Prematurity risk in association with human papillomavirus infection

Simona-Daniela Popescu[1,2], Andreea Mădălina Bănică[1,2], Simona Vlădăreanu[1,2], Alina-Gabriela Marin[1,2], Radu Vlădăreanu[2,3]

1. Neonatology Department, "Elias" University Emergency Hospital, Bucharest, Romania

2. Department of Obstetrics, Gynecology and Neonatology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

3. Obstetrics-Gynecology Department, "Elias" University Emergency Hospital, Bucharest, Romania

Corresponding author:
Alina-Gabriela Marin
E-mail: alina_2830@yahoo.com

Abstract

Prematurity is an important cause of neonatal morbidity and mortality. Recent studies have shown that human papillomavirus (HPV) infection also extends to the newborn. During pregnancy, the risk of obstetric complications, such as preterm premature rupture of fetal membranes (PPROM), prematurity, preeclampsia and spontaneous abortion, increase through inflammatory changes induced in trophoblast cells and, thus, through histopathologically identified placental abnormalities. The prevalence of HPV is increasing among young population, with a peak around the age of 25 years old. In addition, other infectious diseases, such as bacterial vaginosis and trichomoniasis, can also act to cause PPROM by similar mechanisms. Worldwide, there are three types of inactivated HPV vaccines (bivalent, quadrivalent and 9-valent), with the latter (Gardasil-9®) being currently the most recommended for use in the general population. Even though HPV vaccination will never reach a 100% coverage, its implementation in national immunization programs worldwide is one of the key solutions needed in order to reduce the impact of prematurity on the newborn.

Keywords: *HPV, prematurity, HPV vaccination, PPROM, placental disfunction, obstetric adverse outcome*

Rezumat

Prematuritatea este o cauză importantă de morbiditate și mortalitate în perioada neonatală. Studiile recente arată că infecția cu papilomavirusul uman (HPV) se extinde și asupra nou-născutului. În timpul sarcinii, riscul de complicații obstetricale, cum ar fi ruptura prematură a membranelor fetale (PPROM), prematuritatea, preeclampsia și avortul spontan, crește prin intermediul modificărilor inflamatorii induse la nivelul celulelor trofoblastice și implicit prin anomaliile placentare identificate histopatologic. Prevalența HPV în populație este în creștere în rândul populației tinere, cu un vârf în jurul vârstei de 25 de ani. De asemenea, alte boli infecțioase, precum vaginoza bacteriană și trichomoniaza, pot cauza PPROM prin mecanisme similare. La nivel mondial, există trei tipuri de vaccinuri HPV inactivate (bivalent, cvadrivalent și 9-valent), acesta din urmă (Gardasil-9®) fiind în prezent cel mai recomandat pentru utilizarea în rândul populației generale. Chiar dacă vaccinarea împotriva HPV nu va atinge niciodată o acoperire de 100%, implementarea acesteia în programele naționale de imunizare de la nivel mondial reprezintă una dintre soluțiile-cheie necesare pentru a reduce impactul prematurității asupra nou-născutului.

Cuvinte-cheie: *HPV, prematuritate, vaccin anti-HPV, ruptura prematură a membranelor fetale, disfuncție placentară, reacții adverse obstetricale*

Submission date:
17.02.2022
Acceptance date:
28.02.2022

Prematuritatea și riscul asociat infecției cu virusul papilomatozei umane

Suggested citation for this article: Popescu SD, Bănică AM, Vlădăreanu S, Marin AG, Vlădăreanu R. Prematurity risk in association with human papillomavirus infection. Ginecologia.ro. 2022;35(1):40-42.

Introduction

Prematurity is a public health problem, being the main cause of perinatal morbidity and mortality in developing countries, which causes about 75% of neonatal deaths, in 50% of cases in the pediatric population also being observed long-term neurological impairment. Annually, around 11% (15 million) of premature births are estimated worldwide, leading to approximately 965,000 neonatal deaths and to 125,000 deaths in children aged 1-5 years old[1-3]. The overall prevalence of HPV infection is 12%, HPV 16 being the most common strain identified, with a worldwide prevalence of 3.2%[4].

