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Human Papillomavirus In Pregnancy

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Abstract

Infections by the human papillomavirus (HPV) have currently increased, becoming a common infection with a significant rise in the population, with pregnant women being the most affected group, posing risks to both the mother and the newborn. HPV during pregnancy can lead to a variety of complications, ranging from mild to severe, representing a risk for both the mother and the fetus. These complications in the mother are attributed to the numerous physiological changes experienced during pregnancy, which can favor the development of pathological alterations. The present research aimed to analyze and synthesize the available scientific evidence to understand how HPV infection can affect pregnancy. The methodology involved a systematic review, where scientific articles from reliable databases were selected. The results revealed that during pregnancy, especially in the first two trimesters, there is a decrease in immunity or immunosuppression, which can increase susceptibility to HPV infection or viral replication. There is a possibility of vertical transmission of HPV from mother to newborn during childbirth, resulting in the appearance of anogenital and laryngeal lesions in the newborn. In conclusion, the accurate diagnosis of HPV infection during pregnancy is essential to manage complications adequately and apply safe treatments, considering the limitation of certain therapeutic approaches during gestation.

Keywords: *HPV, Pregnancy, Cervical Cancer, HPV Infection, Genital Warts, Anogenital Lesions.*

Introduction

Human papillomavirus (HPV) is a common viral infection that affects a large percentage of the world's population, although most HPV infections are transient and asymptomatic, certain subtypes of HPV have been associated with an increased risk of develo[1]ping cervical cancer and other gynecological complications (1). Among vulnerable populations, pregnant women represent a particular interest group, as HPV infection during pregnancy raises important questions about the potential effects on the mother and fetus (2).

HPV infection is caused by a virus that is usually transmitted through direct contact, either through the skin or mucous membranes, BPH virus infection is the most common sexually transmitted infection and places young women at high risk (3). Although the vast majority of cases disappear spontaneously within 1 to 2 years, persistent HPV infection remains a

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serious concern, as it has been repeatedly linked to the development of multiple malignancies, including cervical, anogenital, and oropharyngeal cancers. In addition, more recent data suggest a detrimental effect of HPV infection on pregnancy, as the hormonal environment and the mother's immune system undergo significant changes during pregnancy, HPV persistence is favored (4).

The period of onset of symptoms from when a person becomes infected with HPV can range from three months to years, turning on and off as time passes (5). On the other hand, the fact that a person does not have clinical manifestations on their genitals does not mean that they are not a carrier of the virus, since people who present with condylomas or genital or anogenital warts show a variety of non-specific symptoms, many are asymptomatic, but are concerned about perianal growths (6). Pruritus is a common complaint, and there may be pain and bleeding in larger lesions, which can become noticeably foul-smelling (5,6).

Among the most notable clinical manifestations are condyloma acuminata, also known as genital or anogenital warts. These benign lesions, usually multiple, have colors ranging from pink to grayish-white, with thread-like or papillomatous projections on their surface (7). They are usually exophytic lesions, either sessile or pedunculated, although in some cases they can be flat. Its main location is the anogenital region, especially in areas more prone to trauma during sexual intercourse. They can also occur in the pubis, inguinal, perineal, perianal areas, anal canal, urethral meatus, vagina, cervix, and oral cavity (8).

There are other expressions of HPV that are not related to the genital region and that are not acquired through sexual contact, these are cutaneous warts, which include vulgar, plantar and flat warts, these are benign, delimited and small epithelial lesions, which can appear anywhere on the surface of the skin, although they are usually more frequent on the hands, soles of the feet, as well as on the face and neck (7,8). Another less common manifestation of HPV infection, which is not linked to sexual contact, is recurrent respiratory papillomatosis, which is a more frequent condition in young children, characterized by the presence of exophytic lesions in the trachea and respiratory tract, which can cause alterations in crying and stridor (9).

According to Mendoza, et al, (10), the Human Papillomavirus (HPV) is the most prevalent sexually transmitted infection globally, affecting more than 290 million women, with a significant proportion of asymptomatic cases (10%-17%). This high prevalence and the association of HPV with potential risks, such as the development of cervical cancer, highlight the need to explore in detail the relationship between HPV infection and pregnancy. It is essential to understand how this infection, particularly common in women of reproductive age, might influence the course of pregnancy and its potential consequences for the mother and fetus (7).

