

# Correlation between human papillomavirus infection and reproduction

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## ABSTRACT

Human papillomavirus (HPV) is one of the most common sexually transmitted infectious viruses among men and women of reproductive age throughout the world. Pregnant women are susceptible during pregnancy and most infections of them are self-limiting infections, which can be removed by their autoimmunity, while the persistent infections are associated with precancerous lesions and cancer of the anogenital mucosa in women and men. In addition, HPV infection may also affect reproductive health and fertility. The effect of HPV on female fertility requires further study, but HPV influences sperm parameters. Furthermore, whether HPV infection alters the effect of assisted reproductive technology and whether there is an association between it and assisted reproductive technology (ART) outcomes is unknown. It is considered that the relationship between HPV infection and spontaneous abortion (SA), assisted reproductive technology (ART) outcomes and spontaneous preterm birth (sPTB) has profound implications for the medical care of pregnant and infertile women. This paper reviews the relationship between human papillomavirus infection during pregnancy and SA, sPTB and ART in reproduction, and reviews the relationship between human papillomavirus and human fertility by summarizing the recent domestic and foreign literature.

**Key words:** human papillomavirus infection; reproduction; spontaneous abortion; assisted reproductive technology; spontaneous preterm birth

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## INTRODUCTION

As a kind of most common sexually transmitted infectious viruses, Human papillomavirus (HPV) had infected human of reproductive age throughout the world [1], which mainly infects the skin and mucosal scaly epithelium. The overall prevalence of HPV infection is estimated to be approximately 12% among women of childbearing age [2, 3], nearly 60% of women carry anti-HPV antibodies in their sera [4]. Domestic studies have shown that 5201 pregnant women were screened for cervical HPV, resulting in 698 positive HPV cases and an infection rate of 13.42% [5]. HPV is a DNA virus that is mostly self-limiting and can be cleared by the infected person's autoimmunity, but its persistent infection can cause carcinogenesis, and is associated with precancerous lesions and cancer of the anogenital mucosa in women as well as men [6]. HPV included high-risk HPV (HR-HPV) and low-risk HPV (LR-HPV) [7].

In order to ensure that the fetus is not rejected by the mother in utero during pregnancy, a large amount of estrogen and progesterone, chorionic gonadotropin and pla-

cental lactogen secreted by the placenta of women can inhibit the maternal immune response, leaving the mother in a state of natural immune tolerance and suppressed cellular immune function, so HPV infection is more likely to occur during this period. It is well-known that sexually transmitted infections are the main cause of infertility, but does HPV infection also have an impact on other aspects of human reproduction such as germ cell quality, germ cell binding, pregnancy success rate, abortion, preterm delivery, and ectopic pregnancy? It has been reported that human papillomavirus (HPV) may influence pregnancy outcome [8, 9]. HPV infection increases the risk of spontaneous abortion as well as ectopic pregnancy, and different genotypes caused by HPV infection may play different roles in adverse pregnancy outcomes [10, 11].

Considering the relationship between HPV infection and spontaneous abortion (SA), assisted reproductive technology (ART) outcomes and spontaneous preterm birth (sPTB) have profound implications for the medical care of pregnant and infertile women, we reviewed the relationship

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between human papillomavirus infection during pregnancy and SA, sPTB and ART in reproduction in this paper, which is reported as follows:

### **HUMAN PAPILLOMAVIRUS AND SPONTANEOUS ABORTION**

Spontaneous abortion (SA) was the most common adverse complication during pregnancy [13, 14]. Depending on the study population involved, the incidence of SA is nearly 12–15% [15] and 80% of SAs occur in the first trimester [16], what's worse, the risk of SA occurrence directly increases with age [17].

Previous studies reported that the prevalence of HPV in the cervix of women with spontaneous abortion was significantly higher than that of normal full-term pregnant women (24.5% vs 17.5%); in a previous study, although the pregnancy memory rate was lower in HPV-positive women, the rate of spontaneous abortion was doubled in 66 women with genital HPV infection [18]. This trend suggests a possible association between spontaneous abortion and HPV infection [19].

At present, some studies have found by summarizing the results of eight cohort and case-control studies [20]: HPV infection may increase the rate of spontaneous abortion by 1.40 [95% confidence interval (CI): 0.56–3.50]; but the pooled OR of three cohort studies and one case-control study (456 subjects in total) was 0.65 (95% CI, 0.21–1.98, I<sup>2</sup> = 64.7%) when only considered HR-HPV infection.

