Original Article

Systematic review and meta-analysis on influence of human papillomavirus infection during pregnancy on premature rupture of membranes and premature delivery

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Background: The increasing infection rate of human papillomavirus (HPV) has resulted in various complex pregnancy-related complications in recent years. HPV can directly pass through the placenta to cause intrauterine infection, leading to premature delivery or the premature rupture of membranes (PROM).

Methods: English databases were searched for randomized control trials (RCTs) on HPV infection and premature delivery and PROM, including PubMed, Medline, Embase, and Cochrane Central Register. The search time was from inception to March 1st 2021, with human papillomavirus, rupture, pregnancy, preterm birth, viral infection, and pregnancy complications as search terms. RevMan5.3 provided by the Cochrane Collaboration was used to perform bias risk assessment.

Results: A total of 7 studies were identified, involving 45,603 patients, including 22,799 cases in the control group, and 22,799 cases in an HPV infection group. The odds ratio (OR) and 95% confidence interval (95% CI) were used to express the results. HPV infection increased the probability of premature delivery (OR =1.81, 95% CI: 1.25–2.62, Z=3.16, P=0.002) and PROM (OR =1.74, 95% CI: 1.45–2.10, Z=5.84, P<0.00001). The P values were all less than 0.05, and the difference was statistically significant.

Discussion: A total of 7 articles were included in this meta-analysis. HPV infection affects the physiology of pregnant women and may lead to PROM and premature delivery.

Keywords: Premature rupture of membranes (PROM); premature delivery; meta-analysis; human papilloma virus (HPV)

Submitted Aug 12, 2021. Accepted for publication Oct 14, 2021.
doi: 10.21037/apm-21-2497
View this article at: https://dx.doi.org/10.21037/apm-21-2497

Introduction

Human papillomavirus (HPV) is a small double-stranded closed circular DNA virus with high host-specific. It is named because some types of HPV can cause papillomas or warts in certain parts of the skin mucosa (1). More than 80% of men and women over 45 years old have a history of HPV infection, and women of young reproductive age are predominantly affected. Pregnant women are more susceptible to HPV infection due to their special endocrine and immune status, and it has been reported that the cervical HPV infection rate in this group is 82%, which is significantly higher than the 10.4% in non-pregnant women (2). The HPV detection rate for pregnant women is 15.53%, which is also higher than the 12.6% of

non-pregnant women and confirms the susceptibility of pregnant women to HPV infection (3,4). HPV infection during pregnancy leads to adverse pregnancy outcomes, such as miscarriage, premature delivery, premature rupture of membranes, preeclampsia and restriction of intrauterine growth and development of the fetus, which seriously affects the health of the newborn and prevents the smooth delivery of the newborn. This is a common concern of obstetricians and pregnant women (5).

In recent years, the pregnancy outcomes resulting from HPV infection have attracted much concern (6). The World Health Organization defines premature delivery as a delivery within 37 gestational weeks, and in developed countries, pregnant women usually have HPV tests at 22 or 24 weeks (7). However, in developing countries, the lower limit for premature babies is 28 weeks of gestation and a birth weight of 1,000 g (8). Factors that induce premature delivery include lower genital duct and urinary tract infections, intrauterine infections, uterine hyperdilatation, uterine malformations, placental and internal organ factors, diarrhea, and other pregnancy complications (9). HPV infection is an important factor in the occurrence of premature delivery and can lead to intrauterine infection (10). When a pregnant woman is infected with HPV, the vaginal environment becomes more susceptible to bacterial disease. Moreover, infection with pathogenic microorganisms in the reproductive duct is associated with premature rupture of the uterine membranes (11). Some scholars found that HPV infection has a great impact on pregnancy outcomes, such as immature delivery, immature membrane rupture, postpartum hemorrhage, puerperal infection, and fetal growth restriction (12,13). Current thinking holds that high-risk HPV infection is closely associated with premature delivery, but the hypothesis has not been verified. Hence, a systematic review of existing studies is necessary to obtain more accurate conclusions to guide clinical practice (14).

