

# HPV and premature delivery risk

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## ABSTRACT

Preterm delivery represents the leading cause of perinatal morbidity and mortality. Among possible etiologies of premature birth are the infectious ones, Human Papilloma Virus (HPV) infection being less documented than others. The available data on the role of HPV infection in premature delivery pathogenesis is limited and controversial. This review article attempts to make an assessment of current information on the risk of premature delivery in women with HPV infection during pregnancy. A systematic literature electronic search for journal articles and guidelines regarding HPV infection during pregnancy was undertaken. The relationship between HPV infection and pregnancy is bidirectional, as physiological changes that occur during pregnancy modulate the mechanisms of HPV infection and HPV infection determine adverse maternal, obstetrical, and fetal outcomes.

**Keywords:** human papillomavirus, preterm delivery, adverse pregnancy outcomes

## INTRODUCTION

Preterm delivery, the leading cause of perinatal morbidity and mortality, represents a tremendous global burden. Worldwide, 1 in 10 babies are born at less than 37 weeks gestation, making preterm birth the greatest contributor to long-term neurological disabilities and life-long consequences in children and the most common reason for hospitalization during pregnancy [1].

The etiology of preterm birth is imperfectly understood. Maternal conditions that increase the risk of preterm birth include cervical incompetence, preeclampsia, pre-gestational and gestational diabetes, obesity, smoking and the use of recreational and illicit drugs. Uterine, placental, or fetal conditions such as uterine anomalies, leiomyoma, placenta previa, placental abruption or fetal birth defects, could be also associated with preterm birth. Infection and inflammation are already known to contribute to preterm delivery etiology. Infectious conditions that increase the likelihood of preterm birth include HIV infection, Chlamydia trachomatis

infection, hepatitis C, syphilis, malaria, bacterial vaginosis and chorioamnionitis. Studies mainly focused on bacterial etiologies, leaving the impact of viral infections on pregnancy, obstetrical and neonatal outcomes less studied, particularly when it comes to human papillomavirus infection (HPV) [2].

Over 200 genotypes of human papillomaviruses have been identified and nearly 40 of them cause genital infections, showing a specific tropism for human epithelial cells both in the skin and mucous membranes. They comprise two groups – low-risk, responsible for papilloma and genital warts, and high-risk, inducing intraepithelial neoplastic and invasive cancer in anogenital, respiratory and upper digestive tract mucosa. The HPV-related malignancy causing the most important morbidity and mortality worldwide is cervical cancer. HPV is considered the most common sexually transmitted infection. It is estimated that more than 80% of sexually active women and men will have an HPV infection at least once [3]. Regardless of that, the most of these infections have no clinical impact, are

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transient and resolve spontaneously within two years by unknown mechanisms [4]. Worldwide, nearly 12% of women have a cervical HPV infection [5]. Some studies suggest that during pregnancy the prevalence of HPV increases [6]. Apart from the increased risk of cervical dysplasia and cancer, recent studies suggest that infection with HPV during pregnancy would be associated with adverse pregnancy outcomes, such as preterm delivery [7,8].

## METHODS

A systematic literature electronic search for reviews and journal articles was undertaken using PubMed and the official websites of Obstetrics and Gynecology and Infectious Diseases associations. Search words were “human papillomavirus”, “HPV”, “pregnancy”, “preterm delivery”, “preterm birth”, “adverse pregnancy outcomes”. Publications were selected based on accessibility to full paper article, quality evaluation, publication year, attempting to select recent studies. The publications used are mentioned in References section.

## EFFECT OF PREGNANCY ON HPV

Pregnant patients have several characteristics specific to pregnancy which predispose them to an increased incidence and risk of complications from infections.

Changes in maternal immune and hormonal status - decreased lymphocyte proliferative response, reduced lymphokine response to alloantigens, reduced number of helper T cells, diminished cell-mediated proliferative cytotoxicity affect maternal susceptibility to infectious disease, for example, HPV [9,10,11].

Studies prove that increased steroid hormone levels during pregnancy increase HPV replication, this hypothesis giving an explanation for the higher incidence of HPV infection during pregnancy [12,13].

Furthermore, pregnancy-specific altered immunity can lead to the persistence of the HPV in cervical cells and to subclinical or mildly symptomatic infections. The proliferation of basal layers of the epithelium of the cervix increases mucus secretions in the cervical glands and activates the metaplasia of the cervical epithelium. Moreover, the columnar epithelium migrates toward the vaginal part of the cervix, being more exposed to infections [14].

