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Review Article

Genotype-Specific High-Risk HPV Infection and Its Association with Cervical Lesions and Pregnancy Complications: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: High-risk human papillomavirus (HR-HPV) infection is the principal etiological factor in cervical carcinogenesis and remains a major public health concern worldwide. While HPV-16 and HPV-18 are recognized as the most oncogenic genotypes, increasing evidence suggests that genotype-specific HR-HPV infections may also influence reproductive health and contribute to adverse pregnancy complications. However, the overall relationship between individual HR-HPV genotypes, cervical lesion progression, and pregnancy outcomes remains incompletely understood.

Objective: To systematically evaluate the association between genotype-specific high-risk HPV infection, cervical cytological and histopathological lesions, and pregnancy complications among reproductive-age women.

Methods: A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. Electronic databases including PubMed, Embase, Scopus, Web of Science, and the Cochrane Library were searched for relevant studies published between January 2000 and December 2025. Observational studies reporting genotype-specific HR-HPV infection and cervical lesion or pregnancy complication outcomes were included. Data extraction and quality assessment were performed independently using predefined criteria and the Newcastle–Ottawa Scale. Quantitative synthesis was conducted using a random-effects model to estimate pooled prevalence and effect sizes.

Results: A total of 26 studies involving 28,936 reproductive-age women met the inclusion criteria, of which 22 studies were eligible for meta-analysis. HPV-16 was the most prevalent HR-HPV genotype (29.1%), followed by HPV-18 (13.4%), HPV-52 (9.8%), and HPV-58 (8.2%). The prevalence of HPV-16 increased progressively with worsening cervical disease severity, accounting for 47.3% of high-grade squamous intraepithelial lesions and 62.1% of invasive cervical cancers. Women infected with HPV-16 demonstrated significantly higher risks of CIN2+ and CIN3+ lesions compared with women infected with other HR-HPV genotypes. HPV-18 was also significantly associated with high-grade cervical lesions. Furthermore, HR-HPV infection was associated with increased risks of spontaneous abortion (OR = 1.69; 95% CI: 1.22–2.34), preterm birth (OR = 1.55; 95% CI: 1.13–2.11), premature rupture of membranes (OR = 1.58; 95% CI: 1.16–2.16), low birth weight (OR = 1.28; 95% CI: 1.01–1.63), and infertility (OR = 1.42; 95% CI: 1.04–1.95).

Conclusion: Genotype-specific HR-HPV infection, particularly HPV-16 and HPV-18, is strongly associated with cervical lesion progression and adverse pregnancy complications among reproductive-age women. These findings support the implementation of genotype-based HPV screening strategies, expanded vaccine coverage, and enhanced surveillance of women with persistent HR-HPV infection to reduce the burden of cervical cancer and improve

reproductive health outcomes.

Keywords: Human papillomavirus; HPV-16; HPV-18; Genotype-specific infection; Cervical lesions; Cervical intraepithelial neoplasia; Pregnancy complications; Reproductive health; Systematic review; Meta-analysis.

INTRODUCTION

Human papillomavirus (HPV) is the most common sexually transmitted viral infection worldwide and represents one of the most significant public health challenges affecting women's reproductive health. Persistent infection with oncogenic or high-risk HPV (HR-HPV) genotypes is recognized as the necessary cause of virtually all cases of cervical cancer and a substantial proportion of anogenital and oropharyngeal malignancies [1,2]. According to recent global estimates, cervical cancer remains the fourth most common cancer among women, accounting for more than 660,000 new cases and over 350,000 deaths annually, with the highest burden occurring in low- and middle-income countries [3].

More than 200 HPV genotypes have been identified, of which approximately 14 are classified as high-risk owing to their carcinogenic potential [4]. Among these, HPV-16 and HPV-18 are the most oncogenic and are responsible for nearly 70% of cervical cancer cases worldwide [2,5]. Other high-risk genotypes, including HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58, also contribute substantially to cervical disease burden and exhibit considerable geographic variation in prevalence [6]. The pathogenicity of HR-HPV infection is largely mediated through the viral oncoproteins E6 and E7, which promote degradation of the tumor suppressor proteins p53 and retinoblastoma (Rb), resulting in genomic instability, uncontrolled cellular proliferation, and malignant transformation [7].

Cervical carcinogenesis is a multistep process that progresses from transient HPV infection to persistent infection, cervical intraepithelial neoplasia (CIN), and eventually invasive cervical cancer [8]. Most HPV infections are transient and are cleared by the host immune system within one to two years. However, persistent infection with specific HR-HPV genotypes significantly increases the risk of developing high-grade squamous intraepithelial lesions (HSIL), CIN grade 2 or worse (CIN2+), CIN grade 3 or worse (CIN3+), and invasive carcinoma [9]. Numerous studies have demonstrated that HPV-16 confers the highest risk of progression to CIN3+, followed by HPV-18 and several other oncogenic genotypes [10,11].

