Ref: Ro J Infect Dis. 2022;25(2)
DOI: 10.37897/RJID.2022.2.3

# Human papillomavirus infection and associated risk of preterm birth

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## ABSTRACT

**Introduction.** The human papilloma virus (HPV) is a virus usually transmitted through mucocutaneous contact directly with the infected organs, resulting in a sexually transmitted infection that exposes particularly young women to a high risk of developing neoplasia of cervical, anogenital, respectively oropharyngeal origin if the virus persists for more than 1-2 years. Our study aimed to detect the correlation between HPV infection and spontaneous preterm labor.

**Materials and methods.** We conducted an observational comparative case-control study in the Department of Neonatology/Obstetrics and Gynaecology of Elias Emergency University Hospital on women diagnosed with HPV infection to assess the risk of preterm labour associated with this infection.

**Results.** The overall group of patients was divided into two groups (confirmed and unconfirmed (or negative) with HPV infection). We observed that, among positive patients, there was a higher incidence of patients infected with a single HPV strain (n=36), followed by patients infected with 2 strains (n=7). Our study revealed the fact that only 4 cases (22.2%) had a history of preterm birth, as opposed to 77.8% (14 cases) who had no associated preterm birth history in the case of HPV genotype 16 positive patients. The data obtained showed no statistical significance (p=0.977).

**Conclusions.** Preterm birth remains one of the leading causes of perinatal mortality and lifetime morbidity worldwide. HPV is a frequently diagnosed viral infection, but clinical studies have observed mixed results regarding the association of HPV 16 and the risk of preterm birth.

**Keywords:** HPV 16, pregnancy, preterm birth, prematurity

## INTRODUCTION

Papillomaviruses are widely distributed worldwide and have a preferential tropism for squamous epithelial cells located in the mucocutaneous barrier. Depending on the genotype involved, HPV infection determines both benign proliferative lesions, such as vegetations or papillomas and the formation of preneoplastic lesions that may evolve and subsequently lead to the development of cervical cancer [1].

HPV types are classified, based on the oncogenicity and the strong association with cervical neoplasia, into two categories: high-risk HPV (genotypes 16, 18, 31, 33, 35, 45 and 59, which account for about 95% of cervical preneoplastic and neoplastic lesions) and low-risk HPV (mainly genotypes 6 and 11,

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*Article History:*
Received: 28 June 2022
Accepted: 30 June 2022

which are responsible for most of the papillomatous lesions).

Regarding the viral structure, the differentiation between these two categories is mainly achieved through the two viral proteins with role in cell transformation and, by extension, the development of invasive lesions – protein E6 (inactivates the p53 tumor suppressor protein and activates the telomerase complex, preventing cell apoptosis) [2] and protein E7 (acts by binding and degrading proteins belonging to the retinoblastoma family) [3].

Of particular note would be the type 16 that presents the highest oncogenic risk, a risk determined by the virus' superior tendency to cause persistent infection. Progression to neoplasia, even in the presence of high-risk strains, is not a mandatory consequence, as this requires additional factors that are related to host immunocompetence and environment [4].

Viral infections of the genital tract can lead to preterm birth either by reducing the barrier protection provided by the cervical mucosa, thus facilitating the ascension of the infection, or by directly inhibiting the trophoblastic function and disrupting the immune system [5,6].

HPV is the most common viral infection of the genital tract, but although in vitro studies [7] and animal models [8] have associated HPV infection with multiple adverse pregnancy outcomes, including preterm birth, clinical studies have observed mixed results regarding this association. This may be due to misclassification of HPV exposure, detection of HPV at inappropriate time points, and insufficient control for confounding factors [9].

Given the high prevalence of HPV infection among women of childbearing age, the mechanistic plausibility of an association between preterm birth and HPV infection, the significant burden of preterm birth, and the availability of effective HPV vaccines as a prevention method, confirmation of this association is of utmost interest [6].

Regarding immunization during pregnancy, HPV vaccine is an inactivated viral vaccine available worldwide as bivalent, quadrivalent and 9-valent, though HPV vaccination with any of them during pregnancy is preferred to be avoided due to limited safety information [10]. If pregnancy is confirmed after the patient in question has initiated the vaccination series, postponement of the remaining vaccine doses is recommended, although the available evidence on inadvertent vaccination during pregnancy does not indicate any increased risk of adverse pregnancy outcomes [11].

