Effect of Pregnancy on HPV Infection and on its Mode of Management

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Abstract

HPV (Human papillomavirus) has long been associated with carcinoma of the cervix. Ranked first as the most common gynecologic cancer and second as the most common cancer in the female population, carcinoma of the cervix has a high incidence of 8.9% in all races with a death rate of 2.8%. It is the second cause of cancer death in females aged between 20 and 39 years. Although most cervical cancers arise from cells infected with HPV, not all females harboring the virus will eventually develop carcinoma of the cervix. While the risk of HPV persistence and its progression to high-grade neoplasia and cancer increases with age, adolescents and young women usually clear most clinical and subclinical HPV infections. Although the exact reason for which regression of HPV infection occurs in some only is not known, the immune system is strongly suspected to be responsible for it. This is supported by the fact that immune suppression, as shown by most researches, has a great impact on the outcome of HPV infection. The aim of this review is to see how pregnancy affects the immune system, the natural history of HPV infection and its mode of management.

INTRODUCTION

HPV infection is highly prevalent in sexually active women worldwide, mostly in the non-vaccinated females, and even among those presenting normal cytology [1]. It is one of the most common sexually transmitted infections in the world. It has been found that most sexually active women will be infected with HPV at least once during their lifetime, with the majority of infections being cleared within 2 years [2,3]. Based on their association with cervical cancer (CC), HPV genotypes are classified as low-risk or high-risk [4]. High-risk (HPV) is a small DNA tumor virus that infects the mucosal squamous epithelium and causes various malignant diseases in humans, including cancers of the cervix [5]. It is well established that persistent infection with high-risk HPV genotypes is the necessary although not a sufficient cause of CC [6]. The involvement of other factors, in addition to HPV, is needed to induce cervical carcinogenesis and adequate immune response is crucial for HPV clearance while immune deficiency favors viral persistence and cervical cancer [7,8]. Only 10-15% of women develop a persistent infection, which is an important risk factor for cervical carcinogenesis [9]. HPV persistence, even for short-time, has been associated with higher risk for cervical intra-epithelial neoplasia, compared to women without a history of HPV infection [10,11]. HPV clearance is more frequent in the first six months after initial infection, with rates of 50-70% per follow-up year [12, 13]. Physiological changes in immunity and other biological parameters (e.g. changes in the levels of different hormones) during pregnancy and postpartum may change the natural history of HPV infection and most authors have found a reduction in HPV positivity during the postpartum period [14].

Effects of the hormonal changes during pregnancy on the cervix and on the immune system that favor HPV infection

HPV dependent carcinogenesis starts with the infection of HPV in episomal form which initiates the transcription of viral gene products. This is followed by subsequent genomic integration of HPV oncogenes into the host genome [15]. Pregnancy can hasten and aggravate infection by high-risk HPV (in particular, by HPV 16) and presents highly suitable conditions for HPV activation, persistence and transformation [16]. Possible biological mechanisms for this could be that the raised levels of estrogen and progesterone during pregnancy which brings the following changes;

