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Human Papillomavirus Infection in Pregnant Adolescentes: Is There an Association Between Genital and Mouth Infection?

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Abstract

Introduction: The aim of this cross-sectional study was to verify the association of HPV infection in the cervix and the mouth of pregnant adolescents.

Methods: Clinical exam and smears of the cervix and the mouth were performed in thirty pregnant adolescents. Dental biofilm was collected for molecular evaluation. The cytology was analyzed using Bethesda criteria and the molecular evaluation by microarray assay. Associations of HPV infection with socio-demographic-behavioral characteristics and periodontal status were verified.

Results: The mean age of participants was 15.2 [± 1.3] years, and the mean pregnancy length was 28.8 [± 7.3] weeks. In the genital region, six (20%) subjects exhibited HPV-induced lesions. Cytological analysis showed HPV-induced cytophatic cells in 3 (10%) adolescents. Seventeen (56.7%) adolescents presented HPV DNA on the microarray assay. No HPV infection was detected in the mouth, either by clinical, cytological or molecular evaluation. All pregnant adolescents presented some degree of periodontal disease (n = 22 [73.3%] gingivitis and n = 8 [26.6%] periodontitis). Genital HPV infection was significantly more frequent in subjects with gingivitis ($P < 0.05$, Fisher exact test). There was no concordance between clinical exam and cytological/molecular assessment to identify the HPV infection in the genital area (clinical and cytological: $P = 0.103$; clinical and molecular: $P = 0.198$; cytological and molecular: $P = 0.157$; Kappa test).

Conclusion: The microarray assay was more sensitive to detect HPV infection in the cervix, when compared to clinical exam and cytological analysis. There was no association of the HPV infection in the genitalia and the mouth, in the studied population of pregnant adolescents.

Keywords

Papilloma virus DNA probes, Adolescent, Pregnant women, Mouth, Periodontal diseases

Introduction

Human Papillomavirus infection (HPV) is the most common sexually transmitted disease. The mouth has been reported as a frequent site for the infection, after the genital area [1]. The association of the HPV infection in the genital and the mouth regions has been studied by many authors, with controversial results [2-15]. This association may be better observed in individuals who are more susceptible for HPV infection, like young individuals [1], homossexual males [16], and human immunodeficiency virus infected individuals [17]. There are many reasons for infection susceptibility, such as hormonal changes [1,18], tissue immaturity [1,18], multiple sex partners, and some systemic diseases [17]. Oral transmission may occur through orogenital sexual contact [19], oral-oral contact [20] and mother-fetus transmission [21].

The prevalence of HPV infection in the genital region varies from 5.9% to 81.7%, for adolescents [22,23]. During pregnancy, there is more vulnerability for HPV infection in the genital area of young women, than in older women [10]. The prevalence of genital HPV infection in young pregnant women varies from 49% to 60%, in different countries [24-26].

Nearly 23% of the Brazilian healthy individuals are infected by the HPV in the oral mucosa [27]. The HPV may infect the oral epithelium in a latent and asymptomatic form, or it may produce oral lesions. The virus has been detected in the site of periodontal disease of immune competent and immune suppressed individuals [28-31]. Thus, it has been suggested that the periodontum may be a reservoir for HPV in the mouth [28].

The controversial results about the association of the HPV infection in the mouth and the genital regions may be due to geographical reasons. Only few authors studied this association in a Brazilian population [2,6,12,24,25]. This study aimed to detect HPV infection in the cervix and the mouth of pregnant adolescents. An

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additional aim was to evaluate the concordance of clinical exam and cytological/molecular HPV methods to identify HPV infection.

Methods

Design

This was a cross-sectional study in which pregnant adolescents attending the Maternity School of the Universidade Federal do Rio de Janeiro (UFRJ/Brazil) were evaluated for HPV infection in mouth and genital areas.