Detailed examination of HPV in pregnant women is essential, as it involves potentially significant health consequences for both the mother and the fetus (8,9). Since hormonal and immune system changes during pregnancy could influence the persistence and development of HPV infection, the following research question arises: What is the impact of human papillomavirus infection on pregnant women? With the aim of analyzing and synthesizing the available scientific evidence, the focus of this research will be to understand how HPV infection can affect pregnancy. This analysis will include crucial considerations, such as the persistence of HPV, hormonal changes characteristic of gestation, and potential complications for both mother and fetus. This research not only seeks to fill a knowledge gap about the interaction between HPV and pregnancy, but also to provide a solid foundation for the development of targeted care and prevention strategies, thereby improving the health and well-being of pregnant women facing this infection.

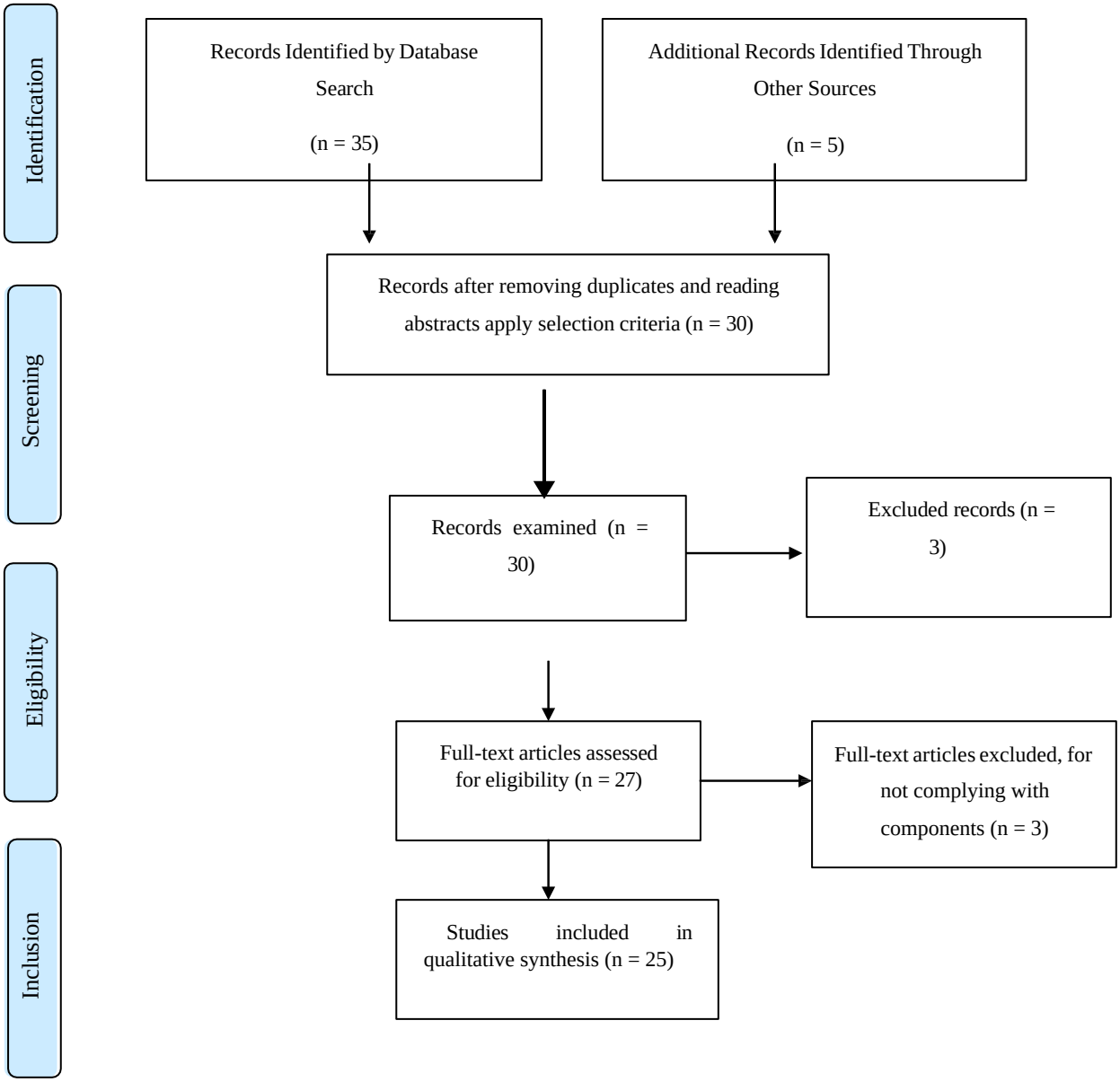
Methods

The research involves a systematic review, where a search was conducted in several recognized databases, including PUBMED, REDALYC, SCIELO, SCOPUS and TAYLOR AND FRANCIS. The search was carried out using the following keywords such as; "Human Papillomavirus", "HPV Infection", "Pregnancy", "Cervical Cancer", "Genital Warts" and "Pregnant Women". Articles published in the range of years from 2019 to 2023 were included, with the aim of ensuring the incorporation of the most recent evidence, likewise, articles published in Spanish and English will be considered. On the other hand, studies with no direct relevance and data related to HPV infection in pregnant women were excluded.

Results

Illustration 1

Article Selection Flowchart



Discussion

When talking about the genetic makeup of HPV, the genome is organized into two classes of genes; early and late. Early genes, such as E1, E2, and E4, code for proteins that regulate viral expression. In contrast, genes E5, E6, and E7 code for oncoproteins, playing a crucial role in host cell transformation. Finally, the late genes, L1 and L2, code for capsid structural proteins, contributing to the formation of the viral envelope (11,12). The genetic structure and makeup of HPV are critical to understanding its ability to infect epithelial cells and its association with various disorders, including cervical cancer risk (12).