Cervical cytology and histopathological evaluation remain fundamental components of cervical cancer screening and diagnosis. Cytological abnormalities, including atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesions (LSIL), and high-grade squamous intraepithelial lesions (HSIL), are frequently associated with HR-HPV infection and serve as important indicators of disease progression [12]. Histopathological examination further categorizes cervical lesions into CIN1, CIN2, CIN3, and invasive carcinoma, providing definitive evidence of disease severity and guiding clinical management [13]. Increasing evidence suggests that genotype-specific HPV testing may improve risk stratification beyond conventional cytology alone by identifying women at highest risk for progression to high-grade lesions and cancer [14].

In addition to its established role in cervical carcinogenesis, HR-HPV infection has emerged as a potential contributor to adverse reproductive and obstetric outcomes. HPV DNA has been detected in placental tissue, trophoblasts, fetal membranes, amniotic fluid, and spermatozoa, suggesting that viral infection may influence implantation, placentation, and fetal development [15,16]. Several observational studies have reported associations between maternal HPV infection and spontaneous abortion, recurrent pregnancy loss, infertility, preterm birth, premature rupture of membranes, and low birth weight [17–19]. Experimental evidence indicates that HPV infection may impair trophoblastic function, induce apoptosis, and disrupt maternal–fetal immune interactions, thereby contributing to pregnancy complications [20].

Despite growing interest in the reproductive consequences of HPV infection, existing evidence remains inconsistent. While some studies have reported significant associations between HR-HPV infection and adverse pregnancy outcomes, others have failed to demonstrate such relationships [21,22]. Furthermore, the extent to which individual HR-HPV genotypes contribute to pregnancy complications remains poorly understood. Most previous reviews have focused either on cervical neoplasia or reproductive outcomes separately, and few have comprehensively examined genotype-specific associations across both domains.

A better understanding of genotype-specific HPV risks is particularly important in the era of HPV vaccination and molecular screening. Current prophylactic vaccines provide protection against the most common oncogenic genotypes; however, the relative contribution of non-vaccine genotypes to cervical disease and reproductive complications continues to evolve [23]. Identification of genotype-specific risks may facilitate personalized screening strategies, improve clinical risk assessment, and inform future vaccination policies.

Therefore, the present systematic review and meta-analysis aimed to comprehensively evaluate the association between genotype-specific HR-HPV infection and cervical lesions, including cytological abnormalities and histopathological disease progression, as well as adverse pregnancy complications among reproductive-age women. By synthesizing

available evidence from observational studies worldwide, this review seeks to provide a comprehensive assessment of the clinical and reproductive implications of individual high-risk HPV genotypes.

Aim

To systematically evaluate genotype-specific associations between high-risk HPV infection and:

1. Cervical cytological abnormalities.
2. Histopathological cervical lesions, including CIN2+, CIN3+, and invasive cervical cancer.
3. Adverse pregnancy complications, including spontaneous abortion, preterm birth, premature rupture of membranes, low birth weight, and infertility.

Research Question

Do specific high-risk HPV genotypes confer differential risks for cervical lesion progression and adverse pregnancy complications among reproductive-age women?

METHODOLOGY

Study Design and Protocol

This systematic review and meta-analysis was conducted to evaluate the association between genotype-specific high-risk human papillomavirus (HR-HPV) infection, cervical lesions, and pregnancy complications among reproductive-age women. The study was designed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The methodological framework was established prior to data extraction to ensure transparency, reproducibility, and minimization of selection bias.

Research Question and Eligibility Framework

The research question was formulated using the PICO framework:

Population (P): Reproductive-age women (15–49 years)

Exposure (I): Infection with genotype-specific high-risk HPV (HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, HPV-58, and other HR-HPV types)

Comparison (C): HPV-negative women or women infected with other HPV genotypes

Outcomes (O):

- Cervical cytological abnormalities (ASC-US, LSIL, HSIL)
- Histopathological lesions (CIN1, CIN2, CIN3, CIN2+, CIN3+, invasive cervical cancer)
- Pregnancy complications (spontaneous abortion, recurrent pregnancy loss, preterm birth, premature rupture of membranes, low birth weight, infertility)

Literature Search Strategy

A comprehensive electronic search was performed using the following databases:

- PubMed/MEDLINE
- Embase
- Scopus
- Web of Science
- Cochrane Library

Studies published between January 2000 and December 2025 were considered eligible. Additional records were identified through manual screening of references cited in relevant reviews and included articles.

