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Does Human Papillomavirus Affect Pregnancy Outcomes? An Analysis of Hospital Data 2012-2014

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Abstract

Objective: To estimate the rate of Human Papillomavirus among pregnant women and its impact on the pregnancy outcomes.

Study design: This was a retrospective cohort study of women who sought prenatal care and later delivered at the Nebraska Medical Center from 2012-2014. Human Papillomavirus infection was based on a cytological cervicovaginal diagnosis (Pap test) report. Bivariate and multivariable analyzes were performed using SAS 9.3.

Results: Of the total sample size of 4824 women, 221 (4.4%) were HPV-positive. Women with Human Papillomavirus infection had increased risk of preeclampsia (adjusted OR: 2.83 95% CI: 1.28-6.26) and were also 1.8 times more likely to deliver preterm compared to women with no Human Papillomavirus infection (adjusted OR: 1.8, 95% CI: 1.15-2.83). Additionally, Human Papillomavirus infection was found to be significantly associated with low birth weight (adjusted OR: 2.58; 95% CI: 1.56-4.27).

Conclusions: Although the prevalence of Human Papillomavirus infection was relatively low in this sample, the study clearly indicated a positive association between Human Papillomavirus infection and adverse pregnancy outcomes. Further research is needed to understand the impact of Human Papillomavirus infection in a larger and diverse sample of women. Also, a closer follow-up of pregnant women affected by Human Papillomavirus infection may be warranted.

Keywords

HPV, Pregnancy, Preterm birth, Low birth weight, Preeclampsia, PROM

Introduction

Human Papillomavirus (HPV) is the most common sexually transmitted infection in the United States [1]. Pregnant women are at higher risk of HPV infection [2] because during pregnancy major physiological and immunological changes take place that modulate the functioning of the immune system and may cause changes in HPV replication [3]. These changes may also make the clearance of HPV much more difficult [1]. HPV infection can impair extra villious trophoblast invasion into the uterine wall by increasing the rate of trophoblast cell deaths and cause placental dysfunction which may result in adverse pregnancy outcomes [4].

One of the potential adverse pregnancy outcomes is preeclampsia, a leading cause of maternal and fetal morbidity and mortality [5]. To date the exact biological mechanism of preeclampsia is still not very well understood. A recent study conducted by McDonnald et al. reported that women infected with high risk (HR)-HPV have a 2-fold higher risk of developing preeclampsia [1]. However, these results were contradictory to the study findings of Cho et al. which found no significant association between HPV and preeclampsia [6]. Another adverse pregnancy outcome is preterm birth. Intrauterine infection may account for 25%-40% of preterm births, but this maybe an underestimate since intrauterine infections are difficult to detect with conventional culture techniques [7]. Few studies have examined the relation of cervical cytology during pregnancy and HPV infection [8-10]. In addition to preterm birth, intrauterine infections can affect the fetal development and cause intrauterine growth restriction that results in low birth weight [11]. Though the association of bacterial infections, including Gonorrhea and Chlamydia, with adverse pregnancy outcomes has been studied before, no studies have focused on their association with HPV infection. Premature rupture of membrane (PROM) is another adverse pregnancy outcome. Recent epidemiological research has found an association between colonization of the genital tract with Chlamydia trachomatis, Neisseria Gonorrhea, B streptococci, and PROM [12]. However, the association between HPV infection and PROM remains unclear.

The inconsistencies in the results of the previous studies may be due to confounding factors like smoking or co-infection with Chlamydia or Gonorrhea that were not controlled for in some studies.

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In this study we controlled for the necessary confounders to examine whether the association would be still significant. The objective of this study is to determine if HPV infection is associated with adverse pregnancy outcomes including preeclampsia, preterm birth, low birth weight, and premature rupture of membrane (PROM).

Material and Methods

This study analyzed hospital data on adult women (18 years and older) who delivered a live birth at an academic medical center between 2012 and 2014. The analysis was restricted to women who had a Pap smear test during pregnancy. The potential subjects were identified based on a query of a hospital patient database. Because de-identified information was used, the University of Nebraska Medical Center Institutional Review Board determined that the study met the exempt research criteria. Women with multipara were included, with each pregnancy considered as an individual observation. However, women with multiple births were excluded from our study since previous studies indicate that multiple births are more likely to have adverse pregnancy outcomes [13]. This resulted in a total of 4824 women (5022 births) in the sample.