The innovation of this paper lies in the fact that it is necessary to explore the correlation between high-risk HPV infection and adverse pregnancy outcomes. Many scholars at home and abroad have conducted a series of observational studies, but the results are not completely consistent, that is, there is controversy over whether there is correlation between the two (15). In this research, the correlation between premature rupture of membranes and premature delivery was analyzed by human papillomavirus infection during pregnancy (16). In this meta-analysis, 7 randomized control trials (RCTs) on the influence of HPV on the premature rupture of membranes (PROM) and premature delivery were included, for the purpose of establishing a theoretical basis for the prevention of PROM and premature delivery during pregnancy and improving the survival rate of pregnant women.

We present the following article in accordance with the PRISMA reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2497).

Methods

Literature retrieval

The Medline, Embase, and Cochrane Central Register of Controlled Trials databases were searched for RCTs on the influence of HPV on PROM and premature delivery published from January 1st, 2001 to March 1st, 2021, with human papillomavirus, PROM, pregnancy, premature birth, viral infection, pregnancy complications, gestational diabetes mellitus, gestational hypertensive disease, chorioamnionitis, cervical dysplasia, preeclampsia, and spontaneous abortion as search terms. Additionally, the symptoms and treatment of other complications during pregnancy were sought.

Inclusion and exclusion criteria

The following inclusion criteria applied: (I) those diagnosed with HPV infection within 3 years before pregnancy to 6 months after delivery; (II) with premature delivery and PROM; (III) RCT; and (IV) published literature.

The exclusion criteria were: (I) Chinese literature; (II) meta-analyses not relevant to the topic; or (III) literature with unclear results and incomplete data.

Literature screening

Initially, some references were eliminated after reading the titles and abstracts. Then, a second screening was performed according to the inclusion criteria and exclusion criteria, and references were traced using a search engine. Finally, a third screening was conducted by reading the full text of the included literature.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature according to seven criteria: (I) whether a randomized method was used; (II) whether

allocation concealment was used; (III) whether the subject and the operator were blinded; (IV) whether the assessor was blinded; (V) whether the results data was complete; (VI) whether the results were reliable; and (VII) other biases. Each item accounted for 1 point, and the total score ranged from 0–7 points. A score of 4–7 points was considered high quality research, and 0–3 was considered low quality research.

Data extraction

Two experts used unified Microsoft Excel to collate data independently, and inconsistency was resolved by discussions or inviting another expert to arbitrate. The following data were collated: (I) research title, first author's name, publication year, and publication name; (II) general information of the research object: region, sample size, gender ratio, and age distribution; (III) observation indicators; and (IV) intervention methods in the control group and experimental group.

Risk of bias and quality assessment of articles

The Cochrane randomized trial risk assessment tool was applied to evaluate the quality of the included articles. The evaluation included the following six items: (I) the random sequence generation method; (II) whether there was bias in the allocation process; (III) whether the blind research was adopted; (IV) whether the results data was complete; (V) whether there was selective reporting of the research results; and (VI) other deviations.

Sensitivity analysis

Sensitivity analysis was used to evaluate whether the results of meta-analysis were stable and reliable, specifically by excluding some controversial studies, low-quality studies or analyzing the same group of data using statistical methods/effect models at different points to observe the changes in meta-analysis results. If the sensitivity analysis does not substantially change the results, the results are reliable. On the contrary, it is suggested that great caution should be exercised in interpreting results and drawing conclusions.

Statistics analysis

RevMan 5.3 software was used to analyze the risk bias of the included literature. The odds ratio (OR) was used as the effect size and 95% confidence interval (CI) was used to express the results. First, a heterogeneity test was perfumed on the included studies, with α=0.1 as the cut-off value. If there was no heterogeneity between the studies ($P>0.1$, $I^2<50\%$), the fixed-effects model was selected for meta-analysis, otherwise, subgroup analysis was then performed. $P<0.05$ was the threshold for significance. When a single risk factor analysis was included in more than 7 articles, a funnel chart was used to analyze the publication bias of the risk factor. RevMan5.3 software was used to analyze publication bias by Begg's and Egger's test methods and if $P>0.05$, it was considered that there was no publication bias.

Results

Literature retrieval results

By searching keywords, 1,969 articles were initially obtained. After reading the titles of the above-mentioned articles, and excluding those that did not meet the requirements, 544 articles were used for the next analysis. After browsing the abstracts of the literature roughly, 76 articles were used for the next analysis. The literature was screened according to the inclusion and exclusion criteria, and 31 articles were used for the next analysis. After downloading and reading the documents, a total of 7 documents were finally used for meta-analysis (17-23). *Figure 1* depicts the flowchart of literature retrieval, and *Table 1* shows the basic information of the included studies. The included studies compared the treatment effects of the two methods according to the main methods used, and the methodological quality of each research in the intervention results was medium or above, at the same level of literature quality, and there was no methodological heterogeneity. Therefore, this systematic review did not conduct sensitivity analysis.