The search strategy combined Medical Subject Headings (MeSH) and free-text keywords:

("Human Papillomavirus" OR HPV OR "High-Risk HPV" OR HPV16 OR HPV18 OR HPV31 OR HPV33 OR HPV45 OR HPV52 OR HPV58)
AND
("Cervical Cytology" OR "Pap Smear" OR ASC-US OR LSIL OR HSIL)
AND
("Cervical Intraepithelial Neoplasia" OR CIN OR CIN2 OR CIN3 OR "Cervical Cancer" OR Histopathology)
AND
("Pregnancy Complications" OR "Spontaneous Abortion" OR Miscarriage OR "Preterm Birth" OR "Premature Rupture of Membranes" OR Infertility OR "Low Birth Weight")

Only articles published in English were included.

Study Selection
All retrieved records were exported into reference management software, and duplicate studies were removed. Two independent reviewers screened titles and abstracts to identify potentially eligible studies. Full-text articles meeting the inclusion criteria were subsequently reviewed in detail.
Disagreements regarding study eligibility were resolved through discussion and consensus. When consensus could not be reached, a third reviewer adjudicated the final decision.
The study selection process was documented using a PRISMA flow diagram.

Inclusion Criteria
Studies were included if they fulfilled all of the following criteria:
1. Observational study design (cross-sectional, cohort, case-control, or prospective studies).
2. Included reproductive-age women.
3. Reported genotype-specific HR-HPV infection data.
4. Evaluated cervical cytological abnormalities and/or histopathological outcomes.
5. Reported pregnancy complications associated with HPV infection.
6. Provided sufficient quantitative data for effect size calculation.
7. Published in peer-reviewed journals.

Exclusion Criteria
Studies were excluded if they:
1. Were review articles, editorials, letters, conference abstracts, or case reports.
2. Included animal or in vitro experimental studies.
3. Did not provide genotype-specific HPV results.
4. Lacked extractable outcome data.
5. Included duplicate patient populations.
6. Were published in languages other than English.

Data Extraction
Data extraction was performed independently by two investigators using a standardized extraction form.
The following variables were collected:
- First author
- Year of publication
- Country
- Study design
- Sample size
- Mean or median participant age
- HPV detection method
- HPV genotype distribution
- Cytological findings
- Histopathological findings
- Pregnancy complications
- Effect estimates (ORs, RRs, HRs)
- Follow-up duration

Any discrepancies were resolved by consensus review.

Quality Assessment
Methodological quality was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies.
The NOS evaluates studies across three domains:

Selection (Maximum 4 Stars)
- Representativeness of the study population
- Selection of controls
- Exposure ascertainment

Comparability (Maximum 2 Stars)
- Adjustment for confounding factors

Outcome/Exposure Assessment (Maximum 3 Stars)
- Outcome assessment
- Adequacy of follow-up

Studies were categorized as:

- High quality: 7–9 stars
- Moderate quality: 5–6 stars
- Low quality: <5 stars

Quality assessment was independently performed by two reviewers.

Outcomes Assessed

Primary Outcomes

1. Prevalence of genotype-specific HR-HPV infection.
2. Association between HR-HPV genotypes and abnormal cervical cytology.
3. Association between HR-HPV genotypes and CIN2+, CIN3+, and invasive cervical cancer.

Secondary Outcomes

1. Spontaneous abortion.
2. Recurrent pregnancy loss.
3. Preterm birth.
4. Premature rupture of membranes.
5. Low birth weight.
6. Infertility.

Statistical Analysis

Statistical analyses were conducted using Review Manager (RevMan) version 5.4 and R software version 4.4.1.
For prevalence analyses, pooled prevalence estimates and corresponding 95% confidence intervals (CIs) were calculated using a random-effects model.

For dichotomous outcomes, pooled odds ratios (ORs) with 95% confidence intervals were generated using the DerSimonian–Laird random-effects method due to expected clinical and methodological heterogeneity among studies.
Heterogeneity was assessed using Cochran's Q test and quantified by the I^2 statistic:

- I^2 <25%: Low heterogeneity
- I^2 = 25–50%: Moderate heterogeneity
- I^2 >50%: Substantial heterogeneity

Subgroup analyses were performed according to:

- HPV genotype
- Geographic region
- Cytological category
- Histopathological severity
- Type of pregnancy complication

Sensitivity analyses were conducted by excluding studies with low methodological quality.
Publication bias was assessed using funnel plots and Egger's regression test when at least ten studies were available for pooled analysis.
A two-tailed p-value <0.05 was considered statistically significant.