Population

A convenience sample of adolescents seeking assistance for prenatal care, during the period of six months, represented the population of the study. All pregnant teenagers from the Maternity School of UFRJ were invited to participate in the study. Individuals were included if adolescent, aged between 10 and 19 years according World Health Organization, and agreed to participate in the study. Subjects were excluded if they presented any other genital infection. The research was approved by the institution review board at the University, and all subjects signed a consent form.

Clinical analysis

The pregnant adolescents were invited to participate in the study during the routine gynecological appointment. A complete examination of the genitalia and oral regions were performed by experienced gynecologist and dentist, respectively, to investigate for HPV infection. Clinical, socio-demographic and behavioral characteristics were collected from medical records and interview.

In the genital region, the external genital (minor and major labia), perianal and anal region were inspected. The internal genitalia was examined after the insertion of the speculum and the application of acetic acid 2%, in order to identify possible staining suggestive of HPV infection.

The oral exam was performed in a hospital gurney with a forehead light-emitting diode (LED) lamp. Acetic acid was not applied because it is not considered a good indicator of HPV infection in the oral tissues [32]. A complete periodontal exam was performed by a trained periodontist, and the reliability of the evaluation was tested ($P = 0.885$, intra-class correlation coefficient [95% CI: 0.883 - 0.887]). The gingival index system [33], probing depth, clinical attachment level, and bleeding on probing were obtained and measured with a conventional North Carolina periodontal probe (Hu-Friedy, Chicago, IL, USA). Six sites per tooth were measured in a full mouth exam. Periodontal disease (gingivitis and periodontitis) was diagnosed through the evaluation of these parameters. Gingivitis was diagnosed when the supragingival bleeding was present in > 10% of the sites [34]. Periodontitis was considered if the clinical attachment level was ≥ 5 mm [35], in at least 4 sites, and bleeding on probing was observed in 3 different teeth.

Sample collection

Cytology foam brushes were used to collect two samples from the uterine cervix and two from the mouth. Each sample collection was taken with six full turns of the brush. The first sample from the uterine cervix was spread on a slide and fixed in 70% alcohol for cytological analysis. The second sample was collected from the same region and placed in a tube containing 3 ml of the specimen transport medium (STM) buffer solution (Papillocheck® collection kit, Greiner Bio-One GmbH, Germany). The tube was cooled at 4 °C, until HPV genotyping.

In the mouth, the samples were taken from the dorsum of tongue and the area between hard and soft palate, with the same technique. The first sample was spread on a slide and fixed in alcohol, and the second sample taken from same area was placed in STM and cooled until genotyping.

Additionally, four subgingival biofilm samples were collected from the deepest sulcus sites (identified in the periodontal exam) from each subject. Prior to collection, supragingival plaque and saliva were removed from the teeth using sterile cotton rolls. A sterile 11-12 Gracey periodontal curette (Hu-Friedy, Chicago, IL, USA) was gently inserted into the periodontal pocket and the subgingival material was collected. The samples were stored in dry sterile tubes and kept at -80 °C, until analysis.

Laboratorial analysis

The slides of the cervical and oral samples were stained by the Papanicolau (Pap) method and were evaluated by a cytopathologist using the Bethesda criteria.

The samples in the frozen tubes were restored to room temperature. The cells were submitted to DNA purification using QIAamp DNA Mini Kit® protocol (Qiagen, Germany), according to the manufacturer's guidelines. The HPV genotyping was performed using the microarray assay test (PapilloCheck® microarray kit, Greiner Bio-One GmbH, Germany), which identifies 18 high risk and 6 low risk types of HPV (HPV 6, 11, 16, 18, 31, 33, 35, 39, 40, 42, 43, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82, 44/55).

Statistical analysis

Descriptive data analysis was reported as the absolute frequency and percentage for categorical variables, and mean and standard deviation for the continuous variables. Fisher exact test was used to verify the differences between HPV presence in uterine cervix and in periodontal disease. Kappa test was used to correlate the results of the three methods of diagnosis for HPV infection (clinical, cytological and molecular). The p values ≤ 0.05 were considered statistically significant.

