Relationship Between Maternal High Risk Human Papillomavirus Infection and Pregnancy Outcomes

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Article

Relationship Between Maternal High Risk Human Papillomavirus Infection and Pregnancy Outcomes

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Abstract: Aim: The aim of this study was to evaluate the relationship between maternal HR-HPV (high risk) infection and pregnancy outcomes. **Materials and Methods:** Among 5840 women who gave birth between 2016-2023, a total of 1042 patients, 146 (14%) HR-HPV (+) and 896 (86%) HR-HPV (-), who had cervical cancer screening test results within 1 year and met the eligibility criteria, were retrospectively evaluated. Age, parity, Apgar score, smoking status, history of premature rupture of membranes (PROM) were retrospectively reviewed from medical records. **Results:** The mean BMI of HR-HPV (+) patients was determined to be 26.2 kg/m2, which was significantly higher than the (-) group ($p<0.001$). The smoking rate of HR-HPV (+) patients was found to be significantly higher than the (-) group ($p=0.04$). No significant difference was found between HR-HPV (+) and (-) patients in terms of PROM rates and preterm delivery rates ($p=0.2$, $p=0.9$ respectively). No significant difference was found between HR-HPV (+) and (-) patients in terms of preeclampsia rates and GDM rates ($p=0.4$, $p=0.6$ respectively). **Conclusion:** We could not clearly demonstrate a relationship between HR-HPV infection and perinatal and neonatal outcomes. Further studies are needed to evaluate the effects of HR-HPV infection on pregnancy outcomes.

Keywords: Human Papillomavirus; pregnancy; preterm delivery; PROM

Introduction

Human papillomavirus (HPV) is known as the most common sexually transmitted infection in adults. [1,2]. Infections during pregnancy and changes in the vaginal flora may affect the emergence of negative pregnancy outcomes [3]. The lifetime probability of acquiring genital HPV is estimated to be greater than 80% by age 45 in both women and men [1]. Fortunately, approximately 80% of HPV infections regress spontaneously within 1–2 years [4]. There are publications in the literature showing that HPV infection is more likely to persist during pregnancy and regress after delivery [5–8]. In vitro and animal experiments show that HPV can complete its full replication cycle in trophoblasts, thereby causing inhibition of blastocyst formation, failure of endometrial implantation, and apoptosis of embryonic cells [9–11]. Placental abnormalities observed in vitro can translate into various adverse pregnancy outcomes in vivo, such as spontaneous abortion, preterm delivery (PTD), or pregnancy-induced hypertension (PIH) [11–14]. However, previous studies have shown different results in the literature regarding the relationship between HPV and adverse pregnancy outcomes [15–17]. Findings from observational studies have yielded ambiguous results. The aim of this study was to evaluate the relationship between maternal HR-HPV infection and pregnancy outcomes.

Materials and Methods

In our study, all women who gave birth in our hospital between 2016 and 2023 and who had cervical cancer screening test results within 3 months before pregnancy were evaluated and a retrospective cohort study was designed. The study was initiated after receiving ethics committee

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approval numbered 2024/318 from the hospital ethics committee. Consent forms were obtained from all patients. Our study was designed according to the Helsinki Declaration. Hybrid Capture II system (Digene Diagnostics Inc., Gaithersburg, MD, USA) was used in our hospital for the detection of HPV infection. Patients who had previously undergone any procedure for cervical dysplasia were excluded from the study. A total of 5,840 patients gave birth in 2016-2023, of which 1042 patients met the eligibility criteria, 146 (14%) were HR-HPV positive and 896 (86%) were HR-HPV negative. Baseline characteristics of all patients included in the study, including age, parity, number of miscarriages, body mass index (BMI), gestational age at birth, Apgar score and birth weight of each newborn, smoking status, history of premature rupture of membranes (PROM), history of preterm delivery, and mode of delivery were retrospectively reviewed from medical records. Preterm delivery was defined as giving birth before 37 weeks of gestation. PROM was defined as rupture of membranes at any time during pregnancy before the onset of labor. Preeclampsia was diagnosed in patients with maternal blood pressure ≥ 140/90 mmHg measured at least six hours apart on two occasions after the 20th week of gestation, no history of hypertension, and concurrent proteinuria (≥ 300 mg/24-hour urine or ≥ 1+ on dipstick test) [18]. Gestational Diabetes Mellitus (GDM) was diagnosed according to the American Diabetes Association (ADA) criteria [19]. Statistical analysis was performed by SPSS version 26.0 (IBM-Inc., Chicago-IL-USA). The normality of the distribution was evaluated with Kolmogorov-Smirnov test. Not normally distributed parameters were analyzed with the Mann-Whitney-U test. Chi-square-test and Fisher precision test were used in the analysis of categorical data. Quantitative data were presented as median (minimum-maximum), and qualitative data were presented as numbers and percentages (%). The p value considered statistically significant was <0.05.