Risk of bias of the included literature

The Cochrane Handbook version 5.3 was used to evaluate the bias risk of the 7 articles included in this meta-analysis. As shown in *Figure 2* and *Figure 3*, Review Manager 5.3 software was used to output the risk bias maps.

Meta-analysis of HPV infection and PROM

As shown in *Figure 4* and *Figure 5*, there were 2 articles

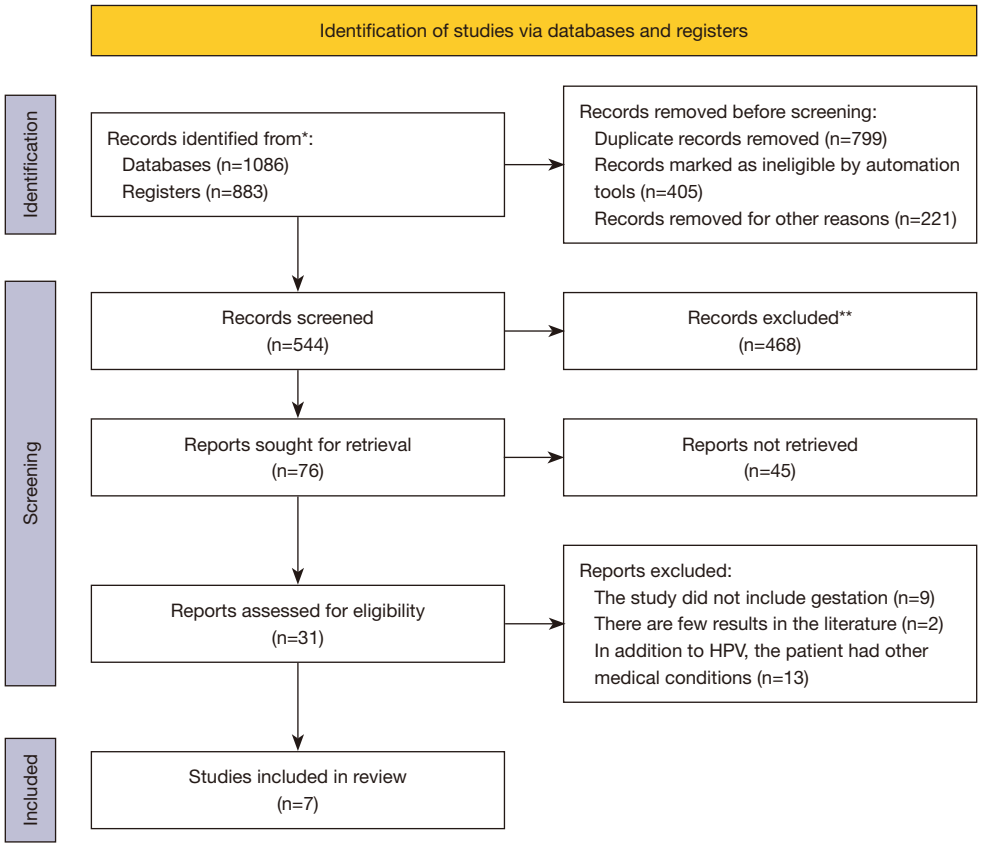

Figure 1 Flowchart of literature retrieval. *, consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers); **, if automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Table 1 Basic information of the included literature

First author	Publication year	Consequences	Age/year	Research duration
Zuo (17)	2011	Cervical cancer premature delivery	12–47	Whole pregnancy
Gomez (18)	2008	PROM	Not clear	36 weeks of pregnancy
Cho (19)	2013	Premature delivery, PROM, preeclampsia, and gestational diabetes (GDM)	Not clear	End of pregnancy
McDonnold (20)	2014	Preeclampsia, premature delivery	Not clear	Prenatal care to the end of pregnancy
Slatter (21)	2015	Premature delivery, preeclampsia, and diabetes	Not clear	Whole pregnancy
Subramaniam (22)	2016	Hypertension during pregnancy, preeclampsia or eclampsia, premature delivery	Not clear	Whole pregnancy
Ambühl (23)	2017	Premature delivery or spontaneous abortion	Over 18	8–22 weeks

PROM, premature rupture of membranes.

