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Papillomavirus infection and preterm birth: chronicle of a broken relationship? (Case series and review of the literature)

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Abstract

Human papillomavirus (HPV) infection is widespread. Approximately 40 HPV serotypes infect ano-genital area, but most infections are asymptomatic and can get cleared spontaneously. HPV clearance is modified during pregnancy. Many information have been published about HPV infection and preterm birth, unfortunately the results are often not corresponding. The aim of this study was to understand whether there is an association between HPV infection and preterm birth. In our study we reported results about 20 pregnant women admitted for preterm birth. We assessed if and how papillomavirus cervical

infection affects pregnancy outcome. HPV prevalence in pregnant women in this case series was 45% (9/20), while 55% pregnant women were found HPV-negative (11/20). There was no difference between HPV positive group and HPV negative group in terms of gestational age at delivery, neonatal weight, Apgar score. Our data, even though from a very small series, confirm the absence of different outcomes due to HPV infection. It has been reported that women with H-SIL have a higher baseline risk for PTB than general population and treatment for H-SIL probably increase this risk further. The research on HPV and PTB should go straight to this direction.

Introduction

Papillomavirus (HPV) is a double-stranded DNA virus, in humans it can cause infections in multi-layer squamous epithelium of the skin and/or mucosae [1]. HPV is the most common sexually transmitted infection in adults [2]. The highest incidence rates occur in young adults, both men and women. Among 150 serotypes, there are low-risk and high-risk HPV, related to cervical, vaginal, vulvar lesions and cancers. Approximately 40 HPV serotypes infect ano-genital region [1], but most infections are asymptomatic and can get cleared spontaneously because of normal competent immune system´s response [3]. Young women aged 20-35 are at higher risk of HPV infection, furthermore this is the age when women are more sexually active and can get pregnant [3]. Pregnancy can promote the persistence of HPV infection because of specific hormonal milieu and immunological "tolerance" process [2]. Recent reports have been published about HPV infection and adverse pregnancy outcomes (miscarriages, PPROM, pre-term birth) [4-6], with not homogeneous results [7-14]. Indeed most of the studies were too much heterogeneous: different examined sample (Pap smear, HPV DNA cervical swab, amniotic fluid, placenta), variable timing of sampling (during pregnancy, post-partum, within 3 years to delivery), mechanism of action evaluated (cervical lesion, placental and membranes infection), moreover there were different outcomes (preterm-birth, PPROM). From the latter data it seems that major risk factor for pre-term birth could lay on HPV-related cervical H-SIL [14]. Thus HPV-infection and high-grade squamous intraepithelial lesion (HSIL) may alter cervical function and competence, possibly increasing the risk of intrauterine infection [15,16]. Both uterus and growing fetus are protected from ascending infection by the cervix, which controls and limits microbial access by the production of mucus, cytokines and anti-microbial peptides (AMPs). If this barrier is compromised, bacteria may enter into uterine cavity leading to preterm birth [16]. In the present study we investigated the prevalence of HPV-DNA in a series of 20 pregnant women admitted for high risk pre-term birth at different gestational age (2nd and 3rd trimester) and followed until delivery (pre-term or at term). We assessed if and how papillomavirus cervical infection affected pregnancy outcome. Pre-term birth diagnosis was based on Italian society of Obstetrics and Gynecology definition "birth before 36 6/7 weeks of gestation" [17].

Methods

Twenty women admitted for threatened PTB were asked for previous Pap smear or HPV status and they signed an informed consent, form September 2019 to December 2019. Those women who were previously diagnosed with HPV infection or had low or high SIL were excluded from this series. Inclusion criteria were: diagnosed threatened pre tem birth, hospital admission, previous normal Pap smear. Sample collection: cervical citology samples were collected by dry swabs, before performing transvaginal scan and/or obstetrical physical evaluation. An Obstetrics and Gynecology resident was instructed to vaginal samples. No lubricants nor saline infusion were used in order to reduce vaginal discomfort. Swabs were immediately put in a sterile plastic container with phosphate buffer saline solution (20cc), shaken, then removed. Storage was kept not underneath 4°C. HPV-DNA extraction and typing: viral DNA was extracted by

magnetic beads and amplified in real time multiplex. PCR amplification detected 14 high risk types (16,18,31,33,35,39,45,51,52,56,58,59,66,68), with a clinic sensibility of 97.5%. Low risk HPV types were revealed but no typed (test result: positive, unknown type).