Results

The mean age of the patients in this study was 28, and no significant difference was found between HR-HPV positive and negative patients in terms of parity and abortion numbers (p=0.8, p=0.8 respectively). The mean BMI of HR-HPV positive patients was determined to be 26.2 kg/m2, which was significantly higher than the negative group (p<0.001). The smoking rate of HR-HPV positive patients was found to be significantly higher than the negative group (p=0.04). No significant difference was found between HR-HPV positive and negative patients in terms of 1-min and 5-min Apgar scores (p=0.7, p=0.7 respectively) (Table 1).

Table 1. Evaluation of demographic and obstetric data according to the presence of HR-HPV.

Variables	HR-HPV positive (n=146, 14%)	HR-HPV negative (n=896, 86%)	p value
Age (years)	28 (18-43)	28 (18-43)	0.8
Parity (n)	1 (1-2)	1 (1-3)	0.8
Abortion (n)	0 (0-2)	0 (0-2)	0.8
BMI (kg/m²)	26.2 (22.6-33.3)	25.3 (20.7-33.3)	<0.001
Smoking habit (n, %)	19 (13%)	70 (7.8%)	0.04
1-min Apgar score	8 (6-10)	8 (6-10)	0.7
5-min Apgar score	8 (6-10)	8 (6-10)	0.7
Gestational age at delivery (weeks)	37 (30-40)	37 (25-40)	0.4

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Birth weight (grams)	3050 (1950-3800)	3100 (1950-3800)	0.1
Delivery mode (n, %)			0.06
Vaginal delivery	97 (66.4%)	664 (74.1%)	
Cesarean section	49 (33.6%)	232 (25.9%)	

HR: High risk, HPV: Human papillomavirus, BMI: Body mass index.

In our study, no significant difference was found between HR-HPV positive and negative patients in terms of preterm delivery rates (p=0.9). No significant difference was found between HR-HPV positive and negative patients in terms of PROM rates (p=0.2). No significant difference was found between HR-HPV positive and negative patients in terms of preeclampsia rates and GDM rates (p=0.4, p=0.6 respectively) (Table 2).

Table 2. Evaluation of adverse pregnancy outcomes according to the presence of HR-HPV.

Variables	HR-HPV positive (n=146, 14%)	HR-HPV negative (n=896, 86%)	p value
Preterm delivery	14 (9.6%)	88 (9.8%)	0.9
PROM	19 (13%)	87 (9.7%)	0.2
Preeclampsia	7 (4.8%)	32 (3.6%)	0.4
GDM	6 (4.1%)	44 (4.9%)	0.6

HR: High risk, HPV: Human papillomavirus, PROM: Premature rupture of the membranes, GDM: Gestational diabetes mellitus.

