater participation of men among the youngest and of women among the oldest[14]. These oscillating tendencies show that, although young people know about STD/Aids and their forms of prevention, HIV infection grows[14].

Regarding the prevalence of hepatitis B and C, it should be taken into account the large proportion of adolescents who did not perform tests or who did not have the result registered, representing loss of information, and, above all, a missed opportunity for the infection prevention, diagnosis and treatment. Expanding the testing and diagnosis of viral hepatitis is extremely important and one of the priorities of the Ministry of Health, because it means more notification and, consequently, more reliable information on the number of existing cases, enabling appropriate interventions planning[15].

In 2010, the northeast region showed the lowest rate of detection of hepatitis B in the country, 2.5 cases per 100,000 inhabitants, which can be the result of both the low diagnoses index and the high underreporting of cases diagnosed in this region. According to the distribution by age group in the same year, it was observed that the rate of detection of hepatitis B cases was higher in females between 15 and 29 years old, higher in boys under 10, and similar between genders in the age group from 10 to 14 years old[15], but in general the rate of detection of hepatitis B was higher in adolescents. With regard to hepatitis C, in 2010, the northeast region also showed lower detection rate than the national, 1.2 cases per 100,000 inhabitants, while the national average for this year was 5.4. In adolescents, the detection rate was similar between sexes[15].

As for the color, there was higher percentage of brown people, which is similar to the findings of a study conducted at the CTA of Feira de Santana, which found more than 70% of brown[9], diverging from the study in a CTA in the south region, which found higher percentage of white users[7,8]. These divergences reflect the existing miscegenation in the different regions[16]. In the present study, the color of more than 2/3 of the adolescents was not registered. The fact that this variable is not investigated in the FE-SI-CTA, as it is recorded only in the entry description form, can contribute to the loss of information. The variables related to race/color indirectly bring important information related to the historical process of social organization, which may indicate situations of iniquities[17], and, therefore, it is essential to register them in health services. Comparing the proportional distribution of Aids cases according to race/color between men and women in Brazil from 2004 to 2013, it is observed that there is no statistically significant difference in proportions by sex, except among those of black color, in which the proportion of infected women is higher than in men[14].

In the analysis of the association between STI and education, less years of study means more prevalence of STIs. Higher schooling represents greater degree of education and empowerment, which favors the adoption of safer[18] sexual practices, as it influences the discernment and decision-making skills. Among the adolescents investigated, there was higher percentage of women in the categories "none" and "4 to 7 years" compared to men, and, in general, men's schooling was higher. This may also be an explanation for the higher percentage of women with STIs, since the knowledge and the ability to process information is an important factor for the infection's prevention.

When the marital status is concerned, despite the predominance of single individuals attended in the service, the percentage of STIs among the married/common-law status was higher than among the single ones, and this variable was statistically associated with the outcome. Considering that the proportion of married women was twice the men's, this could also be a factor that would explain the higher percentage of STIs among them, since married women/common-law trust their partners and tend not to use condom or use it in an inconstant[9] way. Similar behavior can be observed in steady relationships, even if they do not configure a conjugal relationship, highlighting that most of these women declared to have a stable partnership (steady partner) and does not use condoms or use them irregularly. The literature revealed that the use of hormonal contraceptives is one factor to be associated with the inconsistent use of condoms with stable partners, suggesting that adolescents use less condoms when they have access to other means of contraception[19].

Regarding the origin of the clientele, sharing information with group of friends and the contact with health professionals proved to be important to encourage the investigation of serological status. On the other hand, it is observed that the dissemination of information in the media had a very small scope and it seems not to achieve the goal of stimulating the adolescent to self-care. This result may be an alert so that the strategy of information disclosure be revised and appropriate, seeking more effective alternatives.

The most frequent exposure type was sexual intercourse, followed by vertical transmission, similar results to those found in a CAT in the southern region[8]. According to the epidemiological bulletin of HIV/Aids among children under 13 years of age, almost all cases had the vertical transmission as the way of HIV infection; among individuals with 13 years old or over, the main route of transmission is sexual, both among men and women[14]. This reflects the nonuse or the inconsistent use of condoms during sexual intercourse, as observed in adolescents who participated in this study, confirmed by the high prevalence of STDs in the year prior to filling out the form, mainly among women. The male condom is the most effective available technology to reduce the sexual transmission of HIV and other sexual[5] transmission. The female condom is a new technology, but very efficient, which can serve as a means to control the difficulties that women have in negotiating the condom use with their sexual partners, although the use is still restricted.

Heterosexual preference predominated in this population, but homosexual and bisexual frequency was approximately five times greater among men, reaching 8%. There is an increased tendency in the proportion of Aids cases in men who have sex with men in the last ten years, from 34.6% in 2004 to 43.2% in 2013, also observed in the age group 13–19 years old[14]. On the other hand, the

proportion of cases among heterosexual men in the same age group shows decrease during that period.

The regular use of condoms with steady partner, in both sexes, was low, reflecting the vulnerability of these adolescents to STI. The most common reasons for not using condom with regular partner, both for girls and boys, were "do not like it", and "trust partner", similar to that observed in a study conducted in the city of Goiânia, GO, Brazil[19]. According to the authors, the trusting partner is probably related to the bond and emotional involvement at the time of the sexual intercourse, added to the fear of jeopardizing the relationship by creating doubts about the fidelity of the partner[19].

The fact of disliking the use of condoms can reflect misinformation or prejudice about the preservative, associating it with the loss of naturalness in the relationship and the discomfort caused by its use. It was noted that the percentage of women who claimed that reason was higher than that of men's. Among the adolescents, the fact that the partner does not accept condoms also had major proportion showing the predominance of male wish, so that the woman still has a little active role on that decision. Among boys, the third alleged motive was "not available at the moment", showing that condom use is not a routine behavior yet.

Likewise, the consistent use of condoms with nonsteady partner was very low in both sexes. The reasons for not using a condom with nonsteady partner reported by adolescents resemble the reasons "do not use with steady partners", "do not like it", "trust partner". Assigning trust to a nonsteady partner shows that female adolescents adopt similar postures with steady partners, revealing an emotional significance to a sporadic relationship. Among female adolescents the motive "partner not acceptance" reinforces the gender behavior, and among boys the unavailability of the condom at the time of sexual intercourse.

Most adolescents revealed the first intercourse at the age of 15 or under, similar to that found in the city of Goiânia[19]. The early start of sexual intercourse (under 15 years of age) is a risk factor to STIs, especially for girls, since many start their sexual intercourse with older men and become more exposed[3,5]. The high percentage of adolescents who reported first sexual experience at the age of 13 or under can also be related to sexual abuse and prostitution situations, since the number of partners in the previous year was high.

The condom use at first sex experience was low, considered the large number of lost data in that category. The precocity of sexual initiation also contributes to the nonuse. This reinforces the importance of the family, the school and the health services in guiding these adolescents to practice safe sex from the beginning of their sexual activities, contributing to the reproduction of this behavior throughout life[20].

It must be considered that this study presents some limitations related to the use of secondary data, such as the reliability of the records and the loss of information. The homogeneity of the group of participants from a CTA can also be seen as a limitation of the study, as it hinders the identification of statistically significant differences.

CONCLUSION

The results identified the high prevalence of STIs, with predominance of syphilis, inconsistent use of condoms, early start of sexual life, greater vulnerability among girls — those with lower levels of education and those involved in stable relationships. The adoption of safer sexual practices, with the correct and systematic use of male and female condoms, as well as the later start of sexual life and the reduction in the number of partners, coupled with actions to rescue the identity, self-esteem and empowerment of adolescents, in particular girls, is an important measure to prevent or reduce the transmission of STIs among young people.

The CTA has a strategic role in the protection of this group, and should be articulated with the health network and schools, bringing information and establishing bonds that favor access to counseling, testing and early diagnosis.

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Conflict of interests

The authors declare no conflict of interests.

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Recurrent vaginal discharge: a myth or a fact?

Corrimento vaginal recorrente: mito ou fato?

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ABSTRACT

Introduction: Vaginal discharge is a frequent gynecological complaint, and may represent a disease or not. A vaginal discharge is considered recurrent when it occurs four or more episodes per year. Among the aetiologies, physiological and infectious conditions are mentioned, being the infectious ones, particularly those caused by *Candida spp.* fungus, the most related to the symptom. Despite the diagnostic and therapeutic resources available, empirical clinical treatments and self-treatments are very frequent and related to ineffective therapeutic results, leading this population to question what the differences regarding women with no symptoms are. **Objective:** To identify sociodemographic, behavioral and microbiological differences between women with recurrent vaginal discharge and asymptomatic women. **Methods:** Cross-sectional study involving 126 women with recurrent discharge complaints (study group) and 155 (control group), totaling 281 evaluated women. The group included women in the menacme, sexually active, and those who fit in the criteria of recurrent vaginal discharge, without definite previous diagnosis, compared with asymptomatic women, who attended an annual routine examination. Pregnant, diabetic and immunosuppressed women were excluded. The study was based on the principle of the null hypothesis, when there are no differences between the two studied groups. **Results:** The average age was 29.95 years, predominantly single and without children. There was no significant difference in the analysis of relationship time with the current partner, numbers of partners throughout life, gender and contraceptive method. There was predominance of normal vaginal flora (type 1) in both groups, with average prevalence of 44.9%. The alkaline vaginal pH was predominant in the study group. **Conclusion:** The null hypothesis was confirmed. Biological, behavioral and sociodemographic differences in the studied populations were not identified. In women with recurrent discharge group, there were no infectious etiologic factors, suggesting that clinical diagnoses are not sufficient for the most efficient management of these situations, indicating laboratory evaluation for these cases in order to improve diagnostic accuracy.

Keywords: vulvovaginitis; vaginal discharge; leukorrhea; gynecological examination; vulvovaginal candidiasis; bacterial vaginosis.

RESUMO

Introdução: O corrimento vaginal é queixa ginecológica frequente, podendo ou não representar doença. Conceitua-se como corrimento vaginal recorrente aquele que ocorre em quatro ou mais episódios ao ano. Entre as etiologias, citam-se condições fisiológicas e infecciosas, sendo as infecciosas, particularmente as causadas por fungo *Candida spp.*, as mais relacionadas ao sintoma. Apesar dos recursos diagnósticos e terapêuticos disponíveis, tratamentos clínicos empíricos e autotratamentos são muito frequentes e associados a resultados terapêuticos pouco efetivos, levando essa população a questionamentos sobre quais diferenças elas teriam em relação a mulheres sem sintomas. **Objetivo:** Identificar diferenças sociodemográficas, comportamentais e microbiológicas entre mulheres com corrimento vaginal recorrente e mulheres assintomáticas. **Métodos:** Estudo transversal envolvendo 126 mulheres com queixa de corrimento recorrente (grupo de estudo) mais 155 controles, totalizando 281 mulheres avaliadas. Foram incluídas no grupo de estudo mulheres no menacme, sexualmente ativas e enquadradas nos critérios de corrimento vaginal recorrente, sem diagnóstico prévio definido, comparadas a mulheres assintomáticas, que compareciam a exame de rotina anual. Foram excluídas as gestantes, diabéticas e imunossuprimidas. Partiu-se de princípio da hipótese nula, em que não há diferenças entre os dois grupos estudados. **Resultados:** A média de idade foi de 29,95 anos, predominando solteiras e sem filhos. Não houve diferença significativa quando analisados: tempo de relacionamento com o atual parceiro, número de parceiros ao longo da vida, sexarca e método anticoncepcional. Houve predomínio da flora vaginal normal (tipo 1) em ambos os grupos, com prevalência média de 44,9%. O pH vaginal alcalino foi predominante no grupo de estudo. **Conclusão:** Confirmou-se a hipótese nula, não se identificando diferenças biológicas, comportamentais e sociodemográficas nas populações estudadas. Não se observaram, no grupo de mulheres com corrimento recorrente, fatores etiológicos infecciosos, sugerindo que diagnósticos clínicos não são suficientes para o manejo mais eficiente dessas situações, indicando-se avaliação laboratorial para esses casos com o objetivo de melhorar a acurácia diagnóstica.

