Regression rate of clinical HPV infection of the lower genital tract during pregnancy after laser CO_2 surgery

A. Frega[1], E. Baiocco[1], S. Pace[1], A. Palazzo[1], R. Iacovelli[1], A. Biamonti[2], M. Moscarini[1], P. Stentella[1]

[1]Department of Gynecology, Perinatology and Childhealth, University" La Sapienza" of Rome
[2]Department of Obstetrics and Neonatology. Cristo Re Hospital, Rome (Italy)

Summary

The objective of the study was to evaluate the effects of laser CO_2 surgery during pregnancy to prevent clinical HPV infection recurrence after delivery and vertical infection.

A case-control study was performed on 280 pregnant women affected by clinical HPV infection treated during pregnancy with 256 women treated three months after delivery. Follow-up was performed for a minimum of three colposcopic examinations for two years. Recurrence rates were calculated considering the number of positive findings for at least one colposcopic examination confirmed by biopsy after a negative control in a year. Statistical comparison of rates was performed by χ^2 and Fisher's exact test. Recurrence rates were higher in the women treated in postpartum ($p < .01$) than in the group treated during gestation ($p < .005$).

Clinical HPV infections treated during the second trimester of pregnancy showed a sensitive decrease in recurrence rate of infection. Rarity of respiratory papillomatosis makes conclusions inconsistent for the prevention of vertical infection.

Key words: Pregnancy; HPV; Laser CO_2.

Introduction

HPV is currently the most widespread infection in the world and its prevalence is estimated differently in the literature, varying from 10% to 60%; this range, even though unexpectedly broad, can be explained if we take into account the great number of diagnostic techniques employed [1-3].

From more than 100 HPV types currently known, some are considered highly oncogenic, whereas others seem to be less pathogenic in that they show a less marked tendency to produce lesions that can lead to neoplastic degeneration [4].

There are reasons to believe that pregnancy, because of the modifications of the immunological and hormonal environment that characterize it, can favor an increased incidence of infections from HPV and HPV-linked lesions. On the other hand it can cause the progression of dysplastic disease towards more evidently carcinomatous forms [5-8].

Another factor that justifies the interest demonstrated by the medical and scientific community regarding the relationship between HPV and pregnancy is given by the possibility, almost unanimously accepted, of a maternofetal transmission of the virus with the related risk for the newborn of developing juvenile laryngeal papillomatosis (JLP - a disease in which papillomas of the larynx and upper respiratory tract cause hoarseness and respiratory obstruction). Estimates for JLP are similarly imprecise, with incidence rates of 0.4 to 1.2 per 100,000 children [7, 9]. Types most frequently involved in JLP are HPV 6 and HPV 11, both among the most commonly observed at the genital level. Furthermore, it has been shown that HPV-positive children born from similarly infected HPV/DNA-positive women, present at the buccal level the same variants of papillomavirus detected in the cervices of their mothers [10].

The currently estimated risk of perinatal transmission is about 50% [11] and anal-genital lesions diagnosed within the first year of life can be considered as acquired perinatally [11-13].

Thus, the combination of the malignant potential of HPV, its high prevalence of infection and the relative diminished gestational immuno-responsiveness confers the importance of generalized clinical and virological significance during pregnancy, in postpartum and pediatric care.

Factors such as pregnancy hormones and diminished immune responsiveness may promote the growth of cervical and vulvovaginal HPV-induced lesions that make complex colposcopic findings needed.

Laser CO_2 vaporization/excission for vulvovaginal warts during gestation is well documented as safe for the mother and fetus with no increased risk of pregnancy complications or preterm birth [14-16].

The objective of the study was to assess the effects of laser CO_2 vaporization/excission to prevent clinical HPV infection recurrence after delivery and the rate of vertical transmission.

Material and Methods

We performed a randomized case-control study comparing 280 pregnant women with clinical HPV infection treated during the second trimester of pregnancy with 256 women treated three months after delivery. Follow-up was carried out with a

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minimum of three colposcopic examinations during gestation and for two years after delivery. Recurrence rates were calculated considering the number of positive findings for at least one colposcopic control confirmed by biopsy after one negative control in year. HPV-DNA testing was not performed. All patients affected by HPV infections underwent biopsy. Patients were submitted to laser CO_2 vaporization/excission during the second trimester from one to three steps. Exclusion criteria were spontaneous regression of condylomatosis or acetowhite lesions without confirmed biopsy. Histologic diagnosis was provided according to the classification proposed by the International Society for the Study of Vulvar Disease. A colposcopic examination was carried out in all patients to rule out the presence of cervical HPV infections or a squamous intraepithelial lesion (SIL). Treatments were performed under local anesthesia. A Zeiss CO_2 laser attached to a Zeiss T 50 colposcope was used, in continuous mode with a power density ranging between 600 and 1200 W/cm^2. Power densities above 1,000 W/cm^2 were used for lesion vaporization, whereas lower power densities were used at the periphery of the excised tissue or to coagulate slight bleeding; the smallest spot size was 0.5 mm. All procedures were performed under colposcopic guidance, with a focal length of 300 mm, after the application of 5% acetic acid. Two weeks later, in the presence of persistent HPV lesions, the patients were submitted again to laser CO_2 surgery.