Discussion

In present study, no significant difference was found in general regarding the pregnancy outcomes of HR-HPV positive women and HR-HPV negative women. Although it is accepted that PROM occurs due to multifactorial reasons, it is thought that infections mainly cause membrane damage and thus play a role in the etiology of PROM. Inflammatory cells, the production of which is stimulated by genital infections, can cause weakening of fetal membranes in pregnant women and therefore PROM [20–22]. Possible cause of membrane damage associated with infection that several organisms synergistically secrete cytokines, such as metalloproteases (MMPs), which degrade collagen and weaken fetal membranes, which may lead to membrane rupture, which begins to lose tissue integrity [23]. It has been shown that MMP-2 is continuously expressed in fetal membranes throughout pregnancy [24,25]. However, it has been shown that it increases with gestational age in amniotic fluid and reaches significantly increased levels at the time of delivery. It has been shown that the increase in MMP-2 may therefore also play a role in PROM [26,27]. Prostaglandins promote cervical changes and PROM by increasing the expression of MMPs in the genital tract, increasing gap junctions between uterine cells, promoting the formation of myometrial oxytocin receptors, and suppressing myometrial progesterone receptor expression. Prostaglandins also increase the expression of cervical interleukin-8 (IL-8), causing neutrophils to release additional MMPs and elastases. MMPs degrade and degrade collagen, and their activity increases in fetal membranes during PROM and labor [28,29]. MMP-2 is also an crucial factor in the spread of cervical cancer by causing degradation of the extracellular matrix. Membrane-associated activated MMP-2 is likely to play a role in the dissemination of cervical cancer precursor cells to surrounding tissues [30,31]. HPV

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is of primary importance in the presence of invasive cervical carcinoma and is associated with increased MMP-2 expression; this association suggests that HPV may be important in MMP regulation [32]. In the literature, HPV infection has been reported to be associated with various changes in tissue organization and architecture, including dysregulation of MMP-2 expression and activity. In addition, various changes can be detected in different molecules of the extracellular matrix (ECM) in HPV associated cervical intraepithelial neoplasia(CIN). While MMP-2 expression was detected in cervical analyses of patients with CIN, it was observed that it was not detected in normal cervix and low-grade lesions [33,34]. On the other hand, CIN 2-3 and cervical cancer showed high MMP-2 expression, supporting the idea that MMP-2 may be an early marker for cervical cancer progression. MMP-2 expression is thought to be effective in the spread of cervical lesions to nearby and distant tissues [33,34]. When the relationship with fetal membranes is investigated, it is thought that HR-HPV can easily be transmitted through proximity to the fetal membrane and therefore the most likely area for membrane rupture is located on the cervix. It is thought that the presence of this degree of close contact may cause HR-HPV infection to develop PROM [35]. However, it is generally thought that inflammatory cells produced by genital infections cause fetal membrane damage and weakening of fetal membranes and PROM in pregnant women [36]. However, various vaginal infections may also increase the risk of HPV infection, which may additionally increase the risk of PROM. Liang et al.'s meta-analysis suggested that vaginal microecology and HPV infection have a close relationship with CIN. Bacterial vaginosis, Chlamydia trachomatis, and Ureaplasma urealyticum were associated with increased HPV infection, while bacterial vaginosis was associated with increased risk of developing CIN [37]. The results on the risk of PROM based on these relationships should be evaluated with caution. In cases where PROM develops in HR-HPV positive women, it is quite difficult to distinguish whether the current condition is caused by HPV or other infections. The cause of PROM in an HR-HPV positive woman may be a non-HPV genital infection, and this detail should not be overlooked. In this study, although the PROM rate was higher in HR-HPV positive women than in HR-HPV negative women, no significant difference was detected. In a systematic review conducted by Niyibizi et al., it was revealed that the prevalence of HPV in pregnant women varied widely between 5.5% and 65% [38]. In the study conducted by Nobbenhuis et al., HR-HPV positive were detected in 50% of women in the first trimester. In the 2nd and 3rd trimesters, the prevalence rates of HR-HPV were determined as 44-45%, respectively [6]. In our study, no difference was observed between the groups in terms of gestational age at delivery. Therefore, there was no confounding factor that would affect the HR-HPV positivity rate based on trimester origin. Ethnicity, choice of detection method, HR-HPV type, study design and risk factors such as maternal age, gestational age, education level, reproductive disease history, a history of alcohol consumption, sexual intercourse history and choice may be the determinants of HPV incidence among publications. In this study, no significant difference was found in terms of age between women with and without HR-HPV infection. In the study conducted by Yang et al., the prevalence of HR-HPV infection reached its peak in two separate periods at the ages of 56-60 and 61-65, and the infection rates were determined as 14.71% and 15.51%, respectively [39]. Considering the peak ages, it is considered normal that there is no difference between the mean age of HR-HPV positive and negative pregnant women in our study. In present study, no difference was found between the parity numbers of HR-HPV positive patients and negative patients. However, it is stated in the literature that parity will be a cofactor for cervical cancer, as well as preinvasive lesions of the cervix [40,41]. In present study, smoking was found to be significantly higher in HR-HPV positive pregnant women. Our results seem to be consistent with the literature, as are the studies in the literature that reveal a clear relationship between HR-HPV infection and smoking [42]. Since cesarean delivery has not been shown to prevent vertical transmission of HPV infections, there is no indication for cesarean section in the presence of HPV [43]. In this study, no significant relationship was found between the presence of HPV and the type of birth, consistent with the literature. This situation was revealed by the fact that the women included in the study underwent cesarean section only for appropriate indications. A meta-analysis by Xiong et al. revealed that high-risk HPV infection is associated with an increased risk of preterm