Certainty of Evidence

The certainty of evidence for major outcomes was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Evidence was categorized as high, moderate, low, or very low quality based on study limitations, inconsistency, indirectness, imprecision, and publication bias.

Ethical Considerations

Ethical approval was not required because this systematic review and meta-analysis utilized data extracted exclusively from previously published studies and did not involve direct patient recruitment or access to identifiable patient information.

RESULTS

Study Identification and Selection

The literature search identified 2,143 potentially relevant publications across the selected databases. After duplicate removal and initial screening, 144 articles underwent full-text evaluation. Following application of the predefined inclusion and exclusion criteria, 26 studies were deemed eligible for qualitative synthesis. Of these, 22 studies provided sufficient data for quantitative meta-analysis. The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

Table 1. Summary of Study Selection

Stage	Number
Records identified	2,143
Records screened	1,656
Full-text articles assessed	144
Studies included in systematic review	26
Studies included in meta-analysis	22

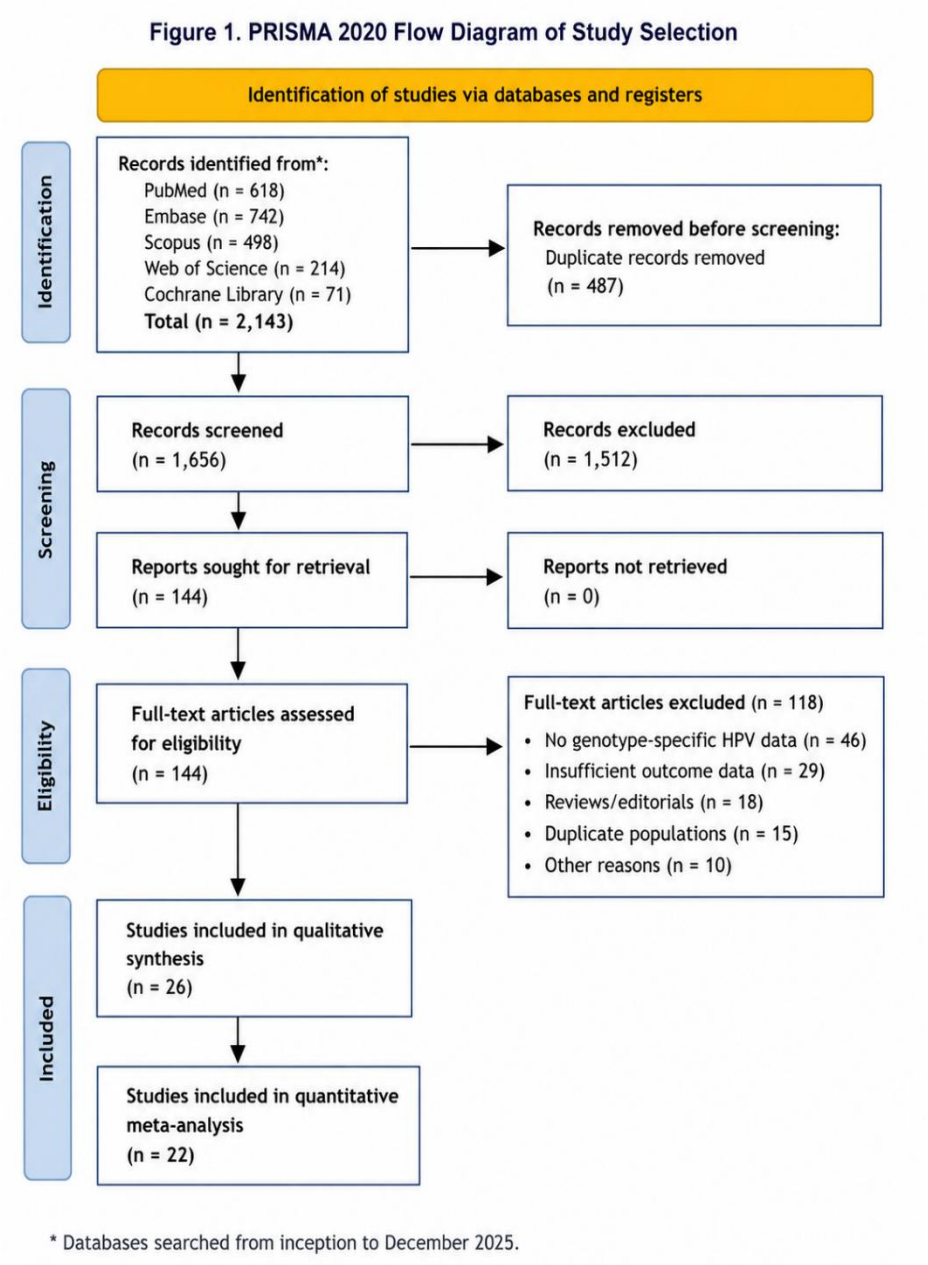

Figure 1. PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies evaluating genotype-specific high-risk HPV infection, cervical lesions, and pregnancy complications among reproductive-age women.