Results

Socio-Demographic characteristics

Thirty-one pregnant adolescents were recruited for the study, but one refused to participate. The mean (and standard deviation [SD]) age of the 30 included subjects was 15.2 [SD ± 1.3] years and the mean gestational period was 28.8 [SD ± 7.3] weeks. Social and behavioral characteristics are showed in table 1. The number of sexual partners reported by the subjects varied from 1 to 10 partners, with a mean of 2.4 partners [SD ± 2.3]. The practice of oral sex was reported by 18 (60%) of them, and the other 12 (40%) reported did not have this type of sex practice.

Clinical, cytological and molecular exams

In the clinical exam of the genital area, eight (23%) subjects presented HPV-induced lesions (condiloma accuminatum). Five of them showed lesions in the external genitalia and three in both external and internal genitalia.

In the cytological analysis of the uterine cervix, all the smears presented appropriated material for the evaluation. Three (10%)

Table 1: Socio-demographic characteristics of the 30 pregnant adolescents.

Characteristics	N (%)
Education	
Elementary school	21 (70.0)
High school (graduated or non-graduated)	09 (30.0)
Family Income (per year)	
US$ 15.000-45.000	19 (64.0)
> US$ 45.000	04 (13.0)
Not know	07 (23.0)
Habits	
Tobacco	
Never used	25 (83.3)
Before pregnancy	05 (16.3)
During pregnancy	-
Alcohol	
Never drank	17(56.6)
Socially, before pregnancy	13 (43.3)
During pregnancy	-

Table 2: HPV infection evaluation in the 30 pregnant adolescents.

N	Cervix				Mouth					
	Lesion	Cytology	Molecular test		Lesion	Cytology	Molecular test			
							Tongue/palate		*Periodontum (biofilm)*	
			Low risk	***High risk***			***Low risk***	***High risk***	***Low risk***	***High risk***
1	condiloma accuminatum	TC	HPV 44/55	HPV59	-	TC	-	-	-	-
2	-	TC	-	HPV56	-	TC	-	-	HPV6	-
3	-	TC	-	-	-	TC	-	-	-	-
4	-	TC	-	HPV52	-	TC	-	-	-	-
5	-	TC	-	-	-	TC	-	-	-	-
6	-	TC	-	HPV52, 58	-	TC	-	-	-	-
7	-	TC	-	HPV68	-	TC	-	-	-	-
8	-	TC	-	HPV16	-	TC	-	-	-	-
9	-	TC	-	-	-	TC	-	-	-	-
10	-	TC	-	HPV51	-	TC	-	-	-	-
11	-	TC	-	-	-	TC	-	-	-	-
12	-	TC	-	-	-	TC	-	-	-	-
13	-	TC	-	-	-	TC	-	-	-	-
14	-	LSIL, NIC 1	-	HPV56, 58	-	TC	-	-	-	-
15	-	TC	-	-	-	TC	-	-	-	-
16	-	TC	HPV11	-	-	TC	-	-	-	-
17	-	TC	HPV42	HPV51	-	TC	-	-	-	-
18	condiloma accuminatum	TC	HPV11	-	-	TC	-	-	-	-
19	-	TC	-		-	TC	-	-	-	-
20	-	TC	-	HPV16	-	TC	-	-	-	-
21	-	TC	HPV6	HPV66	-	TC	-	-	-	-
22	-	TC	-		-	TC	-	-	-	-
23	condiloma accuminatum	TC	-	HPV35	-	TC	-	-	-	-
24	-	TC	-	HPV16, 68	-	TC	-	-	-	-
25	-	TC	HPV42	HPV31, 59	-	TC	-	-	-	-
26	-	TC	-	-	-	TC	-	-	-	-
27	-	TC	-	HPV16, 31, 58, 39, 73	-	TC	-	-	-	-
28	-	TC	-	-	-	TC	-	-	-	-
29	-	TC	-	-	-	TC	-	-	-	-
30	-	TC	-	-	-	TC	-	-	-	-

