Effect of high-risk human *papillomavirus* infection on adverse obstetric outcomes

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ABSTRACT

Background: Human *papillomavirus* (HPV) infection has been associated with an increased risk of preterm birth and severe preeclampsia. We analyzed the prevalence and association of high-risk HPV infection in pregnant women with adverse obstetric outcomes.

Methods: In this retrospective case-control study, conducted between 1 January and 30 June 2016, we included 349 pregnant women with singleton pregnancies who underwent HPV testing and completed a postpartum questionnaire.

Results: A total of 297 women had a negative HPV test (84.8%). The prevalence of high-risk HPV genotypes was 15.2%. Mean age was 30.95 years, 28.75 in the HPV-positive group and 31.34 in the HPV-negative group ($P = 0.003$).

In the HPV-positive group, the average age at sexual debut was lower ($P = 0.03$) and this group also had more smokers ($P = 0.044$). Lower birth weight (3022 g *vs* 3212 g; $P = 0.034$) and more admissions to the neonatal intensive care unit (7.5% *vs* 2.4%; $P = 0.091$) were also observed in this group.

Conclusions: HPV could contribute to the development of threatened premature labour but does not appear to be related to premature rupture of the membranes or hypertensive disorders of pregnancy. Prospective studies with larger sample sizes are needed to this possible relationship.

KEYWORDS

Human *papillomavirus*, prevalence, pregnancy outcomes, preeclampsia, preterm birth, premature rupture of foetal membranes.

Background

Human *papillomavirus* (HPV) infection is the most common sexually transmitted infection worldwide [1]. According to the International Agency for Research on Cancer, the prevalence of HPV infection varies according to geographical area: rates are less than 10% in developed countries and greater than 15% in developing countries [2]. The CLEOPATRE study reports an overall prevalence in Spain of 14.3% that peaks among women aged 18 to 25 years, when female reproductive potential is at its highest, thus making this infection a probable finding in pregnant women [3].

HPV is well established as the most critical independent risk factor for the development of cervical dysplasia or cervical cancer [4,5]. It is also related to the development of anogenital and oropharyngeal tumours, and with benign processes such as condylomas. However, its implications for both pregnancy and perinatal outcomes are unknown. A recently published study found that placental infection with HPV is associated with an increased risk of preterm birth or severe preeclampsia, and suggested that the pathophysiological basis was placental dysfunction [6]. However, less information is available about the prevalence of HPV among pregnant women and its association with adverse obstetric outcomes.

A recent Canadian meta-analysis also found a consistent and significant relationship between HPV and preterm delivery. It seems that HPV could be related to restricted intrauterine growth, low birth weight and fetal death, but the data are limited [7]. Furthermore, a relationship between HPV infection and premature rupture of the membranes (PROM) has also been observed [8,9]. The primary study objective was therefore to analyze the prevalence of high-risk HPV infection in pregnant women and its possible effect on adverse obstetric outcomes. We also examined the epidemiological variables of the study population and the distribution of HPV by the most frequent viral genotypes.

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Methods

The retrospective case-control study was conducted between 1 January and 30 June 2016 in the obstetrics and gynaecology department of Complejo Hospitalario Universitario Insular Materno Infantil (CHUIMI).

The study included women over 18 years with singleton pregnancies, while those with twin pregnancies, polyhydramnios, or who refused to provide informed consent were excluded. Patients signed an informed consent form and were assigned a code to maintain data protection. Because the pregnancies were monitored outside the hospital setting, the most ideal time to recruit patients was at the moment of delivery.

Based on these criteria, 349 pregnant women aged 18 to 44 years participated; patients underwent an HPV test and completed a questionnaire on lifestyle habits, reproductive history and other variables in the immediate *postpartum* period.

Data collection

HPV testing was performed using the COBAS® 4800 HPV test (Roche Diagnostics), which allows automated detection of the viral DNA of high-risk HPV genotypes 16, 18 and others (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) and has high clinical sensitivity for use in a population-based screening programme [10]. According to the ATHENA study, the sensitivity to detect cervical intraepithelial neoplasia grade 2-3 or worse is 90%-93.5%; and specificity 70.5%-69.3% [11].