The vaginal flora specifically presents an imbalance that,
together with the dampness particular to that area, favors the development of infectious agents, including HPV. Also, during pregnancy, there occur anatomical modifications of the genital tract such as hypertrophy and congestion of the cervix, which increase, and is followed by metaplasia. The squamo-columnar junction undergoes alterations and maintains the transformation zone (TZ) on the exo-cervix (ectopy) for many years as a result of which this area of immature squamous metaplasia becomes more susceptible to the development of HPV infections and pre-neoplastic lesions [17]. These hormones also alter the local immune microenvironment of the cervix and sensitizes the TZ to cervical cancer formation. The squamous epithelium of the cervix is composed of keratinocytes (primary target of HPV) and a type of immature dendritic cell (DC, the Langerhans cells (LC), which are important for the immuno-surveillance of the squamous epithelium [18]. Estradiol and progesterone influence the APC (antigen-presenting cell) functions of DC, with estradiol generally suppressing APC function, which may be due to decreased recruitment of DC or due to hormone-induced TGF-β production that maintains DC in an immature state [19]. Moreover, in the transformation zone, estradiol has a high rate of conversion to 16α-hydroxyestrone [20, 21] which covalently bind and activate ERα, Estrogen receptor alpha, ERα is necessary for the genesis and continued growth of cancer and its expression in stromal cells is required for disease progression [22-24]. The activated ERα is assumed to bind to responsive elements within the LCR (Long control region) and further induce E6 and E7 transcription to maintain HPV gene activity [21, 25]. Thus, it is hypothesized that both HPV and estradiol enhance the effects of each other, either directly through functional ERs (Estrogen responsive elements) in the viral genome or indirectly encourage uncontrolled cellular proliferation, thus enhancing malignant proliferation [26]. This synergistic combination between estrogen and HPV has been described as the strongest factor in such carcinogenic transformations [22-27,30].

In addition, estrogen has a well-known mitogenic activity which can be amplified by viral oncoproteins [31]. It has been shown to stimulate the proliferation of human keratinocytes by promoting the expression of cyclin D2 and inducing G1 to S phase progression in the cell cycle [32]. Moreover, estrogen inhibits the oxidative stress-induced apoptosis in keratinocytes by promoting expression of the anti-apoptotic protein bcl-2 [33]. It can also induce direct DNA damage via its catechol metabolites [34] and HPV infection has shown to considerably increase the formation of these potentially carcinogenic estrogen metabolites [20]. In addition, there is increasing evidence that estrogen has the property to influence the immune system by acting on the cytokine production [35]. Estradiol has been shown to inhibit the expression of GM-CSF in the U2OS cell line through its interaction with ERα and to decrease this production via contact with ERβ [36].

Progesterone has also been shown to act on cytokine production to affect the immune system [35]. It increases the production of IkBα, an inhibitor of NFκB [37] and has an inhibitory effect on GM-CSF secretion [38]. The immune suppression caused mainly by the increased progesterone, which is necessary for maintaining a fetus during pregnancy, further predisposes a woman to the acquisition and development of lesions induced by HPV [16,17,39]. Researches in molecular biology have also found an interaction between progesterone and HPV. It is known now that HPV 16 encodes a protein located in the region of E6 and E 7 reading frames that cooperate with activated as oncogene to transform primary cells [40]. The LCR of HPV 16 is reported to contain a deoxyribonucleic acid sequence that enhances response to both progesterone and glucocorticoids thereby increasing E 6 and E 7 transcription [41]. E6 and E7 once proteins bind to p53 and Rb, respectively, and surpass the host defense system [42-44]. In pregnancy, the elevated progesterone level increases HPV gene expression, giving rise to larger numbers of viral copy and multiplication of virus-transformed cells [45]. During the first trimester, there is a low immune response to HPV, thus accounting for the higher frequency of persistence of the virus. This deficient response, however, undergoes an intense recovery at the beginning of the third trimester, with reinforcement during the postpartum period to eventually lead to regression of the infection [46].

Furthermore, in cervical carcinogenesis, HPV DNA is often integrated into the host genome, leading to the loss of E2 gene. HPV E2 is a modulator of HPV gene expression and an inducer of apoptosis [47]. It was found that E2 and E7 proteins can induce apoptosis in transformed cells [48] and that progesterone and estrogen increase the levels of E2 and E7-induced apoptosis [49]. However, with the loss of E2 in HPV infection, cell proliferation might increase [47]. In addition, in the absence of E2, these hormones have been found to be a possible risk factor for cervical carcinogenesis through their effects on HPV gene expression [50].

