

The effect of human papilloma virus on women reproductive system, pregnancy outcome of mothers: a review

Abstract

Human papillomavirus is a type of sexually transmitted virus that is common in people with factors such as multiple sexual partners, a weakened immune system caused by anxiety, or alcohol and tobacco users. This virus (human papilloma) causes negative effects on vaginal and cervical epithelial cells, sperm quality and other fertility parameters. Human papilloma virus can exist in the seminal fluid caused by ejaculation and play a role in the fertility quality of men. Different viruses may directly or indirectly infect male gametes, sperms. Decreased fertility quality is caused by changes in sperm structure, increased sperm DNA fragmentation, and increased sperm aneuploidy. As a result, it causes a decrease in the quality of fertility in women and men and failure of assisted reproductive methods, and pregnancy complications such as frequent miscarriages, premature births and weight loss at birth. HPV causes precancerous cells, low-grade and high-grade cancer (LSIL-HSIL).

Keywords: pregnancy, fertility reduction, human papilloma virus

Introduction

Human papilloma virus is a common virus transmitted through sex in people with weak immune system, multiple partners and unhealthy lifestyle. This virus infects the genitals (vagina and cervix), the anus. This sexually transmitted virus may also affect the oral mucosa in people who have multiple partners and have oral sex.¹³ Therefore, its occurrence rate is high in both sexes regardless of the socio-economic status. According to the type (high-risk and low-risk), HPV is responsible for causing benign lesions (warts or papilloma) and cervical intra-epithelial neoplasia (CIN1, CIN2, CIN3), which if there are risk factors such as high-risk lifestyle, hookah, alcohol consumption, several sexual partners failure to use condoms may cause infections that are resistant to treatment and eventually lead to cancer.^{4,5} The most common high-risk types of this virus are 16, 18, and 31, while HPV 6 and 62 were the most common low-risk (LR) types in a study. These viruses disappear by chance and spontaneously if the immune system is strengthened within 1-2 years. If this virus becomes resistant in the body, it causes serious and very dangerous injuries, especially in people of reproductive age, because it frequently becomes anogenital with multiple malignancies, including cervical cancer.^{6,7} Determination and diagnosis of HPV type is very important in the diagnosis of fertility quality.⁸ Later studies show a relationship between the papilloma virus and the decrease in the quality of reproductive factors and, as a result, the failure of assisted reproductive technologies.^{8,9} The aim of this study is to investigate the effects of human papilloma virus on fertility quality. In the Garola study, they concluded that HPV in the male partner was positive for ART (assisted reproductive technology) success in each cycle of IUI (Intrauterine insemination), WIVF (a similar correlation between reduced pregnancy rates and HPV DNA positivity in semen samples from male partners in treated infertile couples) with IVF (In Vitro Fertilization) was reported by Perino et al.¹⁰ A laboratory study showed that the papilloma virus can have a negative effect on the development of the fetus, and consequently increase the rate of miscarriage in couples treated with ART. In our study, no association between HPV infection of male, female or both partners and higher abortion rate was identified in ART-treated couples or in couples with spontaneous pregnancy.¹¹

HPV and Semen

New studies show that the human papilloma virus can exist in the seminal fluid caused by ejaculation and play a role in the fertility quality of men. More than 170 types of this virus have been identified, and among them, less than 40 types can infect the genital area such as the cervix.¹² Different viruses may directly infect male gametes, sperms or indirectly. Decreased fertility quality is caused by changes in sperm structure, increased sperm DNA fragmentation, and increased sperm aneuploidy. Significantly reduces sperm motility. This could be due to HPV-driven DNA fragmentation in spermatozoa, which leads to apoptosis. In several studies, HPV semen infection was found to be associated with significantly lower sperm motility due to an increase in the number of anti-sperm antibodies binding on the sperm surface. The places affected by different variants of the virus include the anus and external genitalia, including the foreskin of the penis, scrotum and penis, vas deferens, epididymis, and testicles.¹³⁻¹⁵ It is believed that one of the most common places where this virus is located in male sperm is in its head. It seems that the presence of glycosaminoglycans and other soluble substances in the head of the sperm causes the binding and interaction of the virus in the sperm of the ovum.¹⁶⁻¹⁸ In addition, it is the equatorial part of the cerasperm that is connected to the plasma membrane of the egg and the membranes of both are combined.¹⁹ Therefore, according to the information shown in the studies, it can be understood that due to the presence of the virus in the cerasperm part and the fusion of the membranes together, it has a negative effect put on fertilization. In addition, it has been shown that the disruption of different parts of the sperm may be dependent on the type of virus. In particular, in a study conducted by Connelly (2001), it was found that types 16 and 31 of this virus cause DNA damage, and for this reason, sperm disorders may have a negative effect on the development of the fetus. In other studies, they concluded that, it seems Type 18, 33 and 6-11 do not seem to have an effect on sperm quality.^{20,21}

