

Mode of delivery does not have a relationship with high-risk HPV positivity

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Summary

Objective: This study aims to evaluate the delivery room data for patients who give birth with standard vaginal delivery and caesarean section (C/S), to estimate whether high-risk (HR) HPV status affected the mode of delivery. **Methods:** Between January 2014 and January 2018, 8,376 pregnant women gave birth in our hospital. Of 8,376 patients, 1,039 pregnant women were aged 30 years and older and had HPV results known. They had a singleton pregnancy and no contraindications for standard delivery. **Results:** C/S rates for all HR HPV groups were lower than for all HPV-negative groups. However, no statistically significant difference was found between HR HPV-positive and HPV-negative patients for C/S rates got all 987 patients (18.75% vs. 24.39%) ($p = 0.463$), 245 primiparous patients (50.0% vs. 59.83%) ($p = 0.629$) and 742 multiparous patients (11.53% vs. 12.56%) ($p = 0.876$). **Conclusion:** HR HPV positivity does not affect normal vaginal labour progress and does not statistically increase C/S rates at the labour ward. Therefore, HR HPV positivity should not be regarded as a negative risk factor for normal vaginal labour progress.

Key words: HPV; C/S transition; NSVD; Labour; Delivery; High-risk HPV.

Introduction

Human Papilloma Virus (HPV) is a small, non-enveloped circular double-stranded deoxyribonucleic acid (DNA) virus [1-3]. The relationship between HPV and cervical cancer is already known [3, 4]. Specifically, HPV types in the high-risk (HR) group (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) are screened by the Ministry of Health of Republic of Turkey through the routine HPV screening program of women over the age of 30. Appropriate referrals are made according to the results [5].

When the obstetric literature on HPV is searched, generally studies are about the vertical transition from mother to the fetus [6, 7]. Also, there are studies about the impact of HPV on pregnancy outcomes such as preterm labour, early membrane rupture [8-10]. Placental and trophoblast infection with HPV lead to immune sensitisation, and an exaggerated immune response generates an inflammatory process causing preterm parturition, so HPV might also be a risk factor for spontaneous preterm birth or spontaneous abortion [9-11]. However, there is no study on whether HPV affects the route of delivery, such as normal spontaneous vaginal delivery (NSVD) and caesarean section (C/S).

This study aims to evaluate whether HR HPV affected the mode of delivery, labour process and progress, by looking at the normal delivery and C/S rates of HR HPV patients that were planned to have NSVD in the birth ward.

Materials and Methods

The study was designed retrospectively. Between January 2014 and January 2018, 8,376 pregnant women gave birth in our second-degree (Bartın, Turkey) state hospital. As shown in Figure 1, 1,039 pregnant women were aged 30 years and older (the oldest was 45), for whom HPV results were known. Patients who were not eligible for normal birth, such as breech, shoulder, oblique, placental presentation, were excluded. Also, all multiple pregnancies were excluded from the trial group, since generally trial of labour to multiple pregnancies is not a preferred method in Turkey. As a result, 987 women remained within the scope of the study. We investigated the medical archive of the patients. Only three years of HPV results before their labour were included in our research group. Since this study aimed to investigate how HR HPV affects the normal labour process, patients who had previous C/S were excluded from the study. When multiple pregnancies were also excluded, 987 women remained within the scope of the study.

Pregnant women aged 30 years and over, with known HPV results in maximum three years range before the labour, with a singleton pregnancy and no contraindications for NSVD, were included in this study. Also, patients diagnosed with cervical dysplasia, cervical infection, patients with a history of cervical biopsy or any other cervical operations, and low-risk HPV positive patients have not been included.

Table 1. — Summary of the study groups, NSVD and C/S rates.

