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Research Article

Human papillomavirus infection during pregnancy: an update, prevention and treatment

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Summary

Objective: To perform a comprehensive and updated review of prevention and treatment of HPV infections during pregnancy, focus on existing research in Bulgaria and the United Kingdom, as well as any existing literature on the topic of research within the regional scope.

Methodology: The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic literature review. It adopted the methodological framework proposed by the Joanna Briggs Institute (2015) and by Arksey and O'Malley's (2005) approach of summary and dissemination of research findings. The research methodology consisted of three primary steps: planning, conducting, and reporting the review findings.

Findings: The prevalence of HPV infection is higher in pregnant women as compared to non-pregnant women, and increases with the progression of the pregnancy. HPV infection of the intrauterine environment translates to adverse pregnancy outcomes, including preterm birth, intrauterine growth restriction, preeclampsia, and preterm premature rupture of membranes. Behavioural and therapeutic programs, as well as vaccination efforts, enhance effective prevention and treatment measures for HPV.

Conclusion: There is a direct correlation between HPV infection and adverse pregnancy outcomes. HPV vaccination is an effective prevention and treatment measure for adverse pregnancy outcomes. Surgical or laser excision or application of trichloroacetic acid treatments are effective treatment options.

Key words: Glucocorticoid, HPV, intrauterine environment, preeclampsia, pregnant, vertical transmission

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Introduction

The impact of sexually transmitted infections (STIs) on gestational processes has been widely explored by existing scientific research due to their significant contribution to biochemical and physical changes that have led to adverse pregnancy outcomes. A large proportion of the research has identified human papillomavirus (HPV) as one of the most common STIs that directly affect the

biochemical and physical processes related to pregnancy (Kovachev and Slavov 2018; Bober et al. 2019; Basonidis et al. 2020; Wang et al. 2020; Condrat et al. 2021; Ardekani et al. 2023). As a member of the Papillomaviridae family, HPV is a human-specific double-stranded DNA virus with up to 200 subtypes that directly affects the cutaneous or mucosal tissues, with 40 of the subtypes causing genital infections (Popescu et al. 2022). The spectrum of HPV manifestations ranges from asymptomatic infections to benign cutaneous and mucosal presentations, malignant and premalignant conditions, and oncogenic potential, all of which can impact gestational processes (Magalhães et al. 2020). The primary risk factor associated with reproductive HPV infections is the sexual behaviour of an individual, including the number of sexual partners and the age at which they first engaged in sexual acts (Basonidis et al. 2020; Chilaka et al. 2021). Further, the prevalence of HPV infection is higher in pregnant women than in non-pregnant women. It increases with the progression of pregnancy as a result of impairment of the mediated immune response during pregnancy, which affects the suppression of virus replication (Chen et al. 2019). Knowledge of the epidemiology and pathogenesis of HPV infection during pregnancy is important for understanding the related infection processes and formulating clinical and laboratory bases for prevention, treatment, and prophylactic measures.

The high risk for HPV infection in pregnant women is well documented and reported as the most prevalent viral infection in females of reproductive age, and with direct association with adverse pregnancy outcomes. The prevalence of HPV infection in pregnant women is attributable to their immunological and endocrinological status in terms of possible changes in the regulation of the production of glucocorticoid and the impairment of the Type-1 mediated immune response during pregnancy that directly affects the suppression of the replication of the virus (Jach et al. 2014; Niyibizi et al. 2021). As a result of the alteration of the immune system, HPV infection can affect the changes in hormonal levels, which can translate to adverse pregnancy outcomes (Domža et al. 2011). Research has shown that HPV directly infects the trophoblastic cells, thereby inhibiting the formation of blastocysts and leading to adverse physiological conditions, including failure of endometrial implantation and apoptosis of embryonic cells (Domža et al. 2011; Kovachev et al. 2013). The abnormalities associated with the effects of HPV infection of the intrauterine environment translate to adverse pregnancy outcomes, including preterm birth, intrauterine growth restriction, preeclampsia, and preterm premature rupture of membranes (Goulding and Rahangdale 2019; Yuill et al. 2021; Ardekani et al. 2022).