Palavras-chave: vulvovaginite; descarga vaginal; leucorreia; exame ginecológico; candidíase vulvovaginal; vaginose bacteriana.

INTRODUCTION

The normal vaginal microbiota is predominantly composed of *Lactobacilli* producing hydrogen peroxide (80 to 95%) and some bacteria. The physiological vaginal discharge, clear or whitish, variable throughout the menstrual cycles and composed by microbiota and cervical fluids, is one of the frequent gynecological complaints confused by women with infectious symptoms, especially those caused by fungi. There is a wide spectrum of differences between what is normal and a vaginal disease, despite the symptoms can be common to both situations[1-4].

Pathological symptoms include infectious causes, such as bacterial vaginosis, vulvovaginal candidiasis and trichomoniasis, corresponding to 90% of cases. These configure vaginal disease that presents, in addition to abnormal vaginal discharge, itching, dyspareunia, and/or odor change[5-7].

Amongst infectious symptoms, bacterial vaginosis is considered the most common lower genital tract infection, with prevalence of approximately 27.5%. It results from the imbalance of vaginal microbiota with excessive growth of normal anaerobic bacteria and reducing concentrations of *Lactobacilli*. It is characterized by a greyish-white, fluid and fetid odor discharge that becomes accentuated after intercourses and/or menstrual period[8-11].

Vulvovaginal candidiasis is present in 20 to 25% of cases of infectious discharge. The clinical symptom is primarily characterized by

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the intense itching. The discharge is white, crumbly, odorless and cheesy-looking, adhered to the vaginal walls. In recurrent cases, predisposing factors are investigated, particularly immunosuppression, and more connected to other species of *Candida albicans* (responsible for 80 to 90% of candidiasis cases)[8-13].

Trichomoniasis is caused by a flagellate protozoan, *Trichomonas vaginalis*, responsible for 10 to 35% of vulvovaginitis. It is characterized by a moderate to a large amount of discharge, yellow-green, pemphigoid, vulvar irritation and/or itching, dysuria and polyuria, hyperemia with reddish plaques in cervix (cervix in strawberry or tigroid aspect) and, less common, pelvic pain[9,11,14].

Symptoms of vaginal itching without pathological discharges should also be observed. These are mostly due to allergic or irritative causes (clothing, toiletries and beauty products), skin disorders and vaginal atrophy. Nonspecific discharges can still result in different concomitant infections[8].

Among adult sexually active women, about 75% have at least one episode of vulvovaginitis in life[3,15]. And to avoid complications, such as the extension to upper genital tract and infertility due to tubal damage, the priority becomes the quick vulvovaginitis recognition and prevention, in order to treat the pathological cases in the most specific way possible[16].

Approximately 5% of women with vulvovaginitis will evolve to recurrent symptoms[17], being defined as recurrent vulvovaginitis the properly diagnosed episodes, clinical and laboratory exams, repeated for at least four times in a period of one year[18,19].

In such cases, empirical treatments with medicinal associations result in low efficiency and frequent return of symptoms[6], aggravated by self-treatments, which in general also contribute to the perpetuation of the irritative symptoms[2,20]. Nyirjesy noted that only 28% of the female population using self-treatment for recurrent candidiasis — when evaluated in a reference service — was diagnosed with this pathology, and 15% presented contact dermatitis caused by the topical medications used[15,21].

Nowadays, the diagnosis and the indication of the appropriate treatment are considered challenges, requiring knowledge of physiology, normal and abnormal vaginal microbiota, and the implementation of a complete diagnosis guideline, especially in recurrent symptoms[1-4].

OBJECTIVE

To evaluate, in the study population composed of women complaining of recurrent vaginal discharge with previous unsatisfactory treatments referred to specialized ambulatory of gynecological infections, the presence of microbiological, etiologic, behavioral and sociodemographic factors that justifies this complaint, comparing the existence of the same factors in control population of asymptomatic women.

METHODS

A diagnosis cross-sectional analytical study was carried out to evaluate the prevalence of *Candida spp*., bacterial vaginosis, trichomoniasis, *Chlamydia* infection, and mycoplasma diagnosis. Study group patients had reported recurrent vaginal discharge (four or more episodes in one year) with various systemic or topical treatments considered unsatisfactory. The control group consisted of asymptomatic women, morbidities-free, who attended various clinics for tests considered annual checkup. The research project was approved by the Ethics Committee in research in Human Beings of the Hospital das Clínicas of the Universidade Federal do Paraná (UFPR), and all subjects of the survey agreed with the participation by signing a written informed consent form.

Inclusion criteria were the following: women over 18 years of age in menacme who met the criteria for recurrent vulvovaginitis without a definite diagnosis submitted to any evaluation or treatment in the last six months for the presented symptoms and recurrent symptoms. Exclusion criteria were as follows: pregnant, diabetic, immunosuppressed, undergoing treatment for any sexually transmitted disease diagnosed in the last six months, menopausal and prepubescent women.

All patients were submitted to previous anamnesis for the collection of sociodemographic, behavioral and clinical information in an adequate instrument of data collection, and then referred to a gynecological examination associated with diagnostic procedures and biological materials collections for microbiological analysis.

The gynecological examination was conducted in accordance with the conventional technique. The complementary examinations and biological materials collections have been made systematically as described next:

1. measurement of vaginal pH with indicator tape in vaginal right wall;
2. collection of material with sterile swab from vaginal sac followed by sowing of culture medium for fungi and smear on blade for Gram and collection of material in test tube with saline for fresh examination;
3. removal of excess of mucus, if necessary, and collection of endocervical secretions with sterile swab in appropriate lamina for direct immunofluorescence for *Chlamydia* followed by sowing in culture medium suitable for mycoplasma;
4. collection of cervical ectocervix smear with Ayre's spatula and with endocervical brush on a lamina and preserved with appropriate fixative;
5. collection of secretion in vaginal sac with the same Ayre's spatula in lamina for amines test.

The vaginal environment pH was determined by placing a universal indicator tape with four turns on the right vaginal wall and interpreted after 10 seconds of contact, according to changes in color, and compared to the standard colorations at the time of collection by the observer. The fresh examination made the quantitative evaluation of epithelial cells, leukocytes, hyphae and trichomonas, with standardized reading by the laboratory. Gram staining was performed using a Gram staining set (set of dyes for differential staining in bacteriology with staining technique, reading and interpretation of standardized results according to international techniques).

The evaluation of mycoplasmas used the mycoplasma kit composed of one tube containing 2 mL of A3XB broth; one tube with 2 mL of MLA broth; one tube with 2 mL of U 10 broth and plates with 10 mL of A7 medium for the isolation, identification and

quantification of urogenital mycoplasmas (*Ureaplasma urealyticum* and *Mycoplasma hominis*).

Chlamydia was evaluated by direct immunofluorescence method after direct staining agent with marked antibodies, using the Biomed Pathfinder *Chlamydia Trachomatis* Direct Antigen Detection System Kit.

The evaluation of fungi was performed in selective culture medium for isolation of pathogenic fungi, mycosel agar, which contains two antimicrobials (cycloheximide and chloramphenicol), and can be used for the selective isolation of pathogenic fungi samples from biological samples potentially contaminated with bacteria and saprophytic fungi. The sample was also seeded by striking the inclined surface of several mycosel agar tubes with a bacteriological ring followed by incubation for up to two weeks at 20 to 25ºC and also at 35ºC. The reading and interpretation depends on the characteristics of the main fungi isolated from clinical materials in mycosel. *Candida albicans* showed good growth of white creamy colonies[22-24].

Cytology criteria based on oncotic Bethesda System were used for cytological diagnostics of normality, Atypical Squamous Cells of Uncertain Significance (ASCUS) and Squamous Intraepithelial Lesions (SIL).

The collected materials were sent on the same day to the laboratory where the analysis was performed, following universal standard techniques.

Statistical analysis occurred through the groups' comparison in relation to the dichotomous variables using Fisher's exact test, and χ^2 test was considered concerning the polytomous variables. The Student's t-test for continuous variables was considered, taking into account the homogeneity of variances. P values less than 0.05 indicated statistical significance. The evaluation was performed by a professional of the Statistics Department of the UFPR.

RESULTS

The results were based on the null hypothesis, *i.e.*, inferred there is no statistically significant difference in the analyzed variables (sociodemographic, behavioral and microbiological ones) among women with recurrent vaginal discharge and the asymptomatic control group.

Sociodemographic information analyzed were age, marital status, number of children and occupation. Among age average, despite a little difference in numeric absolute terms, there was statistical difference between the study and control groups (p=0.0258). Regarding marital status, there was significant prevalence of unmarried women in relation to married women in both groups, with significant predominance of married women in the study group (p=0.0258). In reference to the number of children, women without children were prevalent in both groups. There was no significant difference between the study group and the control group (p=0.5249). Concerning occupation, women who work outside home predominated in both groups. There was no significant difference between the study group and the control group (p=0.6670). **Table 1** describes the sociodemographic information.

From a behavioral standpoint, the following information were evaluated: number of partners by the time of the examination, sexarche age, time of sexual relationship with the current partner, smoking and use of contraceptive methods.

When assessing the number of partners, there was predominance of women with two to five partners over a lifetime and those who have had a unique partner in both groups. There was no significant difference between the study group and the control group (p=0.4361).

Regarding the age of sexual activity onset, the average age was 17.95 years old in the study group and 18.34 years old in the control group. There was no significant difference between the study group and the control group. The statistical test result indicated the non-rejection of the null hypothesis at 5% significance level (p=0.2044).

When evaluating the time of sexual relationship with the current partner, the percentage of women who were stable with the same partner for more than one year was prevalent in both study and control groups. There was no significant difference between the study group and the control group (p=0.4119).

The use of contraceptives showed predominance of hormonal methods, followed by not using any method. There was no significant difference between the study group and the control group (p=0.6097). Smoking was also prevalent in both groups, with no significant

Table 1 – Sociodemographic information of study group and control group in absolute and relative values.

	Study group (n=126)		Control group (n=155)		p
Average age	**28.86 years old**		**30.84 years old**		**0.0258**
	n	**%**	**n**	**%**	
Marital status					
Married or common-law	56	44.4	36	23.2	0.0258
Single ou divorced	70	55.6	119	76.8	
Children					
No children	63	50.0	64	41.9	
1 child	37	29.4	51	32.9	0.5249
2 or more children	26	20.6	40	25.2	
Occupation					
No	30	23.8	33	21.3	0.6670
Yes	96	76.2	122	78.8	
Number of partners					
1	45	35.7	61	39.3	
2 to 5	66	52.4	71	45.8	0.4361
6 to 10	9	7.1	18	11.6	
More than 10	6	4.8	5	3.2	
Time of relationship					
Up to one year	8	6.4	6	3.9	
More than one year	108	85.7	137	88.4	0.4119
No partner	10	7.9	12	7.7	
Contraceptive method					
Hormonal	71	56.3	80	51.6	
Non-hormonal	17	13.5	27	17.4	0.6097
None	38	30.2	48	31.0	
Smoker					
No	113	89.7	144	92.9	0.3933
Yes	13	10.3	11	7.1	

difference between the study group and the control group (p=0.3933). The data of the behavioral variables were mentioned in **Table 1**.