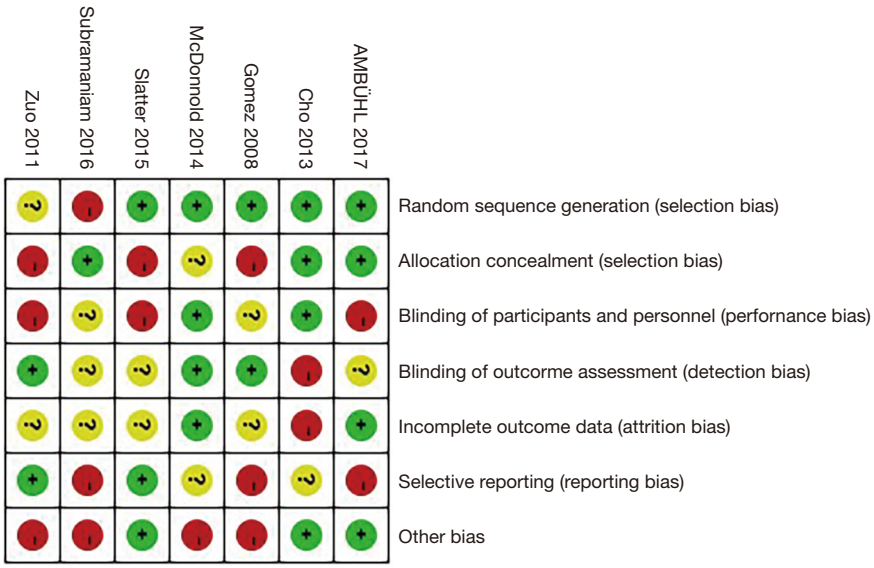

Figure 2 Bias risk assessment results of included literature.

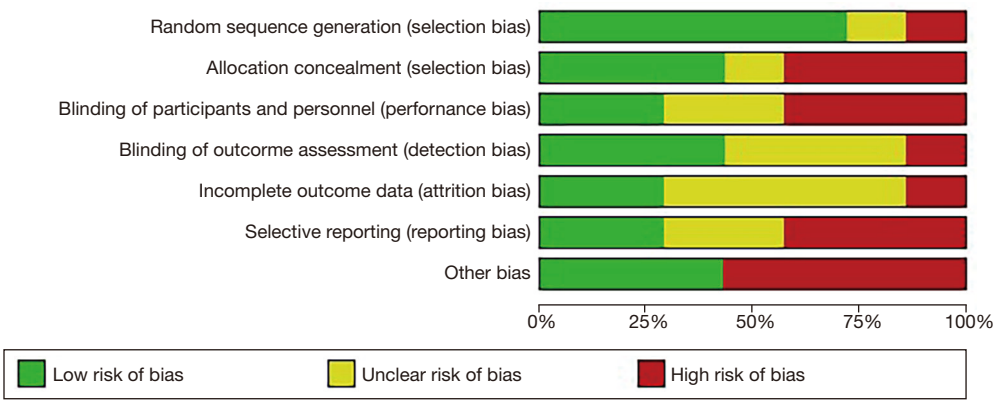

Figure 3 Bar chart showing the bias risk assessment results of the included literature.

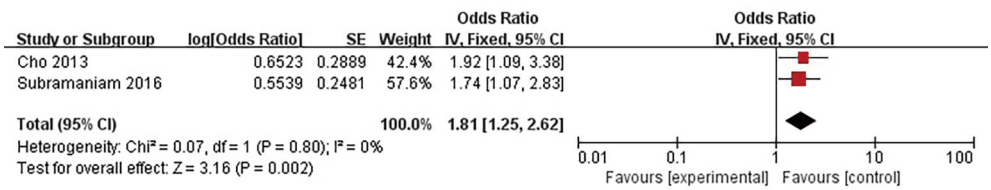

Figure 4 Forest plot of premature rupture of membranes in two groups.

with premature rupture of membranes as the outcome index, and both of which were cohort studies. Meta-analysis of each included data showed that there was no statistical heterogeneity (I^2=0%, P=0.80), and a fixed effect model (FEM) was used for analysis. The results of the combined effect model showed that pregnant women with high-risk HPV infection had a higher incidence of premature rupture of membranes than the negative control group, and the