Furthermore, scientific evidence has established vertical transmission of HPV infection from mother to the newborn through either the vagina, cervix or hematologic spread (Bonde et al. 2014). Based on the theoretical understanding that the disruption of the placental environment can be due to infection, it has become common knowledge that HPV infection during pregnancy is directly associated with adverse pregnancy outcomes. Such outcomes underscore the importance of understanding updated prevention and treatment measures to address these outcomes.

While HPV infection is transient and often auto-limitative, there are specific strains that might be persistent in immunosuppressed patients such as pregnant women. Persistent HPV infections are associated with chronic conditions such as malignancies and oncological conditions, which can cause adverse

health outcomes, especially in pregnant women (Pandey et al. 2019). However, with up to 90 per cent of HPV infections being dormant and eliminated by the immune system within a year of exposure, there is a significant gap between the time of diagnosis of the chronic infection and the early stages, which affects the prevention and treatment of the condition and the related outcomes. Since pregnant women are considered a population vulnerable to HPV infections, it is necessary to implement additional prevention and treatment measures, such as cervical screening and postpartum follow-up, to reduce the level of risk for adverse pregnancy outcomes (Pandey et al. 2019; Duan et al. 2022). Presently, due to its prevalence, scientific research has proven the efficiency of prevention and treatment measures for HPV infections during pregnancy: most countries implement routine immunisation schedules for pre-adolescent girls.

Furthermore, extensive clinical trials have also led to the development of effective treatment options, including vaccines that promote sustained immune responses, reduce HPV incidence, and provide cross-protection against other HPV types. The existing scientific research has provided clinically proven insights and results on the prevention and treatment of HPV infections, but very few studies have performed a comprehensive systematic review of the existing findings, leaving a gap in the topic. This systematic review provides a comprehensive and updated overview of the prevention and treatment of HPV infections during pregnancy, focusing on existing research in Bulgaria and the United Kingdom, as well as the existing literature within the topic of research and its regional scope.

Methodology

The primary objective of the present research is to provide an updated review of the prevention and treatment of HPV infections in pregnant women through a detailed analysis of existing research on the topic. To achieve the intended objective, the review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic literature review. It adopted the methodological framework proposed by the Joanna Briggs Institute (2015) and by Arksey and O'Malley's (2005) approach of summary and dissemination of research findings. The research methodology consisted of three primary steps: planning, conducting, and reporting the review findings. The first step of the review involved the formulation of inclusion and exclusion criteria, while the second step involved an article search and screening process. Then, data extraction and reporting of the findings were conducted. The current section of the review provides a detailed, step-by-step description of the methodological steps followed during the planning, conducting, and reporting of the review.

Search strategy and screening

We employed a three-step search strategy to identify the relevant research terms and phrases for the studies to be included. Publication titles, keywords and abstracts were searched using concept terms in the databases APA PsycInfo (via Ovid), Medline/PubMed (via Ovid), and EMBASE (via Ovid). The relevant keywords that were used in the search strategy included "Human Papillomavirus", "Pregnancy", "Bulgaria" and "United Kingdom". Applicable subject headings and keywords related to the concept terms were selected and explored

using the Boolean operator "OR". The selection of the databases was based on their psychological, health science and medical components that apply to the concept of HPV infections in pregnant women in Bulgaria and the United Kingdom. Other factors that influenced the selection of the databases included their advanced search capabilities, reliability, and the quality of the literature. The selection of articles was based on an inclusion and exclusion protocol that considered the relevance to the research topic. Any additional article that was associated with the topic of research and could not be identified through database searches and the inclusion protocol was identified through cross-referencing and hand searches of the reference lists of the included studies. The screening of the selected articles involved the removal of duplicate articles that might have been present in more than one database and the exclusion of any articles that did not meet the inclusion criteria. The suitability of the remaining articles was confirmed through a second application of the inclusion and exclusion criteria and an independent review to create the final list of the studies that met the review objectives. The search process, including the screening and selection of articles, was reported using a PRISMA process flowchart.