## MATERIALS AND METHODS

We conducted an observational comparative case-control study in the Department of Obstetrics and Gynaecology of Elias Emergency University Hospital on women diagnosed with HPV 16 strain infection to assess the risk of preterm labour associated with this infection. Therefore, we prospectively evaluated whether vaginal HPV infections during pregnancy and was independently associated with preterm birth.

Premature birth was defined as birth before the age of 37 weeks of gestation.

## RESULTS

The overall pool of patients was divided into two groups (confirmed and unconfirmed (or negative) with HPV infection). We observed that, among positive HPV patients, there was a higher incidence of patients infected with a single HPV strain (n=36), followed by patients infected with 2 strains (n=7). Only one case associating 6 HPV strains was also detected.

The main target assessed was the risk of preterm birth associated with HPV infection. Thus, we made a parallel between the group of patients with HPV

**TABLE 1.** Comparison of preterm birth risk between positive vs negative patients

nasteri_prem *HPV_status Crosstabulation

| | | | HPV_status | | Total |
|---|---|---|---|---|---|
| | | | negativa | pozitiva | |
| nasteri_prem | nu | Count | 45 | 38 | 83 |
| | | % within nasteri_prem | 54.2% | 45.8% | 100.0% |
| | | % within HPV_status | 91.8% | 77.6% | 84.7% |
| | | % of Total | 45.9% | 38.8% | 84.7% |
| | da | Count | 4 | 11 | 15 |
| | | % within nasteri_prem | 26.7% | 73.3% | 100.0% |
| | | % within HPV_status | 8.2% | 22.4% | 15.3% |
| | | % of Total | 4.1% | 11.2% | 15.3% |
| Total | | Count | 49 | 49 | 98 |
| | | % within nasteri_prem | 50.0% | 50.0% | 100.0% |
| | | % within HPV_status | 100.0% | 100.0% | 100.0% |
| | | % of Total | 50.0% | 50.0% | 100.0% |

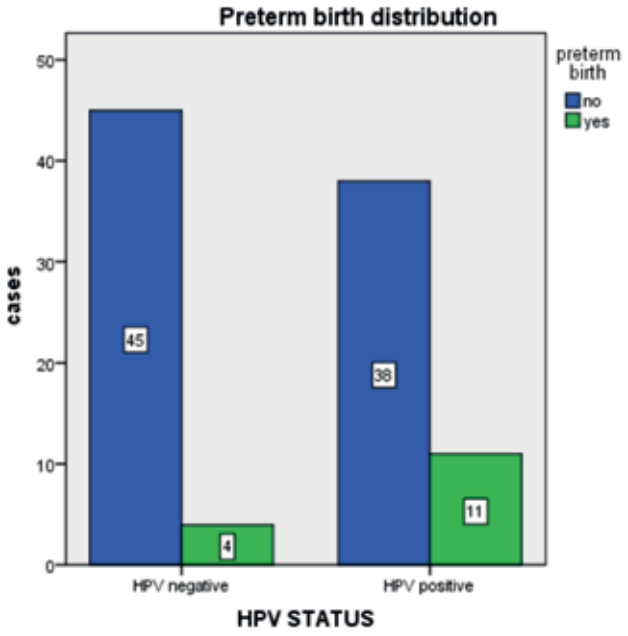


**FIGURE 1.** Distribution of preterm births by HPV infection status

infection and without HPV infection to identify the background preterm birth risk of the patients.

Thus, we observed that in the group of HPV positive patients 22.4% of them (n=11) associated with preterm birth compared to the group of HPV negative patients of which only 8.2% (n=4) associated with preterm birth. In this case, the difference was statistically significant (p=0.050).

We compared the risk of premature birth determined by the type of HPV-infecting strain.

We targeted 25.0% (n=4) of the group of patients infected with low-grade HPV strains that were associated with preterm birth. On the other hand, 21.2% (n=7) of the group of patients infected with high-grade HPV strains associated with preterm birth. However, the percentages obtained are not statistically significant (p=0.766).

We have followed a parallel between the presence of HPV 16 and the risk of premature birth among these patients.

Thus, in the case of HPV genotype 16 positive patients only, 4 cases (36.4%) had a history of preterm birth, as opposed to 14 cases (36.8%) who had no associated preterm birth history. The data obtained showed no statistical significance (p=0.977)

## DISCUSSIONS

In our study, we followed a number of 49 HPV-positive pregnant women, making correlations between HPV infection and the risk of preterm birth, compared to a control group, HPV-negative pregnant women.