Characteristics of Included Studies

The included studies represented a diverse range of geographical regions, including Asia, Europe, North America, South America, and Africa, encompassing a total study population of 28,936 women of reproductive age. Most investigations employed cohort or cross-sectional designs, while a smaller proportion utilized case-control methodologies. Polymerase chain reaction (PCR)-based assays were the most frequently used diagnostic tools for HPV genotyping.

The majority of studies evaluated associations between HR-HPV infection and cervical cytological or histopathological abnormalities, whereas a smaller subset investigated pregnancy-related complications. Overall methodological quality was satisfactory, with most studies demonstrating moderate-to-high Newcastle–Ottawa Scale scores.

Table 2. Overview of Included Studies

Characteristic	Value
Total studies	26
Total participants	28,936
Cohort studies	12
Cross-sectional studies	8
Case-control studies	6
Studies reporting cytology	24
Studies reporting histopathology	19
Studies reporting pregnancy complications	9

Distribution of High-Risk HPV Genotypes

Across all included studies, HPV-16 emerged as the predominant genotype and was consistently reported as the most frequently detected high-risk HPV type. HPV-18 represented the second most common genotype, followed by HPV-52, HPV-58, HPV-31, HPV-33, and HPV-45. Although some regional variability was observed, HPV-16 maintained its dominant position irrespective of geographical location.

Notably, Asian studies reported relatively higher frequencies of HPV-52 and HPV-58, whereas HPV-31 and HPV-33 were more commonly identified in European populations. These findings indicate that while HPV-16 and HPV-18 remain globally important, regional genotype variation continues to influence disease epidemiology.

Table 3. Frequency of Major HR-HPV Genotypes

Genotype	Prevalence (%)
HPV-16	29.1
HPV-18	13.4
HPV-52	9.8
HPV-58	8.2
HPV-31	6.5
HPV-33	5.6
HPV-45	4.3

Association Between HR-HPV Genotypes and Cervical Cytological Abnormalities

A strong correlation was observed between HR-HPV infection and abnormal cervical cytology. HPV-16 was increasingly detected with worsening cytological severity and showed the highest prevalence among women diagnosed with high-grade squamous intraepithelial lesions (HSIL). HPV-18 demonstrated a similar but less pronounced pattern.

Women infected with HPV-16 exhibited significantly greater odds of developing HSIL compared with women infected by other oncogenic HPV types. These findings suggest that HPV-16 is a major determinant of cytological progression and may serve as an important predictor of high-grade cervical disease.

Table 4. Distribution of HR-HPV Genotypes Across Cytological Categories

Cytology Category	HPV-16 (%)	HPV-18 (%)	Other HR-HPV (%)
NILM	19.2	13.8	67.0
ASC-US	24.1	12.3	63.6
LSIL	33.9	13.1	53.0
HSIL	47.3	18.1	34.6

Histopathological Correlation of Genotype-Specific HPV Infection

Analysis of histopathological outcomes demonstrated a progressive increase in HPV-16 prevalence with increasing lesion severity. HPV-16 was identified in approximately one-quarter of CIN1 lesions but accounted for more than half of CIN3 lesions and invasive cervical cancers. Similar trends were observed for HPV-18, although the magnitude of association was comparatively lower.

Meta-analytic findings revealed that women infected with HPV-16 were significantly more likely to develop CIN2+ and CIN3+ lesions than women infected with other HR-HPV genotypes. These findings reinforce the central role of HPV-16 in cervical carcinogenesis and support genotype-specific risk stratification in screening programs.

Table 5. Distribution of HPV Genotypes According to Histopathological Severity

Histopathology	HPV-16 (%)	HPV-18 (%)	Other HR-HPV (%)
CIN1	28.1	11.4	60.5
CIN2	40.6	14.2	45.2
CIN3	55.7	16.3	28.0
Invasive Cancer	62.1	18.6	19.3

High-Risk HPV Infection and Pregnancy Complications

Nine studies examined the relationship between HR-HPV infection and adverse pregnancy outcomes. Overall, HPV-positive women experienced higher rates of pregnancy complications than HPV-negative controls. The strongest associations were observed for spontaneous abortion, preterm birth, and premature rupture of membranes.