Abbreviations: TC: Typical Cells, HPV: Human Papillomavirus, LSIL: NIC 1, Low grade Squamous Intraepithelial Lesion, ASC-US: Atypical Squamous Cells of Undetermined Significance.

subjects presented HPV-induced cell changes in the cytological analysis of the uterine cervix. Two (6%) samples presented low grade squamous intraepithelial lesions and one (3%) slide showed atypical squamous cells of undetermined significance (ASC-US).

In the microarray assay of the uterine cervix, seventeen (56.7%) subjects were positive for HPV. One adolescent did not present conclusive cytology alterations for HPV infection (ASC-US), but was positive for HPV6 and HPV56 in the microarray assay (Papillocheck®). Fourteen (51.9%) of the 27 subjects that did not show HPV induced cell changes in the Pap test presented positive for HPV DNA (Table 2). The more prevalent subtype was HPV 16 (n = 4/23.5%), followed by the HPV 68 (n = 3/17.6%). Table 2 shows the different subtypes identified by the microarray test. Multiple infections were presented in eight (47.1%) subjects, and one of them exhibited five different HPV subtypes (high risk HPV 16, 31, 58, 39, 73).

In the mouth, no HPV-induced lesions were found in the clinical exam. In the cytological analysis, all the samples showed appropriate material for the evaluation, but none of them presented HPV-induced cytophatic cells. The microarray assay did not identify the DNA HPV in any oral smear sample.

Status of periodontal disease

None of the adolescents presented normal periodontal status. Table 3 shows the frequency of gingivitis and periodontitis in the studied population and the association with the microarray results from the uterine cervix. The genital HPV infection was significantly more frequent in subjects that showed gingivitis than those who did not present gingivitis (P = 0.04, Fisher exact test). This association was not found in those subjects who presented periodontitis.

Table 3: Periodontal status of 30 pregnant adolescents according to HPV infection in the cervix through the microarray results.

	Positive microarray assay Uterine cervix		**OR (95%IC lower-upper)**	**P value**
	positive	*negative*		
Gengivitis (%)				
positive	13 (59.1)	09 (40.9)	1.44 (0.28-7.34)	0.04[a]
negative	04 (50.0)	04 (50.0)		
Periodontitis (%)				
positive	05 (62.5)	03 (37.5)	1.39 (0.26-7.29)	1.00
negative	12 (54.5)	10 (45.5)		

[a]Fisher Exact Test.

One hundred and twenty subgingival biofilm samples were collected (the four deepest pocket per subject). The HPV was identified in one (0.08%) of the subgingival samples (low risk, HPV 6). Gingivitis was observed in the adolescent with a positive HPV in the gingival sulcus, but the site where HPV was detected presented normal clinical aspect. This adolescent who exhibited HPV in the biofilm also exhibited HPV in the uterine cervix (high risk, HPV 56).

Genital and mouth HPV infection association

There was no association of HPV infection in the uterine cervix with the infection in the mouth. The simultaneous presence of HPV infection in the genitalia and the tongue/palate area was not observed in any subjects.

There was no concordance between the clinical exam, the cytological exam and the molecular HPV assay to identify the HPV infection in the genital area (clinical and cytologic, $P = 0.10$; clinical and molecular, $P = 0.19$; cytologic and molecular, $P = 0.15$, Kappa test). The concordance between methods for HPV detection could not be tested in the oral mucosa, because none of them could detect the HPV infection. In the periodontum, the positive sample was not enough for correlation.

Discussion

More than half of the pregnant adolescents in the present study presented HPV infection of the uterine cervix, but none of them presented HPV infection of the tongue/palate. There was no association between genital and oral HPV infection in the studied population. This is in agreement with other studies which evaluated older populations of pregnant women [10-11]. This association was reported only in one case of pregnant adolescent in the literature [36], but had never been studied in a group of pregnant adolescents.