SA is closely associated with histological chorioamnionitis (HCA) and HPV infection [21]. It has been considered that HPV can be transmitted through the blood and cross the placental barrier when it infects the mother, thereby inducing SA [22]. Thus, in order to further verify the reliability of this hypothesis, some studies examined the HPV infection rate in the chorionic villi of the main septate surface between mother and embryo/fetus and found that the HPV infection rate in the chorionic villi was low (4–7%) [23–25]. In addition, *in vitro* studies have shown that HPV can replicate in trophoblast cells, suggesting that the virus may not be strictly keratinocyte-specific [26, 27], indicating that HPV has a low propensity for chorionic villi. There is a great variability in the detection rate of HPV-DNA in amniotic fluid, cord blood, cervical tissue as well as fetal membranes, ranging from 4–75% [28, 29]. Many studies on cord blood, amniotic fluid, and fetal membranes also do not support this idea [30, 31]. Therefore, the hypothesis that HPV-infected pregnant women possibly cause SA by virus crossing the placental barrier has been greatly questioned. The reported results on the relationship between human papillomavirus (HPV) and SA are conflicting, and this may be due to the interference of confounding factors, such as HPV detection methods and risk factors or other sexually transmitted infections.

Another statement is that the gene expression of HPV can increase embryonic DNA fragments, leading to abnormal embryonic development. In addition, HPV-DNA infection can increase the apoptosis rate of trophoblast cells, change placental viability and adhesiveness, reduce implantation of the placenta into the uterine wall, interfere with hematogenous descending route, and affect embryo implantation, which causes the occurrence of early abortion [32]. However, this statement is also controversial. In a case-control study carried out by Italian scholars, the effect of HPV infection on recurrent spontaneous abortion was explored. This study showed that women without a historic recurrence had a higher rate of HPV infection and a longer clearance cycle process of HPV infection. It was speculated that the possible reason was that women with recurrent abortion had a more sensitive immune response and a stronger clearance of foreign bodies, which could timely remove HPV and played a protective role [33].

A META study [20] in 2018 negated the association between HPV and pregnancy/SA rate by searching the relevant literature up to December 16, 2016, indicating that HPV did not affect the pregnancy outcome after MAR. Some other studies, including those reporting a high incidence of HPV in women experienced SA also negated the effect of HPV in pregnancy outcomes [34]. Thus, there was probably no association between SA and HPV infection. However, the gestational age of aborted fetuses was positively correlated with the viral load of fetuses as well as the matrix metalloproteinase 2 (MMP-2) gene expression rate, indicating that the abortion timing was correlated with HPV viral load [35].

Overall, HPV probably infect the placenta but does not have an impact on embryonic outcome. Therefore, the association between SA and HPV infection, and the relationship between HPV and SA needs further study.

### **HUMAN PAPILLOMAVIRUS AND ASSISTED REPRODUCTIVE TECHNOLOGY**

Assisted reproductive technology is the abbreviation of Assisted Reproductive Technology, which refers to techniques that use medical aids to make infertile couples pregnancy, including Artificial Insemination (AI), In Vitro Fertilization and Embryo Transfer (IVF-ET), and two major categories of their derivative techniques. The World Health Organization (WHO) assessed that about one of every seven couples had reproductive disorders. Recent surveys in China suggested that domestic infertility accounted for 10% of married couples, increased by more than double the 4.8% surveyed in 1984, and the incidence was on the rise. This is because China is more affected by the concept of succession, and most families are eager to have children, leaving infertile couples under great psychological pressure, even leading to divorce, extramarital relationships and other family and

social problems. The direct effect of ART is to make sterility couples fulfill their desire to conceive and have children, so that the related problems caused by infertility can be solved.

ART requires both husband and wife to have healthy gametes. Some studies [36] have found that the positive rate of HR-HPV in oocyte donors was higher than that in infertile women receiving IVF treatment by studying the HPV infection of female partners and oocyte donors in infertile patients. These results indicate that there is no correlation between HR-HPV infection and pregnancy rate or miscarriage rate in female patients treated with IVF and normal subjects. The outcomes of female partners with HPV-positive does not seem to affect the success of assisted reproductive technology (ART), and treatment for HPV prior to IVF is not recommended, as longer treatment times and increasing age can instead reduce ovarian function, leading to poor IVF outcomes [37].

One study [38] reported that there was a 15.9% overall miscarriage rate in HPV-negative couples ( $p < 0.001$ ). Therefore, was a highly statistically significant correlation between pregnancy loss rate and positive HPV DNA testing in the male partner of infertile couples.