As for the microbiological profile, the analyzed data are described in **Table 2**. They are: the type of flora, the presence of fungi, the presence of infection by *Chlamydia*, trichomoniasis infection and mycoplasma infection.

The type of vaginal flora prevalent in both groups was type I (normal), according to Spiegel et al.[25]. There was no statistically significant difference between the types of flora when the study group and the control group were compared (p=0.6140), confirming the null hypothesis.

The prevalence of bacterial vaginosis was similar in both groups (16.67% in the study group and 15.48% in the control group), with no significant difference between the two groups (p=0.8704), confirming the hypothesis of nullity.

Concerning the presence of fungi in culture, there had been higher positivity in the study group with tendency towards statistical significance, which shows a difference between the two populations (p=0.0572).

The presence of endocervical *Chlamydia* presented low prevalence in both groups, with no statistical significance between them (p=0.5890).

The vaginal trichomoniasis presented very low prevalence in both groups, with no significant difference between them (p=0.4484).

In the control group, there was a discreetly higher prevalence of mycoplasmas. However, there was no statistical significance between the groups (p=0.5890).

The alkaline vaginal pH (above 4.5) proved to be the most prevalent in both study and control groups, followed by the normal vaginal pH (between 3.5 and 4.5). No significant difference was observed between the groups (p=0.7301).

Table 2 – Microbiological profile information analyzed in the study and control groups in absolute and relative values.

	Study group (n=126)		Control group (n=155)		p
	n	%	n	%	
Flora					
Normal	53	42.1	74	47.7	
Intermediate	39	30.9	45	29.0	0.6140
Abnormal	34	27.0	36	23.3	
Fungi					
Negative	110	87.3	146	94.2	0.0572
Positive	16	12.7	9	5.8	
Chlamydia					
Negative	124	98.41	154	99.4	0.5890
Positive	2	1.59	1	0.6	
Trichomonas					
Negative	125	99.2	155	100	0.4484
Positive	1	0.8	0	0	
Mycoplasma					
Negative	113	89.69	131	89.5	0.5890
Positive	13	10.31	24	10.5	
pH					
<3.0	2	1.6	2	1.3	
3.5 to 4.5	59	46.8	72	46.4	0.7301
>4.5	65	51.6	81	52.2	

DISCUSSION

The present study examined 281 women attended in ambulatory with gynecological infections. Among them, 126 belonged to the study group, as had previously presented clinical diagnosis of recurrent pathological discharge, while women of the control group were asymptomatic.

The sociodemographic profile of both groups (with and without recurrent vaginal discharge) was similar, showing that women with recurrent vaginal discharge are young, unmarried, without children, non-smoker, in use of hormonal contraceptive, with remunerated activities out of home, which is compliant with the literature, representing the modern woman starting an independent adult life[8,26].

The sexual behavior, evaluated by the start of sexual activity, the number of previous partners and the time of the last relationship, was also similar between groups and remained according to studies already described. No behavioral habit was inconsistent between the populations[20].

The microbiological analysis showed minimal alteration in both groups, contrary to the expected, especially in the study group. Regardless of the presence of recurrent vaginal discharge, the normal flora (type 1) was predominant. The incidence of abnormal vaginal flora in the study group (27%) was slightly lower than that one showed by Camargo et al. (34% of abnormal flora), and was slightly higher than the control group of this study, 23.2%[6], but without statistical difference between the asymptomatic control group, showing no differences in the composition of the vaginal microbiota[10,14,21].

The presence of fungi in vaginal secretion was higher in the study group (12.7%) than in the control group (5.81%), with tendency to statistical significance (p=0.0572), reinforcing greater colonization by *Candida spp.* fungi in the recurrent discharge group, in which this agent has been the most prevalent representative. This analysis suggests a more detailed investigation in the involvement of fungus in the genesis of recurrent vaginal discharge.

The presence of mycoplasmas, *Chlamydia* and trichomonas was much lower than the expected in both groups, suggesting low prevalence or low accuracy of previous clinical diagnoses[6,26]. The same pattern found by Di Bartolomeo et al. reports similar results, demonstrating that approximately half the women with recurrent vaginal discharge did not confirm pathogenic microbiota for fungal, bacterial and trichomoniasis infections[27]. Microbiological findings recommend new prevalence studies and also consider the non-utilization of molecular biology tests as a limitation factor for this sensitivity.

The cytopathological examination can be an accessory tool and with relative specificity for the recognition of alterations in the vaginal flora, indicating that it is an acceptable diagnostic criterion in the analysis of this symptom, being validated when it shows descriptive alterations in the microflora pattern[28-30].

The normal vaginal pH, between 3.5 and 4.5, produced by *Lactobacilli* protects against infections by pathogenic microbiota, being its verification an integral part of Amsel clinical criteria for the evaluation of vaginal discharge and diagnosis of vaginitis and infectious vaginoses[1]. The prevalence found was pH above 5 in both groups, which did not show any relation with increased prevalence of bacterial vaginosis and other vaginal infections.

As limitations of the diagnosis, we considered the non-utilization of molecular biology tests, a fact that could possibly be

associated with the underdiagnoses of some agents, especially *Chlamydia* and mycoplasma.

As perspectives, we observed that, although some syndromic approaches took into account the epidemiological data as a diagnostic key, in the studied population these epidemiological differences were not demonstrated, guiding the eventual revision of this type of approach.

CONCLUSION

Recurrent vaginal discharge is a frequent complaint in gynecological practice. Women in this condition do not generally present biological, behavioral and sociodemographic differences in relation to asymptomatic women, and might have been considered carriers of recurrent infections by *Candida* or other infections in clinical assessments of low accuracy.

Women with this symptom are labeled as carrying an abnormal recurrent infectious discharge, such as recurrent vaginal candidiasis, making difficult to understand their individual, physiological and pathological vaginal nature, leading to inappropriate treatments and self-treatments with the use of topical and systemic anti-infective medications.

Due to the way that recurrent vaginal discharge is often handled, the diagnosis of recurrent vulvovaginitis is still a myth that should be better explored by both clinical and scientific assistance.

In view of these results, it can be recommended the most detailed and objective clinical and laboratorial evaluation for the clinical management of these cases, involving detailed complete anamnesis and vaginal microbiological evaluation, preferentially through molecular biology methods. Similarly, detailed explanations about the vaginal microbiota and its physiological and pathological behavior and recommendations regarding drug management should be intensified by the clinical assistance to these women.

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Conflict of interests

The authors declare no conflict of interests.

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Lipodystrophy and metabolic parameters of people living with HIV

Lipodistrofia e parâmetros metabólicos de pessoas vivendo com HIV

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ABSTRACT

Introduction: Since the earliest reported cases in the United States, Acquired Immunodeficiency Syndrome (AIDS) remains one of the major challenges to global health. **Objective:** To evaluate the metabolic parameters and clinical manifestations of lipodystrophy in patients with lipodystrophy syndrome associated with the use of antiretroviral therapy. **Methods:** A cross-analytical study carried out from December 2015 to June 2016, in a public reference hospital for the care of HIV patients, in the city of Belém, state of Pará, Brazil. The sample consisted of HIV positive serology patients in treatment with antiretrovirals and lipodystrophy. Interviews were conducted and a research protocol plus laboratory analysis applied. **Results:** A total of 54 patients was included, 68.5% male and 31.5% female, aged 26–72 years, average of 53.07 years (standard deviation — SD±10.41). Among the clinical forms of lipodystrophy, the mixed one was the most prevalent (72.2%). As for dyslipidemia, 30.8% of the patients presented isolated hypertriglyceridemia, 26.9% mixed dyslipidemia, 19.2% low high-density lipoprotein (HDL-c) and 17.3% without dyslipidemia. Regarding the glycemic profile, 28.3% of the patients were diabetic, 28.3% had altered fasting glycaemia and 5.6% had altered fasting glycaemia and glucose intolerance. **Conclusion:** The clinical form of mixed lipodystrophy was the most prevalent. In this study, there was no association between the lipid profile and the clinical forms of lipodystrophy. However, follow-up of these patients is necessary to avoid possible complications and risks of cardiovascular events.

Keywords: HIV; lipodystrophy; antiretroviral therapy, highly active.

RESUMO

Introdução: Desde os primeiros casos relatados nos Estados Unidos, a *Acquired Immunodeficiency Syndrome* (AIDS) ainda continua sendo um dos grandes desafios para a saúde global. **Objetivo:** Avaliar os parâmetros metabólicos e as manifestações clínicas da lipodistrofia em pacientes com síndrome lipodistrófica do HIV, associada ao uso de terapia antirretroviral. **Métodos:** Estudo transversal analítico realizado de dezembro de 2015 a junho de 2016 em hospital público de referência no atendimento de pacientes HIV, em Belém, Pará, Brasil. A amostra foi composta de pacientes com sorologia positiva para o HIV em tratamento com antirretrovirais e lipodistrofia. Foram realizadas entrevistas e foi aplicado um protocolo de pesquisa mais análise laboratorial. **Resultados:** Foram incluídos 54 pacientes, 68,5% masculinos e 31,5% femininos, com idade entre 26 e 72 anos e média de 53,07 anos (desvio padrão — DP±10,41). Entre as formas clínicas da lipodistrofia, a mista foi a de maior prevalência (72,2%). Quanto à dislipidemia, verificou-se que 30,8% dos pacientes apresentaram hipertrigliceridemia isolada, 26,9% dislipidemia mista, 19,2% lipoproteína de alta densidade (HDL-c) baixo e 17,3% sem dislipidemia. Quanto ao perfil glicêmico, 28,3% dos pacientes são diabéticos, 28,3% apresentaram glicemia de jejum alterada e 5,6% glicemia de jejum alterada e intolerância à glicose. **Conclusão:** A forma clínica da lipodistrofia mista foi a mais prevalente. Nesta pesquisa, não houve associação entre o perfil lipídico e as formas clínicas de lipodistrofia, contudo faz-se necessário o seguimento desses pacientes, para evitar possíveis complicações e riscos de eventos cardiovasculares.

Palavras-chave: HIV; lipodistrofia; terapia antirretroviral.

INTRODUCTION

After more than 30 years since the first reported cases in the United States, the Acquired Immunodeficiency Syndrome (AIDS) is still one of the major challenges for the global health[1]. According to data from the World Health Organization, there are about 36.7 million people living with HIV in the world, 3.3 million of them in the Americas. Despite it reflects the increase of new HIV infections, there is also a significant expansion of access to antiretroviral treatment, which has helped to reduce AIDS-related deaths, especially in recent years[2].

Brazil has registered an average of 40 thousand new cases of AIDS in the past five years. The proportional distribution of the identified cases shows concentration in the Southeast and South, corresponding to 52.3 and 20.1% of the total cases, respectively — the Northeast, North and Midwest correspond to 15.4, 6.1 and 6.0% of the total cases, respectively[2]. The social organization of the space and the economic and cultural inequalities in the structure of the Brazilian society are the main factors that have determined and conditioned the receptiveness and vulnerability to the maintenance and dissemination of the epidemic of various transmitted diseases in the country[3].