The information on HPV infection and selected adverse pregnancy outcomes was extracted from medical records. HPV infection was based on patient's laboratory reports. Patients with atypical squamous cells of undetermined significance (ASCUS) in addition to low/high grade intraepithelial lesions on Papanicolaou smear were considered to be HPV-positive. The outcomes of interest were PROM, preterm birth, low birth weight and preeclampsia. PROM was defined as the rupture of the membrane prior to the onset of labor. Preterm birth was defined as birth before 37 weeks of gestation. Infant weight of less than 2500 gram at the time of birth was characterized as low birth weight. Preeclampsia was defined as the presence of either systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg on two occasions at least 6 hours apart, along with proteinuria (an abnormal amount of protein in urine).

Bivariate analysis was performed to assess the relationship between HPV infection and demographic and clinical variables. Logistic regression was performed to assess the relationship between HPV infection and each of following pregnancy outcomes, after adjusting for demographic and clinical variables: PROM, preterm birth, low birth weight and preeclampsia. The demographic and clinical variables were either those that were significantly different between the infected and non-infected groups, or were based on the prior knowledge of their association with both HPV infection and the outcome. These variables included age, race, smoking, and infection with either Chlamydia or Gonorrhea, mode of delivery, gestational age, gestational diabetes, chronic hypertension, previous preterm birth, previous abortions, and obesity prior to pregnancy. A two-sided p-value of less than 0.05 was considered significant.

Results

Of the total sample of 5022 observations, 221 (4.4%) tested positive for HPV. Table 1 shows significant differences in demographic and clinical characteristics between HPV infected and non-infected groups. Over 40% of HPV infected women were in the age group 20-24 years compared to only 23.3% of uninfected women in that age category. About 30% of women with HPV infection were Black compared to 16.0% of women who were not infected. Close to 20% of HPV infected women were a smoker compared to 6.9% of uninfected women. HPV infected women were also at higher risk of Chlamydia and gonorrhea infection compared to non-infected women. HPV infected group had a statistically higher percentage of vaginal delivery compared to the non-infected group (87.8% vs. 81.9%, p = 0.025). Finally, the percentages of women with previous preterm delivery and previous abortion were higher in HPV infected group than non-infected group (13.8% vs. 8.1% for preterm delivery, 28.6% vs. 22.5% for abortion).

Pregnancy outcomes and odds ratios are shown in table 2. The crude odds ratios were significant for preeclampsia (OR: 2.37; 95% CI: 1.11-5.06), preterm birth (OR: 1.64; 95% CI: 1.15-2.32) and low birth weight (OR: 2.71; 95% CI: 1.86-3.94) and remained significant after adjusting for demographic and other variables that were believed to confound the association based on prior studies. HPV-positive women were 2.8 times more likely to develop preeclampsia compared to HPV-negative women (adjusted OR: 2.80; 95% CI: 1.26-6.21) after adjusting for age, race, previous preterm birth, gestational age, gestational diabetes, chronic hypertension, infection with Chlamydia and Gonorrhea, previous abortions and delivery type. Women with HPV infection were 1.79 times more likely to deliver preterm (adjusted OR: 1.79; 95% CI: 1.14-2.82) and 2.56 times more likely to deliver low birth weight infants (adjusted OR: 2.56; 95% CI: 1.56-4.26) compared to uninfected women, after adjusting for other covariates. Although the odds of developing PROM were higher among infected women compared to uninfected, the association was not statistically significant (OR: 1.39, 95% CI: 0.54-3.58).

Table 1: Demographic characteristics according to maternal human papillomavirus (HPV) status.

