

Effect of a *Coriolus Versicolor*-based Vaginal Gel on High-grade Cervical Lesion During Pregnancy

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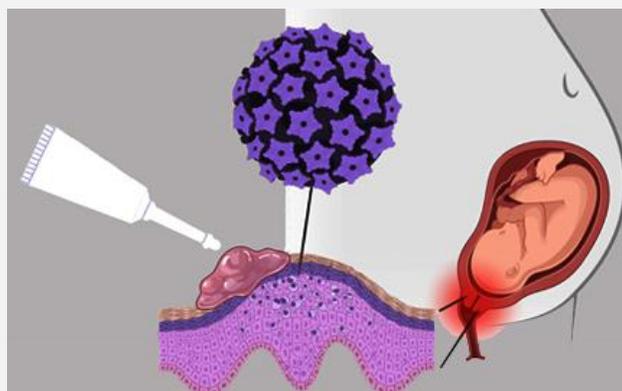


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ABSTRACT

The prevalence and incidence of Human Papillomavirus (HPV) infection rates are highest among sexually active young women. Pregnancy is regarded as a mild immunosuppressed and hormonally altered state that is a risk factor for HPV infection, viral persistence, and the development of high-grade squamous intraepithelial lesions (HSIL), which is a prerequisite for invasive cervical cancer development. Importantly, HPV infection and surgical treatments of HPV-related lesions are risk factors for perinatal miscarriage and thus, guidelines such as the Spanish Association of Cervical Pathology and Colposcopy (AEPCC) do not recommend the excisional treatment of histologic HSIL (CIN 2 or CIN 3) in pregnant women. As a consequence, conservative, non-invasive and safe treatments for pregnant women are an unmet medical need that must be addressed. Here we report the clinical case of a 26-year-old pregnant woman diagnosed with histologic HSIL, and a positive PCR test for HPV serotypes number 31, 39, and 45. The patient was treated daily with a *Coriolus versicolor*-based vaginal gel (Papilocare®) for 21 days, followed by a 7-day resting period, and 2 months of treatment on alternate days. The patient was able to carry her pregnancy to term and had a vaginal birth without complications. Six months postbirth, cytology showed a regression from HSIL to low-grade squamous intraepithelial lesions (LSIL), and a new PCR test showed HPV negativized in two serotypes, with only type 45 remaining.



Keywords: Cervical Lesion, human papillomavirus, pregnancy

1. Introduction

Human papillomavirus (HPV) is one of the most frequently sexually transmitted infections, with 50–80% of cases occurring within two-three years following the first sexual contact [1,2]. The virus affects two million women in Spain, 28.8% of whom are aged 18 to 25 years old [3]. More than 200 types of HPV have been identified, 14 of them classified as high-risk (HR) variants and are the main cause of virtually all precancerous cervical lesions and cervical cancers among women [4,5]. Several risk factors have been identified that increase the incidence of HPV. Between them, the pregnancy has been described as a mild hormonal and immune system disturbance that favors cervical HPV infection and persistence [6, 7]. The balance between pro- and anti-inflammatory response changes during pregnancy, such as steroidal hormone concentrations, including progesterone and estrogens, gradually rise. Pro-inflammatory responses are more intense during the first trimester of pregnancy, which is known as the "open wound phase," while anti-inflammatory responses are more prevalent during the second and third-trimester phases when the body is preparing for delivery [8] (Figure 1).

Some studies have reported an increased incidence of HSIL lesions in pregnant women compared to general populations [9]. The clinical consensus agrees that although excisional treatment is recommended for HSIL cases, this is not the case for pregnant women due to the increased risk of miscarriage [10-12]. As a consequence, most of the

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medical guidelines, such as the Spanish Association of Cervical Pathology and Colposcopy (AEPCC) recommend a conservative approach of watchful waiting [13].

The aim of this clinical case is to illustrate the effectiveness of a *Coriolus versicolor*-based vaginal gel as a conservative treatment for HPV infection in a 26-year-old pregnant woman with HSIL lesions and a positive PCR test for HPV serotypes number 31, 39, and 45