Many of these diseases have hit large geographic isolation areas, as in the Amazon region[3], since in the past five years (2012 to 2016) the Northern region reported the average of 4,200 cases per year, noted that from 2007 to 2017 there were 14,275 new cases notifications[2].

This scenario demonstrates that the inequalities of the Brazilian society favors spreading the human immunodeficiency virus infection in the country, revealing an epidemic of multiple dimensions that over time showed significant transformations in the virus epidemiological profile[4]. With the arrival of antiretroviral therapy (HAART), also known as strongly active antiretroviral therapy in the 90s, there was deep impact on the natural history of HIV infection, as it significantly reduced morbidity and mortality by opportunistic infections and neoplastic diseases, but started a set of modifications known as HIV Lipodystrophy Syndrome (HIVLS)[5-7]. This clinical event consists of complex metabolic endocrine changes that can be associated

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with a significant increase in cardiovascular risk[8]. The antiretroviral drugs used in the treatment of HIV infection now totalize 21, and can be currently divided into five classes for clinical use: nucleoside analogue reverse transcriptase inhibitor (NARTI), non-nucleoside analogue reverse transcriptase inhibitor (NNRTI), protease inhibitors (PI), fusion inhibitors (FISH) and integrase inhibitors (II)[9].

Studies have been showing that the drugs used in HAART tend to raise levels of lipids, redistribute body fat and show insulin resistance. The use of HAART is considered the main cause for dyslipidemia, because with its introduction there is a change in the dyslipidemia profile with the aggravation of hypertriglyceridemia and an increase of total cholesterol and fractions, except high-density lipoprotein (HDL-c) and the state of insulin resistance[10].

The HIVLS is a side effect of the use of HAART, characterized by the redistribution of body fat. The clinic lipodystrophy was defined as a peripheral lipodystrophy, with or without central fat accumulation, evaluated by patients and doctors, showing three distinct forms, according to the distribution pattern of the body fat: lipoatrophy, lipohypertrophy and mixed form (simultaneous development of lipoatrophy and lipohypertrophy)[11-13].

OBJECTIVE

To evaluate the metabolic parameters according to the clinical forms of lipodystrophy in patients with HIV lipodystrophy syndrome associated with the use of HAART in outpatients of a reference public hospital in the state of Pará, Brazil.

METHODS

The study population consists of patients living with lipodystrophy syndrome associated with HIV, from the city of Belém and countryside of the state of Pará, assisted at Hospital Universitário João de Barros Barreto (HUJBB), in Belém, Pará, Brazil. The study occurred in the period from December 2015 to June 2016, and was approved by the Ethics Committee of the Center for Tropical Medicine (NMT) at the Universidade Federal do Pará, under Protocol no. 1,438,726.

Participants were included in the study after elucidation of the procedures and goals of the research and the proper signature of a free term of consent. This population consists of people of both sexes, over 18 years old, in treatment with HAART, for more than one year in a row, not inmates, non-pregnant women and functionally independent for their daily life activities, excluding those without positive serology for HIV/AIDS and those who were not within the research criteria. A cross-sectional analytical study was performed in a specific time period.

The research's participants were divided into three groups:

- patients with lipoatrophy: fat loss in the face, legs and limbs (associated or not with prominence of subcutaneous veins);
- patients with lipohypertrophy: accumulation of fat in neck, known as *hump* or *buffalo hump*, breast or abdomen;
- patients with mixed syndrome: association between fat loss and fat accumulation.

The lipoatrophy was identified by the spontaneous report of patient before the presence of relevant morphological changes to the face (loss of Bichat and/or preauricular fat cushion), arms, legs, and abdominal subcutaneous tissue. The lipohypertrophy was defined as the progressive increase in waist circumference, breasts size or back or cervical fatty cushions, or supraclavicular fat accumulation. Later on, a questionnaire containing demographic data, medical history, personal habits, family history and anthropometric measurements was applied.

All patients were examined by the physician in charge, as well as the standardized measures of weight (kg), height (m), and blood pressure (mmHg), measured and weighed without shoes and wearing light clothes. Laboratory fasting procedures for analysis of serum levels of total cholesterol (mg/dL), HDL-c (mg/dL), low-density lipoprotein (LDL-c) (mg/dL), triglycerides (mg/dL), glucose (mg/dL) and insulin (μ IU/mL) were performed in the HUJBB laboratory, since they are already part of the routine of patients' follow-up in the lipodystrophy ambulatory.

The cut-off points for normality of the biochemical tests were established according to the Brazilian Society of Cardiology: total cholesterol <200 mg/dL, triglycerides <150 mg/dL, HDL-c >60 mg/dL and LDL-c <160 md/dL[14]. The values regarding glycemic indexes have been established by the Brazilian Society of Diabetes: blood glucose normal <100 mg/dL, fasting blood glucose altered >100 and <127 mg/dL, oral glucose intolerance ≥140 and <200 mg/dL after overload[15].

The statistical analysis of the results was performed by the BioStat 5.0 and Epi Info 3.5.2 software, through the G-nonparametric test, qualitative variable. The quantitative variables were analyzed by parametric tests (ANOVA) or nonparametric (Kruskal-Wallis), according to the distribution of the variables with normal or nonparametric distribution. Values $p<0.05$ were considered significant.

RESULTS

We included 54 patients, 68.5% male. In relation to the distribution by age, we included patients between 26 and 72 years old, the average of 53.07 years old (standard deviation — SD±10.41). Regarding the distribution of body fat associated with the lipodystrophy syndrome, the clinical form of mixed lipodystrophy was the most prevalent in ambulatory, reaching 72.2%, the lipoatrophy, 24.1%, and the lipohypertrophy, 3.7%.

When we related lipodystrophy to sex (**Table 1**), the most frequent clinic form was the mixed one in both genders (67.6%

Table 1 – Lipodystrophy classification according to sex of patients undergoing antiretroviral therapy*, Belém (PA), Brazil, 2016.

	Male		Female	
	Frequency	Percentage (%)	Frequency	Percentage (%)
Lipoatrophic	11	29.7	2	11.8
Lipohypertrophic	1	2.7	1	5.9
Mixed	25	67.6	14	82.3
Total	37	100.0	17	100.0

*Test G (p=0.3580).

males, and 82.4% female). In this study, there was no association of sex (p=0.3580) with the lipodystrophy form. The standard therapeutic scheme in studied cases shows that 22.2% made use of nucleoside reverse transcriptase inhibitor (NRTI)+PI; 18.5% NRTI+NRTI+PI; and 18.5% NRTI+NNRTI, in which the NRTI (96.3%) and PI (64.8%) were the most used antiretroviral drugs in the therapeutic scheme of patients of this study (**Table 2**). The time of HAART use was of at least two years and the highest 21 years, with the average of 12.9 years (SD±4.6). As for the distribution of patients, it occurred according to the dyslipidemia classification (**Figure 1**).

There was higher prevalence of hypertriglyceridemia (30.8%), followed by mixed dyslipidemia (26.9%), low HDL-c (19.2%), without dyslipidemia (17.3%) and 5.8% isolated hypercholesterolaemia, being the latter the less frequent class.

By analyzing the lipid profile (**Table 3**), total cholesterol (TC) showed value from 115 to 629, HDL-c (mg/dL) from 21 to 156, LDL-c (mg/dL) from 41 to 241 and triglycerides (mg/dL) 64 and 3,555, minimum and maximum values, respectively. There was no association in the relationship of the lipid profile with the clinical forms of lipodystrophy (**Table 4**).

As for the glucose tolerance profile, 28.3% of the patients are diabetics, 28.3% presented fasting glucose altered, 5.6% presented fasting glucose altered and glucose intolerance, and 37.7% showed no change in glycemic profile (normoglycemia). As regards the use of lipid-lowering, 57.4% made use of lipid-lowering (fibrate and/or statin).

DISCUSSION

In this study, all participants were patients with lipodystrophy syndrome and made use of HAART, most male (68.5%). Similar studies in patients with lipodystrophy also identified high prevalence in males (67.0 and 60.8%, respectively)[8,16]. The average age of patients was of 53.07 years old ±10.41; in other studies, results similar to 44.11 years old ±9.84 and 44.2 years old ±9.4[17,18]. The prevalence of lipodystrophy evaluated in several studies ranged from 32.4 to 65% in HIV-infected patients in ambulatory follow-up and positively related to the use of antiretrovirals[16,19].

Table 2 – Therapeutic scheme pattern in the studied cases, Belém (PA), Brazil, 2016.

Class of antiretroviral	Frequency	Percentage (%)
INNTR + PI	2	3.7
INTR + INNTR	10	18.5
INTR + INNTR + PI	3	5.5
INTR + INTR + INNTR	9	16.7
INTR + INTR + INNTR + PI	1	1.9
INTR + INTR + PI	10	18.5
INTR + INTR + PI + II	1	1.9
INTR + INTR + PI + PI	2	3.7
INTR + INTR + PI + PI + II	2	3.7
INTR + PI	12	22.2
INTR + PI + PI	2	3.7
Total	54	100.0

INNTR: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors; INTR: nucleoside reverse transcriptase inhibitors; II: integrase inhibitors.

Differences in the prevalence rates can be attributed to age, gender, type or time of anti-retroviral therapy. Lipodystrophy syndrome is defined by the redistribution of body fat according to the patient's own report and confirmed in clinical examination.

Among the clinical forms, the mixed lipodystrophy was the most prevalent in this study, 72.2%. Similar data, 52.0 and 49.9%, respectively, were found with mixed lipodystrophy[17,18]. When morphological changes are correlated to sex, both male and female, the mixed lipodystrophy was the most prevalent (67.6 and 82.4%, respectively). In the present study, there was no association of sex (p=0.3580) with the form of lipodystrophy (**Table 1**). In another study conducted in the Southeast region of Brazil, in the Centre of Testing and Monitoring

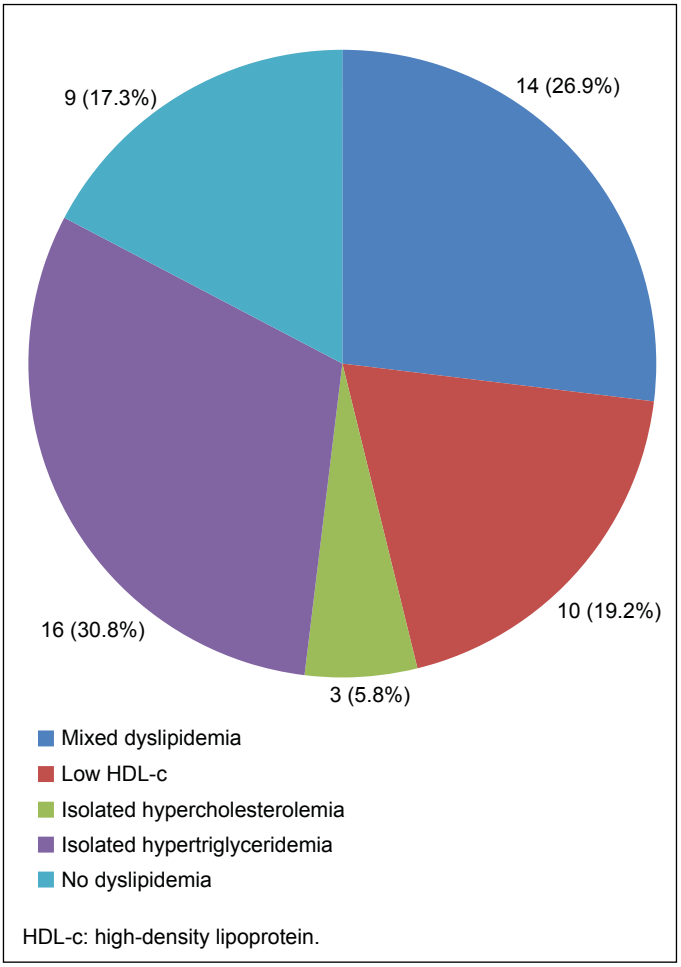

Figure 1 – Classification of dyslipidemia in lipodystrophy syndrome patients secondary to antiretroviral therapy, Belém (PA), Brazil, 2016.