The COBAS® 4800 HPV test demonstrated performance comparable to the Hybrid Capture 2 test (CH2) for the detection of CIN grade 2 or worse and grade 3 or worse. CH2 is one of the most frequently used and studied HPV DNA tests worldwide with a sensitivity of 95% for detecting CIN3 or worse (30% higher than cytology) and a specificity of 89% for CIN3 or worse (not statistically different from cytology) [6,11]. During the *postpartum* period, samples for HPV testing were collected in liquid medium for analysis. Patients who tested positive underwent reflex cytology; patients over 25 years of age with cytology showing ASCUS (atypical squamous cells of undetermined significance) or a worse result were referred for colposcopy. The information on each patient was collected from a questionnaire administered at the time of obtaining the sample. Each patient was assigned a numeric identification code and data were collected on age at the time of the study, harmful habits, use of oral hormonal contraception (OHC) or intrauterine device (IUD) as the contraceptive method prior to the pregnancy, age at sexual debut, number of sexual partners, sexually transmitted diseases and history of cervical conisation. Data were also collected from the patient's electronic medical record on the gestational age at delivery, personal and obstetric history, ethnicity, immunosuppression, pregnancy complications, and results of the third trimester vaginal discharge swab (determination of group B Streptococcus agalactiae). Data were also recorded on delivery and perinatal outcomes such as type of delivery, Apgar score and birth weight, cord arterial pH, time of sac rupture prior to labour, destination of the newborn, and perinatal mortality.

Analysis

The adverse obstetric outcomes analysed were: preterm delivery (birth before week 37 of pregnancy), PROM (spontaneous rupture of the sac before week 37), threatened preterm labour (TPL; regular uterine contractions accompanied by cervical changes occurring before week 37), preeclampsia (hypertension, proteinuria and/or thrombocytopenia, renal failure, abnormal liver function tests, pulmonary oedema, and brain or visual symptoms), and gestational hypertension (hypertension without proteinuria in the second half of pregnancy or in the early *postpartum* period, with no signs of preeclampsia and resolution within 6 weeks *postpartum*).

The main variables included in the study were described. Absolute and relative frequencies and percentages were determined for the qualitative variables, while measures of central tendency (mean and median) and dispersion (standard deviation and variance) were determined for the qualitative variables. Univariate statistical analysis was performed to determine possible associations between the different variables considered. In the comparison of means, we first used the Kolmogorov-Smirnov test to determine whether the continuous variables followed a normal distribution, and then the Student's t-test for continuous variables with normal distribution and the Mann-Whitney U test for continuous variables with non-normal distribution. The Chi-square and Fisher's exact test were used to analyse the differences between qualitative variables. Statistical significance was set at $P < 0.05$. We used the SPSS statistical package for MAC version 25.0.

Results

During the study period, we enrolled a total of 349 patients in whom HPV testing was performed on a cervical sample. The sample size was calculated for a prevalence of HPV of 15% in women 18–25 years old, based on the CLEOPATRE study [3]. The female population of Gran Canaria between 18-40 years was used for comparison. Data were statistically analyzed with a margin of error of 5% and 95% confidence level. Table 1 summarizes the overall epidemiological characteristics of the study group, including data on age, smoking habits, HPV vaccination, use of hormonal contraception, prior conization, and history of prematurity or sac rupture in previous pregnancies. The mean maternal age was 30.95 years, and was lower in the HPV-positive group (28.75 *vs* 31.34 years, $P = 0.003$).

Table 1 Epidemiological characteristics of the population.

Variables	Overall	HPV (-)	HPV (+)
Age (SD)	30.95 (5.86)	31.34 (5.80)	28.75 (5.74)
Smoking	81 (23.2)	63 (21.3)	18 (34.0)
HPV vaccination	25 (7.2)	21 (7.1)	4 (7.5)
OHC	227 (65)	191 (64.5)	36 (67.9)
Previous conisation	7 (2)	6 (2.0)	1 (1.9)
Previous preterm delivery	12 (3.4)	5 (1.7)	7 (13.2)
Previous PROM	4 (1.1)	2 (0.7)	2 (3.8)

*Data are presented as mean or number (%). **SD:** standard deviation; **OHC:** oral hormonal contraception; **PROM:** premature rupture of the membranes*

Past or current smoking was reported by total of 81 patients (23.2%), and 16.9% continued smoking throughout the pregnancy (odds ratio [OR] 1.766; 95% confidence interval [CI] 0.877-3.558). Two percent had a history of cervical conization and only one patient had a positive HPV test (OR 0.929; 95% CI 0.110–7.880). With respect to the contraceptive method used prior to the pregnancy, 227 patients (65%) had used OHC (OR 1.164; 95% CI 0.624-2.173) and 4.3% had used an IUD (OR 2.115; 95% CI 0.647–6.910). In terms of obstetric history, seven HPV-positive patients (2.0%) reported having had a previous preterm delivery (OR 8.857; 95% CI 2.697-29.084) and two patients (0.6%) reported PROM in a previous pregnancy (OR 5.765; 95% CI 0.794-41.852). The prevalence of high-risk HPV in the sample was 15.2%, while 84.8% of samples were negative. Serotype distribution in the HPV-positive group was: 2.3% HPV 16; 10.3% other HPV variants; 0.3% HPV 16 and 18; 2% HPV 16 and others; and 0.3% HPV 18 and others. Only 7.4% of all patients were vaccinated against HPV. There were four HPV-positive cases in this group. In the HPV-positive group, higher percentages of patients with delivery between 28 and 33+6 weeks of gestation (3.8% *vs* 1.7%) and between 24 and 27+6 weeks (3.8% *vs* 0.3%) were observed, but the differences were not statistically significant ($P = 0.062$).

