Vertical transmission of the human papillomavirus: a systematic quantitative review

Transmissão vertical do papilomavírus humano: uma revisão sistemática quantitativa

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Abstract

In order to better understand the exact mode and risk of vertical transmission in asymptomatic pregnant women, as well as the relationship between HPV transmission and mode of delivery, we have proposed this systematic quantitative review of prospective cohort studies. A comprehensive search was performed in the Cochrane Library, MEDLINE, LILACS, CANCERLIT, and EMBASE, as well as in the reference lists from the identified studies. Nine primary studies, which included 2,111 pregnant women and 2,113 newborns, met our selection criteria and were analyzed. A positive HPV test in the mother increased the risk of vertical HPV transmission (RR: 4.8; 95%CI: 2.2-10.4). We also observed a higher risk of HPV infection after vaginal delivery than after cesarean section (RR: 1.8; 95%CI: 1.3-2.4). The results of this meta-analysis showed the HPV DNA-positive rate only after birth, but an HPV DNA-positive neonatal sample does not necessarily indicate infection; it could merely indicate contamination (perinatal HPV contamination may have occurred). Infants born through vaginal delivery were at higher risk of exposure to HPV.

Systematic Review (Publication Type); Meta-Analysis; Vertical Transmission; Papillomavirus

Introduction

Human papillomavirus (HPV) infection is highly common among sexually active young adults, with an estimated prevalence between 20.0% and 46.0% [1]. HPV oncogenic types are the principal cause of cervical cancer, because they are capable of inducing cellular immortalization with transformation to the malignant phenotype and loss of tumor suppressor genes [1,2]. In children, the virus can cause recurrent respiratory papillomatosis (RRP), a benign and rare disease almost always caused by one of two HPV types, HPV6 or HPV11. However, cervical cancer is an aggressive neoplasm that produces considerable morbidity [3,4].

The association between sexual activity and cervical cancer has been known. It is also well recognized that high-risk HPV is spread by sexual activity [1]. There is growing evidence that HPV infection is acquired through non-sexual routes, and that one potential route is mother-to-child transmission in the perinatal period [5,6,7,8]. Although epidemiological trials suggest the possibility of non-sexual transmission, there is evidence of vertical transmission, presumably occurring during passage of the fetus through an infected birth canal. The virus could also be transmitted by ascending infection, principally after premature rupture of membranes [5,6,7]. Elective cesarean delivery could benefit infants of HPV DNA-positive mothers by reducing the

neonatal contamination rate [8]. However, whether cesarean delivery could prevent transmission of the virus from HPV-positive mothers remains to be determined [8].

In order to better understand the exact mode and risk of vertical transmission in asymptomatic pregnant women, as well as the relationship between HPV transmission and mode of delivery, we have proposed this systematic quantitative review.

Methods

Search strategy

We conducted a complete search of MEDLINE (OVID version) (1966 to April 2004), CINAHL (1982 to April 2004), LILACS (1980 to April 2004), EMBASE (Excepta Medica Database – 1980 to April 2004), Cochrane Central (1984 to April 2004). The following key words were used: HPV, pregnancy, newborn infants, vertical transmission, maternal-fetal transmission, perinatal infection, and perinatal transmission. Reference lists of all available primary studies were reviewed to identify additional relevant citations. There were no language restrictions. We attempted to contact the respective authors.

Selection criteria

This was a review of prospective cohort studies including pregnant women from all races and ages which examined transmission of HPV infection to newborns. HPV infection was investigated by polymerase chain reaction (PCR) in the maternal cervix between 20 and 40 weeks of gestation, and in the newborn infant's oral mucosa and/or genital area at delivery. Retrospective cohort studies, case-control studies, and case-series were excluded.

Three outcomes were measured: (1) HPV prevalence in pregnant women and newborns in each trial; (2) risk of mother-to-child HPV transmission defined as a positive HPV test (PCR); (3) risk of mother-to-child HPV transmission according to mode of delivery.