Route of delivery	All patients (987 patients)				Multiparous (742 patients)				Primiparous (245 patients)			
	Number of cases		HR HPV +	HPV -	Number of cases		HR HPV +	HPV -	Number of cases		HR HPV +	HPV -
NSVD	748	26	722	649	23	626	99	3	96			
C/S	239	6	233	93	3	90	146	3	143			
C/S Rate (%)	24.21	18.75	24.39	0.463	12.53	11.53	12.56	0.876	59.59	50	59.83	0.629
Totally Count of patients	987	32	955	742	26	716	245	6				

NSVD: Normal Spontaneous Vaginal Delivery; C/S: Cesarean.

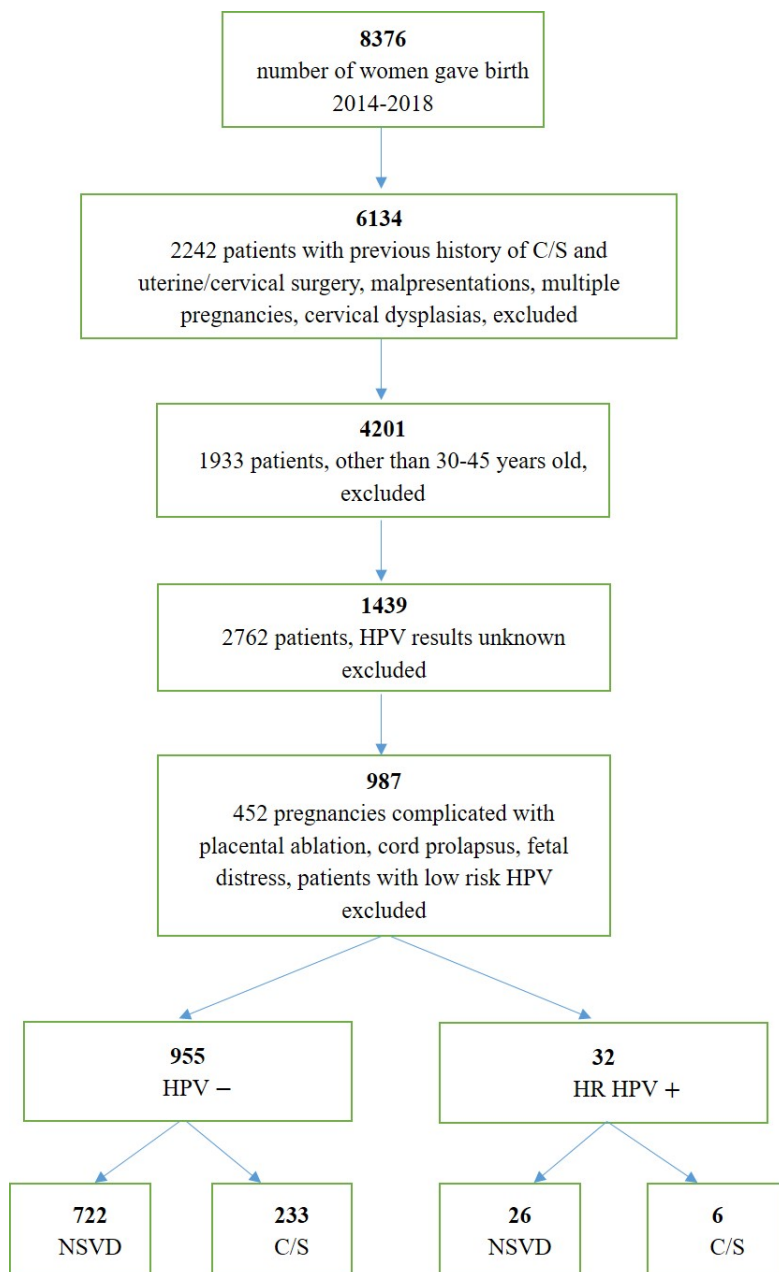


Figure 1. — Summary of the study groups' formation.