Some authors explain that HPV presents as a small virus without an envelope, which belongs to the DNA type. Its circular genome is composed of approximately 7500 to 8000 base pairs. Interestingly, HPV lacks genes that encode a viral DNA polymerase or other enzymes that would normally control the synthesis of its own DNA. Instead, HPV tends to rely on the host cell's genetic machinery to replicate (3,4,12).

The HPV capsid has an icosahedral shape with a diameter ranging between 50 and 60 nm, which is made up of two structural proteins, L1 and L2, which are organized into 72 capsomers, this protein structure is essential for the protection of the genetic material of the virus (12). In terms of its genetic material, HPV DNA encodes eight early-expression proteins or genes, i.e., E1 to E8, which play a crucial role in regulating viral expression, and two late-expression proteins (L1 and L2), which are responsible for capsid formation (13).

Human papillomavirus (HPV) infection undergoes a transition into a dormant state by activating specific genes such as E1, E2, E6, and E7. This activation allows the virus to maintain its genome and trigger cell proliferation. In this phase, infected cells differentiate and migrate from the basal layer to the epithelial stratum spinosum, stimulating viral genome replication. The collaboration of the E4 protein, in conjunction with other genes, leads to the production of virions within the cell nucleus. This process evolves towards a phase of active replication without manifesting a lytic phase, taking advantage of the particular characteristics of the cell for its propagation. The release of new virions occurs when cells in the stratum corneum break off, leading to uncontrolled cell proliferation. Crucially, this cycle depends on interaction with the host cell, the immune system, and certain risk factors (10,12,14)

Of all known HPV types, about 35 have been identified in both benign and malignant lesions in the anogenital region in women. Among these genotypes, it is worth noting that 15 of them are directly linked to the development of cervical cancer, especially those considered to have a high oncogenic index when they show their ability to contribute to cell proliferation and when certain cofactors converge. This collaboration between high-risk genotypes and cofactors is associated with the development of intraepithelial neoplasms and, ultimately, invasive cervical cancer (14,15).