The reviewed studies were identified independently by four investigators (L. R. M., A. B. M. E., R. R. Z. and O. B. S.). All trials which appeared relevant on the basis of "title", "abstract", and "MeSH headings" were selected for full review by three independent reviewers. Articles were only rejected on initial screening if it could be determined from the title or abstract that the article was not a report of a prospective cohort study. Final inclusion and exclusion was made with reference to a checklist, which consisted of items based on the selection criteria.

Quality assessment

All articles meeting the eligibility criteria were assessed for their methodological quality. This assessment involved scrutinizing study designs and relevant features of population, test, and reference standards [9,10]. Each trial's quality was assessed by two different methods. In the first method the results were summarized using the Ottawa-Newcastle system [10], in particular the use of stars awarded for each criterion in three domains (cohort selection, cohort comparability, and outcome) (Table 1). Studies were further assessed for methodological quality with reference to the Oxford Center for Evidence-Based Medicine Levels of Evidence Classification rubric [11]. Only studies with Oxford Evidence Levels 1 to 3 were considered classified as high-quality, while those with levels 4 and 5 were excluded. These features included the data collection and patient selection methods, definition of a positive HPV test (PCR) in pregnant women and newborns, and presence of verification bias [12,13,14,15].

Data extraction

English-language articles were assessed by 2 reviewers (L. R. M. and A. B. M. E.) and those published in other languages were evaluated independently by 2 different reviewers (R. R. Z. and O. B. S.) following translation (when necessary). Disagreements were resolved by consensus, and when this was not possible, by arbitration with a fifth reviewer (M. C. B.).

From the potentially relevant articles, four reviewers independently selected the studies (based on the full-text format) for inclusion in this review. Thus, three outcomes were considered: (1) HPV prevalence in pregnant women and newborns; (2) risk of mother-to-child HPV transmission; (3) risk of mother-to-child HPV transmission according to mode of delivery. HPV prevalence data were calculated separately for sources with positive and negative results. Transmission risk data were abstracted as 2x2 tables (newborns HPV-positive/negative versus mothers HPV-positive/negative). Similarly, a contingency table was produced for

Table 1

Ottawa-Newcastle quality assessment scale cohort studies [10].

Domains, cohort studies	Characteristics
Selection	1 – *Representativeness of the exposed cohort* a) truly representative of the average _____ (describe) in the community* b) somewhat representative of the average _____ in the community* c) selected group of users d) no description of the derivation of the cohort 2 – *Selection of the non exposed cohort* a) drawn from the same community as the exposed cohort* b) drawn from a different source c) no description of the derivation of the non-exposed cohort 3 – *Ascertainment of exposure* a) secure record* b) structured interview* c) written self report d) no description 4 – *Demonstration that outcome of interest was not present at start of study* a) yes* b) no
Comparability	5 – *Comparability of cohorts on the basis of the design or analysis* a) study controls for _____ (select the most important factor)* b) study controls for any additional factor*
Outcome	6 – *Assessment of outcome* a) independent blind assessment* b) record linkage* c) self report d) no description 7 – *Was follow-up long enough for outcomes to occur?* a) yes* b) no 8 – *Adequacy of follow-up of cohorts* a) complete follow-up – all subjects accounted for* b) subjects lost to follow-up unlikely to introduce bias – smal number lost - > _____ % (select an adequate %) follow-up, or description provided of those lost)* c) follow-up rate < _____ % (select an adequate %) and no description of those lost d) no statement

* A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability.

mother-to-child HPV transmission risk according to mode of delivery (newborns HPV-positive/cesarean versus newborns HPV-positive/vaginal delivery).

Statistical aspects

To evaluate agreement between study eligibility and methodological quality assessment, the observed percentage agreement and κ coefficient for inter-rater reliability were calculated [12]. HPV prevalence rates in pregnant women and newborns were calculated by pooled estimates in each trial. For two other outcomes, in each trial we constructed 2x2 contingency tables. Relative risk (RR) and the respective 95% confidence intervals (95%CI) were calculated for all effect size estimates for both individual studies and pooled estimates. Summary risk estimates were calculated using a general-variance-based fixed effect model (assessed with a homogeneity test), and the relative risks were pooled with a random effects model in cases of heterogeneity [14,15]. We tested for homogeneity of the combined effect sizes by the χ^2 test, with $p < 0.05$ indicating significant heterogeneity [14,15]. When the 2x2 tables contained 0 cells, 0.5 was added to each cell to enable our calculations to be made. Data analyses were done using the Comprehensive Meta-Analysis and Review Manager software (RevMan).