The prevalence of HPV in the population is increasing among young people, with a peak around the age of 25 years old, but after that age the number of cases identified will decrease. About 80% of HPV infections go into spontaneous remission within 1-2 years of onset.

Regarding pregnancy, HPV persists throughout pregnancy and remits postnatally. One of the explanations found in the literature is that, during pregnancy, increased levels of maternal steroid hormones contribute to the changes in the immune status, thus facilitating "maternal-fetal immune tolerance", but increasing the risk of acquiring infections[5].

HPV infection and pregnancy outcome

HPV infection is associated with adverse pregnancy outcomes, such as miscarriage, preterm premature rupture of the membranes (PPROM), prematurity, preeclampsia, and the risk of vertical transmission of infection to the fetus. This link has been confirmed by the identification of the virus in placentas from pregnancies with preterm infants. Histopathologically, placental abnormalities associated with HPV infection, such as chorioamnionitis and lymphohistiocytic villous

inflammation, were identified, particularly in pregnancies complicated by preeclampsia or prematurity[6].

Among the characteristics of HPV infection, of particular importance are the prolonged latency in the body and the periodic detectability. Viral persistence defines two or more positive HPV tests over a period of time, and viral latency means that, although the infection is undetectable by conventional methods, HPV is not cleared from the body, which may influence the infectious status of HPV patients. These characteristics can also lead to cervical intraepithelial neoplasia which must be treated by loop electrosurgical excision techniques or cold knife conization, thus associating increased susceptibility to late miscarriage or preterm birth; the physiopathological mechanisms incriminated include cervical scarring with subsequent loss of cervical plasticity, reduction in tensile strength due to loss of cervical stroma and increased risk of infection due to cervical gland loss[5].

Risk factors for prematurity, such as smoking, cocaine use, low socioeconomic status, infections, multiple pregnancies, stress, functional defects of the cervix, history of preterm birth, low maternal Body Mass Index and African race, have been described in the literature. However, the main causes attributed to prematurity are lower genital tract infections such as bacterial vaginosis and trichomoniasis.

Recently, studies have shown a particular interest in HPV infection and its associated risk of prematurity.

A retrospective study analyzed cervical cytological samples, maternal HPV status and histopathological findings of placentas obtained from pregnancies complicated by prematurity. The study results demonstrate that the infection with high-risk HPV strains for cervical cancer is a risk factor for prematurity and placental abnormalities[7].

A recent retrospective study has shown that, in association with HPV infection, PPROM increases the risk of prematurity. The study included a large cohort of pregnant women (2153), 38.5% of whom were diagnosed with HPV. PPROM was found in 2.88% of cases.

Literature data demonstrate that pregnancies complicated by PPROM are associated with a higher percentage of inflammatory markers compared to term pregnancies, determined by the presence of HPV in choriodecidual tissue[8].

The trophoblast is responsible for facilitating the attachment of the placenta to the uterine wall and for establishing a low flow resistance circulation at this level. Damage to trophoblast cells by HPV causes placental dysfunction through cell apoptosis and impaired adhesion and subsequent compromised placental circulation with hypoxia and eventually even intrauterine growth restriction.

Secondly, this interaction between the trophoblast and virus may act as a trigger for the immune system, causing an exaggerated inflammatory response, with collagen degradation and fetal membrane fissure or rupture[9-11].

The trophoblast also secretes pregnancy-associated plasma protein-A in the first trimester of pregnancy, and its low levels correlates with an increased risk of preterm birth and PPROM. Thus, it can be used to indirectly check the degree of trophoblastic impairment in HPV-infected pregnant women[11].

Studies have shown that matrix metalloproteinase 2 (MMP2), which stimulates the synthesis and release of prostaglandins with the triggering of uterine contractions, has a strong influence on the choriodecidual inflammation process. Recently, a positive correlation has been reported between elevated MMP2 levels and HPV infection among pregnant women, suggesting that the virus may influence the regulation and expression of MMP2 and can be used as an indicator in the assessment of pregnant women at risk for HPV[10,12].