A growing number of evidence concurred to identify that HPV-infected male partners play a non-negligible role in infertility. The presence of HPV in the DNA of infertile men has been found to correlate with sperm motility, sperm count and semen pH in their semen [38, 39]. HPV infection in male partners appears to be a predictor of negative pregnancy outcomes in ART procedures [40, 41]. In fact, in a study of infertile couples, the miscarriage rate in couples underwent ART was 2:1 when comparing the seminal HPV infection group to couples without infection, and HPV DNA was detected in semen samples of a significant proportion of these infertile couples underwent ART [40]. After HPV vaccination, the sperm motility of HPV-positive male partners can be improved, and the pregnancy rate also can be significantly increased [42]. Besides, sperm washing techniques maybe improved pregnancy rates in ART procedures [43, 44].

The equatorial plate region of the sperm head is the site of sperm binding to oocytes, and in vitro studies have found that the equatorial plate is the binding site for sperm HPV L1 capsid protein and sperm surface glycosaminoglycan synthase 1 [45]. Therefore, sperm perhaps play a role as a vector in the process of HPV transfection into oocytes during fertilization, and sperm infected with the HPV E6/E7 gene can penetrate oocytes and transfect viral DNA into oocytes, followed by HPV viral gene activation and transcription in oocytes [46]. Infected spermatozoa possibly would function as a carrier of HPV DNA within the reproductive tract and oocyte and could have deleterious effects during fertilization.

## HUMAN PAPILLOMAVIRUS AND SPONTANEOUS PRETERM BIRTH

Spontaneous preterm birth (sPTB) is defined as delivery between 28 and less than 37 weeks of gestation. Neonates delivered at this time are called preterm infants and weigh 1000 to 2499 g. Preterm birth accounts for 5% to 15% of total deliveries in China, and about 15% of preterm infants die in the neonatal period. In the past two decades, sPTB is increasing worldwide, and late preterm births, which comprise more than 70% of all preterm births, account for much of the increase. Preterm infants have imperfect development of various body systems and are prone to multisystem serious diseases, which are characterized by high mortality and morbidity [47]. Risk factors for sPTB include advanced maternal age, advanced spouse age, multiparous women, placenta previa, placental abruption, fetal membranes, gestational diabetes, and hypertensive disorder complicating pregnancy [48].

The placental barrier is one of the three major barriers in the human body that protects against many microorganisms, thereby allowing the fetus in the utero to be well protected. However, several studies have shown that viral infection maybe lead to pregnancy loss [49, 50] and consequently to preterm birth. In addition, HPV infection in the upper genital tract was found to be an important cause of sPTB [51]. By reviewing the clinical data of 2480 patients with abnormal placenta during the past 11 years, it was found that reactive, infectious, atypical and dysplastic cytological changes during pregnancy were significantly associated with placental abnormalities. In addition, all other changes were significantly associated with sPTB except dysplastic cytological changes. The presence of HR-HPV DNA was significantly associated with premature delivery and abnormal placentation. These findings indicated that HPV infection in cervix was a risk factor for premature delivery [52]. It has also been found that women with HR-HPV infection had a higher incidence of premature rupture of the membranes (PROM) than those without HR-HPV. HR-HPV infection was associated with an increased risk of PROM (OR, 2.380; 95% CI, 1.103–5.134) [53]. There are also several reports [54, 55] showing that HPV infection during pregnancy increased the risk of spontaneous preterm delivery or placental abnormalities. The overall prevalence of HPV in normal pregnancies was 17.5% (95% CI, 17.3–17.7) for cervix, which was significantly lower than sPTB (47%,  $p < 0.0001$ ). In all cases, normal pregnancies have lower rate of HPV positive than placental tissues of sPTB (8.3% vs 24.9%). Another META analysis included 1719 participants showed that HR-HPV infection was a risk factor for sPTB, with a pooled OR of 2.84 (95% CI, 1.95–4.14;  $I^2 = 23.5\%$ ).

In summary, HR-HPV infection is a risk factor for sPTB. In the process of fertilization binding, sperm possibly will

play a role as a carrier in the process of HPV transfection into oocytes, and have a harmful effect during fertilization, thus affecting the outcome of ART. In addition, HPV perhaps infect the placenta, but will not influence embryo outcome. The association between SA and HPV infections still need further research.

### **Ethics approval and consent to participate**

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of The Eighth People's Hospital Hebei Province.