In Turkey, women aged between 30 and 65 years are invited for HPV screening by primary level health staff (family physicians, KETEM screening centres and in state hospitals as well) every five years. All screening processes are free of charge. The sample for HPV testing was taken with a brush and put into 5 ml of Standard Transport Medium, HPV DNA specimen collection kits (Qiagen HC2) for HPV DNA analysis. For women who are HPV positive by Hybrid Capture2 (Qiagen), genotyping is performed with the CLART kit (Genomica) [5].

Our study was approved by the ethics committee for clinical studies of Zonguldak Bülent Ecevit University, Turkey, with the approval number of 2018-239-19/12-5 after all permissions were taken from provincial health directorate and state hospital of Bartın.

Before the study began, all human participants gave informed consent for HPV testing and inclusion in the study. We investigated the medical archive of the patients, medical notes, and progress, namely follow-up notes of 8376 pregnant women who gave birth.

Statistical analysis was performed by using the SPSS programme 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Pearson Chi-square test was used for comparison of HR HPV-positive and HPV-negative. A *p*-value of less than 0.05 was considered statistically significant.

Results

Our study consisted of two parts. First; HPV results of 987 pregnant women who fulfilled the inclusion criteria, whether they were multiparous or primiparous, were recorded. Women positive for HR HPV formed HR HPV-positive group while women negative for HPV were included in the HPV-negative group. In this study, we sought to find whether there is a difference in the delivery route in HR HPV-positive and HPV-negative patients, according to the delivery room chart reviews.

As a subgroup analysis, only the primiparous women, who gave birth to their first baby in this trial, were included. Two hundred forty-five pregnant women who met the criteria mentioned above were evaluated according to HPV status and NSVD and C/S rates, as explained above. Also, as another subgroup analysis, 742 multiparous women that met the appropriate criteria were included. HPV status and NSVD and C/S rates were investigated, as well.

Out of 987 pregnant women (30-45 years old, primiparas or multiparas) that had no contraindication for NSVD, 748 delivered by NSVD and 239 had to undergo C/S. The rate of the C/S of this group was 24.21% (Table 1).

In the subgroup analysis, there were 245 primiparous women aged 30-45. The rate of C/S in this group was strikingly high (59.6%), alerting about soared C/S ratios. Ninety-nine NSVD and 146 C/S were performed. Of 245 patients, six were HR HPV-positive, and 239 were negative. The HR HPV rate for this subgroup is 2.4%. No statistically significant difference was found between HR HPV-positive and negative patients in terms of NSVD and C/S percent-

ages. However, the paucity of HR HPV-positive patients in this group might affect the statistical results ($p = 0.629$).

The other subgroup analysis included 742 multiparous women aged between 30-45 years. Because this subgroup was multiparous, the C/S ratio was low, 12.5%, as expected. Of the 742 patients, 26 were HR HPV-positive, and 716 were negative. The HR HPV ratio of this subgroup was 3.5%. No statistically significant difference was encountered between the NSVD and C/S rates of the multiparous HR HPV-positive group and HPV negative group ($p = 0.876$).

Discussion

As it is already known, HPV is the most common sexually transmitted infection in adults [12]. In previous researches, maternal infections, inflammation [13], and changes in vaginal bacterial microbiota [14] have been recognised as an underlying cause of major adverse pregnancy outcomes: miscarriage [15], spontaneous preterm birth [16], and hypertensive disorders related to pregnancy [17, 18].

Nimrodi *et al.*'s population-based cohort showed no association between positive HPV testing (Pap smear) and obstetric complications such as preterm delivery, cervical insufficiency, placental abruption, premature rupture of membranes (PROM), preterm PROM (PPROM), neonatal small for gestational age (SGA) and preeclampsia, in a population with 1.3% HPV infection [19]. According to that study, the only finding that came almost to a statistical significance was the relationship between evidence for HPV infection in Pap-smear and cervical insufficiency [19].

However, as we emphasised above, maternal HR HPV presence and relation to the labour progress was not mentioned in the literature, according to our knowledge. This study is the first study questioning the HR HPV effect on the labour process and progress in the delivery room.