Serotypes 16 and 18 are classified as oncogenic or high-risk due to their association with cervical dysplasia. The presence of these genotypes has been observed in approximately 70% of squamous cell carcinomas of the cervix. In addition to their involvement in cervical cancer, these serotypes are responsible for recurrent laryngeal papillomatosis, conjunctival lesions and are associated with about 90% of genital warts (15). On the other hand, the types of HPV called alpha produce clinically visible lesions on the mucous membranes and skin, while the HPVs called beta and gamma are the main responsible for persistent subclinical skin lesions secondary to infections acquired in early childhood, which tend to occur very frequently, because the child's immune system is still immature and it is easier for the virus to be contracted in areas such as the soles of the feet, face or hands, giving rise to papillomas(16).

Endocervical curettage (LEC) is a procedure performed to obtain a more complete sample of cells from the cervix, which may indicate that changes in cervical cells that could be

caused by HPV infection are being investigated. Cervical Intraepithelial Neoplasia (CIN), which is a term used to describe abnormal cell changes in the cervix, is also seen. Persistent HPV infection is one of the main risk factors for the development of CIN lesions, as certain types of HPV can lead to changes in cervical cells that, over time, can progress to precancerous lesions. On the other hand, cancer in situ (CIS) involves the presence of cancer cells in their original place, without invading surrounding tissues (17,18).

To obtain an accurate diagnosis, inspection and palpation are important components, the clinical diagnosis is primarily based on the performance of the Pap smear, which consists of performing a Pap smear to extract a cell sample from the cervix(5)The diagnosis of infection caused by the papillomavirus in general is usually simple, Because they are lesions that are easy to recognize, for example, a wart on the sole of the foot with a hard layer, and black dots, which are capillaries that have coagulated, color changes, the presence of masses, painful induration or ulceration should be noted(7,8). High-resolution anoscopy (HRA) is used by many centers around the world as an adjunct to digital rectal inspection and examination. Sometimes the diagnosis is a little more complicated and is usually not so simple, which is why a skin biopsy or microbiological diagnostic tests are performed (12).

HPV infection is highly associated with non-sexual routes of transmission and transmission, detecting HPV DNA in the placenta, ovaries, and endometrium, revealing that HPV could be transmitted at the time of fertilization of the egg (7). Both placental and chorionic tissue can be affected hematogenously, and therefore HPV can initially affect amniotic cells, followed by the fetus. Therefore, HPV can be transmitted by intrauterine transmission and the possible route is through the maternal genital tract and HPV DNA has been reported to be found in the umbilical cord and amniotic fluid.

Likewise, HPV has been detected in oral scrapings, the percentage has been more than 50% of the children positive, resulting in infected with the same type of HPV detected in the genital region of the mother at the time of delivery (8). Therefore, HPV can be transmitted from the mother's genital region to the child's oral cavity during childbirth (6). Due to the fact that a large number of patients are unaware of the existence of this virus and the complications that its contagion entails, it is very important that patients undergo the Pap smear, colposcopy and PCR for HPV, even before a pregnancy, so that it can be known whether or not they are carriers of the virus. as well as what specific type of HPV virus is found in your body and in this way, avoid further complications, since from the beginning of pregnancy, the fetus is in contact with the virus through the placenta, the umbilical cord and the amniotic fluid(9,10).

During pregnancy, especially in the first two trimesters, a decrease in immunity or immunosuppression is observed, attributable to the fertilization process, this phenomenon leads to immunological and anatomical changes in the uterine canal as part of physiological adaptation, gradually increasing susceptibility to HPV infection or viral replication (11). It is important to note that most women overcome this process, and transient changes in immunity tend to be corrected. However, about 20% of patients may continue to develop condylomas, which implies a risk of transmitting the virus to the neonate (3,4,5).

This type of transmission is characterized by HPV-induced lesions, which encompass anogenital and laryngeal areas. Several authors state that intrauterine transmission of HPV has been suspected, leading to laryngeal or oral papillomatosis, and the presence of vulvovaginal secretions in HPV-positive mothers is related to vertical transmission of the virus at the time of delivery (8,9,10). It is crucial to note that the likelihood of infection transmitted from mother to child depends largely on the viral genotypes present in the mother. Although HPV serotypes 6 and 11, which are considered to be low risk, do not usually cause serious lesions or significant clinical significance, the condylomas associated with these serotypes are highly contagious. Therefore, there is an increased risk of the

newborn contracting laryngeal papillomatosis during delivery due to direct contact with the affected genital areas (12,13).