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delivery [44]. A study by Kovács et al. revealed a relationship between HPV infection and preterm delivery [45]. In present study, no significant relationship was found between the presence of HR-HPV and preterm delivery. In a retrospective cohort study by McDonnold et al., they revealed that the risk of developing preeclampsia was two times higher in women with HR-HPV [14]. However, this study only investigated one association to prove causality, and more extensive prospective studies are needed and adjustment for secondary risk factors such as ethnicity, smoking, chronic kidney disease or chronic hypertension is needed [14]. In the study on Human Papillomavirus E6/E7 Expression in Preeclampsia, they provided evidence that HPV E6/E7 is expressed in the placenta of women with preeclampsia. This finding, combined with the findings that HPV infects trophoblastic cells from the first trimester, reveals the potential role of HPV infection in early placental development. The placental origin of preeclampsia is well known, but further research is needed to prove the decisive role of HPV in placental dysfunction and thus to prove that HPV is a definitive causative agent of pregnancy complications [46,47]. In a cohort study by Subramaniam et al., HPV was not an independent factor in PIH [48]. In present study did not reveal a significant association between the presence of HR-HPV and the development of preeclampsia. Due to insufficient data on the association between maternal HPV infection and preeclampsia or other pregnancy-induced hypertensive disorders, HPV is not a definitive risk factor at this stage and further research is needed. Given the importance of the role of trophoblast cells in the normal development and function of the placenta, placental HPV infection may likely increase the risk of a placental dysfunction syndrome such as GDM [49,50]. In studies conducted in the literature, placentas with known pregnancy complications such as GDM were examined and a relationship with HPV infections was revealed [11,51]. In the study conducted by Niyibizi et al., no association was found between placental HPV infection and GDM [52]. In present study, no significant relationship was found between the presence of HR-HPV and the risk of GDM. In this study, patients with PROM and PPROM were not evaluated in two separate groups. This can be considered as a limitation of our study. When evaluated only in terms of PROM, the presence of perinatal and neonatal effects is clear. However, prospective studies with large patient numbers evaluating PROM and PPROM in two separate groups are needed. Although the presence of PROM was found to be higher in the presence of HR-HPV infection, it was shown that there was no statistically significant relationship. Therefore, a large-scale study on the relationship between HR-HPV infection and PROM is needed. The cross-sectional design of our study limits our ability to determine the effect of HR-HPV infection on adverse pregnancy outcomes. Information on the sexual intercourse history of the pregnant women included in the study, choice and number of sexual intercourses, condom use and other active sexually transmitted infections could not be effectively accessed due to the retrospective design of our study. These factors may directly increase the risk of PROM and also constitute additional risk factors for HR-HPV infection. We observed a lower prevalence of HR-HPV infection in pregnant women compared to the literature. We could not clearly demonstrate a relationship between HR-HPV infection and perinatal and neonatal outcomes. We found a non-significant increase in risk in PROM. Further studies are needed to evaluate the effects of HR-HPV infection on pregnancy outcomes.

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