Table 3 – Lipid profile of lipodystrophy syndrome patients secondary to antiretroviral therapy, Belém (PA), Brazil, 2016.

Lipid profile	Average and standard deviation	Minimum and maximum
Total Cholesterol (mg/dL)	213.78±73.27	115 and 629
HDL-c (mg/dL)	49.58±19.56	21 and 156
LDL-c (mg/dL)	115.17±37.35	41 and 214
Triglycerides (mg/dL)	283.88±477.52	64 and 3,555

HDL-c: high-density lipoprotein; LDL-c: low-density lipoprotein.

of Presidente Prudente, in São Paulo state, no significant statistical differences in the occurrence of lipodystrophy among categories of sex (p=0.140) and age group (p=0.964) were observed[20].

According to recommendation by the national coordination of Sexually Transmitted Diseases (STD)/AIDS, the initial recommended therapy consists of two NRTI associated to one NNRTI or PI. Initial schema changes may be necessary due to therapeutic failure, toxicity or intolerance to treatment. In relation to the use of drugs, 96.3% of participants of this study made use of NRTI and 64.8% of PI.

A similar result was found in Guimarães et al.[21], in which 98.5% of the patients made use of NRTI and 46.3% of PI, and in Diehl et al. [19], in which 99.9% were users of NRTI and 65.5% of PI. The time of HAART was of at least two years, and a maximum of 21 years, with average of 12.9 years (SD±4.6).

A similar study in the Northern region of Brazil, in the Centre of Attention on Acquired Infectious Diseases (Centro de Atenção à Saúde em Doenças Infecciosas Adquiridas — CASADIA) and in the Reference Unit Specialized in Special Infectious and Parasitic Diseases (Unidade de Referência Especializada em Doenças Infecciosas Parasitárias Especiais — UREDIPE), in Belém, Pará State, reported that all patients used HAART during the average time of 8.49 years (SD±4.31), using therapeutic schemes with two or more classes of antiretroviral drugs, and 69.6% was on treatment for more than seven years[18].

Another study in Southeastern Brazil, in the city of Ribeirão Preto, São Paulo state, observed that time of treatment with antiretrovirals was from 2 to 13 years, the average time of 7.5 years (SD±2.70)[9]. The group with increased use of HAART showed the highest proportion of individuals with lipodystrophy, a result that strengthens the relation of time of medicine use with the emergence of the syndrome[20].

In the association of antiretroviral use and dyslipidemia, a study in São Paulo with 319 HIV-patients divided into groups of those who made use of HAART and those who did not, showed that concentrations of total cholesterol, triglycerides and glucose were statistically higher among patients who used HAART[22].

These studies allow us to infer that the greater the use of HAART, the greater the repercussions related to lipodystrophy, dyslipidemia and fasting glucose.

The present investigation observed that most patients on antiretroviral therapy (82.6%) showed a change in the lipid profile (total cholesterol levels, LDL-c, triglycerides and low HDL-c), agreeing with studies in which the dyslipidemia associated with HIV infection is characterized by a significant increase of plasma levels of triglycerides, total cholesterol and reduced HDL-c in patients using HAART[15,17,23].

With the coming of HAART, especially with the use of PI, lipid profile change occurs with elevated triglycerides values, total cholesterol, lipoproteins of very low and low density (VLDL-c and LDL-c), leading to a decreased HDL-c, leaving these patients at risk of developing diabetes, hypertension and cardiovascular risk[20,24,25].

Studies estimate that the prevalence of dyslipidemia in HIV patients during HAART can range from 67.5 to 77.5% and can be influenced by several factors, including the type of study, the sample type and time of HAART[9,26,27]. It was observed prevalence of hypercholesterolemia from 31 to 47% and hypercholesterolemia from 47 to 71%[25].

A study with 268 HIV patients in a university hospital in Rio de Janeiro concluded that in male patients the prevalence of dyslipidemia is greater when compared to the female, and that family history of hyperlipidemia is directly related to both the occurrence of dyslipidemia and the time of use of HAART by patients[9].

The present research (**Table 3**) showed that the overall average of total cholesterol, LDL-c and triglycerides are high and HDL-c low, showing a lipid profile change. Studies show that metabolic abnormalities are characterized by a highly atherogenic lipid profile, with increase of total cholesterol and LDL-c, triglycerides and reduced HDL-c[28].

Evidences accumulate in the direction of pointing out that the HIV/AIDS infection itself plays the main role in the lower HDL-c rates[26,29,30]. When assessing the glucose tolerance profile, 62.7% of the patients have altered glycemic profile, in which 28.3% of them are diabetics and 33.9% have altered fasting glycaemia and glucose intolerance. Studies carried out in different regions of Brazil, as the Hospital de Clínicas da Universidade Estadual de Londrina, in 2008, where 8% are diabetics, found out that 15% showed fasting glucose >100 mg/dL and 23% had modified glucose. In the university hospitals of the states of Pernambuco and Santa Catarina, in which 5.7 and 8% are diabetics, respectively, the researchers revealed lower prevalence when compared to the present research[19,23,25].

Dyslipidemia in HIV carrier making use of HAART therapy is characterized by a high level of VLDL (the biggest transporter of triglycerides), LDL-c and reduced HDL-c level[3].

The authors even suggest that factors that would lead HIV patient to dyslipidemia are not yet elucidated. It is not exactly known if it occurs directly by the use of HAART or if it is the product of several factors, such as antiretroviral treatment, genetic predisposition, diet and exercise, or other factors, as the host's response to HIV infection[8,17,20].

The present study did not find association between lipid profile and clinical forms of lipodystrophy (**Table 4**), in spite of these

Table 4 – Lipid profile as to the Lipodystrophy Classification in Lipodystrophy Syndrome patients secondary to antiretroviral therapy. Belém-PA, 2016

Lipid profile	Lipodystrophy classification			p
	Lipoatrophic	Lipohypertrophic	Mixed	
Total Cholesterol (mg/dL)	183.78±55.67	221±38.18	215.73±80.80	0.4603*
HDL-c (mg/dL)	46.54±10.04	58±8.48	50.21±22.20	0.4744**
LDL-c (mg/dL)	127.12±42.28	132.5±55.86	110.83±35.15	0.3651*
Triglycerides (mg/dL)	230.27±177.88	152±48.08	311.07±550.44	0.4314**

*ANOVA; **Kruskal-Wallis; HDL-c: high-density lipoprotein; LDL-c: low-density lipoprotein.

parameters are changed at the time of the interview (p>0.005). According to the studies, the HIV infection itself and HAART promote these changes in the metabolic profile of these patients, leading to dyslipidemia in HIV carrier who makes use of HAART[5,21]. When checked the use of lipid-lowering, 57.4% make use of fibrate and/or statin. Diehl et al. observed that 13% made use of lipid-lowering and 70% of patients presented lipodystrophy[19]. The treatment of dyslipidemia in HIV-infected patients deserves special attention in the safety of the drug interaction between antiretrovirals and lipid-lowering drugs.

CONCLUSION

The clinical form of mixed lipodystrophy was the most prevalent in both sexes. In this research, there was no association between lipid profile and clinical forms of lipodystrophy. However, it is necessary to observe these patients to avoid possible complications and risk of cardiovascular events.

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Conflict of interests

The authors declare no conflict of interests.

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Does the use of probiotics in pregnant women with premature rupture of membranes improve the maternal and perinatal outcome? A systematic review

O uso de probióticos em gestantes com rotura prematura de membranas ovulares melhora o desfecho materno e perinatal? Uma revisão sistemática

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ABSTRACT

Introduction: Premature rupture of membranes (PROM) is a condition that affects 8–10% of all pregnancies, and contributes with 20–40% of preterm deliveries. Evidence shows that changes in the vaginal microbiota may also have a favorable impact on the decrease in the prevalence of PROM, and that expectant treatment may be an appropriate approach to reduce morbidity in these cases. **Objective:** To investigate whether the use of probiotics in pregnant women with premature rupture of ovary membranes improves the maternal and perinatal outcome. **Methods:** This is a systematic review, developed from articles published between January 2001 and August 2018, which justify the use of probiotics in pregnant women with PROMto improve maternal and perinatal outcome. **Results:** Some studies have shown a potential role of probiotics in modulating vaginal bacterial communities, reducing rates of cesarean section and PROM, and increasing the latency and weight of newborns in pregnant women with PROM. However, in other studies, there was no confirmation of changes in the vaginal microbiota from the use of oral probiotics. **Conclusion:** There are benefits in the administration of probiotics to the mother-fetus binomial. However, there are still doubts about routes of administration, choice of strains and period of use. More studies are necessary to settle them.

Keywords: probiotics; premature rupture of fetal membranes; pregnancy; microbiota.

RESUMO

Introdução: A rotura prematura de membranas ovulares é uma condição que afeta 8–10% de todas as gestações e contribui com 20–40% dos partos prematuros. Evidências mostram que mudanças na microbiota vaginal podem ter impacto favorável na diminuição de sua prevalência, e o tratamento expectante pode ser uma abordagem adequada para reduzir a morbidade nesses casos. **Objetivo:** Investigar se o uso de probióticos em gestantes com rotura prematura de membranas ovulares melhora o desfecho materno e perinatal. **Métodos:** Trata-se de uma revisão sistemática desenvolvida com base em artigos publicados no período de janeiro de 2001 a agosto de 2018, que justificam o uso de probióticos em gestantes com rotura prematura de membranas ovulares para melhorar o desfecho materno e perinatal. **Resultados:** Alguns estudos mostraram potencial atuação dos probióticos em modular comunidades bacterianas vaginais, em reduzir taxas de cesarianas e rotura prematura de membranas ovulares, além de aumentar o período de latência e peso do recém-nascido de gestantes com esse quadro. Porém, em outros trabalhos, não houve confirmação de mudanças na microbiota vaginal pelo uso de probióticos orais. **Conclusão:** Há benefícios na administração dos probióticos sobre o binômio mãe-feto, contudo ainda há dúvidas sobre vias de administração, sobre escolha das cepas e sobre tempo de uso. Mais estudos precisam ser realizados para dirimi-las.

Palavras-chave: probióticos; ruptura prematura de membranas fetais; gravidez; microbiota.

INTRODUCTION

Premature rupture of membranes (PROM) is a condition that affects 8–10% of all pregnancies, and since prematurity is the most frequent consequence of PROM[1], it acts as a cause of 20–40% of preterm deliveries[2]. When rupture occurs at an earlier gestational age, between 24–36 weeks, expectant management may be a suitable approach to reduce the morbidity associated with prematurity[3]. However, it is a difficult decision to make. On the one hand, the anticipation of labor prevents infections in the newborn; on the other hand, the prolongation of this pregnancy may allow a greater maturation of the fetus and reduce the risk of complications associated with preterm birth[2,3].