Characteristics	Infected (%)	Uninfected (%)	p-value*
Total	221 (4.4)	4801 (95.6)	-
Age			< 0.001
≤ 19	12 (5.4)	392 (8.2)	
20 - 24	91 (41.2)	1119 (23.3)	
25 - 29	57 (25.8)	1536 (31.9)	
30 - 34	35 (15.8)	1215 (25.3)	
≥ 35	26 (11.8)	539 (11.2)	
Race/Ethnicity			< 0.001
White/Caucasian	113 (51.6)	3140 (67.1)	
Black/African American	69 (31.5)	751 (16.0)	
AI/AN/PI	11 (5.0)	84 (1.8)	
Hispanic	4 (1.8)	139 (2.9)	
Others	21 (9.6)	435 (9.3)	
Unknown	1 (0.5)	133 (2.8)	
Smoking			< 0.001
Yes	39 (17.7)	332 (6.9)	
No	182 (82.4)	4469 (93.1)	
Obeseβ			0.462
Yes	95 (58.6)	1165 (54.7)	
No	67 (41.4)	963 (45.3)	
Infection with Chlamydia and Gonorrhea			0.002
Yes	8 (3.6)	43 (0.9)	
No	213 (96.4)	4758 (99.1)	
Mode of delivery			0.025
Vaginal	194 (87.8)	3930 (81.9)	
Cesarean(C-section)	27 (12.2)	871 (18.1)	
Previous preterm deliveryβ			0.003
Yes	30 (13.8)	383 (8.1)	
No	188 (86.2)	4370 (91.9)	
Previous Abortions			0.047
Yes	57 (28.6)	989 (22.5)	
No	142 (71.4)	3400 (77.5)	

β: Missing information for some of the observations
*P-value of < 0.05 was considered significant

Table 2: Prenatal Outcomes among HPV-positive pregnant women.

Outcomes	Total Sample size	Prevalence of HPV (%)	Crude OR	95% CI	Adjusted OR$^{\delta}$	95% CI
PROM	94	5.3	0.94	0.38-2.34	1.39	0.54-3.58
Preeclampsia	67	11.9	2.37	1.11-5.06	**2.80***	1.26-6.21
Preterm Birth	625	6.6	1.64	1.15-2.32	**1.79**$^{\tau}$	1.14-2.82
Low Birth Weight	356	10.1	2.71	1.86-3.94	**2.56**	1.55-4.26

δ: Adjusted for age, race, smoking, previous preterm, gestational age, infection with Chlamydia and Gonorrhea, previous abortions, delivery type, gestational diabetes and chronic hypertension
τ: Preterm birth was not adjusted for gestational age
*: Except for preeclampsia all other outcomes were additionally adjusted for preeclampsia

Comments

This study was designed to investigate the association of HPV infection with adverse pregnancy outcomes. The overall prevalence of HPV among pregnant women in this study was 4.4%. However, the prevalence is lower when compared to previous studies conducted in U.S. [14,15]. One of the reasons could be that previous studies that reported the higher prevalence of HPV among pregnant women were conducted in the pre-vaccination era (before 2006). Additionally, there is no recommended screening for HPV among pregnant women [16]. Interestingly, in this study the prevalence of HPV among whites was higher than other ethnic/racial groups contrary to the national rates (51.6% vs. 31.5%). A study conducted by Dinh et al. indicated that there is a higher prevalence of genital warts among whites compared to black [17]. Since most genital warts are the result of HPV, the presence of these in pregnant women would likely prompt healthcare professionals to perform HPV testing on these women. This might be the reason for higher prevalence of HPV infection among whites in our study data.

Our study results indicate that HPV infection is significantly associated with adverse pregnancy outcomes including preeclampsia, preterm birth, and low birth weight, but not with premature rupture of membrane. After controlling for demographic and clinical variables, we observed that HPV-positive women were 2.80 times more likely to develop preeclampsia compared to HPV-negative women. The association remained significant after adjusting for confounding factors. Our study results were consistent with other studies that reported HPV as a risk factor for preeclampsia [1,18]. A study conducted by McDonnald et al. [1] was scrutinized for not adjusting for co-infections, leading to concern that HPV may not be the main cause of the adverse outcome but rather a contributing factor to other infections [19]. In our study we adjusted for co-infection with Chlamydia and Gonorrhea and still observed a significant association. However, our study results were contradictory to the results of a case-control study that found no difference in the detection of HR-HPV from placentas of women with preterm severe preeclampsia and controls [4]. This could be possible if HPV infection present in uterine decidua can still affect uteroplacental function [1].