Sensitivity analysis

To evaluate the stability of the overall risk estimate, a sensitivity analysis was performed by iteratively eliminating each study and calculating the resulting RR [15]. The robustness of the results was tested by repeating the analysis using different statistical models (fixed and random effects model) [15]. We did not use funnel plots because there are numerous and confounding factors that may introduce heterogeneity in the context of observational meta-analysis [15].

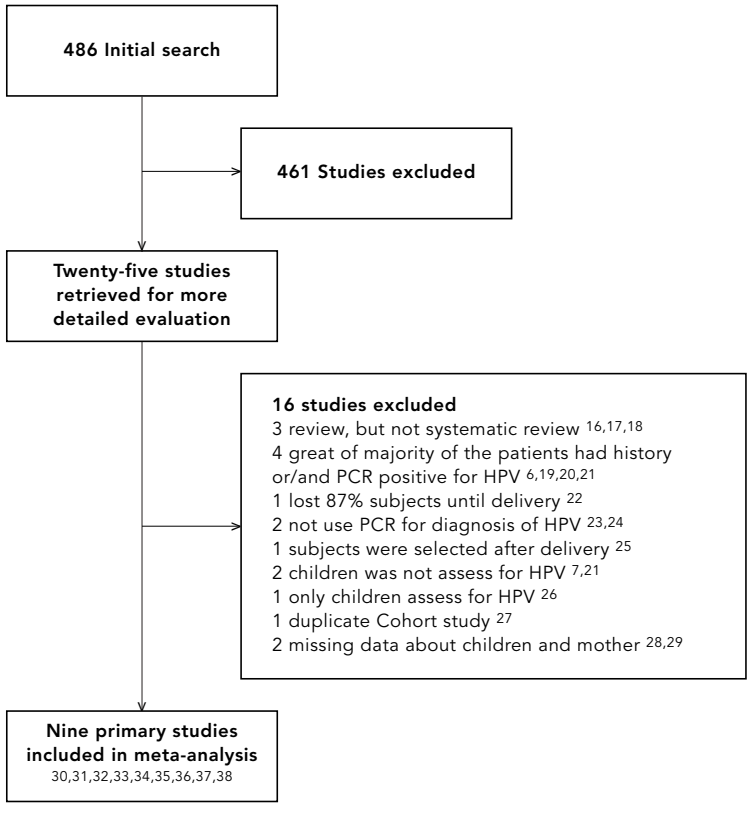
Results

Study identification and eligibility

Figure 1 summarizes the study selection process. Our initial search identified 486 articles. Twenty-five met the initial eligibility criteria, and full-text articles were retrieved. We excluded 16 studies [6,7,16,17,18,19,20,21,22,23,24,25,26,27,28,29], leaving 9 included in the analysis [30,31,32,33,34,35,36,37,38], involving a total of 2,111 pregnant women and 2,113 newborns. Inter-rater agreement for study eligibility was 79.0% (κ = 0.64), indicating good agreement [12].

Figure 1

Study selection process.



Study description

Table 2 summarizes the details of participants, outcomes, and quality assessment of the studies selected for meta-analysis. Participants' ages across studies ranged from 16 to 45. All nine were prospective cohorts from a narrow population, but included sufficient details and diagnostic reference standards [30,31,32,33,34,35,36,37,38]. There were six studies with high methodological quality, satisfying greater than 86.0% of the criteria for study quality (seven or more stars for each quality criterion in the Ottawa-Newcastle system) [30,31,32,33,34,36]. However, two trials were classified as level 3B, because details of the patient population including age were not reported [37], and the sample size was small (n = 30) [38].

Table 2

Characteristics and assessment of quality of studies.