### **Authors contribution**

Conception and design of the research: Duan LL, Yin H, Ju YM. Acquisition of data: Yin H, Li QY, Zhou LJ. Analysis and interpretation of the data: Duan LL, Mi XR. Statistical analysis: Duan LL, Yin H, Ju YM. Obtaining financing: None. Writing of the manuscript: Duan LL, Yin H, Ju YM. Critical revision of the manuscript for intellectual content: Ju YM.

All authors read and approved the final version of the manuscript.

### **Conflict of interest**

All of the authors had no personal, financial, commercial, or academic conflicts of interest separately.

## **REFERENCES**

- Bosch FX, Broker TR, Forman D, et al. authors of ICO Monograph Comprehensive Control of HPV Infections and Related Diseases Vaccine Volume 30, Supplement 5, 2012, authors of the ICO Monograph 'Comprehensive Control of HPV Infections and Related Diseases' Vaccine Volume 30, Supplement 5, 2012, Authors of the ICO Monograph 'Comprehensive Control of HPV Infections and Related Diseases' Vaccine Volume 30, Supplement 5, 2012. Comprehensive control of human papillomavirus infections and related diseases. *Vaccine*. 2013; 31 Suppl 8: 11–31, doi: [10.1016/j.vaccine.2013.07.026](https://doi.org/10.1016/j.vaccine.2013.07.026), indexed in Pubmed: [24229716](https://pubmed.ncbi.nlm.nih.gov/24229716/).
- Ault KA. Epidemiology and natural history of human papillomavirus infections in the female genital tract. *Infect Dis Obstet Gynecol*. 2006; 2006 Suppl: 40470, doi: [10.1155/IDOG/2006/40470](https://doi.org/10.1155/IDOG/2006/40470), indexed in Pubmed: [16967912](https://pubmed.ncbi.nlm.nih.gov/16967912/).
- de Sanjosé S, Diaz M, Castellsagué X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. *Lancet Infect Dis*. 2007; 7(7): 453–459, doi: [10.1016/S1473-3099\(07\)70158-5](https://doi.org/10.1016/S1473-3099(07)70158-5), indexed in Pubmed: [17597569](https://pubmed.ncbi.nlm.nih.gov/17597569/).
- Liu G, Markowitz LE, Hariri S, et al. Seroprevalence of 9 Human Papillomavirus Types in the United States, 2005–2006. *J Infect Dis*. 2016; 213(2): 191–198, doi: [10.1093/infdis/jiv403](https://doi.org/10.1093/infdis/jiv403), indexed in Pubmed: [26320259](https://pubmed.ncbi.nlm.nih.gov/26320259/).
- Wang HY, Hong Y, Hu Y, et al. A multicenter study on cervical cancer screening and maternal-fetal transmission of human papillomavirus in pregnant women. *Jiangsu Medical Journal*. 2015; 24: 2958–2960.
- zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. *Virology*. 2009; 384(2): 260–265, doi: [10.1016/j.virol.2008.11.046](https://doi.org/10.1016/j.virol.2008.11.046), indexed in Pubmed: [19135222](https://pubmed.ncbi.nlm.nih.gov/19135222/).
- Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. *Infect Agent Cancer*. 2009; 4: 8, doi: [10.1186/1750-9378-4-8](https://doi.org/10.1186/1750-9378-4-8), indexed in Pubmed: [19486508](https://pubmed.ncbi.nlm.nih.gov/19486508/).
- Bober L, Guzowski G, Moczulska H, et al. Influence of human Papilloma Virus (hPV) infection on early pregnancy. *Ginekol Pol*. 2019; 90(2): 72–75, doi: [10.5603/GP.2019.0012](https://doi.org/10.5603/GP.2019.0012), indexed in Pubmed: [30860272](https://pubmed.ncbi.nlm.nih.gov/30860272/).