HPV and pregnancy

Since the mother's immune system is low during pregnancy, this virus may increase due to the weakness of the immune system during this period. The adverse consequences of pregnancy in infected

women include: premature birth, abortion, suppression of pregnancy-induced hypertension (PIHD), Intrauterine growth restriction (IUGR) and low birth weight, premature rupture of membranes. (PROM) and fetal death. Therefore, identifying effective ways to eliminate this virus and fight against it will optimize pregnancy outcomes and improve fetal health development.¹⁻⁴ Studies show that the presence of HPV during fertility treatment has a negative effect on the results of assisted reproductive methods and causes (a decrease in the quality and quantity of pregnancy and the risk of premature birth and miscarriage). Therefore, the faster diagnosis and determination of the type of this virus in men and women is very useful because of the rapid diagnosis of infertility, at least idiopathic infertility, before performing assisted reproductive methods. Studies show that this virus increases the risk of infection and progression to intraepithelial lesions in women over 30 years old. Two studies showed that one way to treat this virus is cervical conization and LEEP, which does not increase the risk of preterm delivery in the next pregnancy.

HPV and early stages embryogenesis

Sperm can transmit the virus to the fetus through the process of fertilization (fusion of membranes). Studies have shown that expression of E6, E7, and L1 genes increases DNA damage and trophoblast death. In a study by Henberg and his colleagues, it was shown that both genotypes 16 and 18 have negative effects in the embryonic stage found that the rate of apoptosis (cell death) in the trophoblast of the affected person is 3 to 6 times higher than that of the trophoblast of a healthy person, which causes.

HPV and assisted reproductive technology (ART)

A person who is infected with this virus during ART treatment may have disorders in the acrosome reaction, between sperm and egg and in fusion. This is due to binding of the virus on the head or tail segments of the sperm, which reduces the function of the acrosome.²²

Type of delivery and mother infected with HPV

Tseng et al. found the overall frequency of HPV transmission from mothers to neonates was 39.7%, and a meaningfully higher rate of infection was observed when infants were delivered vaginally compared with cesarean. Detection of HPV DNA in semen, endometrium, and ovaries indicates the possibility of transmission even before conception. Another possible way to infect the fetus is to transfer the virus into the womb or before birth. Due to the presence of DNA of this virus in the amniotic fluid, placenta and umbilical cord blood and the close contact of the fetus with the cervical and vaginal canals of the patient during childbirth can cause perinatal transmission.²³

Colposcopy and HPV

Human papillomavirus infection is the main cause of cervical malignancy and cancer. More than 40 variants of this virus cause infection in the genital area.² These variants include high-risk and low-risk types, which are responsible for progressing to neoplasia and cervical cancer, and the low-risk type, which rarely leads to cancer, is capable of causing genital warts. Persistent infection with HPV is considered the most important predictor of CIN 2 or 3. High-risk variants are associated with more than 80% of cervical cancers and CIN2/3. The most common and clinically relevant genotypes in the population are HPV 16 and 18, which account for more than 70% of all cervical cancer cases. 41-67% of high-grade cervical lesions and 32-16% of low-grade cervical lesions.^{3,5} Among the non-cancerous variants of human papilloma virus, types 6 and 11 are the most

common and involve more than 90% of the genitals. These low-risk variants are primarily responsible for respiratory papilloma (RRP) and a small proportion of low-grade cervical cell abnormalities. (Pap smear), colposcopy or HPV test. In Poland, cytology examination is recommended for all women between 25 and 59 years old at 3-year intervals.²⁴ Women with abnormal pap smear results such as ASCUS, LSIL, should be referred for colposcopy or biopsy. Colposcopy examination is very effective for detecting cervical changes with a high grade, but due to poor reproducibility and lower specificity, it has made it difficult to diagnose patients with CIN 1/2. The conditions for performing colposcopy and pap smear include not having intercourse in the past two days and not using vaginal gel and cream.²⁵⁻³¹

HPV-vaccination and fertility

Fertility fears about HPV vaccination among women with HPV have been reported in a qualitative study. In this study, it was investigated that the person's fear is the loss of fertility after receiving the vaccine. The World Health Organization (WHO) has cited a systematic review and concluded that there is no scientific relationship between HPV vaccination and infertility, and accidental HPV vaccination during pregnancy cannot lead to adverse pregnancy outcomes or harm to the fetus. The World Health Organization recommends preventing HPV vaccine injection during pregnancy. And if the injection occurs in pregnant women, there is no need to intervene and worry.