In addition, we found that HPV-positive women were 1.8 times more likely to deliver preterm compared to HPV-negative women. Our study results were consistent with the results of a previous study conducted by Zhuang Zuo that reported a significant association between HPV and preterm birth [20]. Though the pathophysiology of preterm birth is not well understood, systemic and/or local inflammation has been suggested as an independent etiological risk factor for preterm birth. Additionally, some in vitro studies have shown that HPV can infect a fetus through the transplacental transmission [21,22]. Trophoblasts are integral cell types of the placenta. It is believed that trophoblasts infected with HPV may alter the cellular characteristics and lead to compromised gestation [23].

Furthermore, our results indicate that HPV infected women were 2.58 times more likely to deliver low birth weight infants compared to women not infected with HPV. Although low birth weight has been associated with other sexually transmitted diseases [24,25], to our knowledge no other study has examined the association of HPV and low birth weight. HPV infection could either take place by ascending infection from the maternal birth canal [21], or it may cross the placenta and cause infection in the fetus. If HPV infection occurs at a crucial moment during the development of the fetus, it may affect the fetal cells and cause intrauterine growth retardation.

In our study, we did not find any significant association between HPV and PROM even after controlling for other covariates. Our study results were contrary to a study conducted by Cho et al. that reported a significant association between HR-HPV and PROM. One of the reasons for this disagreement with results could be that the other study was conducted in Korea and the study sample had a very high prevalence of HR-HPV compared to our study (14.1% vs. 4.4%). Additionally, the study does not mention what HR-HPV types were included. Furthermore, the study did not adjust for smoking, which has been reported to be a very strong risk factor for both PROM and HPV [26-29]. Our findings are important because currently there is no vaccination or recommended screening for HPV among pregnant women. Our study results indicate that the presence of HPV during pregnancy may cause adverse pregnancy outcomes, suggesting the necessity of understanding the impact of HPV vaccination on pregnant women.

A number of limitations should be considered when interpreting the results of this study. First, in this study women with ASCUS were assumed to be a result of HPV infection though they could be a result of other factors. This assumption may have resulted in overestimation of this study results. Second, although we had information on current smoking status, we did not know their status prior to pregnancy, which may mask the true exposure to tobacco. Previous researchers have found that the prevalence of HPV varies by gestational age [29,30]. A study conducted by Lee SM et al., detected HPV DNA in 14% of pregnant women in the first trimester, 18% in the second trimester and 10% in the third trimester [30]. This indicates that the HPV infection may be triggered by hormonal or other effects of pregnancy like immunosuppression [29]. While our study was unable to account for gestational age of infection, future studies may consider taking the time point of HPV infection into account. Another limitation of the data was lack of information on vaccination status of these women which may have a confounded the association between HPV and adverse obstetric outcomes. Additionally, this study was unable to take into account the infection with bacterial vaginosis which is also associated with poor pregnancy outcomes.

Despite these limitations, the study has a number of strengths. Since the exposure and outcome status were based on obstetric records/laboratory test, this information was more reliable compared to self-reported data. In summary, the data from this study suggest that HPV infection is associated with adverse pregnancy outcomes including preeclampsia, preterm birth, and low birth weight. From a clinical standpoint, this may highlight the health benefits of HPV vaccination for young girls and adolescents females prior to pregnancy as well as for young boys and men. One of the priorities should be to improve HPV vaccination rates through better education and awareness campaigns among the patient population. In addition, policymakers should consider mandating HPV testing among pregnant women. Concurrently, there should be a close follow-up of HPV-positive women and their fetus. Mandating HPV vaccination may be challenging based on the 2007 experience in Texas, where Governor Rick Perry order mandating the HPV vaccine for young girls, but the legislators in Texas passed H. B. 1098 to override the executive order. However, it is crucial to implement necessary measures in place in order to improve the health of pregnant women. Future studies need to be conducted in larger and more diverse samples of women to better understand the impact of HPV infection.

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