- Rahimkhani M, Mordadi A, Gilanpour M. Detection of urinary Chlamydia trachomatis, Mycoplasma genitalium and human papilloma virus in the first trimester of pregnancy by PCR method. *Ann Clin Microbiol Antimicrob*. 2018; 17(1): 25, doi: [10.1186/s12941-018-0276-7](https://doi.org/10.1186/s12941-018-0276-7), indexed in Pubmed: [29866110](https://pubmed.ncbi.nlm.nih.gov/29866110/).
- Xiong YQ, Mo Y, Luo QM, et al. The Risk of Human Papillomavirus Infection for Spontaneous Abortion, Spontaneous Preterm Birth, and Pregnancy Rate of Assisted Reproductive Technologies: A Systematic Review and Meta-Analysis. *Gynecol Obstet Invest*. 2018; 83(5): 417–427, doi: [10.1159/000482008](https://doi.org/10.1159/000482008), indexed in Pubmed: [29649818](https://pubmed.ncbi.nlm.nih.gov/29649818/).
- Wang BJ, Gong Z, Hu ZX, et al. Human Papillomavirus and Pregnancy Related Problems. *Journal of International Obstetrics and Gynecology*. 2020; 3: 258–261.
- Ault KA. Epidemiology and natural history of human papillomavirus infections in the female genital tract. *Infect Dis Obstet Gynecol*. 2006; 2006 Suppl: 40470, doi: [10.1155/IDOG/2006/40470](https://doi.org/10.1155/IDOG/2006/40470), indexed in Pubmed: [16967912](https://pubmed.ncbi.nlm.nih.gov/16967912/).
- Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. *J Clin Virol*. 2005; 32 Suppl 1: S16–S24, doi: [10.1016/j.jcv.2004.12.008](https://doi.org/10.1016/j.jcv.2004.12.008), indexed in Pubmed: [15753008](https://pubmed.ncbi.nlm.nih.gov/15753008/).
- zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. *Virology*. 2009; 384(2): 260–265, doi: [10.1016/j.virol.2008.11.046](https://doi.org/10.1016/j.virol.2008.11.046), indexed in Pubmed: [19135222](https://pubmed.ncbi.nlm.nih.gov/19135222/).
- Paavonen J, Eggert-Kruse W. Chlamydia trachomatis: impact on human reproduction. *Hum Reprod Update*. 1999; 5(5): 433–447, doi: [10.1093/humupd/5.5.433](https://doi.org/10.1093/humupd/5.5.433), indexed in Pubmed: [10582782](https://pubmed.ncbi.nlm.nih.gov/10582782/).
- Gray-Swain MR, Peipert JF. Pelvic inflammatory disease in adolescents. *Curr Opin Obstet Gynecol*. 2006; 18(5): 503–510, doi: [10.1097/01.gco.0000242952.87125.69](https://doi.org/10.1097/01.gco.0000242952.87125.69), indexed in Pubmed: [16932044](https://pubmed.ncbi.nlm.nih.gov/16932044/).
- Cohain JS, Buxbaum RE, Mankuta D. Spontaneous first trimester miscarriage rates per woman among parous women with 1 or more pregnancies of 24 weeks or more. *BMC Pregnancy Childbirth*. 2017; 17(1): 437, doi: [10.1186/s12884-017-1620-1](https://doi.org/10.1186/s12884-017-1620-1), indexed in Pubmed: [29272996](https://pubmed.ncbi.nlm.nih.gov/29272996/).
- Hellberg D, Nilsson S. IVF and HPV. *Fertil Steril*. 2007; 87(6): 1498; author reply 1498, doi: [10.1016/j.fertnstert.2007.01.135](https://doi.org/10.1016/j.fertnstert.2007.01.135), indexed in Pubmed: [17544657](https://pubmed.ncbi.nlm.nih.gov/17544657/).
- 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, doi: [10.1155/2016/3086036](https://doi.org/10.1155/2016/3086036), indexed in Pubmed: [27110088](https://pubmed.ncbi.nlm.nih.gov/27110088/).