It is known that alterations in the vaginal microbiota, in the early stage of gestation, can be a predictor for abortions and for premature births[1,4]. There is also evidence that restoration of the vaginal microbiota may also have a favorable impact on the decrease in the prevalence of PROM, since there is clear association with vaginal infections[1]. Some of the probable mother-fetus contact sites that may promote infection are: amniotic fluid, placenta, fetal membranes and umbilical cord[5].

There are bacteria that are commensal and which are present in the placenta in non-pathological situations. With the development of techniques of molecular biology and bacterial genetics, it has been possible to reveal the great diversity of the microbiome of the whole reproductive tract and, in particular, the detection of bacteria in the uterine cavity by polymerase chain reaction (PCR) technique[5,6].

Satokari et al.[6] demonstrated the presence of two strains, *Bifidobacterium* and *Lactobacillus rhamnosus*, by deoxyribonucleic acid (DNA) analysis in 34 samples of placentas collected shortly after delivery. It is known that *Bifidobacterium* and *L. rhamnosus* are part of the normal intestinal microbiota in adults. The bacterial DNA of the two strains was detected in almost all placenta samples, regardless of the type of delivery. It is believed that exposure of the

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newborn to intestinal bacteria may be the beginning of the development of the infant immune system[6].

The systemic inflammatory response of the fetus varies according to the intrauterine microbiota, and occurrences of fetal injury and other sequelae of target organ damage may contribute to premature labor, as well to immunomodulation and strengthening of the immune system[4]. Groups of bacteria that cause bacterial vaginosis, for example, confer an inflammatory response in the newborn much larger than any microorganism alone, whereas *Lactobacilli* appear to have anti-inflammatory properties[4]. *Lactobacilli* protect vagina from pathogenic organisms, producing antimicrobial agents such as hydrogen peroxide and bacteriocins, compete for nutrients, adhesion to the epithelial surface and keep vaginal pH low[7]. These aspects were confirmed by Fichorova et al.[4], analyzing 25 biomarkers collected from blood and placenta samples, in which they observed that *Lactobacilli* were more related to anti-inflammatory cytokines, while pathogenic bacteria, such as *Gardnerella sp*. and other ones linked to bacterial vaginosis, were more related to inflammatory cytokines. Therefore, placental colonization of specific bacteria, such as probiotics, during the initial phase of gestation may have promising effects to prevent preterm birth and complications of prematurity[4].

A group of researchers followed 256 women during pregnancy and followed her infants in the first 24 months of life to identify whether the administration of probiotics to the mother could alter maternal and perinatal outcomes. Probiotics have been associated with reduced risk of gestational diabetes mellitus, improved immune regulation of the newborn and the intestinal barrier function, and reduced risk of intestinal infection and of childhood allergic diseases. Considering the maternal microbiota as the first contact for the development of the child's microbiota, it is important to recognize the intestine as a key organ involved in host homeostasis[8].

Probiotics seems to be beneficial to the mother-fetus binomial. However, there are still doubts about routes of administration, choice of strains and time of use.

OBJECTIVE

This review proposes to look for what there is in the scientific literature on the influence of probiotic use on the outcome of gestation in PROM.

METHODS

A systematic review of articles published from January 2001 to August 2018 was conducted in the MEDLINE, Latin American and Caribbean Health Sciences Literature (Lilacs), Cochrane Library, Highwire Stanford and Embase databases. We also searched at the Center for Reviews and Dissemination (CRD), the clinical trials, the Brazilian Registry of Clinical Trials and PROSPERO, looking for some previous systematic or ongoing systematic review on the topic. In these latter databases, no records were found. In addition, a search was made in the references used by the selected articles, of some studies that fit the criteria of inclusion and exclusion.

The search was performed using combinations of keywords: "fetal membranes, premature rupture" [MeSH Terms] (OR "fetal" [All Fields] AND "membranes" [All Fields] AND "premature" [All Fields] AND "rupture" [All Fields]) OR "premature rupture fetal membranes" [All Fields] OR "fetal" [All Fields] AND "membranes" [All Fields] AND "premature" [All Fields] AND "rupture" [All Fields] OR "fetal membranes, premature rupture" [All Fields]) AND "probiotics" [MeSH Terms] OR "probiotics" [All Fields] OR "probiotic" [All Fields].

Articles were selected by means of eligibility criteria. Priority was given to original articles published in Portuguese, Spanish and English, whose object of study were pregnant women with premature rupture of membranes and using probiotics as an intervention factor. Review articles, with themes different from the proposed objective, in languages other than those previously mentioned or published before 2001 were excluded.

Two reviewers participated in the selection of articles, according to the recommendations of the Brazilian Medical Association[9]. Initially, the studies were selected from the title. Next, a detailed analysis of the abstracts was carried out in order to restrict the selection only to those that fulfilled the inclusion criteria. All selected articles were included in the survey. All selected articles were included in the survey. If any of the studies generated disagreement among the reviewers, a third reviewer would be chosen for the evaluation and whether or not this study would be included. Finally, all selected articles make up the research sample.

RESULTS

The search initially returned 111 results, but, after applying the inclusion and exclusion criteria, 16 articles were selected. Then, after a qualitative evaluation, another 10 articles were excluded, totaling six articles included in this review (**Figure 1**). The most relevant results of each study are shown in **Chart 1**.

DISCUSSION

Rautava et al.[10] conducted a randomized, placebo controlled clinical trial of 43 women between June 2007 and November 2009. These women were divided into three groups: a placebo; a group in use of a strain of *Bifidobacterium lactis*; and a third group using *B. lactis* and *L. rhamnosus*. The objective was to verify the interaction between microbes and the maternal-fetal interface and whether

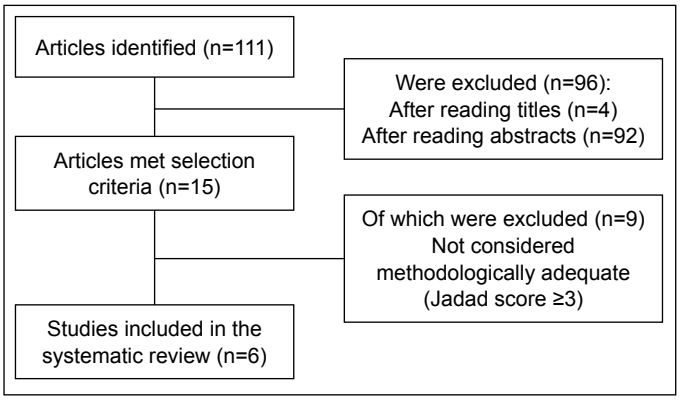

Figure 1 – Selected studies flowchart.

this could be modulated by oral administration of probiotics to mother during pregnancy, in order to bring benefits to the mother-fetus binomial. In order to analyze the composition of the microbiota, samples of amniotic fluid and placenta were collected during cesarean section. Toll like receptor (TLR) genes were identified by Array PCR. TLRs are membrane proteins that are part of the innate immune system and, through the exposure of pathogens, contribute to the signaling of inflammatory cytokines[11]. Microbial DNA was detected in the placenta samples of the three groups and in 6 of the 14 samples of amniotic fluid (43%). Maternal supplementation of probiotics was associated with statistically significant changes in the expression of the TLR gene in the placenta and in particular TLR 1 and 7, as well as reduction of TLR 4. There was also reduction of TLR 1 and 6 in the fetal gut in the group in use of *B. lactis* and *L. rhamnosus*. The authors concluded that the presence of bacterial DNA in the amniotic fluid and in the placenta affects the expression of the TLR gene in the fetal gut and that is essential for the maturation of its immune system. Besides that, the modulation of the inflammatory process, as well as the consequent signaling of TLR in the maternal-fetal unit through the use of specific strains, may result in a fetal metabolic and immunological programming.

If there are benefits in this approach, what would be the best and optimal time to do it? Several studies have tried to answer this question. In a pilot, placebo-controlled and non-randomized study conducted by Vitali et al.[12], the impact of daily oral probiotic supplementation on the vaginal microbiota and immune system of healthy women during the late gestation phase was evaluated. Twenty-seven women were followed for four weeks, between 33 and 37 weeks' gestation, divided into two groups. The intervention group used a probiotic pharmaceutical compound containing four strains of *Lactobacilli*, three strains of *Bifidobacterium* and one of *Streptococcus thermophilus*. The analysis of the vaginal microbiota before and after the intervention was performed by real-time PCR analysis; besides, inflammatory cytokines were analyzed in the vaginal fluid by Luminex immunoassay. Differences in the intervention group's microbiota compared to placebo suggest a potential role for probiotics in modulating vaginal bacterial communities. Compared to the intervention group, the placebo group had reduction of *Bifidobacterium* (related to vaginal health) and increase of *Atopobium*, mainly near the 37th week (bacteria related to bacterial vaginosis). In addition, in the probiotic group, women who previously had *Streptococcus agalactiae* positive after treatment did not present it any more. In this group, there was also greater reduction of inflammatory cytokines. Therefore, they concluded that there is stabilization of vaginal immunity during pregnancy that can be attributed to the intake of probiotics.

Other studies were similar to that of Vitali et al.[12], but with a better delineated search of more solid scientific evidence. A randomized, triple blind, placebo controlled trial published by Gille et al.[13] also sought to verify if the use of oral probiotics could maintain or restore the vaginal microbiota in healthy pregnant women. There were selected 320 pregnant woman with less than 12 weeks, and then they were divided into two groups and followed up for eight weeks. The product contained two strains *L. rhamnosus* and *Lactobacillus reuteri* showed good oral tolerability. Vaginal swabs were collected before and after treatment and the microbiota was

Chart 1 – Original studies conducted between 2001 and 2018 on the use of probiotics in premature rupture of membranes (PROM) and their outcomes.

Study	Year ofpublication	Study design	Women (n)	Method of analysis	Results
Rautava et al.[10]	2012	RCT	43	PCR array QIA amp DNA Placenta and LA samples	Bacterial DNA in LA and in the placenta affects TLR expression in the fetal gut Microbial interaction with TLR is essential for a healthy immune system
Vitali et al.[12]	2012	Pilot study, non-randomized	42	PCR, DGGE and PCR - real time Vaginal swab before and after the intervention	Probiotics reduce pro-inflammatory cytokines in the treated group Placebo group: increase of *Atopobium* (linked to BV) and reduction of *Bifidobacterium* (linked to health)
Gille et al.[13]	2016	RCT	320	Swab vaginal Nugent score	Oral probiotic did not modify the vaginal microbiota Lower prematurity rate in the treatment group
Di Pierro et al.[14]	2016	Non-randomized trial	406	Swab retal/vaginal Statistical analysis	*Streptococcus agalactiae* reduction (6%) PROM reduction (30%) Reduction of cesarean section rate (5.51 / 10.39%) Reduction of umbilical pH (0 / 6.09%)
Daskalakis et al.[15]	2016	RCT	106	GA at birth Birth weight Latency period	Treatment group: GA increase Weight gain at birth Increased latency period
Kavak et al.[16]	2014	Non-randomized trial	40	APGAR 5th min GA at bith Birth weight Latency period	Treatment group: Increase GA Increased latency Increase of APGAR 5 minutes Weight gain at birth 3 cases of chorioamnionitis in the placebo group and none in the probiotic group

RCT: randomized clinical trial; PCR: polymerase chain reaction; QIA: quantitative immune analyzer; DNA: deoxyribonucleic acid; LA: amniotic liquid; DGGE: denaturing gradient gel electrophoresis; GA: gestational age; TLR: Toll like receptor; BV: bacterial vaginosis.

classified according to Nugent score. There was no difference in the vaginal microbiota of the two groups before and after the intervention. In addition, rates of bacterial vaginosis were not significantly different, neither there was divergence in the Nugent score between the groups. However, in relation to the secondary outcomes, the prematurity rate reduced in the treatment group (3.8%) compared to the placebo group (5.0%). The authors concluded, however, that the study did not confirm in pregnant women significant changes in the vaginal microbiota with the use of oral probiotics, different outcomes from the results found in non-pregnant women[13].