**Oral contraceptive use (OC) and the associated risk of cervical pre-cancer and cancer**

To further strengthen the role of estrogen and progesterone, and consistent with results from previously published pooled analyses, studies have revealed strong and positive associations between OC use and risk of cervical cancer and pre-cancer; specifically, the risk increases with duration of use and decreases with cessation of use [51-53]. The IARC (International Agency for Research on Cancer) collaborative study found a relative risk of 1.6 for long-term OC users while Moreno et al. [52], observed a stronger association (Odds ratio=4.0). In addition, these two studies also found a reduced risk of cervical cancer for women who ceased OCs (Relative ratio = 0.8 and Odds ratio = 0.5, respectively). Gierisch et al. [54], also found an increased risk of CC associated with the duration of oral contraceptive in women with an HPV infection. The association between OC use and CC risk is due to estrogens and progesterogens which interact with hormone receptors, mainly progesterone, present in cervical tissue and modulate the natural history of HPV infection. Sex steroid hormones are thought to enhance the expression of HPV 16 E6 and E7 oncogenes, in the same way as what happens in pregnancy, thus stimulating the degradation of p53 tumor suppressor genes and increasing the ability of the viral DNA to transform cells and induce carcinogenesis [51,55].

**Mode of management during pregnancy**

Most studies show a higher postpartum regression rate of CIN (Cervical intraepithelial lesion) in pregnant patients than in the
non-pregnant group. These report regression rates between 37 and 74 % for pregnant women at the time of postpartum follow-up [56-61]. Many theories to explain these high regression rates have been put forward and among the most common ones are;

1. The typical hormonal pattern during pregnancy which induces viral activation that subsequently leads to increased spontaneous regression rates after delivery, where the hormone levels return to normal [61].

2. The regression rates could be increased because of multiple cervical biopsies performed during the antepartum follow-up, thus giving the appearance of spontaneous regression [60].

3. A correlation between CIN course and mode of delivery is suspected to account for the higher rate of regression of cervical dysplasia with vaginal delivery compared with cesarean section (67 versus 13 %) [60,62]. This can possibly be explained by the loss of the dysplastic cervical epithelium during cervical ripening and the passage of the fetus through the birth canal [58,63].

In the past, pregnant women with high-grade CIN were treated by cone biopsy [64]. It is now reported that cone biopsy in pregnancy is associated with unfavorable pregnancy outcomes namely excessive bleeding and spontaneous abortion [65]. On the other hand, the relationship between deliberative excision procedure (LEEP) and preterm birth continues to be debated, with some studies showing increased risk, but others not [66]. However, due to the high regression rates towards the end of pregnancy and in the postpartum, it is nowadays accepted that most patients may safely undergo expectant management if invasive disease has been ruled out [67]. But still, it remains fundamental that close monitoring is continuously done for these pregnant HPV-infected patients during the antenatal period and postpartum by conducting regular gynecological examinations namely PAP smear, colposcopy and colposcopy-guided biopsy (CGB) [56-61].

For pregnant patients with biopsy-proven CIN, it is considered reasonable to monitor them with cytology and colposcopy every 8 to 12 weeks (or every trimester) until term, although there is no definite scientific evidence to support any recommendation regarding a specific frequency of follow-up. If indicated, definitive treatment may be completed 6 to 8 weeks postpartum [68]. Before 24 weeks of gestation, the treatment for invasive carcinoma of cervix is the same as for non-pregnant women. For patients diagnosed few weeks prior to fetal viability, pregnancy may be continued until the earliest fetal viability, after which therapy is undertaken. If diagnosis of invasive disease is made at the time of fetal viability, radical Cesarean hysterectomy can be offered or the fetus can be delivered and treatment instituted thereafter [65].

CONCLUSION

Experimental, virological and immunological studies strongly suggest that sex hormones play an important role, in addition to HPV infection, in the development of cervical pre-neoplastic and neoplastic lesions. The effect of the hormonal changes during pregnancy on the natural history of HPV infection has helped researchers to some extent to understand the interaction between the two. However, further knowledge about the interaction between sex hormones and HPV, at molecular level, is required before new anti-neoplastic therapeutic or preventive strategies can be developed.

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