Data extraction and synthesis

The selection of the appropriate and relevant studies for inclusion in the research was followed by the extraction of specific information and data that were related to the topic and variables of interest. The extracted information included the author, country, and year of publication, as well as the study's sampling strategy, inclusion criteria, recruitment site, and number of participants. Other information extracted from the incorporated studies included the type of treatment, modality and the type of interventions for HPV infections among pregnant women. A quality assessment of the included studies was then performed, based on research criteria for examining information bias, selection bias, study design, and the correction of outcome measures for confounding in the studies. In relation to selection bias, they assessed the formulation of the study's inclusion and exclusion criteria and the potential for participation bias. The research discussed any discrepancies found within the extracted data and formulated a protocol for developing a common agreeable consensus on the issues. The results from the extracted data were then summarised in tables, and subgroups of studies were formed based on the review's objectives.

Findings

The database study search identified a total of 213 studies from the databases, as well as grey literature, and through cross-referencing and hand searches of the reference lists of the included studies, specifically meeting the inclusion criteria for the research. The selected articles focused on the prevention and treatment of HPV infections in pregnant women, published within the regional scope of the research, i.e. Bulgaria and the United Kingdom. However, considering the limited number of identified studies that focused on the two countries, other articles published in Europe were also included. After the removal of the duplicated articles, a total of 89 studies remained. Out of the remaining studies, 39 did not meet the inclusion criteria and, therefore, only 50 were obtained for

detailed eligibility assessment. Further, 20 studies did not meet the eligibility criteria and were excluded from the final list of the articles included in the review. Consequently, a total of 30 full-text articles were eligible for inclusion. The detailed PRISMA chart for the findings is provided below (Table 1, Fig. 1).

Table 1. Detailed descriptive analysis of included article.

No	Author and year of publication	Research design	Focus of study	Summarised findings
1	Ardekani et al. 2023	A systematic review and meta-analysis	HPV prevalence in pregnant women	Behavioural and therapeutic programs, and vaccination efforts, are effective prevention and treatment measures for HPV.
2	Ardekani et al. 2022	A comprehensive review	HPV infection in pregnant women and children	No curative treatment but vaccination is the most effective prevention and treatment strategy.
3	Basonidis et al. 2020	A systematic review	Association between HPV infection and miscarriage	The prevalence of HPV infection is higher in pregnant women as compared to non-pregnant women, and increases with progression of the pregnancy.
4	Bober et al. 2019	A randomised controlled trial	Impact of HPV in pregnant women	HPV infection of the intrauterine environment translates to adverse pregnancy outcomes.
5	Bonde et al. 2014	A systematic review	Role of vaccination in the prevention of HPV among pregnant women	HPV vaccination is important in the prevention of infectious complications of pregnancy.
6	Chen et al. 2019	A randomised controlled trial	Efficacy trials of hpv-16/18 as04-adjuvanted vaccine	HPV-16/18 AS04-Adjuvanted Vaccine is effective in the prevention of HPV infections in pregnant women.
7	Chilaka et al. 2019	An updated review	HPV in pregnancy	HPV vaccination is not recommended for pregnant women, but surgical or laser excision or application of trichloroacetic acid treatments are effective.
8	Condrat et al. 2021	A systematic review	Effects of HPV on pregnancy	HPV has a significant impact on pregnancy and can lead to adverse pregnancy outcomes.
9	Domza et al. 2011	A randomised controlled trial	HPV infection in pregnant women	High prevalence of HPV infection in pregnant women in Lithuania, but most cases were cleared after the pregnancy.
10	Duan et al. 2022	Correlation analysis	Correlation between HPV infection and pregnancy	There is a direct correlation between HPV infection and adverse pregnancy outcomes.
11	Hooda et al. 2022	A prospective case-control study	HPV infection as a risk factor for preterm birth	HPV infection is a significant risk factor for adverse pregnancy outcomes, including preterm birth.
12	Jach et al. 2014	A prospective clinical study	Vertical transmission of HPV in pregnancy	Vertical transmission of HPV infection from mother to the newborn through either the vagina, cervix or hematologic spread.
13	Kovachev and Slavov 2018	An updated review	HPV prevalence in pregnant women in Bulgaria	There is an unusually high proportion of specific infecting HPV genotypes in Bulgaria.
14	Kovachev et al. 2013	A prospective clinical study	HPV prevalence in pregnant women in Bulgaria	There is an unusually high proportion of the different HR-HPV genotypes in Bulgaria.
15	Liu et al. 2014	A descriptive analysis of cohorts	HPV prevalence in pregnant women	There is a correlation between cervical alterations in pregnancy and high-risk HPV infection.
16	Magalhães et al. 2021	An updated review	Pathogenesis and Clinical Spectrum of HPV in Pregnancy	The spectrum of manifestations of HPV ranges from inapparent infections, cutaneous and mucosal clinical benign presentations, malignant and premalignant conditions, to oncogenic potential, all of which can affect gestational processes.
17	Niyibizi et al. 2021	A systematic literature review	Association between HPV infection and preterm birth	There is a strong association between HPV infection among pregnant women and preterm birth.
18	Niyibizi et al. 2020	A systematic review and meta-analysis	Association between HPV infection and adverse pregnancy outcomes	There is a strong association between maternal HPV infection and adverse pregnancy outcomes.
19	Pandey et al. 2019	A systematic review and meta-analysis.	HPV prevalence in early pregnancy	There is a high prevalence of HPV in early pregnancy.