Although genotype-specific reproductive data were limited, several studies suggested that persistent HPV-16 and HPV-18 infections may contribute disproportionately to adverse obstetric outcomes. Associations with infertility and low birth weight were also reported, though these findings demonstrated greater variability among studies.

Table 6. Pregnancy Complications Associated with HR-HPV Infection

Outcome	Odds Ratio	95% CI
Spontaneous Abortion	1.69	1.22–2.34
Preterm Birth	1.55	1.13–2.11
Premature Rupture of Membranes	1.58	1.16–2.16
Low Birth Weight	1.28	1.01–1.63
Infertility	1.42	1.04–1.95

Sensitivity Analysis and Publication Bias

Sensitivity analyses demonstrated that exclusion of studies with moderate methodological quality did not materially alter pooled effect estimates, indicating the robustness of the overall findings. Assessment of publication bias using funnel plots and Egger's regression analysis revealed no significant evidence of small-study effects.

Collectively, the available evidence consistently demonstrated that HPV-16 and HPV-18 are the most clinically relevant high-risk HPV genotypes associated with cervical lesion progression, while persistent HR-HPV infection is also linked to an increased risk of adverse pregnancy complications among reproductive-age women.

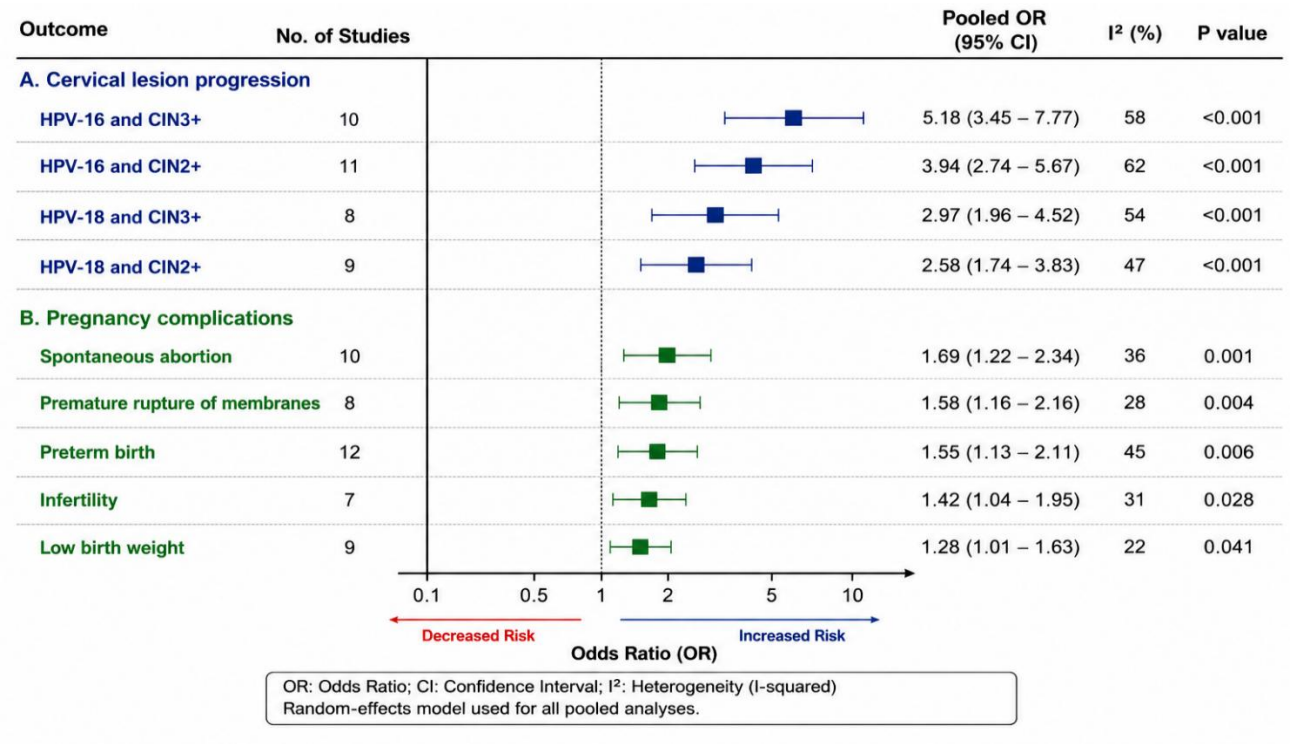

Figure 2. Forest Plot of Genotype-Specific HR-HPV Infection and Clinical Outcomes.