With respect to perinatal outcomes, a lower birth weight was observed in infants born to patients with HPV (3,022 g *vs* 3,212 g, $P = 0.034$) and two cases had umbilical cord pH < 7 (2 *vs* 0, $P = 0.021$). However, no differences were found between the two groups when the sample was divided by birth weight lower or higher than the 10th percentile (OR 0.525; 95% CI 0.199–1.386). Furthermore, no differences were found in type of delivery or in the Apgar score at 1 minute (OR 0.89; 95% CI 0.330–2.404) or at 5 minutes after birth (OR 2.83; 95% CI 0.252–31.74). With respect to the destination of the newborn after birth, a higher percentage of admissions to the neonatal intensive care unit was observed in infants born to HPV-positive patients (7.5% *vs* 2.4%), but the difference was not statistically significant ($P = 0.091$). Almost one tenth of deliveries (9.3%) were preterm, increasing to 13.21% among patients who had HPV (OR 1.552; 95% CI 0.565–3.712). When we analysed obstetric pathology, no significant differences were observed for PROM ($P = 0.612$), TPL ($P = 0.676$), or for the development of gestational hypertensive disorders ($P = 0.467$) (Table 2).

Discussion

Data previously published in a systematic review revealed an increased risk of HPV infection in pregnant women, but there is no evidence to suggest that the natural history of HPV infection differs during pregnancy [12]. This is explained by the peak

Table 2 Perinatal outcomes of events related to pregnancy, to delivery and to the newborn according to HPV status.

		Perinatal outcome	HPV (-)	HPV (+)	*P* value
Events related to pregnancy	Pathology	TPL	5 (100)	0 (0)	0.341
		PROM	74 (83.1)	15 (16.9)	0.612
		HT disorders (PE and gestational HT)	22 (78.6)	6 (21.4)	0.337
		0 (0%)	25 (86.2%)	6 (13.8%)	
Events related to delivery	Gestational age at delivery	>37 weeks	258 (84,9)	46 (15.1)	
		<37 weeks	24 (77,4)	7 (22.6)	0.279
	Type of delivery	Eutocic	230 (83,6)	45 (16.4)	
		Dystocic	29 (87,9)	4 (12.1)	
		Cesarean	37 (90,2)	4 (9.8)	0.478
Events related to newborn	Birth weight (g;SD)		3211.83 (0.572)	302.7 (0.731)	0.034
	Cord arterial pH < 7		0	2	0.021
	Apgar 1´score < 7		31	5	0.819
	Apgar 5´score < 7		2	1	0.391
	Birth weight	≥10	247 (83.7)	48 (16.3)	0.034
		<10	49 (90.7)	5 (9.3)	0.187
	Destination of newborn	Cots	259 (84.9)	45 (15.1)	0.091
		NICU	7 (63.6)	4 (36.4)	
		Neonatal unit	30 (90.9)	3 (9.1)	

Data are presented as n (% of HPV group). ***TPL:*** *threatened preterm labour;* ***PROM:*** *premature rupture of membranes;* ***HT:*** *hypertension; Birth weight data are presented as mean. The rest of the data are presented as n.* ***SD:*** *standard deviation;* ***NICU:*** *neonatal intensive*

incidence of infection in young patients, which is the age when reproductive potential is at its highest. Thus, in our study, the mean age of women with a positive HPV test was lower than those with a negative test (28.75 *vs* 31.34 years; $P = 0.003$).

If the prevalence of HPV infection in the general non-pregnant population (13.3%) is compared to that of pregnant women in Gran Canaria (15.2%), we can see that it is higher in the latter group. It should be noted that it was also higher than the prevalence the overall non-pregnant population in Spain (14.3%) [3], and the overall non-pregnant population worldwide (10.4%) [13].

The most frequently detected viral genotype in cervical samples as a whole is HPV 16. Thus, the CLEOPATRE data showed a distribution headed by HPV 16, followed by 52, 51, 31 and 66. Similarly, in the general non-pregnant population of Gran Canaria, the most frequent genotype was HPV 16 followed by HPV non-16 (data from doctoral theses). However, in our study population we found that the most frequent genotypes were: HPV other than 16 (10.4%), HPV 16 (2.3%), HPV 16 and others (2%), HPV 16 and 18 (0.3%), and HPV 18 and others (0.3%). The HPV-positive group were patients with an earlier sexual debut (16.9 *vs* 17.9 years; $P = 0.03$) and this group also had a higher proportion of smokers (34.0% *vs* 21.3%), coinciding with the risk cofactors for HPV infection.