Study	Year	Age (range)	Subjects		Mother HPV+		Newborn HPV-		Follow-up	Newcastle-Ottawa assessment [10]								Oxford evidence level [11]
										Selection			Compa-rability	Outcome				
			Mother	Infant	n	%	n	%		1	2	3	4	5	6	7	8	
Bandyopahyay et al. [30]	2003	20-39	135	135	38	36.8	14	10.0	12 months	*	*	*	*	*	*	*	–	2B
Pakarian et al. [31]	1994	17-37	31	32**	20	65.0	12	39.0	6 weeks	*	*	*	*	*	*	*	*	2B
Puranen et al. [32]	1997	18-40	105	106**	42	39.0	39	37.0	Delivery	*	*	*	*	*	*	*	*	1B
Smith et al. [33]	2004	18-45	574	574	172	30.0	9	1.6	6 months	*	*	*	*	*	*	*	–	1B
Tenti et al. [34]	1999	16-43	711	711	37	5.5	11	1.5	18 months	*	*	*	*	*	*	*	*	1B
Tseng et al. [35]	1998	17-45	301	301	68	22.5	27	9.0	Delivery	*	*	*	*	*	*	–	–	2B
Watts et al. [36]	1998	16 > 30	151	151	95	63.0	8	5.2	36 months	–	*	*	*	*	*	*	*	2B
Xiaoping et al. [37]	1998	Not reported	73	73	26	35.6	5	19.0	Delivery	–	*	*	*	*	*	–	–	3B
Xu et al. [38]	1995	22-36	30	30	16	53.3	14	46.6	Delivery	–	*	*	*	*	*	–	–	3B
Total			2,111	2,113	514/ 2,111	24.3	139/ 2,113	6.5										

* The use of stars awarded for each criterion was based on the Ottawa-Newcastle system [10];
** One set of twins.

HPV prevalence in pregnant women

In vertical transmission studies, which included mothers who were positive and negative for HPV by PCR, the percentage of positive mothers varied from 5.5% to 65.0%, with a pooled estimate of 24.3% (95%CI: 22.0-26.0) (Table 2). Our meta-analysis showed 139 PCR HPV-positive newborns, with a transmission rate varying from 1.5% [21] to 46.6% [25] and a combined rate of 6.5% (95%CI: 5.0-8.0).

Mother-to-child HPV transmission risk

The combined relative risk for mother-to-child HPV transmission was 7.3 (95%CI: 2.4-22.2; test for heterogeneity $\chi^2 = 46.3$, df = 8, $p < 0.001$) [30,31,32,33,34,35,36,37,38]. Due to substantial heterogeneity, studies were also pooled with a random effects model, and sensitivity analysis was processed. Two studies with observed frequency equal zero in 2x2 tables [34,37], three studies with more than 40.0% of HPV-positive mothers [31,36,38], and one that failed to satisfy the study quality criteria (≥ 87.0%) of the Ottawa-Newcastle system [35] were excluded. Thus, after sensitivity analysis, the pooled relative risk from three studies [30,32,33] was 4.8 (95%CI: 2.1-10.9). There was homogeneity between these studies ($\chi^2 = 3.4$, df = 2, $p = 0.18$) (Table 3; Figure 2).

HPV transmission risk and mode of delivery

Seven studies compared vaginal delivery and cesarean section in HPV-positive women [30,32,33,34,35,37,38]. The combined relative risk for transmission according to mode of delivery was 1.8 (95%CI: 1.3-2.4). There was statistical homogeneity between studies ($\chi^2 = 4.20$, df = 6, $p = 0.6$), and both the fixed and random effect models produced the same values (Table 4; Figure 3).

Discussion

This was the first systematic review to evaluate vertical HPV transmission. The results of this review showed that there is a risk of mother-to-child HPV transmission when the mother presents a positive HPV test. Pooled mother-to-child HPV transmission was 6.5% and was higher after vaginal delivery than cesarean section (18.0% versus 8.0%). The combined relative risk of mother-to-child HPV transmission from nine studies was 7.3 (95%CI: 2.4-22.2), but there was great heterogeneity between these studies [30,31,32,33,34,35,36,37,38]. Therefore, in this and nearly all other meta-analyses, there was extensive clinical heterogeneity, because all studies were observational. This shows that simply combining the results of studies into one overall estimate can be misleading, and that

Table 3

Infection of HPV in mother and newborn infants and risk of transmission.