## EFFECT OF HPV ON PREGNANCY

Possible mechanisms of adverse pregnancy outcomes, such as preterm delivery, could be explained by placental abnormalities. In vitro studies suggest

that the replication cycle of HPV that occurs in trophoblasts could lead to inhibition of blastocyst formation, apoptosis of embryonic cells and endometrial implantation deficiency [15-19].

Placental development disorders which are attributed to HPV infection would explain the risk for intrauterine growth restriction, preterm delivery or miscarriages [20,21].

Another possible mechanism for premature rupture of membranes and therefore premature delivery could be the membrane damage caused by the cytokines, such as metalloproteases (MMP), secreted by several organisms responsible for infections. MMP, MMP-2 in particular, degrade collagen and can determine membrane rupture by weakening their extracellular matrix. MMP-2 is also known to play an important role in the invasion of cervical cancer through the same mechanism. Therefore, there could be an association between HPV infection pathogenesis and premature rupture of membranes [22-24].

Several studies reported different pregnancy outcomes, such as preterm premature rupture of fetal membranes, fetal growth restriction, low birth weight, intrauterine fetal death, hypertensive disorders of pregnancy. Despite noteworthy relations between HPV infection and these adverse outcomes, the authors concluded that preterm birth can be considered highly associated, preterm premature rupture of fetal membranes could be associated but the relation to fetal growth restriction, low birth weight, intrauterine fetal death needs further studies [7,19].

## EFFECT OF HPV INFECTION ON PREGNANCY OUTCOMES

There were conducted several studies which tried to assess the effect of HPV infection on pregnancy outcomes.

A Danish study published in 2016 tried to demonstrate the association between the presence of HPV and spontaneous abortion and preterm delivery. Their conclusion was that HPV prevalence was higher in pregnancies with adverse outcomes as those investigated [8].

A systematic review and meta-analysis on the association between HPV and adverse pregnancy outcomes was published in 2020. The data suggest that HPV is associated with preterm birth, supports a possible association with intrauterine growth restriction, preterm premature rupture of fetal membranes, low birth weight and fetal death, but it doesn't explain a relation between HPV and spontaneous abortion and pregnancy-induced hypertensive disorders [19].

Caballero at al. published in 2018 a retrospective cohort study which aims to determine whether ma-

ternal infection with high-risk HPV increases the risk of preterm premature rupture of membranes and secondarily to determine if this infection increases the risk of preterm delivery due to mechanisms other than preterm premature rupture of membranes. The conclusions of the study were that HPV infection would be associated with an increased risk of preterm premature rupture of membranes and subsequently to preterm delivery and neonatal morbidity, but HPV wouldn't appear to have any other adverse effect on preterm delivery outside of preterm deliveries resulted from preterm premature rupture of membranes [25].

A Swedish retrospective population-based study released in 2021 investigated the associations of treated and untreated HPV infection with preterm delivery and neonatal mortality. The researchers found that HPV infection is associated with an increased risk of premature delivery, preterm premature rupture of membranes and neonatal mortality and treatment for cervical intraepithelial neoplasia was associated with higher risk for preterm delivery [26].

One of the most recent notable study on the association between HPV infection among pregnant women and preterm birth was conducted by Heritage Study Group and was published in 2021. The study's results suggested that persistent high-risk HPV infection is associated with elevated risk of preterm delivery, separately from history of cervical treatment [27].

Aside the studies mentioned before, which support the association between HPV and premature

delivery there are several studies with dissimilar results. A study published in 2019 that used Scottish Health Data concluded that HPV-associated high-grade cervical disease was linked to preterm birth, but HPV infection or low-grade cervical disease were not associated with preterm delivery, therefore HPV infection in the absence of cervical disease wouldn't be a risk factor [28]. In 2016 in The American College of Obstetricians and Gynecologists Journal was published a retrospective cohort study whose objective was to compare rates of preterm birth and pregnancy-induced hypertension in women with and without HPV infection. The authors' conclusion was that HPV infection was not an independent risk factor for preterm birth or pregnancy-related hypertension [29].

## CONCLUSIONS

It would be of great importance if apart of what we already know about HPV infection and its implication in cervical cancer, the involvement of HPV in pregnancy outcomes would be cleared. Currently, there is a possibility to prevent infection and disease caused by HPV through vaccination. Consequently, the possible adverse pregnancy outcomes could be minimized.

Further studies would be helpful in order to establish certain information on the role of HPV infection in preterm delivery's pathogenesis and to develop and implement health strategies, to mobilize resources and to raise awareness.

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