- Xiong YQ, Mo Y, Luo QM, et al. The Risk of Human Papillomavirus Infection for Spontaneous Abortion, Spontaneous Preterm Birth, and Pregnancy Rate of Assisted Reproductive Technologies: A Systematic Review and Meta-Analysis. *Gynecol Obstet Invest*. 2018; 83(5): 417–427, doi: [10.1159/000482008](https://doi.org/10.1159/000482008), indexed in Pubmed: [29649818](https://pubmed.ncbi.nlm.nih.gov/29649818/).
- Srinivas SK, Ma Y, Sammel MD, et al. Placental inflammation and viral infection are implicated in second trimester pregnancy loss. *Am J Obstet Gynecol*. 2006; 195(3): 797–802, doi: [10.1016/j.ajog.2006.05.049](https://doi.org/10.1016/j.ajog.2006.05.049), indexed in Pubmed: [16949414](https://pubmed.ncbi.nlm.nih.gov/16949414/).
- Racicot K, Mor G, Silasi M, et al. Viral infections during pregnancy. *Am J Reprod Immunol*. 2015; 73(3): 199–213, doi: [10.1111/aji.12355](https://doi.org/10.1111/aji.12355), indexed in Pubmed: [25582523](https://pubmed.ncbi.nlm.nih.gov/25582523/).
- Tognon M, Tagliapietra A, Magagnoli F, et al. Investigation on Spontaneous Abortion and Human Papillomavirus Infection. *Vaccines (Basel)*. 2020; 8(3), doi: [10.3390/vaccines8030473](https://doi.org/10.3390/vaccines8030473), indexed in Pubmed: [32854278](https://pubmed.ncbi.nlm.nih.gov/32854278/).
- Sarkola ME, Grénman SE, Rintala MAM, et al. Human papillomavirus in the placenta and umbilical cord blood. *Acta Obstet Gynecol Scand*. 2008; 87(11): 1181–1188, doi: [10.1080/00016340802468308](https://doi.org/10.1080/00016340802468308), indexed in Pubmed: [18972230](https://pubmed.ncbi.nlm.nih.gov/18972230/).
- Matovina M, Husnjak K, Milutin N, et al. Possible role of bacterial and viral infections in miscarriages. *Fertil Steril*. 2004; 81(3): 662–669, doi: [10.1016/j.fertnstert.2003.08.020](https://doi.org/10.1016/j.fertnstert.2003.08.020), indexed in Pubmed: [15037417](https://pubmed.ncbi.nlm.nih.gov/15037417/).
- You H, Liu Y, Agrawal N, et al. Multiple human papillomavirus types replicate in 3A trophoblasts. *Placenta*. 2008; 29(1): 30–38, doi: [10.1016/j.placenta.2007.08.005](https://doi.org/10.1016/j.placenta.2007.08.005), indexed in Pubmed: [17905430](https://pubmed.ncbi.nlm.nih.gov/17905430/).
- Ambühl LMM, Villadsen AB, Baandrup U, et al. HPV16 E6 and E7 Up-regulate Interferon-Induced Antiviral Response Genes ISG15 and IFIT1 in Human Trophoblast Cells. *Pathogens*. 2017; 6(3), doi: [10.3390/pathogens6030040](https://doi.org/10.3390/pathogens6030040), indexed in Pubmed: [28869524](https://pubmed.ncbi.nlm.nih.gov/28869524/).
- Ruffin MT, Bailey JM, Roulston D, et al. Human papillomavirus in amniotic fluid. *BMC Pregnancy Childbirth*. 2006; 6: 28, doi: [10.1186/1471-2393-6-28](https://doi.org/10.1186/1471-2393-6-28), indexed in Pubmed: [16952308](https://pubmed.ncbi.nlm.nih.gov/16952308/).
- Chisanga C, Eggert D, Mitchell CD, et al. Evidence for Placental HPV Infection in Both HIV Positive and Negative Women. *J Cancer Ther*. 2015; 6(15): 1276–1289, doi: [10.4236/jct.2015.615140](https://doi.org/10.4236/jct.2015.615140), indexed in Pubmed: [26865986](https://pubmed.ncbi.nlm.nih.gov/26865986/).