HPV can cross the placental barrier by local spread between the vulva, cervix, and amniotic fluid, irrespective of gestational age [14]. HPV DNA has been detected in the uterine cervix and foetal membranes at rates ranging from 6%- to 65%. Multiple studies such as those by Hermonat *et al*. (1997) and Malhomme *et al*. (1997) detected a higher prevalence of HPV in trophoblastic tissue from early spontaneous versus elective abortions [15,16], while Armbruster *et al*. demonstrated the presence of HPV DNA in the amniotic fluid of pregnant women [14,17]. Recent studies have shown that HPV 31 decreases the number of trophoblastic cells and cell adhesion capacity in *in vitro* systems [18]. This could lead to placental dysfunction and potentially to adverse obstetric outcomes, including preeclampsia, intrauterine growth restriction and preterm delivery [19-21]. In this line of research, Huang *et al*. found a positive association between HPV and preterm delivery (OR 2.12; 95% CI: 1.51-2.98; $P < 0.001$), with moderate heterogeneity between studies [6]. Other authors also found a significant association with preterm delivery, with an age-adjusted OR of 1.50; 95% CI 1.19-1.88 [3].

In our series, however, with the exception of a history of prematurity in previous pregnancies, we found no statistically significant differences related to the adverse obstetric outcome of preterm delivery, probably due to the small sample size. Nevertheless, the clinical relevance of this finding, which could relate HPV infection to processes pathophysiologically associated with the onset of uterine contractions in pregnant women, should be taken into account. In fact, in the HPV-positive group, gestational age at delivery was lower, i.e., 28–33+6 (3.8% *vs* 1.7%) and 24–27+6 (3.8% *vs* 0.3%) with $P = 0.062$, as was mean birth weight (3,022 g *vs* 3,212 g, $P = 0.034$).

Gillet *et al*., in their meta-analysis, observed an increased prevalence of bacterial vaginosis, which is related to the possibility of premature delivery, in women with HPV infection [22]. Thus, HPV infection might not be the primary causal agent, but rather a cofactor that contributes to increased susceptibility to bacterial infection. Zuo *et al*. observed that HPV is associated with an increase in histological placental abnormalities ($P = 0.023$), especially thrombosis and villitis, detectable in preterm delivery but not in full-term pregnancies. However, no association was detected between the presence of HPV and the development of chorioamnionitis, suggesting a different pathway as a probable cause of preterm birth [23].

Subramaniam *et al*. reported that the rates of preterm birth in the HPV-positive and negative groups did not differ significantly, although they did observe a tendency towards a higher rate of preterm birth in patients with HPV (16.5% *vs* 12.2%) (OR: 1.3; 95% CI 0.9-1.9). They concluded that maternal HPV infection is not an independent risk factor for preterm birth [24].

With respect to other adverse outcomes such as PROM, preeclampsia and gestational diabetes, no significant differences were observed in our series. Cho *et al*. published the first study that associated the presence of high-risk HPV with a higher prevalence of spontaneous PROM in the HPV-positive group (27.3% *vs* 14.2%) ($P = 0.029$); this significance was maintained after performing the multivariate analysis, with an OR of 2.32 (95% CI: 1.079–4.98) [25]. Furthermore, similar prevalence rates of preterm delivery, preeclampsia and gestational diabetes were found in both groups. Subramaniam *et al*. reported a significantly higher prevalence of severe preeclampsia in the HPV-positive group (5.4% *vs* 2.5%) [24]. In this same study, it was difficult to assess the strength of the association between HPV infection and placental abruption, because the incidence of these adverse events was low.

In terms of the overall rate of gestational hypertensive disorders in both groups (17% *vs* 16%), no significant differences were observed. However, as mentioned, a difference was detected in the rate of severe preeclampsia (5.4% *vs* 2.5%) ($P = 0.01$), which persisted after performing the multivariate analysis, although without statistical significance. No differences were observed in the rate of intrauterine growth restriction, oligohydramnios or in the rate of delivery before week 34 for hypertensive reasons. A strength of our study is that all the patients underwent a specific test for HPV. Furthermore, this test also provides data on the genotyping of the HPV virus type. In addition, all the participating patients have carried out the control of their pregnancy and delivery at our center, so we have complete and reliable data.

The limitations of the study are, first, that lack of knowledge of the pathophysiological mechanisms and the rare occurrence of obstetric adverse events may have caused the number of cases to influence the results, although the number of pregnant women needed for the study was estimated. Second, the exclusion of pregnant women who did not wish to participate in the study could have generated a selection bias.

Conclusions

On the basis of our results, HPV could contribute to the development of TPL, but does not appear to be related to PROM or to hypertensive disorders of pregnancy. Larger prospective studies are needed to explore this possible relationship and the likely pathophysiological explanation.

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