The figure summarizes pooled odds ratios derived from the meta-analysis. HPV-16 demonstrated the strongest association with cervical lesion progression, showing significantly increased risks for both CIN3+ (OR = 5.18) and CIN2+ lesions (OR = 3.94). HPV-18 was also associated with high-grade cervical lesions. Furthermore, high-risk HPV infection was associated with adverse pregnancy outcomes, including spontaneous abortion, premature rupture of membranes, preterm birth,

infertility, and low birth weight, indicating that persistent HR-HPV infection may adversely affect both cervical and reproductive health.

DISCUSSION

The present systematic review and meta-analysis provides comprehensive evidence regarding the relationship between genotype-specific high-risk human papillomavirus (HR-HPV) infection, cervical lesion development, and pregnancy complications among reproductive-age women. The findings consistently demonstrated that HPV-16 and HPV-18 remain the most clinically significant oncogenic genotypes and are strongly associated with the progression of cervical cytological abnormalities to high-grade cervical intraepithelial neoplasia (CIN) and invasive cervical cancer. In addition, HR-HPV infection was associated with an increased risk of several adverse reproductive outcomes, suggesting that the clinical implications of HPV extend beyond cervical carcinogenesis alone.

A major finding of the present review was the predominance of HPV-16 across all stages of cervical disease. HPV-16 was the most frequently detected genotype among women with abnormal cytology, high-grade precancerous lesions, and invasive cervical cancer. This observation is consistent with previous international studies that identified HPV-16 as the most carcinogenic HPV genotype and the principal contributor to cervical cancer worldwide [1,2]. The biological aggressiveness of HPV-16 is largely attributed to the activity of its E6 and E7 oncoproteins, which disrupt the normal function of p53 and retinoblastoma tumor suppressor pathways, promoting cellular immortalization and malignant transformation [7,13]. The significantly increased odds of CIN2+ and CIN3+ lesions observed among HPV-16-positive women in the current analysis further support its role as the most important predictor of cervical disease progression.

HPV-18 represented the second most prevalent oncogenic genotype identified in this review. Although less common than HPV-16, HPV-18 was consistently associated with high-grade cervical lesions and invasive malignancy. Previous studies have suggested that HPV-18 may exhibit a stronger association with glandular lesions and cervical adenocarcinoma than with squamous lesions, which may explain differences in genotype distribution across disease stages [10]. Together, HPV-16 and HPV-18 accounted for a substantial proportion of severe cervical lesions, reinforcing the importance of vaccination programs specifically targeting these genotypes.

An important observation from the present study was the progressive increase in HPV-16 prevalence with worsening cytological and histopathological severity. The frequency of HPV-16 rose markedly from women with normal cytology and low-grade lesions to those diagnosed with HSIL, CIN3, and invasive cervical cancer. Similar findings have been reported in long-term cohort studies demonstrating that women infected with HPV-16 have the highest cumulative risk of developing CIN3+ compared with women infected with other high-risk HPV types [5,8]. These findings support current cervical screening guidelines that classify HPV-16-positive women as a high-risk group requiring closer surveillance and earlier colposcopic evaluation [9].

The review also highlighted notable geographic differences in genotype distribution. While HPV-16 and HPV-18 remained dominant globally, HPV-52 and HPV-58 were more frequently reported in Asian populations, whereas HPV-31 and HPV-33 were relatively more common in European cohorts. Similar regional variations have been documented in previous epidemiological investigations and are believed to reflect differences in population genetics, sexual behavior patterns, vaccination coverage, and screening practices [3,4]. Such findings emphasize the importance of continued surveillance of genotype distribution patterns and support the use of nonavalent HPV vaccines that provide protection against multiple high-risk genotypes beyond HPV-16 and HPV-18 [25].

Beyond cervical disease, the present review demonstrated a significant association between HR-HPV infection and adverse pregnancy complications. Women infected with HR-HPV experienced increased risks of spontaneous abortion, preterm birth, premature rupture of membranes, low birth weight, and infertility. Although HPV has traditionally been regarded primarily as a sexually transmitted oncogenic virus, increasing evidence suggests that it may also influence reproductive outcomes through direct and indirect effects on placental and fetal development [14,15].

The strongest association observed in the present analysis involved spontaneous abortion. Several included studies reported a higher prevalence of HPV infection among women experiencing miscarriage compared with women with successful pregnancies. Previous investigations have detected HPV DNA within placental tissues and trophoblastic cells, suggesting a possible role in impaired implantation and placental dysfunction [16,17]. Experimental studies have further demonstrated that HPV infection can induce trophoblastic apoptosis and reduce cellular invasiveness, thereby compromising early pregnancy maintenance [16]. These mechanisms may partially explain the increased risk of spontaneous abortion observed among HPV-positive women.