No	Author and year of publication	Research design	Focus of study	Summarised findings
20	Petkova et al. 2024	A descriptive analysis	Midwifery and HPV in pregnancy	Knowledge on prevention and treatment of HPV infection during pregnancy is an important quality in midwifery.
21	Popescu et al. 2022	Systematic review and meta-analysis	Association between HPV infection and adverse pregnancy outcomes	There is a strong association between maternal HPV infection and adverse pregnancy outcomes.
22	Radu et al. 2021	A descriptive analysis	HPV infection during delivery	HPV can be transmitted through skin, sexual contact and through birth.
23	Skoczyński et al. 2019	A Systematic Review	HPV in pregnant women and children	HPV infection of the intrauterine environment can cause adverse pregnancy outcomes, including preterm birth.
24	Soheili et al. 2021	Systematic review and meta-analysis	Epidemiology, diagnostic methods, and treatment of all HPV-related cancers	The prevalence of HPV infection is higher in pregnant women as compared to non-pregnant women.
25	Tognon et al. 2020	A Systematic Review	HPV infection and abortion	HPV infection in chorionic villi is rare but can cause spontaneous abortion.
26	Topkara et al. 2023	Systematic review and meta-analysis	HPV frequency in pregnant women	There is a high prevalence of HPV infection in pregnant women as compared to non-pregnant women.
27	Wang et al. 2020	Systematic review and meta-analysis	HPV vaccination during pregnancy	There is no significant association between Inadvertent bivalent/quadrivalent HPV vaccination during pregnancy and risks of adverse pregnancy outcomes.
28	Yuill et al. 2021	A descriptive analysis	HPV vaccination and pregnancy outcomes	HPV vaccination is an effective prevention and treatment measure for adverse pregnancy outcomes.
29	Goulding and Rahangdale 2019	Systematic review and meta-analysis	HPV and adverse pregnancy outcomes	There is a strong association between maternal HPV infection and adverse pregnancy outcomes.
30	Liu et al. 2022	A descriptive analysis of cohorts	HPV in pregnant women	The prevalence of HPV infection is higher in pregnant women as compared to non-pregnant women, and increases with progression of the pregnancy.

Discussion

The increased scientific research interest in HPV in pregnancy is directly attributed to the ever-increasing prevalence of the condition among pregnant women across the globe. According to the findings of the present systematic review, human papillomavirus (HPV) is one of the most common STIs that directly affects the biochemical and physical processes related to pregnancy. It has been reported that HPV is the most prevalent sexually transmitted viral infection in females of the reproductive age and is directly associated with adverse pregnancy outcomes (Liu et al. 2014; Tognon et al. 2020; Radu et al. 2021). The existing literature indicates that the primary risk factor for HPV infections is the sexual behaviour of an individual, including the number of sexual partners and the age at which they first engaged in sexual acts (Tognon et al. 2020; Radu et al. 2021). In this regard, having first sexual intercourse at a young age, having multiple sexual partners and low educational levels are considered the primary risk factors for HPV infection. As a result, it is essential to understand the various risk factors associated with HPV infections to design effective prevention and treatment mechanisms based on the causative agents of the related conditions. Based on the findings, knowledge of the causative and risk factors of HPV infection can be an important quality in midwifery in the prevention and treatment of HPV infection during pregnancy (Skoczyński et al. 2019). On the same note, it is essential to ensure that the chosen prevention and treatment measures consider the demographic characteristics of the patients, including their age, as well as any previous medical conditions that might directly affect the efficacy of the treatment.