Gupta, et al (18), conducted a systematic review of the literature that demonstrated a wide variation in the prevalence of HPV in pregnant women, which can be attributed to changes in the hormonal environment and decreased immunity. In addition, in several populations, several types of HPV have been found to be associated with premature rupture of membranes, preeclampsia, fetal growth restriction, preterm birth, and placental abnormalities (9). During pregnancy, the change in the hormonal environment and the immune response may favor the presence and persistence of HPV infection (8,9).

It should be noted that young women have a maximum risk of HPV infection, since in the age group between 25 and 35 years women are more sexually active and although most of them are asymptomatic and the viruses disappear spontaneously due to a strong immune system, it is very common that during pregnancy immunosuppression occurs, reactivating the virus and lesions (18,19). Therefore, it is associated as an important risk factor that the mother has a history of active lesions at the time of birth, as well as the premature rupture of membranes that exceeds four hours of evolution before birth, these two factors have been associated with the fact that newborns can trigger this virus with greater risk (20).

HPV infection during pregnancy can trigger complications, including miscarriage, preterm birth, premature rupture of membranes, preeclampsia, and restriction of fetal growth and intrauterine development (11). In recent years, pregnancy outcomes resulting from HPV infection have raised much concern (20). Factors that induce preterm labor include lower genital duct and urinary tract infections, intrauterine infections, uterine hyperdilation, uterine malformations, placental and internal organ factors, diarrhea, and other pregnancy complications.

HPV infection is a major factor in the occurrence of preterm birth and can lead to intrauterine infection. When a pregnant woman becomes infected with HPV, the vaginal environment becomes more susceptible to bacterial diseases. Therefore, infection by pathogenic microorganisms in the reproductive tract is associated with premature rupture of uterine membranes. (17,18,19). Some scholars found that HPV infection has a major impact on pregnancy outcomes, such as immature delivery, rupture of immature membranes, postpartum hemorrhage, puerperal infection, and fetal growth restriction (20,21).

It is important to note that, during pregnancy, the virus remains active, and many of the pregnant patients are unaware of this fact. Generally, lesions occur in the genital, bulbar and perianal areas, which are activated during pregnancy because the body's defenses are weakened, affecting the immune system (15,16). This maternal pathology affects the fetus and neonate, since, as mentioned above, during pregnancy there is a diminished immunity, causing the reactivation of the virus and lesions.

In this regard, Bober, et al (21), estimated that the probability of contracting HPV infection during pregnancy is twice as high, including both activations of viruses that previously remained in the latent phase and new primary infections (10). Of the known HPV types, HPV types 16, 18, 31, 33 and 35 are most frequently activated and HPV infection in early pregnancy may be a cause for miscarriage as HPV has been shown to effectively attack syncytiotrophoblast cells which play a critical role in human reproductive biology. This is what they mention (17:19). The route of infection could be vertical ascending, i.e., transmitted transparently, through the vagina, when the neonate passes through the birth canal, or after birth, however, the possibility of a descending hematogenous infection through the blood should also be considered (21).

Pooled data analysis in this study revealed that pregnant women with high-risk human papillomavirus (HPV) infection had a higher incidence of premature rupture of membranes compared to those in the negative control group (1,2). Similarly, it was observed that

women with high-risk HPV infection were more likely to experience premature rupture of membranes compared to the negative group, and this difference between the two groups was statistically significant (7,8). Consequently, the impact of HPV on pregnant women implies a greater propensity to suffer premature rupture of membranes during pregnancy.

A review of the literature shows that there is a relationship between infections, changes in the vaginal microbiota during pregnancy and the human papillomavirus (HPV), which is why some authors highlight the attention that is being paid to these factors as possible triggers of adverse pregnancy outcomes (21). The vaginal microbiota, being a key component of the uterine environment, emerges as a factor of interest in the investigation of pregnancy complications (22). In addition, in vitro experiments suggest that HPV may complete its replication cycle in trophoblasts, which could contribute to inhibition of blastocyst formation, failure of endometrial implantation, and apoptosis of embryonic cells (23).