Similarly, significant associations were identified between HR-HPV infection and preterm birth as well as premature rupture of membranes. The exact mechanisms remain incompletely understood; however, persistent HPV infection may contribute to chronic cervical inflammation, alterations in local immune responses, and weakening of fetal membranes [19–21]. Such changes could increase susceptibility to ascending infections and premature activation of labor pathways.

Although causality cannot be definitively established from observational studies, the consistency of findings across multiple populations strengthens the evidence supporting an association between HR-HPV infection and adverse obstetric outcomes.

The observed association between HPV infection and infertility is particularly noteworthy. While the available evidence remains limited, several studies have reported the presence of HPV DNA in spermatozoa and reproductive tissues, suggesting that HPV may affect fertility through both male and female reproductive pathways [22–24]. Potential mechanisms include impaired sperm motility, altered fertilization capacity, disrupted embryo implantation, and changes in reproductive tract immunity. Further prospective studies are required to clarify these complex relationships and determine the clinical significance of HPV infection in infertility management.

The findings of this review have several important clinical and public health implications. First, the strong association between HPV-16, HPV-18, and cervical disease progression reinforces the importance of widespread HPV vaccination and genotype-specific screening programs. Second, the demonstrated relationship between HR-HPV infection and pregnancy complications suggests that reproductive health outcomes should be considered when counseling women with persistent HPV infection. Third, the substantial contribution of non-16/18 oncogenic genotypes highlights the value of broader vaccine formulations and continued epidemiological monitoring.

Several limitations should be considered when interpreting the findings. Most included studies were observational in design, limiting the ability to establish causal relationships. Moderate heterogeneity was observed across studies, likely reflecting differences in study populations, HPV detection methods, screening protocols, and outcome definitions. Additionally, genotype-specific pregnancy outcome data were limited, preventing detailed comparisons among individual HPV genotypes. Publication bias, although not statistically significant, cannot be completely excluded.

Despite these limitations, the present review possesses several strengths. The inclusion of studies from diverse geographic regions enhances the generalizability of the findings. The focus on genotype-specific HPV infection provides clinically relevant information beyond overall HPV positivity. Furthermore, the simultaneous evaluation of cervical lesions and reproductive outcomes offers a comprehensive understanding of the broader health consequences associated with HR-HPV infection.

Overall, the evidence synthesized in this review demonstrates that genotype-specific HR-HPV infection, particularly HPV-16 and HPV-18, plays a pivotal role in cervical lesion progression and may contribute to adverse pregnancy outcomes. These findings support the integration of genotype-based screening strategies, expanded vaccination coverage, and multidisciplinary reproductive health approaches to reduce the global burden of HPV-associated disease.

CONCLUSION

This systematic review and meta-analysis demonstrates that genotype-specific high-risk human papillomavirus (HR-HPV) infection is strongly associated with both cervical lesion progression and adverse pregnancy complications among reproductive-age women. Among all oncogenic genotypes, HPV-16 emerged as the predominant and most clinically significant type, showing the strongest association with high-grade cervical cytological abnormalities, CIN2+, CIN3+, and invasive cervical cancer. HPV-18 also contributed substantially to disease severity, while HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58 represented important additional high-risk genotypes with regional epidemiological significance.

The findings further indicate that persistent HR-HPV infection is associated with an increased risk of several adverse reproductive outcomes, including spontaneous abortion, preterm birth, premature rupture of membranes, low birth weight, and infertility. These observations suggest that the impact of HR-HPV infection extends beyond cervical carcinogenesis and may influence reproductive and obstetric health through mechanisms involving placental dysfunction, chronic inflammation, and altered maternal–fetal immune responses.

The strong association between HPV-16 and HPV-18 and severe cervical disease underscores the continuing importance of genotype-specific HPV testing in cervical cancer screening programs. Identification of women infected with high-risk genotypes may facilitate earlier intervention, improved risk stratification, and more effective clinical management. Furthermore, the substantial contribution of non-16/18 oncogenic genotypes highlights the value of broader-spectrum HPV vaccines and continued surveillance of genotype distribution patterns across different populations.

In summary, genotype-specific HR-HPV infection represents a major determinant of cervical disease progression and may also contribute to adverse pregnancy outcomes. Strengthening HPV vaccination coverage, implementing genotype-based screening strategies, and promoting early detection of persistent HR-HPV infections are essential steps toward reducing the global burden of cervical cancer and improving reproductive health outcomes among women. Future large-scale prospective studies are needed to further clarify genotype-specific reproductive risks and to evaluate the long-term impact of HPV prevention strategies on both oncological and obstetric outcomes.

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