Thus, we observed that in the work group, HPV infection was associated with preterm birth in 22.4% of cases (n=11), compared, in the control group, preterm birth was associated in 8.2% of cases (n=4), statistically significant result (p=0,05).

The literature data are contradictory. In the study conducted in 2008, Gomez and colleagues detected DNA-HPV more frequently in placentas from spontaneous preterm deliveries than in placentas from controls (p=0.03). HPV infection of extravillous trophoblast induces cell death, placental dysfunction and is associated with adverse pregnancy outcomes, including spontaneous preterm delivery [7]. Another study, published in 2016, evaluates HPV infection as a risk factor for preterm birth and the conclusion was that the rate of preterm birth was not significantly different between HPV-positive and HPV-negative women (16.5% compared with 12.2%) [12].

Another risk factor associated with preterm birth is represented by the intervention at the level of the cervix, which has the consequence of shortening its length.

**TABLE 2.** Comparison according to the presence of infection with LR versus HR strains

nasteri_prem *Tulp_risk_H_L Crosstabulation

| | | | Tulp_risk_H_L | | Total |
|---|---|---|---|---|---|
| | | | LR | HR | |
| nasteri_prem | nu | Count | 12 | 26 | 38 |
| | | % within nasteri_prem | 31.6% | 68.4% | 100.0% |
| | | % within Tulp_risk_H_L | 75.0% | 78.8% | 77.6% |
| | | % of Total | 24.5% | 53.1% | 77.6% |
| | da | Count | 4 | 7 | 11 |
| | | % within nasteri_prem | 36.4% | 63.6% | 100.0% |
| | | % within Tulp_risk_H_L | 25.0% | 21.2% | 22.4% |
| | | % of Total | 8.2% | 14.3% | 22.4% |
| Total | | Count | 16 | 33 | 49 |
| | | % within nasteri_prem | 32.7% | 67.3% | 100.0% |
| | | % within Tulp_risk_H_L | 100.0% | 100.0% | 100.0% |
| | | % of Total | 32.7% | 67.3% | 100.0% |

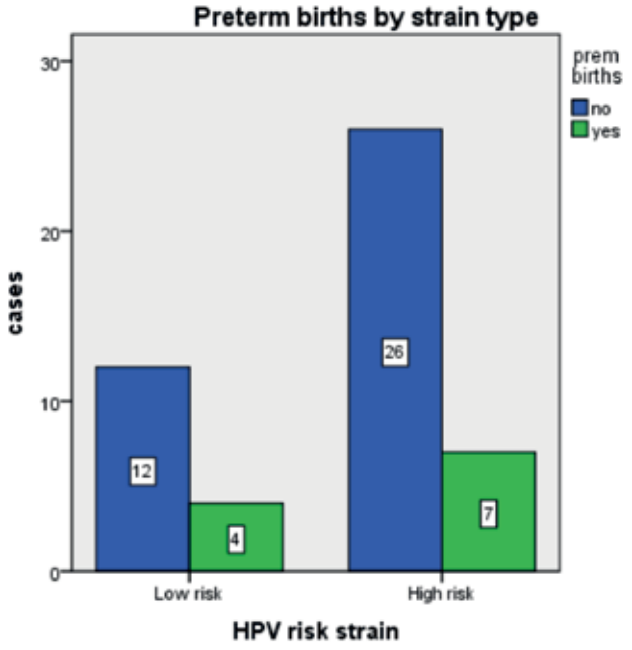


**FIGURE 2.** Distribution of premature births by strain type

In this sense, Miller et al. described recently (2016) an increased risk of prematurity in cervical dysplasia with excisional procedure [13]. One explanation of the independent risk associated with loop electrosurgical excision procedure is that this procedure causes a cervical collagen remodelling that, in turn, is associated with preterm birth [14]. The study does not take into account other factors that can influence the result: the presence of other genital infections associated with HPV and also does not specify HPV strain.

In our study lot, of the 11 patients with preterm birth, 5 (45%) had interventions on the cervix, 3 of them (60%) were with HPV16 stain.