Several studies have explored the possible association between human papillomavirus (HPV) infection and preeclampsia, generating conflicting results. A case-control study conducted by (2) included 108 subjects, and found that the prevalence of HPV DNA in placental samples from preeclampsia cases was comparable to that of the control group. However, the studies (7,8) found no association between HPV DNA and preeclampsia in their cohorts. It is important to note that the increase in steroid hormones during pregnancy may have an impact on the alteration of the immune system, contributing to increased susceptibility to infections, including that caused by HPV (22).

Through the literature of this research, it was also evidenced that the screening of cervical intraepithelial lesions during pregnancy, using cytology, can be more complicated due to the physiological changes typical of this period (23). The detection of abnormal cytologies during pregnancy poses diverse scenarios, where it is estimated that a significant proportion will experience regression, possibly influenced by cervical trauma during childbirth or temporary changes in the cervical epithelium (22,23). In the context of HPV infection, these physiological changes and the possible presence of abnormal cytologies could have specific implications. On the one hand, spontaneous regression of lesions could be more frequent, possibly due to the repair mechanisms and inflammatory response associated with pregnancy. However, the persistence of lesions is also a real-world scenario, which could be especially relevant if the lesions are caused by high-risk HPV types.

Treating HPV during pregnancy presents specific challenges due to the need to ensure the safety of the fetus. In cases where the infection does not cause significant cervical lesions, physicians may opt for a closer observation and monitoring approach during pregnancy, evaluating any changes in cervical lesions(1,3). If more serious injuries requiring treatment are detected, the intervention may be postponed until after delivery to avoid possible complications during pregnancy, as certain procedures, such as conization or laser surgery, could increase the risk of problems during pregnancy(6).

Recommended treatment approaches for pregnant women with human papillomavirus (HPV) infection include less invasive options due to concerns about fetal safety. Cryotherapy and combination therapy, laser treatment, local resection, and topical use of trichloroacetic acid or bichloroacetic acid are some of the preferred alternatives (20,21,22) However, certain treatments, such as imiquimod, fluorouracil, and podophyllin, are contraindicated during pregnancy due to their potential adverse effects on the fetus, such as neurotoxicity, myelotoxicity and malformations (24,25). On the other hand, interventions, such as cryotherapy, have been shown to be effective, with studies supporting their high efficacy of 92.9% (22,24). However, it is noted that more invasive procedures, such as conization or therapeutic resection, are associated with a significant risk of preterm birth, underscoring the importance of careful and personalized management during pregnancy (25).

Conclusions

In conclusion, human papillomavirus (HPV) presents itself as a significant challenge during pregnancy, especially due to the waning immunity seen in the first trimesters. HPV infection can trigger obstetric complications, including miscarriages, preterm births, premature rupture of membranes, preeclampsia, and fetal growth restriction. Although most women manage to overcome transient changes in immunity, about 20% may experience the persistence of condylomas, increasing the risk of transmission to the neonate.

Prenatal care should ensure the quality of life of the mother and child, considering the transmission and treatment of the virus. Treatments during pregnancy, such as cryotherapy and laser, should be carefully selected, avoiding those that may have adverse effects on the fetus. HPV infection during pregnancy is a relevant issue that requires specialized care to mitigate its potential impacts on maternal-fetal health.

Detailed understanding of the relationship between waned immunity during pregnancy, changes in the vaginal microbiota, and HPV persistence offers valuable information for healthcare professionals, enabling them to make informed decisions about the management and treatment of infected pregnant women. In addition, the identification of potential triggers and risk factors contributes to prevention and the design of more effective antenatal care strategies.

Given the prevalence of HPV and its potential impact on maternal-fetal health, this article highlighted the need for more focused care during pregnancy, underscoring the importance of early detection, appropriate treatment, and consideration of preventive measures. Ultimately, this work seeks to raise awareness of the complexity of HPV infection in the context of pregnancy, promoting a comprehensive and proactive approach to improving health outcomes for both mothers and newborns. Providing a comprehensive review of the literature, the clinical and obstetric relevance of this infection is highlighted, evidencing its association with a variety of adverse outcomes, from miscarriages to complications in delivery and fetal development.

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