Results

A total of 20 samples were collected and examined. HPV prevalence in pregnant women in this case series was 45% (9/20), while 55% pregnant women were found HPV-negative (11/20). All samples were positive for high risk HPV type, but one. (Resulted positive for low risk HPV). Among high-risk HPV positive pregnant women three of them showed coinfection: 45-52, 39-56, 35-59. Most frequent type in this short series was HPV45 (3/9) followed by HPV16 (2/9) (Table 1). Three HPV negative women and three HPV positive women had a preterm premature rupture of membranes (PPROM), respectively 27% and 33%. There was no difference between HPV positive group and HPV negative group in terms of gestational age at delivery, neonatal weight, Apgar score (Table 2). The sample size is quite small, but we decided to stop the study because of the costs of HPV DNA evaluation. Furthermore management and treatment didn´t differ between positive or negative cases.

Discussion

Human Papillomavirus infection is widespread; lifetime probability of genital HPV infection is estimated to be more than 80% [2]. It´s commonly well known that almost 80% of HPV infections resolve spontaneously within 2 years, but pregnancy represents a condition with altered and slow viral clearance [4]. Given the high clearance rate of HPV genital infections and the different reaction of immune system during pregnancy, measuring viral exposure out of the pregnancy could lead to bias and not clear results [18]. More bias could come up because of heterogeneity of studied population, type of samples, outcomes, kind of studies (review, cross sectional case series..). Thus published results are often in contrast and inconsistent (Table 3). Lawton [18] reported reduced risk of preterm birth in women vaccinated against HPV. Mosbah and Ambuhl studying a population of pregnant women showed a relationship between HPV infection and poor pregnancy outcome [13,19]. A review by Huang *et al*. demonstrates higher risk for preterm birth due to HPV infection only for Caucasian women, not for Asian population [12]. But it´s mandatory to remind that HPV infection could be a source of anxiety for pregnant women and their family [2]. Health professional should have the possibility to reassure pregnant women asking for their own HPV infection and related pregnancy risks. Despite the small number of this case series, in our opinion it represents the actual scenario. Latter data from Aldhous *et al*. [14] from Scottish population registry demonstrate that HPV infection doesn´t involve any adverse pregnancy outcome, but H-SIL and related therapies on the cervix do. In absence on any associations between HR - HPV infections alone or low grade cervical disease, and considering that most of high grade cervical lesions would have been treated, Authors [14] postulated that H-SIL treatment represent a risk factor for preterm birth. Hypothesis supported previously by many authors who considered Leep as preterm birth risk factor [20-22]. Our data, even though from a very small series, confirm the absence of different outcomes due to HPV infection. Limitations of our data come from small size of study population, timing of HPV testing at the moment of PPROM or threaten of preterm labor.

Conclusion

Papilloma virus studies in relation to preterm birth PTB prevention and management represent a great challenge. Early identification of high risk women would allow prophilactic measures, reducing social and health costs. HPV infection prevalence in general population is variable but higher than PTB prevalence rate worldwide. HPV prevalence has been demonstrated to be dependent on the tissue

type tested and the geographical location of the study population analyzed. However, the number of studies investigating HPV infection on material from spontaneous abortions and spontaneous preterm deliveries is limited [19]. We are aware that pathogenetic mechanism of first trimester abortion and PTB, even very early, could be totally different, in terms of papillomavirus action. It´s well established and reported women with CIN (cervical intraepithelial neoplasia) have a higher baseline risk for PTB than the general population and the treatment for CIN probably increase this risk further. The risk for PTB is probably higher when excisional techniques are used than for ablative treatments. Also, the risk of PTB appears to increase with multiple treatments and increasing amounts of tissue removed [23]. It should be kept in mind that a simple detection of papilloma virus never is equal to a real causative role in the adverse outcome of a pregnancy [19]. Based on Ambuhl´s review, it could be stated that HPV is more prevalent in pregnancy with adverse outcome. But it could be speculated as well that pregnancies with adverse outcome represent a bias because considering only at risk population group. Case series of this study is a clear example: among PTB high risk women (diagnosed by cervicometry and modification of cervix) HPV prevalence has resulted 45%. Accepting a role for HPV in preterm labor's pathogenesis, secondary biomolecular changes or hiatrogenic weakening of the cervix we can presume that HPV vaccination could lead to significant preterm birth reduction. As a consequence the potential global public health impact could be considerable [18].