Thirty-two of 987 pregnant women was HR HPV-positive, and 955 of 987 pregnant women were HPV-negative. In HPV negative group, 722 of them had NSVD, 233 of them had C/S. In HR HPV positive group, 26 of them had NSVD, 6 of them had C/S (Table 1). The HR HPV rate in this population is 3.2%. The HR HPV rate of Bartın, the city that our study took place, is 4%. Turkey HR HPV rate is between 2-8% in different studies [20-24]. Our study cohort also had a similar HR HPV-positive ratio (3.2%). Of those patients, no statistically significant difference was found between HR HPV-positive and HPV-negative patients in terms of NSVD and C/S percentages ($p = 0.463$).

In the literature, it is known that there may be a connection between HPV infection and cervical insufficiency. However, HPV detection with Pap smear leaves much to be desired so that no definitive result can be recorded [19]. In our study, the presence of HPV was not reported only according to the findings on Pap-smear but with definitive laboratory results. In our study; maternal HR HPV positiv-

ity was not found to be a risk for need of C/S, suggesting that uterine contractions and cervical response to the uterine contractions are not affected by HR HPV infection. In this sense, it is the first study regarding this association in the literature.

The mechanical features of the cervix are mainly aroused from its collagen content instead of smooth muscle content of the cervix, consisting of 15% of the cervix during pregnancy [25]. Cervical softening is the result of degradation of collagen by collagenase within the cervix and is affiliated with an increase in water content, making it susceptible to ripening [25].

Agents such as interleukin-8 have a selective effect stimulating the release of Matrix Metalloproteinase (MMP-8) granules and thus secreting collagenase [25].

Tumour invasion requires the degradation of the basement membrane and interstitial extracellular matrix [26]. Davidson et al. found a more pronounced *up*-regulation of MMP-2 in cervical carcinomas and a weaker one - in cervical intraepithelial lesions [27]. Also, Brummer et al. found a relationship between HR HPV and MMPs [26].

Considering that HPV could activate MMP, we hypothesized that the virus could promote cervical dilation and ease the progression of labour. With dilated cervix and activated MMP, cervix could quickly ripen, so HPV-positive patients could be more prone to give birth by NSVD with less need for C/S. Our results showed a positive relationship between HR HPV positivity with the progress of normal delivery, in the sense of less C/S transition rate in comparison with the HPV-negative group, albeit statistically insignificant. This result could depend on the paucity of the HR HPV positivity in our region and patients, such as only 6 HR HPV-positive pregnant women were in a primiparous group in our study.

Also, according to another view, HR HPV positivity may disturb physiological changes of cervix in normal labour progress, although we could not show which of the hypothesis was right. Also, by this second hypothesis, progressively increasing C/S rates could be postulated in this manner as well.

A significant limitation of this study is the retrospective design of the research, and as cervical cancer screening concern, only HR HPV subtypes are being screened. Therefore, we could not make subgroup analysis for HPV subtypes other than HR HPVs.

Zuo *et al.* found that cervical infection with HR HPV detected using HPV DNA testing had been associated with thrombosis and villitis in placental examinations and strongly associated with preterm birth [8]. However, in our study, we investigate full-term pregnant women and their cervical changes in the delivery room, which is not investigated in other studies up to now.

As a conclusion to this study, HR HPV positivity does not affect normal vaginal labour progress and does not statistically increase C/S transition rates at the labour ward. Therefore, HR HPV positivity should not be regarded as a negative risk factor for normal vaginal labour progress.

Authors' Contributions

All authors equally contributed to this study. All authors read and approved the final version of the manuscript

Ethics Approval and Consent to Participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (ZBEU Ethics Committee approval number: 2018-239-19/12-5) and with the Helsinki Declaration of 1964 and its later amendments.

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Conflict of Interest

The authors declare no conflict of interest.

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