Di Pierro et al.[14] conducted an open, non-randomized, placebo-controlled study in which 406 pregnant women were followed up, divided into two groups, from January to December 2015, between 30–40 weeks. The objective was to evaluate the effect of the use of oral probiotics in the last weeks of pregnancy in relation to the influence on cesarean rates, PROM and pH analysis of fetal umbilical artery. The product used was composed of two strains of *Lactobacillus*, one strain of *Bifidobacterium* and one strain of *Enterococcus faecium*. Vaginal and rectal swabs were collected between 36 and 37 weeks for *Streptococcus agalactiae* in order to perform the statistical analysis of the data already mentioned. Vaginal and rectal swabs were positive for *S. agalactiae* in 27/127 (21%) of the women in the treatment group and 76/279 (27%) in the control group. No case of PROM was identified in the treatment group against 87 (31.2%) in the control group. Regarding cesarean rates, 7 (5.51%) in the treatment group and 29 (10.39%) in the control group. And in the pH analysis of the pathological umbilical artery, no case was identified in the treatment group against 17 (6.09%) in the control group. Thus, reduction of the positivity rates for *S. agalactiae* was observed: reduction by about 30% of PROM, reduction of the cesarean section rate and reduction of the pH of the pathological umbilical artery. These data lead the authors to conclude that, despite the limitations of the study because it is not randomized and it presents heterogeneous groups, there are benefits in the use of probiotics at the end of pregnancy, besides good tolerability.

Daskalakis et al.[15] conducted a prospective, randomized study aimed to identify the efficacy of vaginal probiotics in combination with conventional treatment already used in pregnant women with premature PROM in order to prevent maternal and perinatal complications. For this purpose, 106 women were followed and divided into two groups. The analyzed variables were: gestational age at birth; duration of the latency period; birth weight; Apgar score in 1 and 5 minutes, in addition to complications related to prematurity (admission to neonatal intensive care unit, necrotizing enterocolitis and neonatal sepsis). In the intervention group, the mean gestational age was 35 weeks *versus* 32 weeks on the placebo group. The duration of the latency period was 5.6 weeks, while in the placebo it was 2.4 weeks; and birth weight 2,439.08 g *versus* 2,004.81 g, higher in the group using probiotics. Thus, the authors conclude that there are clearly benefits in the association of probiotics with the standard antibiotic regimen as a conservative treatment of PROM[15].

A study with a design similar to Daskalakis et al.[15] had already been published in 2014. Kavak et al.[16] conducted a non-randomized clinical trial from July 2011 to June 2013 with pregnant women with premature PROM (between 23 and 31 weeks). There were selected 40 pregnant women, divided into two groups, with treatment and placebo, and their data were analyzed retrospectively. The objective was to evaluate the efficacy of the use of vaginal probiotics (strain *Lactobacillus casei* and *L. rhamnosus*) in combination with conventional antibiotic treatment for patients with PROM who were on conservative treatment. The factors evaluated were: gestational age at birth, latency period and birth weight, and the Apgar score at the 1st and 5th minute. Comparing the two groups, there were statistically significant differences in the following aspects: gestational age at birth (31.5 weeks in the treated group while in the placebo group it was 28.1 weeks); latency period (41.4 *versus* 12.3 days, respectively); and birth weight (1,947 in the treatment group *versus* 1,320 g in the placebo group). Despite having a much lower sample, this study presented similar conclusions to the investigation by Daskalakis et al.[15]. The authors concluded that the addition of probiotics to this group of women reduced laboratorial infection parameters, as well as maternal and fetal adverse effects and rates.

CONCLUSION

The research has shown that there are benefits in the use of probiotics during gestation, through changes in vaginal microbiota, for maternal and perinatal outcomes. However, some studies still rely on small samples and heterogeneous scenarios. Larger and better-designed studies are needed to make possible to have a more definitive conclusion and so to be replicated for the general population. It is important to highlight that these studies allow us to guide the best way and the ideal moment to introduce this supplementation during prenatal care.

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Conflict of interests

The authors declare no conflict of interests.

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Exclusively oral manifestation of secondary syphilis

Manifestação exclusivamente oral de sífilis secundária

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ABSTRACT

Introduction: Syphilis is at an epidemic level in the Brazilian public health and it occurs, mainly, in the genital region. However, about 5% of the syphilitic lesions are oral. **Objective:** To report a clinical case of secondary syphilis with exclusively manifestation in the oral cavity. **Case report:** A 32-year-old woman who attended the Dentistry Clinic of the Universidade Estadual do Oeste do Paraná (UNIOESTE) complaining of "sores in the mouth". Physical examination revealed a number of ulcerated, pseudomembranous and painful lesions at apex, lateral border, belly, floor and lingual frenulum. After the diagnostic hypothesis of syphilis was raised, serological tests for human immunodeficiency virus (HIV) 1, HIV-2, Venereal Disease Research Laboratory (VDRL) and complete blood count were requested. With the positivity up to the 1/32 titration of the VDRL examination, the patient was referred to the Parasitic Infectious Diseases Center of Cascavel, where a general physical examination and antibiotic therapy with benzathine penicillin were carried out. Subsequent to the drug treatment, the patient returned to the UNIOESTE Dentistry Clinic, where the total remission of the lesions was observed, confirming the diagnosis of secondary syphilis exclusively in the mouth. **Conclusion:** This report illustrates the importance of each phase of the disease, noting that in some cases the manifestations of the infection may be solely oral, with the dentist having a notable role in the diagnosis and reference to the adequate treatment, and the responsibility to control the necessary diagnostic procedures.

Keywords: syphilis; oral manifestations; sexually transmitted diseases.

RESUMO

Introdução: A sífilis encontra-se em estado epidêmico na saúde pública brasileira. Ela ocorre principalmente em região genital, todavia cerca de 5% das lesões sifilíticas são orais. **Objetivo:** Relatar um caso clínico de sífilis secundária com manifestação exclusivamente em cavidade oral. **Relato de caso:** Mulher, 32 anos, compareceu à Clínica de Odontologia da Universidade Estadual do Oeste do Paraná (UNIOESTE) com queixa de "feridas na boca". Ao exame físico, observaram-se inúmeras lesões ulceradas, pseudomembranosas e doloridas em ápice, borda lateral, ventre, assoalho e frênulo lingual. Depois de levantada a hipótese diagnóstica de sífilis, foi solicitada a realização de exames sorológicos para vírus da imunodeficiência adquirida (HIV) 1, HIV-2, Venereal Disease Research Laboratory (VDRL) e hemograma completo. Com a positividade até a titulação de 1/32 do exame VDRL, a paciente foi encaminhada ao Centro de Doenças Infecto-Parasitárias de Cascavel, sendo ali realizados exame físico geral e antibioticoterapia com penicilina benzatina. Posteriormente ao tratamento medicamentoso, a paciente retornou à Clínica de Odontologia da UNIOESTE, sendo observada a remissão total das lesões, confirmando o diagnóstico de sífilis secundária exclusivamente bucal. **Conclusão:** O relato ilustra a importância do conhecimento das características clínicas de cada fase da doença, ressaltando que em alguns casos as manifestações da infecção podem ser unicamente orais, tendo o cirurgião-dentista notável papel no diagnóstico e referência ao tratamento adequado, além da responsabilidade de dominar as manobras diagnósticas necessárias.

Palavras-chave: sífilis; manifestações orais; infecções sexualmente transmissíveis.

INTRODUCTION

Syphilis is a systemic bacterial infection caused by spirochete *Treponema pallidum*. Their means of transmission are most closely linked to the sexual contact, the vertical transmission from mother to fetus and hematogenous via, through blood transfusion, in rare cases[1].

The *T. pallidum* ethiopathogeny is related to the production of mucopolysaccharidoses that dissolve mucopolysaccharides — responsible for the union of vascular cells — , thus allowing the passage to perivascular spaces, promoting collapse, thrombosis, vascular obstruction and necrosis[2].

Chancre is the initial lesion of the infection and is characterized as an eroded and ulcerated lump, painless, with bases and hardened margins, measuring approximately 1 to 2 cm in diameter, which marks the site of the microorganism inoculation and usually manifested 21 to 30 days after contamination[3], accompanied by multiple and bilateral ganglionary reaction, non-suppurative, of hard and painless nodules[1]. It most often affects the ano-genital and oral areas[3], and most of extragenital chancres occur in the mouth (40–70%)[4].

Following primary syphilis, secondary syphilis arises along with a variety of systemic signs: pharyngitis, myalgia, arthralgia, prostration, headache and generalized lymphadenopathy[5]. Manifesting itself four to six weeks after the onset of chancre and having spontaneous remission three to 12 weeks after the onset of symptoms, secondary syphilis presents a range of extremely heterogeneous lesions, which labeled the disease as the "great copycat". Generally, the first impressions of this stage show generalized rash involving all the trunk and extremities, including injury and palmar-plantar known as syphilitic roseolas[4].

Mucosal plaques are most commonly observed in the mouth: painful, oval, serpiginous, slightly elevated erosions with erythematous borders, usually covered by a whitish membrane. They occur due to areas of intense exocytosis and spongiosis of the mucosa[3]. Another frequently observed in secondary syphilis is the canine condyloma lata, with characteristics very similar to mucous plaques, but with a nodular and firm surface[4].

Over the course of two years of infection, secondary syphilis alternates between periods of onset and remission of symptoms, until a large latency period sets in[1]. The reactivation of the disease corresponds to the tertiary stage of syphilis, which affects 30% of patients with secondary syphilis untreated, and more serious complications are registered[6]: syphilitic gum, neurosyphilis and cardiovascular syphilis[4].

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Syphilitic gum is characterized as a destructive lesion, mostly painless, nodular, which invades the mucosa underlying tissues. In the oral cavity, the hard palate is the place of greatest involvement, having palatal perforation and oral-sinus communication results of its destructive capacity[4].

In 20 years, a type of syphilis with high mortality rate was observed. From 1998 to the present day, 160,000 cases of congenital syphilis were reported in children under 1 year of age in the Brazilian territory[7]. It occurs by transplacentary transmission of the mother to the fetus at any stage of the disease, and the risk of contamination is proportional to the amount of bacteria in the maternal blood circulation. The mortality reported in the infected conceptuses is about 40%[1]. The congenital syphilis stigmas can be observed in the maxillofacial complex, and systemically. The neonate may present ectodermal alterations, mucocutaneous rash, osteochondritis, periostitis, rhinitis, destruction of the vomer bone, Hutchinson's incisors and muriform molars[3].