Conclusion

The present paper reviewed the effects of human papilloma virus on male and female fertility and assisted reproductive methods.³²⁻³⁷ HPV infection of type 52 was identified as the most common form of the virus in couples undergoing assisted reproduction.³⁸⁻⁴⁰ The main reason for the failure of ART methods, including IVF and IUI, is because of frequent HPV, so the vaginal environment is affected by these factors and makes the conditions for assisted reproductive treatments difficult.⁴¹⁻⁴² Therefore, midwives advise married women over the age of 30 to perform cervical cancer screening (Pap smear) once every three years. Finally, daily consumption of Powerfit, Vitalact capsules and quitting smoking, hookah, and alcohol are recommended.

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Conflicts of interest

The authors declared no conflicts of interest.

References

1. Carmen EC, Lidia Filip, Mirela Gherghe, et al. Maternal HPV infection: effects on pregnancy outcome. *Viruses*. 2021;13(12):2455.
2. McQuillan G, Kruszon MD, Markowitz LE, et al. Prevalence of HPV in adults Aged 18–69: United States, 2011–2014. *NCHS Data Brief*. 2017;1(280):1–8.
3. Sehnal B, Zikan M, Nipcová M, et al. The association among cervical, anal, and oral HPV infections in high-risk and low risk women. *Eur J Obstet Gynecol Reprod Biol*. 2019;4:100061.
4. Otter S, Whitaker S, Chatterjee J, et al. The human papillomavirus as a common pathogen in oropharyngeal, anal and cervical cancers. *Clin Oncol*. 2019;31(2):81–90.
5. Park E, Kim JY, Choi S, et al. Carcinogenic risk of human papillomavirus (HPV) genotypes and potential effects of HPV vaccines in Korea. *Sci Rep*. 2019;9(1):12556.