30. Worda C, Huber A, Hudelist G, et al. Prevalence of cervical and intrauterine human papillomavirus infection in the third trimester in asymptomatic women. *J Soc Gynecol Investig.* 2005; 12(6): 440–444, doi: [10.1016/j.jsjg.2005.03.003](https://doi.org/10.1016/j.jsjg.2005.03.003), indexed in Pubmed: [16140235](https://pubmed.ncbi.nlm.nih.gov/16140235/).
31. 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, doi: [10.1016/j.fertnstert.2010.11.047](https://doi.org/10.1016/j.fertnstert.2010.11.047), indexed in Pubmed: [21167483](https://pubmed.ncbi.nlm.nih.gov/21167483/).
32. Bober L, Guzowski G, Moczulska H, et al. Influence of human Papilloma Virus (hPV) infection on early pregnancy. *Ginekol Pol.* 2019; 90(2): 72–75, doi: [10.5603/GP.2019.0012](https://doi.org/10.5603/GP.2019.0012), indexed in Pubmed: [30860272](https://pubmed.ncbi.nlm.nih.gov/30860272/).
33. Ticconi C, Pietropoli A, Fabbri G, et al. Recurrent miscarriage and cervical human papillomavirus infection. *Am J Reprod Immunol.* 2013; 70(5): 343–346, doi: [10.1111/aji.12156](https://doi.org/10.1111/aji.12156), indexed in Pubmed: [24102829](https://pubmed.ncbi.nlm.nih.gov/24102829/).
34. Skoczyński M, Goździcka-Józefiak A, Kwaśniewska A. Prevalence of human papillomavirus in spontaneously aborted products of conception. *Acta Obstet Gynecol Scand.* 2011; 90(12): 1402–1405, doi: [10.1111/j.1600-0412.2011.01189.x](https://doi.org/10.1111/j.1600-0412.2011.01189.x), indexed in Pubmed: [21585342](https://pubmed.ncbi.nlm.nih.gov/21585342/).
35. Mosbah A, Barakat R, Nabel Y, et al. 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.* 2018; 31(6): 720–725, doi: [10.1080/14767058.2017.1297403](https://doi.org/10.1080/14767058.2017.1297403), indexed in Pubmed: [28264621](https://pubmed.ncbi.nlm.nih.gov/28264621/).
36. Jaworek H, Zborilova B, Koudelakova V, et al. Prevalence of human papillomavirus infection in oocyte donors and women treated for infertility: An observational laboratory-based study. *Eur J Obstet Gynecol Reprod Biol X.* 2019; 4: 100068, doi: [10.1016/j.eurox.2019.100068](https://doi.org/10.1016/j.eurox.2019.100068), indexed in Pubmed: [31517300](https://pubmed.ncbi.nlm.nih.gov/31517300/).
37. Eppel W, Worda C, Frigo P, et al. Human papillomavirus in the cervix and placenta. *Obstet Gynecol.* 2000; 96(3): 337–341, doi: [10.1016/s0029-7844\(00\)00953-4](https://doi.org/10.1016/s0029-7844(00)00953-4), indexed in Pubmed: [10960622](https://pubmed.ncbi.nlm.nih.gov/10960622/).
38. Foresta C, Garolla A, Zuccarello D, et al. Human papillomavirus found in sperm head of young adult males affects the progressive motility. *Fertil Steril.* 2010; 93(3): 802–806, doi: [10.1016/j.fertnstert.2008.10.050](https://doi.org/10.1016/j.fertnstert.2008.10.050), indexed in Pubmed: [19100537](https://pubmed.ncbi.nlm.nih.gov/19100537/).
39. Cao X, Wei R, Zhang X, et al. Impact of human papillomavirus infection in semen on sperm progressive motility in infertile men: a systematic review and meta-analysis. *Reprod Biol Endocrinol.* 2020; 18(1): 38, doi: [10.1186/s12958-020-00604-0](https://doi.org/10.1186/s12958-020-00604-0), indexed in Pubmed: [32381092](https://pubmed.ncbi.nlm.nih.gov/32381092/).
40. 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, doi: [10.1016/j.fertnstert.2010.11.047](https://doi.org/10.1016/j.fertnstert.2010.11.047), indexed in Pubmed: [21167483](https://pubmed.ncbi.nlm.nih.gov/21167483/).
41. Hermonat PL, Han L, Wendel PJ, et al. Human papillomavirus is more prevalent in first trimester spontaneously aborted products of conception compared to elective specimens. *Virus Genes.* 1997; 14(1): 13–17, doi: [10.1023/a:1007975005433](https://doi.org/10.1023/a:1007975005433), indexed in Pubmed: [9208451](https://pubmed.ncbi.nlm.nih.gov/9208451/).
42. Garolla A, De Toni L, Bottacin A, et al. Human Papillomavirus Prophylactic Vaccination improves reproductive outcome in infertile patients with HPV semen infection: a retrospective study. *Sci Rep.* 2018; 8(1): 912, doi: [10.1038/s41598-018-19369-z](https://doi.org/10.1038/s41598-018-19369-z), indexed in Pubmed: [29343824](https://pubmed.ncbi.nlm.nih.gov/29343824/).