OBJECTIVE

To report the clinical case of secondary syphilis with exclusively oral manifestations.

CASE REPORT

Female patient D. M. U., 32 years old, leucoderma, smoker for 16 years, without extrabucal alterations, attended the Clinic of Stomatology of the Universidade Estadual do Oeste do Paraná (UNIOESTE), in the city of Cascavel, state of Paraná, with main complaint of "painful wounds in the mouth".

Intraoral examination revealed multiple ulcerated lesions, covered by whitish membranes and surrounded by a discrete erythematous halo that affected the region of the apex and dorsum of the tongue (**Figure 1**), tongue lateral border of the right and left and lingual frenulum (**Figure 2**). The complaint of painful symptomatology was evident, and the patient reported evolution of five months for the lesions. When asked about a periodic visit to the gynecologist, the patient reported having had a consultation in the six months preceding the search for care at the Clinic of Stomatology, where no alterations had been observed. There was also a report that the three years previously to the onset of the lesions were marked by the absence of sexual intercourse.

In view of the diagnostic hypothesis of syphilis mucous plaques, a request for serological tests for human immunodeficiency virus (HIV) 1, HIV-2 and Venereal Disease Research Laboratory

Figure 1 – Lesions in apex and dorsum of the tongue prior to the treatment.

Figure 2 – Ulcerations in lateral right and left border and lingual frenulum prior to treatment.

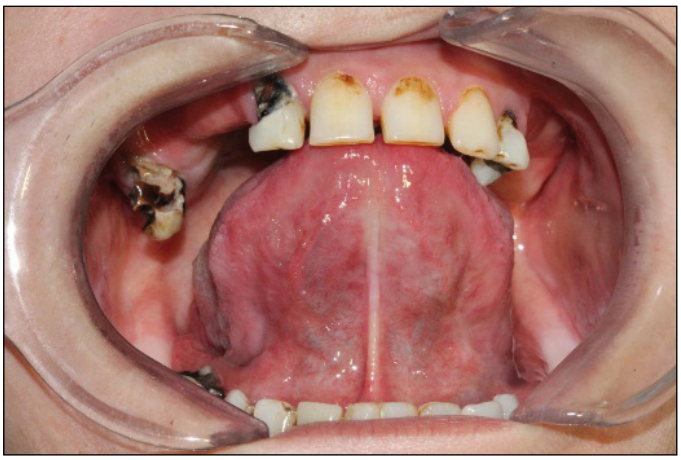

Figure 3 – Remission of lesions in lingual apex, dorsum and frenulum after treatment.

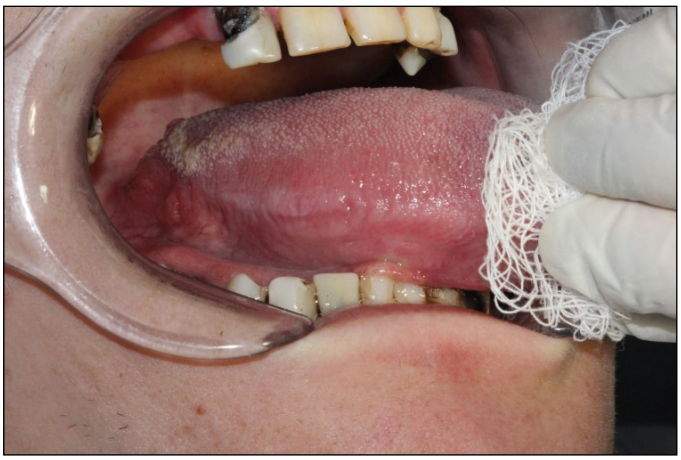

Figure 4 – Remission of lesion in lateral right tongue border after treatment.

(VDRL) was held, in addition to complete blood count. The results revealed absence of alterations in the blood count and negativity to HIV-1 and HIV-2. However, the VDRL test showed positivity up to 1/32 titration.

The patient was referred to the Specialized Center for Parasitic Infectious Diseases (Centro Especializado de Doenças Infecto-Parasitárias — CEDIP), in the city of Cascavel, where the infectology team performed a general physical examination, noting the absence of extraoral lesions and confirming the diagnosis of secondary syphilis. After antibiotic therapy with benzathine benzylpenicillin 2.4 million IU IM, the patient returned to the Clinic of Stomatology of UNIOESTE, where the total remission of all lesions was observed (**Figures 3, 4 and 5**). At the end of the treatment, a serological test was carried out showing the efficacy of antibiotic therapy and serological cure of the patient.

DISCUSSION

In the last five years, Brazil has faced increasing numbers of syphilis notification. It can be attributed to a greater readiness of access to rapid testing, reduction of condom use — largely related to improved antiviral therapy for HIV/acquired immune deficiency syndrome (AIDS) and reduced deaths from the disease — , health professionals' resistance to administering penicillin in the basic attention, worldwide shortage of the antibiotic, as well as the implementation of compulsory notification of syphilis cases[7].

Although oral manifestations of syphilis are more likely to be observed in the secondary phase, all stages of the disease may exhibit oral lesions[6]. Primary syphilis has chancre as the most characteristic injury. In secondary syphilis, mucous plaques and condyloma lata play an important role of the spectrum of lesions observed. In tertiary syphilis, syphilitic gum, with its power of destruction, the tongue becomes atrophic, lobulated, fissurated, and with leucoplastic plaques dorsally. And the oral stigma of congenital syphilis is mostly reflected in the changed morphology of incisors that exhibits a shape similar to a screwdriver and molars with cuspid projections resembling blackberries[3].

The diagnosis of syphilis is related to the investigation through non-treponemic tests — VDRL and rapid plasma reagin (RPR) — and treponemic ones, such as fluorescent treponemal antibody absorption test (FTA-ABS), microhemagglutination assay for *Treponema pallidum* (MHTP) and enzyme-linked immunosorbent assay (ELISA). Dark field microscopy, silver impregnation and cytopathology have doubtful diagnostic value and are not much recommended, since the oral cavity has other treponema species that can be mistaken with *T. pallidum*[5]. In the present case, the diagnosis was based on the clinical findings and on the VDRL reagent result, since at the end of the antibiotic therapy the lesions had total remission, and the histopathological analysis was dispensable by means of biopsy. It is worth to notice, however, the importance of this type of examination to favor additional evidences of the diagnosis of syphilis in controversial cases[4].

Figure 5 – Remission of lesion in lateral left tongue border after treatment.

With the diagnosis of secondary syphilis, questions were raised about the clinical chronology of the disease. This phase manifests from three to 12 weeks after the onset of the chancre[4], and alters periods of outbreak and remission of symptoms over the course of two years until a large period of latency is installed[1]. A possible untruth about sexual practices was speculated, since this information characterizes an embarrassing subject and allows the patient to exercise the right to preserve his/her privacy.

It is believed, however, that periods of absence of characteristic inflammatory symptoms of the infection may occur and are caused due to some particularities of *T. pallidum*. Although the bacterium expresses numerous lipoproteins that would be capable of awakening and activating defense cells, they are covered by a fragile membrane that does not have lipopolysaccharides, a highly pro-inflammatory glycolipid, capable of activating immune responses. The populations of *T. pallidum* are extremely heterogeneous, containing bacterial specimens that can bind to antibodies and others that are not capable of such immunologic activity. This set of distinct characteristics causes the spirochete to proliferate and disseminate systemically, without activating the immune system, being a microorganism with a complex capacity of "furtive pathogenicity"[8]. Thus, although three years of possible primary infection have been reported, the diagnosis of secondary syphilis was plausible.

The peculiarity of the presentation of isolated oral lesions of the disease motivated a literary survey in the MEDLINE and PubMed databases, by means of the keywords "isolated oral syphilis", "oral syphilis" and "rare oral syphilis manifestation", also seeking cases of exclusively oral syphilis. The period corresponding to the 50 recent years of scientific production was analyzed, and the existence of only five cases registered that fit in the investigated situation was found[9-13]. No information about any possible factor that provides this situation — it is only speculated that the popularization of the practice of unprotected oral sex may have enabled the increase in the incidence of oral syphilitic lesions (not necessarily as isolated manifestation)[3] — , as well as some statistical data referring to the percentage of incidence of the same clinical presentation (absence of extraoral manifestation of syphilis), was found, being the oral exclusivity considered an extremely rare characteristic of the infection[6].

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Conflict of interests

The authors declare no conflict of interests.

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Virtue is in the middle
Aristotle

The goal of philosophy to the Greek, contrary to what one would imagine, was the pursuit of the *good life*: a life worthy of being lived. Aristotle was admittedly one of the greatest philosophers of ancient Greece and, like the other philosophers of that time, a natural scientist. He was a mathematician, a biologist, a climatologist and also a doctor. Nowadays his axiom "virtue is in the middle" can still be used for habits, such as diet, exercise, balance between work, family and leisure.

Would his axiom apply to the Brazilian Public Health System (Sistema Único de Saúde – SUS) regarding the treatment of sexually transmitted diseases? The authors would be inclined to answer "yes".

The SUS, which aims to provide universal care and prevention at no cost for people according to their location within a particular neighborhood or region, provides undeniable benefits. Knowledge of the family situation and problems provides an opportunity for prevention, early identification of vulnerability to different conditions and diseases and, in theory, the pursuit of the good life. All this helps in preventing referrals to multiple services and unnecessary displacements, which has positive consequences in terms of convenience, costs and reduction of absenteeism — especially relevant when looking at the high unemployment rates the country is experiencing.

It is known, however, that sexually transmitted diseases are still accompanied by severe stigma and discrimination. In times of the availability of appropriate control of human immunodeficiency virus (HIV) infection, stigma is reported to be the worst problem to be faced by people living with HIV. It is no less for other sexually transmitted diseases, regardless of whether they are curable or those which have chronic conditions accompanied by deep psychosocial impact for long periods or even definitively.

At this point, regionalization becomes a problem. Patients with sexually transmitted diseases are justified in their resistance to be treated in a place where health agents from the community many times might be friends, even members of their family. It is known that secrecy and confidentiality, due to the lack of a bioethics culture, as well as the structural conditions of the services, can often be insufficient. Finally, the efficiency of the services is quite far from the ideal, either due to training deficiencies, lack of supplies, and or discomfort because of sexual nature of the problems. In addiction, many health professionals who work in Family Health Strategy are specialists and do not perfectly ft into the idea of solving most of the community's problems as general practitioner would.

That said, we must ask ourselves: where and how are people with sexually transmitted diseases currently being treated? Although of very debatable scientific value and lacking verification through the use of appropriate methods, we describe a common situation in our daily practice. We often find people who waited too long to get an appointment in the health unit of their region. When it happens, the interaction with the health professional results in referral, which is accompanied with its unfavorable consequences. On the other hand, more recently, primary health care protocols include performing rapid tests for HIV infection, syphilis and hepatitis B and C increased very much the benefts of this visit to the health center.

Would then the middle be the virtue? We must support and strengthen regional services whenever they can be effective, where supplies, medicines, and trained and sensitive professionals are guaranteed. In services with these characteristics, people with sexually transmitted diseases and their partners who feel comfortable will also have benefits. And where services have no such requirements? We recommend the installation of the so-called open door services, which also can provide training, surveillance and generation of local knowledge, especially regarding ethyological agents and its patterns of antibiotic resistance.

It is urgent to effectively know where and how people with sexually transmitted diseases are being treated. We consider it an imperative of operational imperative.

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