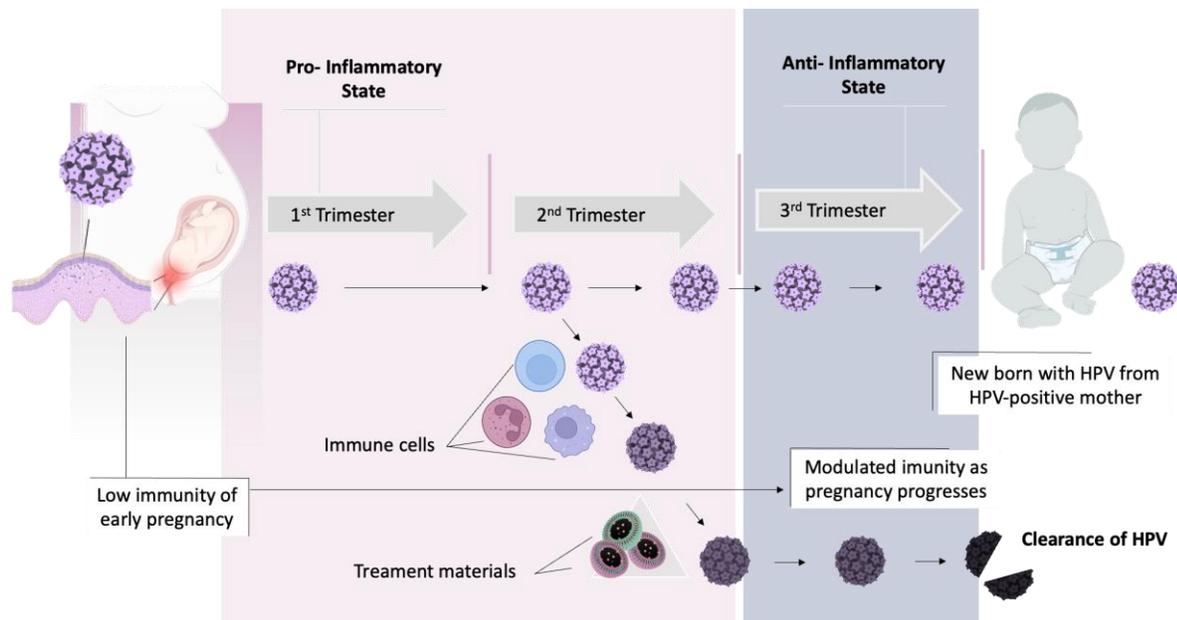


Figure 1. HPV clearance and persistency during pregnancy and postpartum.

2. Methods

2.1. Patient

A 26-year-old woman visiting for a pregnancy check-up without a relevant medical background or surgical operations, no known allergies to any medication, vaccinated for HPV with Gardasil® 4 at 14 years old with two doses (0 and 6 months).

2.2. Reproductive and gynecological history

The patient was a 6+3 weeks-pregnant case, G1P0A0. Contraceptive pill method used for 5 years. Cytology was performed on the first visit as the patient had never had any cytological examinations under the National Health System protocol and showed cytological alterations consistent with HSIL. The presence of HPV was measured through a PCR assay and tested positive for 3 HPV serotypes [31,39,45]. TaKaRa PCR Human Papillomavirus Detection Set (TaKaRa, Kusatsu, Japan) is used. The viral strains found were HR-HPV and related to cervical cancer.

2.3. Physical examination and differential diagnosis

The patient went under a colposcopy examination, which showed an irregular white plaque on the anterior lip (AP), around two centimeters in size, flame-shaped, and both act white and Lugol's resulted positive for pre-cancerous lesions. After that, a biopsy was taken on the area of the AP, showing an HSIL with a detached basal lamina.

2.4. Treatment and evolution

The Spanish Society of Cervical Pathology and Colposcopy (AEPCC) guidelines does not recommend the excisional treatment of histologic HSIL (CIN 2 or CIN 3) during pregnancy as it is a risk factor for miscarriage. Hence, conservative treatment with, a *Coriolus versicolor*-based vaginal gel, Papilocare® [3,7–11] was administered. Posology was based on the laboratory recommendations, meaning twenty-one consecutive days followed by a resting period of seven days, and then two months of treatment on alternate days. After 3 months of treatment, colposcopy was performed

finding a reduction of the lesion from 2 cm to a less than 0.5 cm acetowhite stained area and the Lugol's staining resulted negative for pre-cancerous cells. In addition, cytology and guided biopsy results revealed LSIL/CIN1. The treatment was continued for another 3 months to complete a total of six months of treatment. In the seventh month, a new colposcopy was performed, showing an almost undetectable LSIL, given this result a biopsy was not taken.

At the ninth month of pregnancy, cytology was performed resulting in LSIL. The patient had a vaginal birth without incidents during week 40+5, giving birth to a healthy baby weighing 3250 grams. At six months from birth, the cytology showed LSIL persistence. Nonetheless, the PCR test showed a negativization of 2 out of 3 HPV serotypes, with only type 45 remaining.

3. Discussion

In this clinical case, a 26 years old pregnant woman with HSIL lesions showed a regression to LSIL and the clearance of 2 out of 3 HR-HPV serotypes after conservative treatment with a *Coriolus versicolor*-based vaginal gel (Papilocare®). Pregnancy has been related to an increased risk of HPV infection and persistency, which is a risk factor for HSIL and increased gestational risks, in particular perinatal death [6, 7]. There are only a few bibliographic references about managing HPV of HSIL lesions during pregnancy and there is a considerable gap of information on this subpopulation [14, 15], all of them being surgical, which different studies and metanalysis have pointed to an increased risk of premature birth as well as miscarriage after subjecting patients to these procedures [16]. In fact, some studies have reported that the incidence of miscarriage during the first trimester increases to 21% after excisional treatment compared to the 10-15% of the general population [10, 17]. As the progression rate from CIN2 to cervical cancer is considered 30-50% and the progression time will usually take longer than the pregnancy period [18,19], conservative, safe nonsurgical treatments that could contribute to the lesion regression or at least halt the progression could cover a medical need.

Papilocare® (Procure Health, Spain), a vaginal gel including *Coriolus versicolor* and other ingredients, has proven to be safe and effective in repairing low-grade cervical lesions and enhancing HPV clearance in in different clinical studies. [20, 21]. Due to its local action over the cervical epithelia and vaginal microbiota it is expected that systemic side effects are less probable. In this sense, this clinical case aligns with previous reports supporting the lack of significant side effects.

4. Conclusions

In this clinical case, a 26 years old pregnant woman was subjected to conservative treatment of cervical HSIL with *Coriolus versicolor*-based vaginal gel (Papilocare®). After 3 months of treatment, the patient showed a regression to LSIL/CIN1. Additionally, PCR showed the clearance of 2 out of 3 HPV serotypes initially identified, this clinical case illustrates how conservative treatment with *Coriolus versicolor*-based vaginal gel might represent a valuable tool to manage HPV lesions in pregnant women.

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