43. Garolla A, Lenzi A, Palù G, et al. Human papillomavirus sperm infection and assisted reproduction: a dangerous hazard with a possible safe solution. *Hum Reprod.* 2012; 27(4): 967–973, doi: [10.1093/humrep/des009](https://doi.org/10.1093/humrep/des009), indexed in Pubmed: [22313870](https://pubmed.ncbi.nlm.nih.gov/22313870/).
44. Fenizia C, Vittori C, Oneta M, et al. Human papillomavirus in spermatozoa is efficiently removed by washing: a suitable approach for assisted reproduction. *Reprod Biomed Online.* 2020; 40(5): 693–699, doi: [10.1016/j.rbmo.2020.01.030](https://doi.org/10.1016/j.rbmo.2020.01.030), indexed in Pubmed: [32295745](https://pubmed.ncbi.nlm.nih.gov/32295745/).
45. Zacharis K, Messini CI, Anifandis G, et al. Human Papilloma Virus (HPV) and Fertilization: A Mini Review. *Medicina (Kaunas).* 2018; 54(4), doi: [10.3390/medicina54040050](https://doi.org/10.3390/medicina54040050), indexed in Pubmed: [30344281](https://pubmed.ncbi.nlm.nih.gov/30344281/).
46. Foresta C, Patassini C, Bertoldo A, et al. Mechanism of human papillomavirus binding to human spermatozoa and fertilizing ability of infected spermatozoa. *PLoS One.* 2011; 6(3): e15036, doi: [10.1371/journal.pone.0015036](https://doi.org/10.1371/journal.pone.0015036), indexed in Pubmed: [21408100](https://pubmed.ncbi.nlm.nih.gov/21408100/).
47. Medley N, Vogel JP, Care A, et al. Interventions during pregnancy to prevent preterm birth: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev.* 2018; 11: CD012505, doi: [10.1002/14651858.CD012505.pub2](https://doi.org/10.1002/14651858.CD012505.pub2), indexed in Pubmed: [30480756](https://pubmed.ncbi.nlm.nih.gov/30480756/).
48. Jiang NN, Zhong LJ. Analysis of high risk factors of very early preterm birth and early preterm birth in pregnant women. *Maternal and Child Health Care of China.* 2021; 36(04): 792–795.
49. Koi H, Zhang J, Parry S. The mechanisms of placental viral infection. *Ann N Y Acad Sci.* 2001; 943: 148–156, doi: [10.1111/j.1749-6632.2001.tb03798.x](https://doi.org/10.1111/j.1749-6632.2001.tb03798.x), indexed in Pubmed: [11594535](https://pubmed.ncbi.nlm.nih.gov/11594535/).
50. Arechavaleta-Velasco F, Koi H, Strauss J, et al. Viral infection of the trophoblast: time to take a serious look at its role in abnormal implantation and placentalation? *Journal of Reproductive Immunology.* 2002; 55(1–2): 113–121, doi: [10.1016/s0165-0378\(01\)00143-7](https://doi.org/10.1016/s0165-0378(01)00143-7).
51. Andrews WW, Goldenberg RL, Hauth JC. Preterm labor: emerging role of genital tract infections. *Infect Agents Dis.* 1995; 4(4): 196–211, indexed in Pubmed: [8665085](https://pubmed.ncbi.nlm.nih.gov/8665085/).
52. Zuo Z, Goel S, Carter JE. Association of cervical cytology and HPV DNA status during pregnancy with placental abnormalities and preterm birth. *Am J Clin Pathol.* 2011; 136(2): 260–265, doi: [10.1309/AJCP93J-MIUEKRPIW](https://doi.org/10.1309/AJCP93J-MIUEKRPIW), indexed in Pubmed: [21757599](https://pubmed.ncbi.nlm.nih.gov/21757599/).
53. Cho G, Min KJ, Hong HR, et al. High-risk human papillomavirus infection is associated with premature rupture of membranes. *BMC Pregnancy Childbirth.* 2013; 13: 173, doi: [10.1186/1471-2393-13-173](https://doi.org/10.1186/1471-2393-13-173), indexed in Pubmed: [24011340](https://pubmed.ncbi.nlm.nih.gov/24011340/).
54. Gomez LM, Ma Y, Ho C, et al. Placental infection with human papillomavirus is associated with spontaneous preterm delivery. *Hum Reprod.* 2008; 23(3): 709–715, doi: [10.1093/humrep/dem404](https://doi.org/10.1093/humrep/dem404), indexed in Pubmed: [18184644](https://pubmed.ncbi.nlm.nih.gov/18184644/).
55. Zuo Z, Goel S, Carter JE. Association of cervical cytology and HPV DNA status during pregnancy with placental abnormalities and preterm birth. *Am J Clin Pathol.* 2011; 136(2): 260–265, doi: [10.1309/AJCP93J-MIUEKRPIW](https://doi.org/10.1309/AJCP93J-MIUEKRPIW), indexed in Pubmed: [21757599](https://pubmed.ncbi.nlm.nih.gov/21757599/).