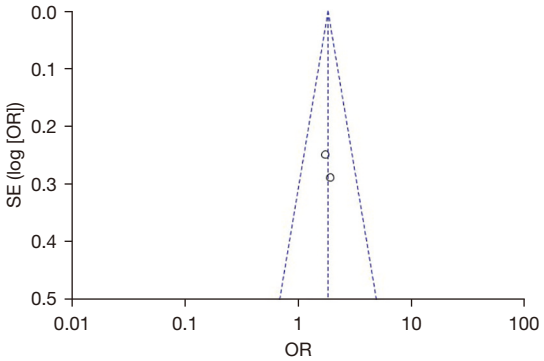

Figure 5 Funnel diagram of premature rupture of membranes. SE, standard error; OR, odds ratio.

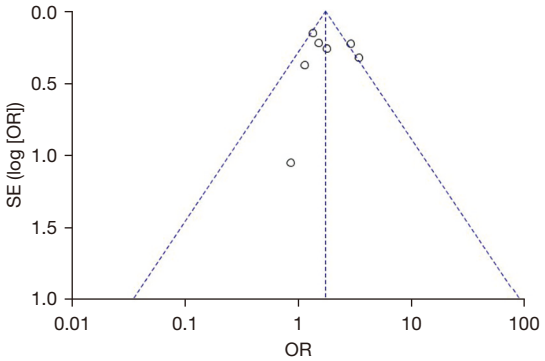

Figure 7 Funnel chart of premature delivery in two groups. SE, standard error; OR, odds ratio.

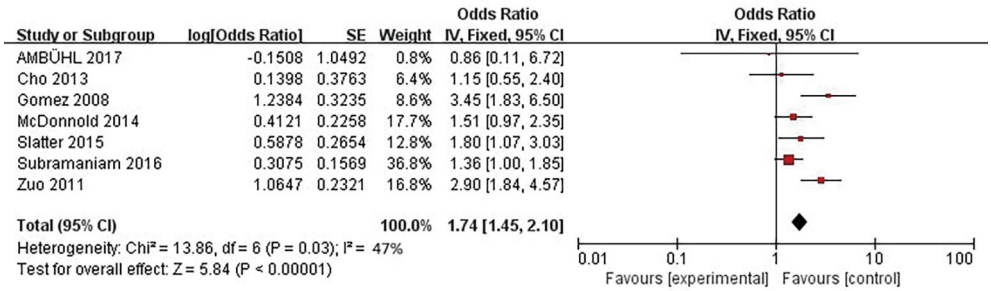

Figure 6 Forest plot of premature delivery in two groups.

difference between the two groups was statistically obvious (OR =1.81, 95% CI: 1.25–2.62, Z=3.16, P=0.002). It can be concluded that women with high-risk HPV infection were more prone to premature rupture of membranes.

Meta-analysis of HPV infection and premature delivery

As shown in *Figure 6* and *Figure* 7, there were 7 articles with preterm birth as the main outcome indicator, all of which were cohort studies. Analysis of the included data showed that there was no statistical heterogeneity (I^2=47%, P=0.03), and the FEM was used for effect size combination. The results showed that the high-risk HPV infection positive group had a higher incidence of preterm birth in the higher-risk HPV negative group, and the difference between the two groups was statistically significant (OR =1.74, 95% CI: 1.45–2.10, Z=5.84, P<0.00001), so women with high-risk HPV infection were more likely to have premature delivery. In the sensitivity analysis of the combined results, none of the articles violated the total combined effect size. In other words, the results obtained were relatively stable. Therefore, a definite conclusion can be drawn: women with high-risk HPV infection were more likely to have premature delivery, so there was no publication bias in the symmetry of the funnel graph.