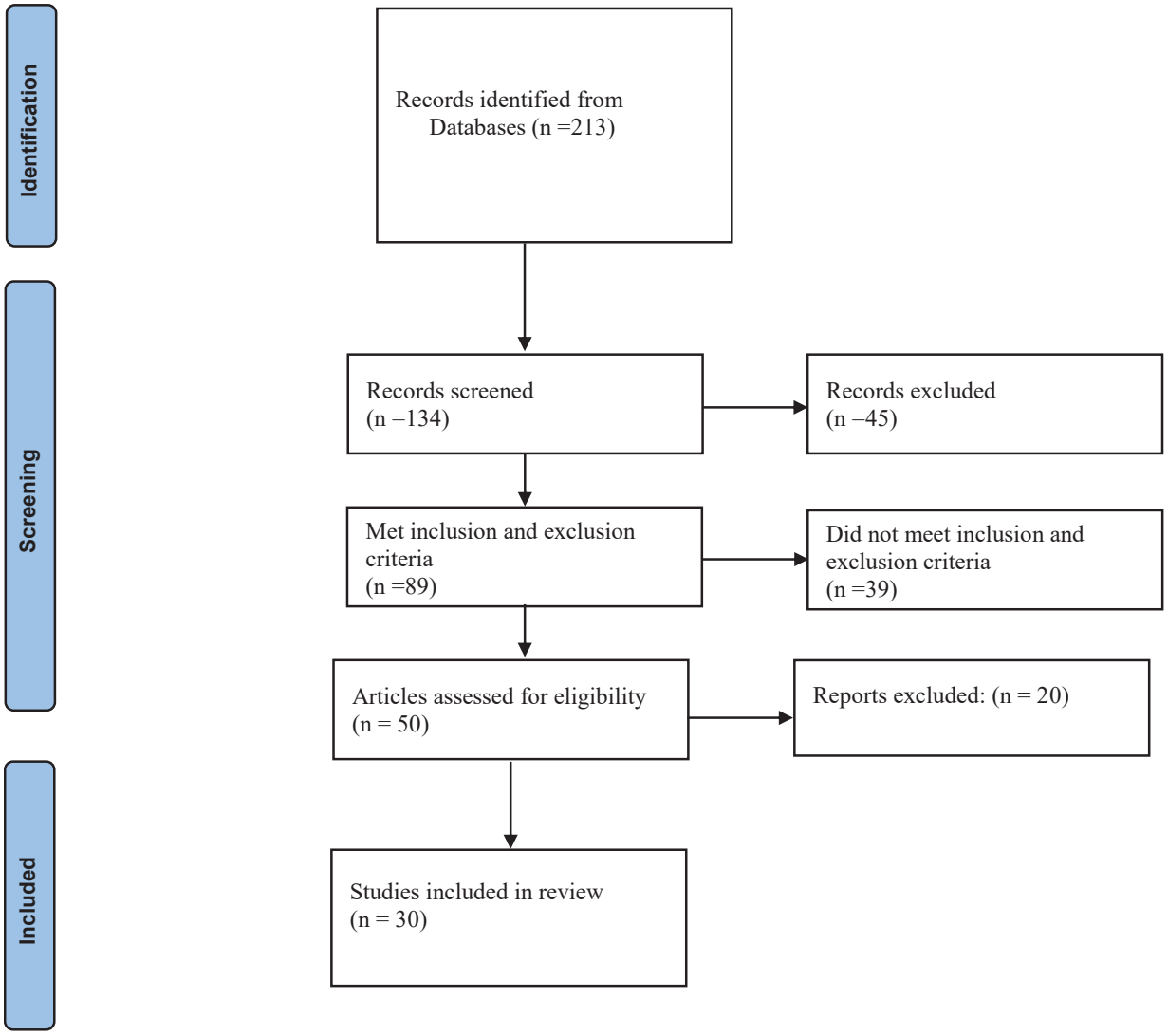

Figure 1. PRISMA flowchart for the review.