The first follow-up was performed four weeks after the procedure and subsequently at six months. Data demographic anamnestic characteristics, size and location of the lesions and follow-up was recorded in our database. HIV-seropositive patients were excluded from the study. Chart reviews of our university hospital medical records from the ear, nose and throat and pediatric departments were used to identify the cases of respiratory papillomatosis due to vertical infection.

Statistical comparison of rates was performed by the chi-square and Fisher´s exact test.

Results

A total of 536 pregnant women with external genital warts were treated between 1998 and 2001, 280 during the second trimester, and 256 within a minimum of three months after delivery. There were 440 vulvar lesions, 43 anoperianal, 80 vaginal and 90 cervical. Two hundred and thirty-two patients needed a second treatment, 40 needed a third and four patients a fourth. In the follow-up three months after delivery in the first group none needed treatment. After six months 14 patients were submitted to a second treatment (8 patients had vulvar lesions and 6 patients had cervical lesions) and 12 months after eight patients (4 patients with vulvar lesions and 4 patients with cervical lesions) needed a third treatment; 13 procedures had to be suspended due to increased blood loss and seven for patient non compliance.

In the second group, until the end of the second trimester and during the third trimester 10.5% (27/256) of the HPV lesions were still growing in size; 66.5% (170/256) were stationary while 23% (59/256) had diminished. Gestational age at delivery in the two groups was 36 ± 2 vs 37 ± 3 weeks and the birthweight was 3,467 ± 300 vs 3,360 ± 282 g, respectively (Table 1).

Recurrence rates were higher in the women treated post-partum (7.9 ± 1.4 vs 4.3 ± 0.9; $p < 01$) than in the group treated during gestation (1.2 ± 0.5 vs 4.4 ± 0.7; $p < 005$). From 499 children's charts recovered from our university hospital medical records from the ear, nose and throat and pediatric department we identified three cases of respiratory papillomatosis from all mothers with cervicovaginal lesions.

Table 1. — *Pregnancy outcome and distribution of lesions.*

	Clinical HPV infection (n = 536)			
	Cervical HPV (n = 90)	Vaginal (n = 80)	Vulvar (n = 440)	Anoperineal (n = 43)
Cesarean section			33.1%	
Vaginal delivery			66.9%	
Previous Birth control			43.9% (12.7)	
Gestational age at delivery			38.47 (2.19)	
Birthweight at delivery			3976.13 (282.96)	

Table 2. — *Variation of HPV+ fetuses at birth in relation to the interval between the breaking of membranes and the end of delivery [10].*

Interval (hrs)	Fetuses	HPV+	%
2	11	0	0
2-4	21	7	31.5
> 4	5	4	80

Discussion

Estimates for genital warts are less precise than those for cancer because of the absence of case reporting and because they often recur after treatment; however, limited data suggest that in the U.S. incidence rates may be as high as 100 per 100,000 [17] with a prevalence of 1.4 million [18].

Identification of HPV types 6 and 11 from both genital warts and respiratory papillomatosis provided evidence for the etiological link between vulvo-vaginal condyloma and JLP [9].

The risk of vertical transmission is linked to the following factors: delivery by the vaginal route [12, 19], maternal viral load [20-22], the time elapsing between the breaking of membranes and the end of delivery in single cases [10] (Table 2).

On the basis of the above considerations, we believe it is important to remove condylomatous lesions at the maternal genital level before women give birth.

However, genital papillomatosis does not seem to require an elective cesarean section because this practice does not bring about important advantages from the point of view of the cost/benefit ratio.

Vaccines still need to be proven to be effective, especially during pregnancy. The imiquimod derivative (Aldara) that induces macrophages to secrete cytokines (IL-2 and INF-α) is applied topically; a 5% preparation is more efficacious and has been approved by the US Food and Drug Administration in non pregnant women whereas safety during gestation has not been tested.

The relative safety and effectiveness of surgical treatment show that this "overtreatment" results in a significant decrease in recurrence. Among all therapeutic

options laser CO_2 surgery has proven efficacy and only rarely do side-effects or important complications occur. Consequently it could be a suitable and effective treatment during gestation. It is well documented as safe for the mother and fetus with no increased risk of pregnancy complications or pre-term birth [14-16]. As a preventive approach for newborn vertical infections results did not reach statistical significance, although the results apparently indicate that in treatment during the second trimester it is protective; while all of the children affected by JLP mothers had cervicovaginal infections, the relative rarity of the pathology needs a larger number of cases to reach a definitive conclusion.

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Address reprint requests to:
A. FREGA, M.D.
Viale Ippocrate, 97
00161 Roma (Italy)