What is known about this topic

- *Women with CIN (cervical intraepithelial neoplasia) have a higher baseline risk for PTB than the general population. Simple detection of papilloma virus never is equal to a real causative role in the adverse outcome of a pregnancy. HPV is more prevalent in pregnancy with adverse outcome.*

What this study adds

- *Absence of different pregnancy outcomes due to HPV infection. CIN treatment could have consequences correlated to PTB.*

Competing interests

The authors declare no competing interests.

Authors' contributions

Laura Giambanco drafted the article. Vito Iannone and Maddalena Borriello enrolled women. Antonella Federica Montalto collected clinical data. All the authors have read and agreed to the final manuscript.

Tables

Table 1: demographic and pregnancy outcome data in HPV-positive group versus HPV-negative group

Table 2: neonatal outcome in HPV-positive group versus negative group

Table 3: conflicting published data

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Table 1: demographic and pregnancy outcome data in HPV-positive group versus HPV-negative group						
Maternal age (years)	**PPROM**	**Gestational age at the time of HPV DNA Test (weeks)**	**Gestational age at delivery (weeks)**	**Neonatal weight (grams)**	**Apgar score**	**HPV DNA Test**
31	No	33	35	2650	9-10	Negative
35	Yes	35	35,4	2500	9-9	45
18	No	32	34,2	2330	9-10	45, 52
35	Yes	31	31,3	1540	9-10	Positive
33	No	29	35	2380	9-10	16
28	No	27	38,6	3870	9-10	Negative
17	No	29	38,3	2850	6-8	39, 56
28	Yes	31,5	33,3	1730	8-9	Negative
41	Yes	36	36,3	3350	9-10	Negative
30	No	28	37,1	2700	8-9	16
27	Yes	24	27	900	5-7	Negative
33	No	27	33,1	2034	8-10	35,59
39	No	30	36,6	2627	9-10	Negative
33	No	28	34,4	2198	9-10	Negative
44	Yes	29	32	1860	7-9	45
36	No	24	36,6	2900	8-10	31
31	No	30	31,3	1720	7-9	Negative
29	No	32	37,2	2930	9-10	Negative
40	No	28	34	2430	8-9	Negative
24	No	33	38,6	3060	9-10	Negative

Table 2: neonatal outcome in HPV-positive group versus negative group		
Neonatal outcome	**HPV+ (9)**	**HPV- (11)**
Gestational age at delivery (weeks) (median)	34	35
Neonatal weight (grams) (median)	2340	2500
Apgar 1 (median)	8	9
Apgar 5 (median)	7	9

Table 3: conflicting published data			
Gomez, 2008	Preterm birth and term birth	Placenta	Significative correlation between HPV infection and PTB
Noehr, 2009	Women with previous pregnancies	Register data	Leep is a risk factor for PTB
Zuo ,2011	Pregnant women	Cervical citology, placenta	HPV infection is risk factor for PTB
Watson, 2012	Women with previous top, ptb,tb	Interview	Leep is a risk factor for PTB
Naresh, 2012	PPROM	Amniocentesis	No relationship with HPV infection
Van Hentenryck, 2012	Women with/without Leep	Register data	Leep is a risk factor for PTB
Cho, 2013	Women who had PTB, gestational diabetes, preeclampsia	Cervical samples	HPV risk factor for PPROM, not for PTB
Huang, 2014	Review	/	HPV infection is a risk factor for PTB only in caucasian women
Subramaniam, 2016	Cervical screening whitin 3 years before delivery	Cervical citology	No association between HPV infection and PTB
Ambuhl, 2016	Sistematic review	/	HPV infection related to adverse pregnancy outcome
Caballero, 2018	Cervical screening whitin 3 years before delivery	Cervical citology	HPV infection related to PPROM
Mosbah, 2018	Pregnant women	/	High risk HPV are risk factors for PTB
Lawton, 2018	HPV vaccinated population	/	Low rate PTB
Pandey, 2018	Pregnant women, 1st trimester	Cervical citology	HPV infection risk factor for PPROM
Aldhous, 2019	Women who had pregnancy	Register data	Leep is a risk factor for PTB
Legenda: PTB: preterm birth; TB: term-birth PPROM: premature-PROM; Leep: Loop Electrosurgical Excision Procedure			