6. Andrea Ciavattini, Chiara Marconi, Luca Giannella, et al. The impact of 9-valent HPV vaccination on couple infertility prevention: a comprehensive review. *Front Med.* 2021;18:700792.
7. Datta J, Palmer MJ, Tanton C, et al. Prevalence of infertility and help seeking among 15000 women and men. *Hum Reprod.* 2016;31(9):2108–2118.
8. Polis CB, Cox CM, Tunçalp Ö, et al. Estimating infertility prevalence in low to middle income countries: an application of a current duration approach to demographic and health survey data. *Hum Reprod.* 2017;32(5):1064–1074.
9. Perino A, Giovannelli L, Schillaci R, et al. Human papillomavirus infection in couples undergoing in vitro fertilization procedures: impact on reproductive outcomes. *Fertil Steril.* 2011;95(5):1845–1848.
10. Hana Jaworek, Vladimira Koudelakova, Ivana Oborna, et al. Impact of human papillomavirus infection on semen parameters and reproductive outcomes. *Reprod Biol Endocrinol.* 2021;19(9):156.
11. Zhangyan Lyu, Xiaoshuang Feng, Ni Li, et al. Human papillomavirus in semen and the risk for male infertility: a systematic review and meta-analysis. *BMC Infect Dis.* 2017;17(1):714.
12. Infertility workup for the women's health specialist: ACOG committee opinion summary number 781. *Obstet Gynecol.* 2019;133(6):1294–1295.
13. Konstantinos Zacharis, Christina Messini, George Anifandis, et al. Human papilloma virus (HPV) and fertilization: a mini review. *Medicina.* 2018;54(4):50.
14. Iran: human papillomavirus and related cancers, fact sheet. *Centre IHI.* 2018.
15. Jersoviene V, Gudleviciene Z, Rimiene J, et al. Human papillomavirus and infertility. *Medicina.* 2019;55(7):377.
16. Souho T, Benlemlah M, Bennani B. Human papillomavirus infection and fertility alteration: a systematic review. *PLoS ONE.* 2015;10(5):0126936.
17. Xiong YQ, Chen YX, Cheng MJ, et al. The risk of human papillomavirus infection for male fertility abnormality: a meta-analysis. *Asian J Androl.* 2018;20(5):493–497.
18. Capra G, Schillaci R, Bosco L, et al. HPV infection in semen: results from a new molecular approach. *Epidemiol Infect.* 2019;147:177.
19. Merckx M, Liesbeth W, Arbyn M, et al. Transmission of carcinogenic human papillomavirus types from mother to child: a meta-analysis of published studies. *Eur J Cancer Prev.* 2013;22(3):277–285.
20. Nohr B, Kjaer SK, Soylu L, et al. High-risk human papillomavirus infection in female and subsequent risk of infertility: a population based cohort study. *Fertil Steril.* 2019;111(6):1236–1242.
21. Joanna ŚK, Krzysztof C, Julia Zaręba, et al. Comparison of HPV testing and colposcopy in detecting cervical dysplasia in patients with cytological abnormalities. *In Vivo.* 2020;34(3):1307–1315.
22. Konstantinos Zacharis, Christina Messini, George Anifandis, et al. Human papilloma virus (HPV) and fertilization: a mini review. *Medicina.* 2018;54(4):50.
23. Ambühl LM, Baandrup U, Dybkær K, et al. Human papillomavirus infection as a possible cause of spontaneous abortion and spontaneous preterm delivery. *Infect Dis Obstet Gynecol.* 2016;2016:3086036.
24. Perino A, Giovannelli L, Schillaci R, et al. Human papillomavirus infection in couples undergoing in vitro fertilization procedures: impact on reproductive outcomes. *Fertil Steril.* 2011;95(5):1845–1848.
25. Spandorfer SD, Bongiovanni AM, Fasioulotis S, et al. Prevalence of cervical human papillomavirus in women undergoing in vitro fertilization and association with outcome. *Fertil Steril.* 2006;86(3):765–767.
26. Pandey D, Solleti V, Jain G. Human papillomavirus (HPV) infection in early pregnancy: prevalence and implications. *Infect Dis Obstetr Gynecol.* 2019;2019:4376902.
27. Andía D, Mozode RF, Villasante A, et al. Pregnancy outcome in patients treated with cervical conization for cervical intraepithelial neoplasia. *Int J Gynecol Obstet.* 2011;112(3):225–228.
28. Ehsanipoor RM, Jolley JA, Goldshore MA, et al. The relationship between previous treatment for cervical dysplasia and preterm delivery in twin gestations. *J Matern Fetal Neonatal Med.* 2014;27(8):821–824.
29. Hernández GC, Smith JS, Lorincz A, et al. High risk human papillomavirus detection and related risk factors among pregnant and nonpregnant women in Mexico. *Sex Transm Dis.* 2005;32(10):613–618.
30. Volpato LK, Siqueira IR, Nunes RD, et al. Association between hormonal contraception and injuries induced by human papillomavirus in the uterine cervix. *Rev Bras Ginecol Obstet.* 2018;40(4):196–202.
31. Tseng CJ, Liang CC, Soong YK, et al. Perinatal transmission of human papillomavirus in infants: relationship between infection rate and mode of delivery. *Obstet Gynecol.* 1998;91(1):92–96.
32. Skoczyński M, Goździcka JA, Kwaśniewska A. Co-occurrence of human papillomavirus (HPV) in newborns and their parents. *BMC Infect Dis.* 2019;19(1):930.
33. Pradhan SR, Mahata S, Ghosh D, et al. Human papilloma virus infections in pregnant women and its impact on pregnancy outcomes: possible mechanism of self clearance. *Human Papillomavirus: Intech Open.* 2020.
34. Bennett KF, Jo Waller, Julia V, et al. The psychosexual impact of testing positive for high-risk cervical human papillomavirus (HPV): a systematic review. *Turk J Obstet Gynecol.* 2019;28(10):1959–1970.
35. Perrin KK, Daley EM, Naoom SF, et al. Women's reactions to HPV diagnosis: insights from in depth interviews. *Women Health.* 2006;43(2):93–110.
36. Kosenko KA, Hurley RJ, Harvey JA. Sources of the uncertainty experienced by women with HPV. *Qual Health Res.* 2012;22(4):534–545.
37. Waller J, McCaffery, Kitchener H, et al. Women's experiences of repeated HPV testing in the context of cervical cancer screening: a qualitative study. *Psychooncology.* 2007;16(3):196–204.
38. McCaffery, Waller J, Nazroo J, et al. Social and psychological impact of HPV testing in cervical screening: a qualitative study. *Sex Transm Infect.* 2006;82(2):169–174.
39. Daley EM, Perrin KM, McDermott RJ, et al. The psychosocial burden of HPV: a mixed method study of knowledge, attitudes and behaviors among HPV+ women. *J Health Psychol.* 2010;15(2):279–290.
40. Pourmohsen M, Simbar M, Nahidi F, et al. Women's experiences of infection with human papillomavirus in the face of disease symptoms: a qualitative study. *Int J Womens Health Reprod Sci.* 2020;8(1):37–45.
41. Kousha AMA, Maleki A, Najmi M, et al. Package of essential non-communicable (PEN) disease interventions for primary health care in Iran "IRAPEN". *Mojassameh.* 2017.
42. Bruni LB-RL, Albero G, Serrano B, et al. ICO information centre on HPV and cancer (HPV information centre). *Hum Papillomavirus Relat Dis.* 2017.