In addition to the HPV, other infectious agents can also act to cause PPROM by similar mechanisms, which is of significant importance when conducting HPV studies, especially those assessing the risk of prematurity. One study demonstrated a strong correlation between HPV infection with high-risk strains and PPROM, but did not analyze the sexual behaviors of the patients enrolled in the study, such as medical history, including infectious history, which may influence the degree of damage to the integrity of the fetal membranes and, thus, the risk of prematurity[10]. The Pap smear is used for global HPV screening and has high specificity and sensitivity. Taking into account the inflammation present during pregnancy, researchers have tried to find an association with HPV infection and the risk of complications, including prematurity. Although conducted on a large study group (15,357 pregnant women), but on a population at low risk for religious reasons (HPV identified in 1.3% of cases), no correlation was found between abnormal results of the Pap smear (used as a surrogate indicator for HPV infection) and prematurity.

The authors of the study have theorized that inflammatory changes identified in test results or even certification of HPV infection during pregnancy could be used as a reference for pregnant women at risk of preterm birth. The importance of screening through Pap smear during pregnancy is based on the results of studies that have shown correlations between HPV infection in the placenta and positive HPV results from Pap smears[9]. The impact that HPV infection can have on pregnancy includes the risk of lower birth weight, depending on gestational age. A study has been carried out in this regard and it has shown that HPV infection, identified at the genital level, through Pap smear as well as at the placental level, is more commonly associated with very low birth weight (VLBW) in 50% of cases and with low birth weight for gestational age in 20% of cases[13].

HPV vaccination – benefits and risks

In regard to adult vaccination against preventable afflictions according to one's environment (including HPV vaccination), it is ideal that individuals would be vaccinated prior to conception, despite the fact that

immunization of pregnant women appears to be as effective as in case of non-pregnant population[14].

Worldwide, there are three types of inactivated HPV vaccines (bivalent, quadrivalent and 9-valent), with the latter (Gardasil-9®) being currently the most recommended for use in the general population. Even though its usage is not recommended during pregnancy due to limited data, and if a woman happens to conceive after the first dose of vaccine, the remaining doses should be delayed until after birth[15,16], there are studies revealing similarities between the cumulative rate of adverse pregnancy outcomes (spontaneous abortion, late fetal death, congenital defect) for both the vaccinated and unvaccinated groups (22.6% versus 23.1%)[17], also with no correlation between spontaneous abortion and the number or timing of doses administered[18].

Lawton et al. conducted a retrospective study on a large population-based cohort (34,994 patients) in which they evaluated the existence of pregnancy risks and benefits of HPV vaccination. They compared vaccinated and unvaccinated pregnant women and studied the risk of prematurity, preeclampsia and intrauterine fetal death. A dose-dependent effect was identified, so that with each dose of vaccine administered, the risk of prematurity is reduced. The vaccine works by decreasing the risk of acquiring HPV infection at the genital level, which prevents placental infection during pregnancy and, thus, the associated risks. The results of this study cannot be generalized as the population enrolled consisted of pregnant women with an average age of 19 years old, as HPV prevalence is much higher at this stage. Further studies are needed in order to determine the efficacy of the vaccine in the population of pregnant women over 25 years old, given the reduction in HPV infection rates in this population[6].

A retrospective study carried out in Montreal examined the effectiveness of the HPV vaccine and whether its use decreases the risk of acquiring infection with the strains included in the vaccine. The authors compared the vaccinated and unvaccinated pregnant women who used the tetravalent vaccine for strains 16, 18, 6 and 11, and demonstrated an approximately 86% efficacy for strains 16 and 18.

For the four strains in the vaccine, the efficacy demonstrated was 61%, but the cohort on which the study was conducted included a relatively small number of HPV 6 and 11 infections, and this may account for the difference in results.

Similar studies conducted in the USA (89% efficacy), Australia (86% efficacy) and Sweden (73% efficacy) have shown that the use of the vaccine is of sufficient benefit to be implemented in national vaccination programs worldwide. Vaccine coverage will never reach 100%, but the authors suggest that it can be improved if given to young people before sexual debut[19].