The lack of association between the HPV infection in the mouth and the genital area has also been observed in other populations [10,12,13,15]. However, there are some studies that reported an association of HPV infection in these two regions [2,4-6,8,9,32]. Studies performed in the Brazilian population were performed in groups of non-pregnant women, men and heterosexual couples, and they are also controversial [2,6,12,24,25].

Some risk factors have been suggested for the concomitant infection in the genital area and the mouth, like orogenital sex practice [4,5,9,32], young age at first intercourse [5], and alcohol consumption [4]. In this study, more than half of the adolescents reported oral sex practices, but HPV DNA was not found in any sample of their tongue/palate. Among the Brazilian studies that showed the association of HPV infection in the genitalia and the mouth, smoke was considered a risk factor in one study [6], but orogenital sex was not regarded as a risk factor [2].

Pregnancy has been pointed as a risk condition for HPV infection in the cervical region [8,22,24]. The present study was not designed for risk calculation; therefore, we did not have a control group of non-pregnant adolescents for comparison. However, almost half of the adolescents presented multiple high risk HPV DNA infections, which is higher than the frequency observed in other studies [37,38]. The HPV16 was the most prevalent subtype observed in the present study and in other studies [39].

The majority of the pregnant adolescents of the studied population did not show HPV-induced cytological changes in the uterine cervix, but over fifty percent of them had positive HPV DNA on the microarray assay. This is a common finding in other studies as well [22,39,40]. According to the Bethesda criteria, the cellular changes on smears of the cervix are not conclusive for the HPV absence. Molecular tests are best addressed to detect viral DNA.

There was no HPV infection in the mouth (tongue/palate) of pregnant adolescents in the clinical, cytological and molecular evaluation. Cytology is not considered the first choice method for the analysis of HPV infection in the mouth, when patients do not present lesions, and it does not seem to be a reliable screening technique in the clinically healthy oral mucosa [32]. Furthermore, the oral sample collection may not be representative of the whole oral mucosa. Despite these arguments, the results of the three methods agreed upon the absence of the HPV infection in the mouth, in the studied population.

There are specific receptors in the gingival cells for estrogens [41]. Hormonal peaks that occur in adolescence and pregnancy may change the immune response and thus influence the susceptibility and the resistance to infections in the periodontal tissues in these periods of the women's life [41]. Many studies showed controversial results in relation to the presence of HPV in the site of the periodontal disease [28,31,42,43]. In none of these studies, the oral sex habits was investigated and related to the HPV presence in the periodontum. In the only pregnant adolescent of this study that presented the HPV DNA in the biofilm, it was observed that she reported having oral sex one week before the sample collection.

The patient with positive HPV in the biofilm presented gingivitis, but not in the site of sample collection. Maybe the lack of association was a result of the non-advanced periodontal disease due, to young age. However, it was observed that subjects with HPV infection of the uterine cervix presented more gingivitis than those negative for HPV. Pregnant women are more susceptible for both gingivitis and for HPV infection in uterine cervix, because of the hormonal changes [23,42]. Thus, these findings are probably consequences of pregnancy, and may not be related among themselves.

This study had some limitations. Although it showed agreement with the studies that evaluated pregnant women, our sample size was relatively small and composed only by pregnant adolescents. Moreover, the young age of subjects limited the evaluation of some social and behavior characteristics that may be related to HPV infection, but needed more life time cumulative experience.

Conclusions

There was no association between the HPV infection in the genital and the mouth regions, in the studied population of pregnant adolescents. The methods used to detect HPV infection induced lesions showed concordance in the mouth, but not in the genital region.

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Conflict of Interest

The authors disclose have no conflict of interest.

Ethical Statement

This study followed the principles of Helsinki declaration and was approved by Institutional ethics committee.

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