Study	Year	Type of HPV (PCR)	Mother HPV positive/negative		Newborn HPV+	Newborn HPV-	Relative risk	95%CI (random model)	*p*
Bandyopadhyay et al. [30]	2003	6, 11, 16, 18, 31, 33, 113, 109, 334, 456, 514	Positive	38	7	31	2.5	0.9-6.7	0.1
			Negative	97	7	89			
Pakarian et al. [31]	1994	16, 18, 31, 33	Positive	20	10	10	1.8	0.6-5.2	0.3
			Negative	11	3	8			
Puranen et al. [32]	1997	6, 11, 16, 18	Positive	42	33	9	8.2	3.7-17.0	< 0.001
			Negative	63	6	57			
Smith et al. [33]	2004	2, 6, 7, 11, 16, 18, 30, 31, 33, 53, 66	Positive	172	6	166	4.6	1.2-18.4	0.01
			Negative	402	3	399			
Tenti et al. [34]	1999	16, 18, 31, 33, 35, 39, 51, 54, 58, 59, 68, 70, 6, 11, 13, 38, 44, 53, 56, 61, 66, 69, 83, 84	Positive	37	11	26	40.8	24.5-6803.0	< 0.001
			Negative	674	0	674			
Tseng et al. [35]	1998	16, 18	Positive	68	37	31	42.2	13.0-132.0	< 0.001
			Negative	233	3	230			
Watts et al. [36]	1998	16, 18	Positive	95	3	92	0.3	0.08-1.4	0.2
			Negative	56	5	51			
Xiaoping et al. [37]	1998	6, 11, 42, 43, 44, 31, 33, 35, 51, 52, 16, 18, 45, 56	Positive	26	11	15	40.8	2.5-667.0	< 0.001
			Negative	47	0	47			
Xu et al. [38]	1995	16, 18, 35	Positive	16	14	2	12.2	1.8-81.0	< 0.001
			Negative	14	1	13			

Figure 2

Mother-to-child HPV transmission risk.