Discussion

This meta-analysis included a total of 7 studies (17-23), one of which was of high-quality and three of which were low-quality. Three studies reported basic data such as age, disease type, and disease stage, but there were no statistically significant differences between the experimental group and the control group (P>0.05). One article (18) introduced a random number table, and another (19) mentioned random grouping according to the pregnancy time. three studies (18,20,21) introduced random methods, but did not mention the measurement blindness, nor did they report the number lost to follow up. The limitations of interventional measures indicated there was measurement bias, and improvements in methodology appear to be required to improve the reliability of studies in the future. Studies have shown

that HPV infection can cause the human body to produce terminal Phospholipids A2 on the fetal cell membrane, and then produce a series of hormones and enzymes, such as tyrosinase protein. These enzymes decompose the fetal membrane matrix and collagen, and eventually lead to the early rupture of the maternal fetal membrane (24). At the same time, the membrane tissue of the infected fetus activates various physiological reactions, synthesizes a large amount of prostaglandin, and stimulates contraction of the uterus. Pathogenic microorganisms invading the human body increase the activity of proteases and reduce the secretion of immune body fluids from the cervix. The premature rupture of the fetal membrane will not only lead to premature delivery of the fetus, but the infection itself will also increase the risk of premature delivery, because inflammatory factors increase, and the neck tube detaches, causing premature delivery. However, whether HPV infection can cause premature delivery remains to be verified, and results to date have varied. In examining 322 cases infected with HPV as research subjects, Lawton *et al.* (25) found HPV infection increased the risk of early membrane rupture and premature delivery. However, Xiong *et al.* (26) found HPV-positive women did not have an increased risk of premature birth compared with HPV-negative women, and that HPV infection did increase the risk of PROM. In another meta-analysis, Bonde *et al.* found HPV infection increased the risk of premature delivery, although there was no discussion regarding PROM in their study (27).

Meta-analysis of the included data in this study showed that pregnant women with high-risk HPV infection had a higher incidence of premature rupture of membranes than those in the negative control group, and women with high-risk HPV infection were more likely to have premature rupture of membranes. In addition, the results of this study showed that the high-risk HPV infection positive group had a higher incidence of preterm birth in the higher-risk HPV negative group, and the difference between the two groups was statistically significant. Therefore, it is said that women with high-risk HPV infection are more likely to have preterm birth. In addition, the Begg's and Egger's methods were applied to test publication bias, and the P values were both greater than 0.05, showing that there was no publication bias. HPV vaccine acts as primary prevention of cervical cancer for the receptor protection. With the deepening of clinical studies on the effectiveness of HPV vaccine in preventing HPV virus infection, universal prophylactic vaccination of HPV vaccine can be widely used to reduce cervical cancer, precancerous lesions, and adverse pregnancy outcomes. Recommended for all women user papilloma virus (HPV) vaccine, because of HPV vaccine clinical trials do not include pregnant women, known HPV vaccination during pregnancy is not recommended, but there are still some people choose to vaccination during pregnancy, especially during the first three months of pregnancy, the one who was unconscious or unable to identify pregnant will inadvertently vaccination. However, the safety of the HPV vaccine in pregnancy needs to be further studied. HPV infection, the second most sexually transmitted disease after gonorrhea, is not only linked to cervical cancer, but also increases the chances of adverse pregnancy outcomes. It hopes to include HPV screening as a physical examination project like gynecological ultrasound, especially in pre-marital examination and pre-pregnancy examination, as early as possible, to reduce the adverse effects of HPV infection.

This meta-analysis included several foreign articles studying various risk factors. However, the treatment time of the 7 included studies is contradictory, which may reduce the power of the results, and there is no report on the randomization method. Therefore, we encourage future researchers in this field to further improve the experimental plan, standardize the specific time, methods, and drugs of periodic interventions, and select high-quality, large-scale samples to obtain more reliable evidence the reliability of their results.

Conclusions

This meta-analysis found that HPV infection can affect the physiological conditions of pregnant women during pregnancy, leading to PROM and premature delivery. The meta-analysis results were basically stable, but there are still the following limitations. Due to differences in retrieval mechanisms, the retrieval may be incomplete. There are also differences in risk factors in distinct references, which may affect the reliability of the results. In addition, the studies included are all publicly published literature, and there may be potential publication bias. We recommend the conduct of more high-quality, multi-center, large-sample original research studies to provide a more reliable theoretical basis for the prevention of complications during pregnancy and improve the survival rate of pregnant women and fetuses.

Acknowledgments

Funding: Key Science and Technology Research Plan of Hebei Provincial Department of Health (20171023).

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2497

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2497). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: B. Draper)

Cite this article as: Wu D, Chen L, Zhen J, Jin X. Systematic review and meta-analysis on influence of human papillomavirus infection during pregnancy on premature rupture of membranes and premature delivery. Ann Palliat Med 2021;10(10):10735-10743. doi: 10.21037/apm-21-2497