Conclusions

The prevalence of HPV, as well as of other infectious diseases, such as bacterial vaginosis and trichomoniasis, is increasing among young population and may also play a role in causing PPROM. Even though HPV vaccination with the latter 9-valent variant of the vaccine (Gardasil-9®) will never reach a 100% coverage, its implementation in national immunization programs worldwide is one of the key solutions necessary in order to reduce the impact of prematurity on the neonate. ■

Conflict of interests: The authors declare no conflict of interests.

References

1. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet. 2008;371(9606):75–84.
2. Nadeau HCG, Subramaniam A, Andrews WW. Infection and preterm birth. Semin Fetal Neonatal Med. 2016;21(2):100–5.
3. Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. Semin Fetal Neonatal Med. 2016;21(2):68–73.
4. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. J Infect Dis. 2010;2(12):1789–99.
5. Niyibizi J, Zanré N, Mayrand M-H, Trottier H. The association between adverse pregnancy outcomes and maternal human papillomavirus infection: a systematic review protocol. Syst Rev. 2017;6(1):53.
6. Lawton B, Howe AS, Turner N, Filoche S, Slatter T, Devenish C, Hung NA. Association of prior HPV vaccination with reduced preterm birth: A population based study. Vaccine. 2017;36(1):134-40.
7. Zuo Z, Goel S, Carter J. Association of cervical cytology and HPV DNA. Status during pregnancy with placental abnormalities and preterm birth. Am J Clin Pathol. 2011;136(2):260–5.
8. Caballero A, Dudley D, Ferguson J, Pettit K, Boyle A. Maternal human papillomavirus and preterm premature rupture of membranes: A retrospective cohort study. J Womens Health. 2019;28(5):606-11.
9. Nimrodi M, Kleitman V, Wainstock T, Gemer O, Meirovitz M, Maymon E, Benshalom-Tirosh N, Erez O. The association between cervical inflammation and histologic evidence of HPV in PAP smears and adverse pregnancy outcome in low risk population. Eur J Obstet Gynecol Reprod Biol. 2018;225:160-5.
10. Cho G, Min KJ, Hong HR, Kim S, Hong JH, Lee JK, Oh MJ, Kim H. High-risk human papillomavirus infection is associated with premature rupture of membranes. BMC Pregnancy Childbirth. 2013;13:173.
11. Gomez L, Ma Y, Ho Mcgrath C, Nelson D, Parry S. Placental infection with human papillomavirus is associated with spontaneous preterm delivery. Hum Reprod Oxf Engl. 2008;23(3):709–15.
12. Mosbah A, Barakat R, Nabiel Y, Barakat G. High-risk and low-risk human papilloma virus in association to spontaneous preterm labor: a case-control study in a tertiary center, Egypt. J Matern-Fetal Neonatal Med. 2017;31(6):1–6.
13. Ford J, Li M, Scheil W, Roder D. Human papillomavirus infection and intrauterine growth restriction: A data-linkage study. J Matern Fetal Neonatal Med. 2019;32(2):279-85.
14. Gonik B, Fasano N, Foster S. The obstetrician-gynecologist's role in adult immunization. Am J Obstet Gynecol. 2002;187(4):984-8.
15. Oshman LD, Davis AM. Human Papillomavirus vaccination for adults: Updated recommendations of the advisory committee on immunization practices (ACIP). JAMA. 2020;323(5):468-9.
16. Petrosky E, Bocchini JA Jr, Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. MMWR Morb Mortal Wkly Rep. 2015;64(11):300-4.
17. Food and Drug Administration. Product approval-prescribing information [Package insert. Gardasil [human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant], Merck & Co, Inc. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2014.
18. Faber MT, Duun-Henriksen AK, Dehlendorff C, et al. Adverse pregnancy outcomes and infant mortality after quadrivalent HPV vaccination during pregnancy. Vaccine. 2019;37(2):265-71.
19. Sarr EHM, Mayrand MH, Coutlée F, et al. Exploration of the effect of human papillomavirus (HPV) vaccination in a cohort of pregnant women in Montreal, 2010-2016. Heliyon. 2019;5(8):E02150.