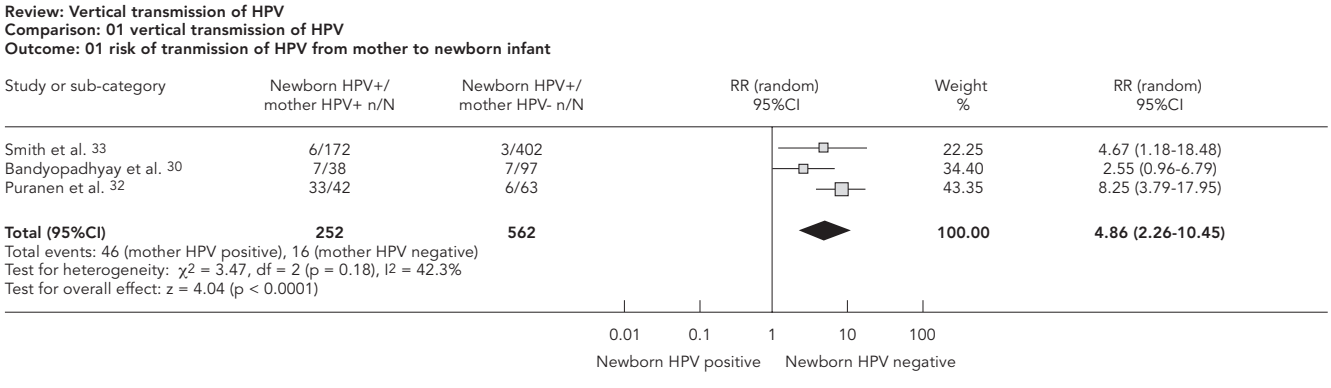


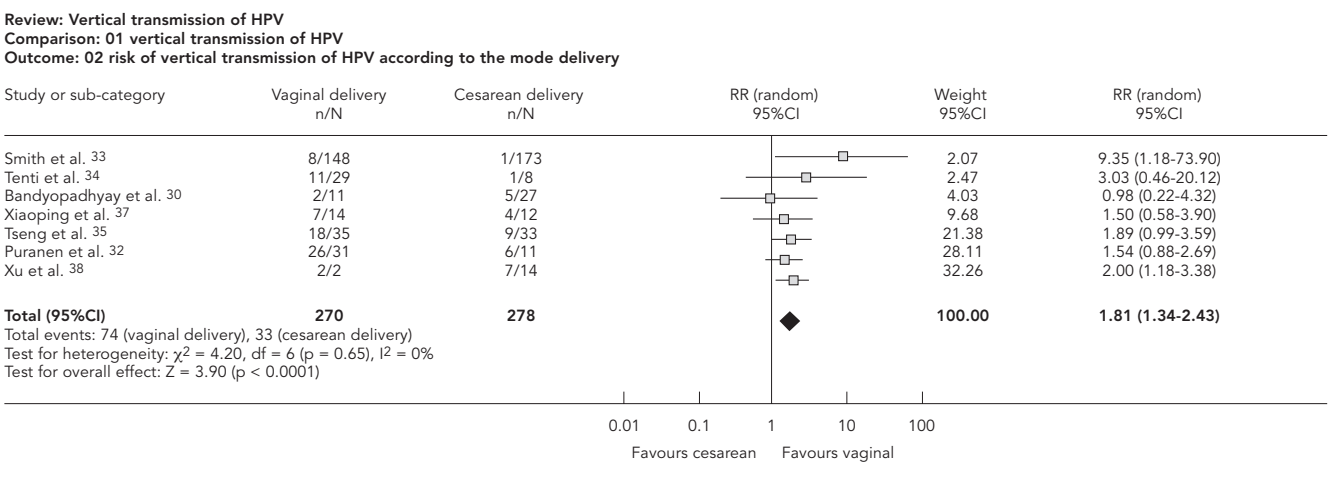
Table 4

Infants born to HPV-positive mothers according mode of delivery.

Study	Year	Type of delivery	Newborn HPV+	Newborn HPV-	RR	95%CI (random model)	p
Bandyopahyay et al. [30]	2003	Vaginal	2	9	0.9	0.2-4.3	0.6
		Cesarean	5	22			
Puranen et al. [32]	1997	Vaginal	26	5	1.5	0.8-2.6	0.04
		Cesarean	6	5			
Smith et al. [33]	2004	Vaginal	8	140	9.3	1.1-73.0	< 0.01
		Cesarean	1	23			
Tenti et al. [34]	1999	Vaginal	11	18	6.9	0.4-105.0	0.1
		Cesarean	0	8			
Tseng et al. [35]	1998	Vaginal	18	17	1.8	0.9-3.5	0.07
		Cesarean	9	24			
Xiaoping et al. [37]	1998	Vaginal	7	7	1.5	0.5-3.9	0.3
		Cesarean	4	8			
Xu et al. [38]	1995	Vaginal	2	0	1.6	0.8-3.4	0.6
		Cesarean	7	7			

Figure 3

Vertical HPV transmission risk according to mode of delivery.



the reasons for heterogeneity need to be understood. The trials differed considerably in patient selection, number, and kind of HPV research, sample size, and duration of follow-up. After sensitivity analysis, the pooled relative risk was 4.8, but with homogeneity between studies [30,32,33].

Tenti et al. [34] and Xiaoping et al. [37] found a large effect size for risk of vertical HPV transmission, because they did not have HPV-positive newborns from HPV-negative mothers (0 cells in 2x2 tables). This probably occurred because one study had a small number of HPV-positive mothers (5.2%) [34], while the other had a limited sample (n = 73) [37]. Three other studies showed more than 40.0% of HPV-positive mothers [31,36,38]. Meanwhile, Xu et al. [38] had a small sample size (30 patients). Some authors have attempted to detect HPV DNA in amniotic fluid [37,38], while two others detected HPV DNA in newborns from swab specimens collected from the oral and/or genital mucosa [30,31,32,33,34,35,36].