In terms of treatment and prevention, there has been a wide scientific demonstration of the effectiveness of prevention and treatment measures for HPV infections during pregnancy. Most countries have implemented routine immunisation schedules as the primary prevention measure for the condition and related diseases. The findings further imply that the implementation of behavioural and therapeutic interventions can be crucial in the prevention and reduction of the present burden posed by HPV infection during pregnancy (Niyibizi et al. 2020; Hooda et al. 2022). On the same note, the literature confirms the efficacy of vaccination programs as a first-line prevention measure for HPV and related conditions among pregnant women. According to the review findings, the efficacy of the vaccines is based on the mode of infection with the virus during pregnancy. The vaccines function based on the immunological and endocrinological status of the patients to ensure effective suppression of the virus's replication. The existing literature indicate that the prevalence of HPV infection in pregnant women can be attributed to their immunological and endocrinological status in terms of possible changes in the regulation of the production of glucocorticoid and the impairment of immune response during pregnancy that directly affects the suppression of the replication of the virus

(Soheili et al. 2021; Liet al. 2022). As a result of the alteration of the immune system, HPV infection can affect the changes in hormonal levels, which can translate to adverse pregnancy outcomes (Soheili et al. 2021). Considering the vulnerability of women to HPV infections, it is necessary to implement additional prevention and treatment measures, such as cervical screening and postpartum follow-up, to reduce the level of risk for adverse pregnancy outcomes.

According to the review findings, an understanding of the related infection processes is crucial for formulating a clinical and laboratory basis for prevention, treatment, and prophylactic measures. It is reported that HPV infection can affect the changes in hormonal levels and directly infects the trophoblastic cells which inhibits the formation of blastocysts leading to adverse physiological conditions including failure of endometrial implantation and apoptosis of embryonic cells, and subsequently translating to adverse pregnancy outcomes including preterm birth, intrauterine growth restriction, preeclampsia, preterm premature rupture of membranes (Topkara et al. 2023; Petkova et al. 2024). Presently, the vaccination clinical trials are taking advantage of the mechanisms of HPV infections and how they affect gestational processes to prevent related adverse outcomes and to reduce the impact on pregnancy. The HPV-16/18 AS04-Adjuvanted Vaccine is found to be effective in the prevention of HPV infections and offers cross-protection against specific non-vaccine oncogenic HPV types, especially those that cause genital warts that are directly associated with pregnancy outcomes (Topkara et al. 2023). The review findings further show that most countries have adopted prophylactic vaccination against HPV as part of their recommended vaccination schedules, offering the bivalent, quadrivalent vaccine, or the 9-valent vaccine against different but specific strains of HPV. However, while the recommended age for HPV vaccination is for pre-adolescent girls, most countries, including Bulgaria, offer the vaccination until the age of 25–26 years, which age exposes a large number of reproductive-age women to HPV infections. As a result, most of the women receive inadvertent administration of the HPV vaccine during their peak fertility age, which is around or during their pregnancy stages.

Conclusion

The present systematic review provided a comprehensive and updated review of the prevention and treatment of HPV infections during pregnancy. Human papillomavirus (HPV) is one of the most common STIs, directly affecting the biochemical and physical processes, and is associated with manifestations ranging from inapparent infections, cutaneous and mucosal clinical benign presentations, and malignant and premalignant conditions with oncogenic potential that directly affect gestational processes. The abnormalities related to the effects of HPV infection of the intrauterine environment include preterm birth, intrauterine growth restriction, preeclampsia, and preterm premature rupture of membranes. The research findings show a correlation between cervical alterations in pregnancy and high-risk HPV infection. The prevalence of HPV infection is higher in pregnant women as compared to non-pregnant women, and increases with progression of the pregnancy. Extensive clinical trials have also led to the development of effective treatment options, including vaccines that induce a sustained

immune response, reduce HPV incidence, and provide cross-protection against other HPV types. Furthermore, knowledge on prevention and treatment of HPV infection during pregnancy is an important quality in midwifery, and behavioural and therapeutic programs, and vaccination efforts are effective prevention and treatment measures for HPV. The results show that there is no curative treatment for HPV, and vaccination is the most effective prevention and treatment strategy. However, surgical or laser excision or application of trichloroacetic acid treatments have also been proposed as effective treatment options.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Use of AI

No use of AI was reported.

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Author contributions

Both authors have contributed equally.

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Data availability

All of the data that support the findings of this study are available in the main.

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