The novel concept is that a viral infection effects the immune modulatory role of the trophoblast and it triggers an exaggerated immune response to bacteria [6]. The HPV infection of the cervix increases the susceptibility to ascending infection, thus confection cu Ureaplasma urealyticum, Mycoplasma, Chlamydia trachomatis is associated with changes in the immune status and preterm birth [6]. In a study conducted in 2013 on mice, Racicot and collaborators, demonstrated that if the cervix is infected with virus, the protection from the upper female reproductive tract is decreased and bacteria from maternal-fetal interface (like U.urealyticum, the most common) are able to reach the pregnant uterus. The authors propose that this reduced protection is due to the decrease in antimicrobials and inflammatory cytokines in the cervix infected with virus [15].

**TABLES 3 and 4.** The risk of premature birth associated with HPV 16

nasteri_prem *T16 Crosstabulation

| | | | T16 | | Total |
|---|---|---|---|---|---|
| | | | nu | da | |
| nasteri_prem | nu | Count | 24 | 14 | 38 |
| | | % within nasteri_prem | 63.2% | 36.8% | 100.0% |
| | | % within T16 | 77.4% | 77.8% | 77.6% |
| | | % of Total | 49.0% | 28.6% | 77.6% |
| | da | Count | 7 | 4 | 11 |
| | | % within nasteri_prem | 63.6% | 36.4% | 100.0% |
| | | % within T16 | 22.6% | 22.2% | 22.4% |
| | | % of Total | 14.3% | 8.2% | 22.4% |
| Total | | Count | 31 | 18 | 49 |
| | | % within nasteri_prem | 63.3% | 36.7% | 100.0% |
| | | % within T16 | 100.0% | 100.0% | 100.0% |
| | | % of Total | 63.3% | 36.7% | 100.0% |

Chi-Square Tests

| | Value | df | Asymp. Sig. (2-sided) | Exact Sig. (2-sided) | Exact Sig. (1-sided) |
|---|---|---|---|---|---|
| Pearson Chi-Square | .001[a] | 1 | .977 | | |
| Continuity Correction[b] | .000 | 1 | 1.000 | | |
| Likelihood Ratio | .001 | 1 | .977 | | |
| FIsher's Exact Test | | | | 1.000 | .633 |
| Linear-by-Linear Association | .001 | 1 | .977 | | |
| N of Valid Cases | 49 | | | | |

a. 1 cells (25.0%) have expected count less than 5. The minimum expected count is 4.04.
b. Computed only for a 2x2 table

In our study, the association with other genital infections was present to 8 patients (16.3%) in the studied group and to 5 patients (10.2%) in the control group. The co-infections were with Ureaplasma urealyticum and Mycoplasma, no infection with Chlamydia trachomatis was detected.

In the most recent multicentre study conducted in Canada, the risk of prematurity is correlated with HPV16/18, independent of other risk factors [16].

The prospective HERITAGE cohort study was conducted at 3 academic hospitals in Montreal, Québec, Canada, 899 pregnant women recruited between November 8, 2010, and October 16, 2016, vaginal HPV DNA detection in the first and third trimesters of pregnancy and placental HPV infection; the objective is the association between HPV infection and preterm birth. Results: Persistent vaginal HPV-16/18 detection was significantly associated with all preterm births. Results were similar when restricting the analysis to participants without a history of cervical intraepithelial neoplasia treatment.

In our study, we also looked for the association between preterm birth and the type of HPV strain, LR – HR, then, the correlation between the presence of the HPV 16 strain and the risk of prematurity.

The results showed that 25% (n=4) of those with LR-HPV were associated with premature birth, respectively 21.2% (n=7) of the group with HR-HPV, the result being statistically insignificant (p=0.766).

Following the association between HPV16 and the risk of prematurity, only 4 cases (22.2%) had a history of preterm birth; the other 14 cases (77.8%) were not associated with prematurity.

Limitations of the study:

- Numerically reduced group
- The pregnant women in the study group were tested positive for HPV before pregnancy, qualitative tests, without monitoring the viral clearance during pregnancy.

## CONCLUSIONS

Preterm birth remains one of the leading causes of perinatal mortality and lifetime morbidity worldwide. HPV is a frequently diagnosed viral infection, but clinical studies have observed mixed results regarding the association of HPV 16 and the risk of preterm birth. Future studies should investigate the association of HPV vaccination and vaccination programs with the risk of preterm birth.

*Conflict of interest:* none declared
*Financial support:* none declared

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