Smith et al. [33] detected pair concordance of HPV types in only one mother/infant pair. Furthermore, one-third of newborns tested positive who were born to mothers who had tested HPV DNA-negative during pregnancy. In some studies there was the possibility of HPV DNA contamination, because they failed to use DNA sequencing, which reduces the probability of false-negative and false-positive results [34]. In addition, there are type-discordant cases between mothers and newborns, suggesting that many of these infants did not acquire the HPV from their mothers [33].

The seven studies that evaluated the association between mode of delivery and vertical HPV transmission showed an increased risk of HPV transmission during vaginal delivery [30,32,33,34,35,37,38]. We found clinical homogeneity in several characteristics. All tested the same hypothesis. They measured similar endpoints and included only HPV-positive mothers with comparable characteristics (such as age and gestational age). According to some authors, cesarean delivery could reduce transmission because it avoids ingestion of infected maternal secretions or blood during fetal passage through the birth canal [8,35]. However, Eppel et al. [7] suggest a possible trans-placental transmission route. We thus need to consider that true infection would have occurred in uterus rather than in the birth canal [39]. We found an 8.0% HPV- positive newborn rate following cesarean section. Therefore, the cesarean delivery would not be effective for protecting newborns from HPV-positive mothers.

This meta-analysis complied with the criteria for performing a rigorous systematic review planned a priori [13,14,15]. This included the use of study quality assessment [10,11] and investigation of homogeneity by fixed and random models to test the robustness of the results [13,14,15]. On the other hand, the potential limitations of this systematic review were the limited number of studies, as well as data which were produced from observational trials. An overall effects measure could be biased, because the confounding factors introducing heterogeneity between studies. Another limitation is that we did not search for unpublished studies.

In this systematic review, the overall results suggest that perinatal HPV transmission occurred and that newborns are at higher risk of exposure to HPV with vaginal delivery as compared to cesarean section. However, because of the heterogeneity, the mathematically pooled results should be interpreted with caution. The results of this meta-analysis showed the HPV DNA-positive rate only after birth, but an HPV DNA-positive sample does not necessarily indicate infection; it could merely indicate contamination with infected maternal cells [13]. In this systematic review, only one study followed infants for an extended period of time (36 months) [37].

In summary, there is insufficient evidence to recommend the generalization of cesarean section for all HPV DNA-positive mothers. The critical question is not how often infants are contaminated with HPV, but how often they are infected with HPV. More studies with better methodological quality, longer follow-up, and HPV testing by DNA sequencing in this area are needed.

Resumo

Para entendimento do modo exato de transmissão vertical e de seu risco em gestantes assintomáticas, bem como a relação entre a transmissão de HPV e o tipo de parto, foi proposta uma revisão sistemática quantitativa de coortes prospectivas. Foi realizada uma busca na Biblioteca Cochrane, MEDLINE, LILACS, CANCERLIT e EMBASE e nas referências dos estudos identificados. Nove estudos, que contaram com 2.111 gestantes e 2.113 recém-nascidos, foram incluídos de acordo com critério de seleção e foram analisados. O teste positivo para HPV na mãe aumentou o risco de transmissão vertical para HPV, com risco relativo (RR = 4,8; IC95%: 2,2-10,4). Foi observado um maior risco de infecção por HPV após parto vaginal (RR = 1,8; IC95%: 1,3-2,4). Os resultados dessa metanálise mostraram uma taxa de positividade para o DNA do HPV somente após o nascimento, porém a taxa de positividade para DNA do HPV em amostras de recém-nascidos não indica infecção; pode indicar apenas contaminação. Concluiu-se que a transmissão perinatal de HPV pode ocorrer e, após parto vaginal, os recém nascidos têm risco maior para exposição ao vírus.

Revisão Sistemática (Tipo de Publicação); Metanálise; Transmissão Vertical de Doença; Papilomavírus

Contributors

L. R. Medeiros, A. B. M. Ethur, R. R. Zanini, and M. C. Bozzetti contributed to all stages in the elaboration of the article. J. B. Hilgert and L. C. Mylius collaborated in the search strategies and methodological quality evaluation of the articles. O. Berwanger evaluated the methodological quality of the articles.

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