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Effect of Pregnancy and Mode of Delivery on HPV Infection and on Cervical Cytological Changes

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Abstract- *Background:* To know if the hormonal changes during pregnancy and the mode of delivery affect HPV (human papillomavirus) infection and on cervical cytological changes concerning the rates of persistence, progression and regression in the postpartum period following hormonal normalization.

Methods: A prospective study was carried out on 57 pregnant women who attended the Nanjing Maternity and Child Health Care Hospital between 2015 and 2017 who were positive for cervical cytological changes and HPV during their antenatal visits by TCT (PAP smear) and hybrid capture test2 respectively. Initial and postpartum results of these tests were compared where the rates of persistence, progression and regression of HPV and the cervical cytological changes were analyzed. For analysis of the results, a control group of 57 nonpregnant patients from the gynecological department was included and followed in this study.

Results: The postpartum evaluation of the pregnant cohort revealed a significantly higher tendency to spontaneous regression as compared to the non-pregnant control group (59.9% versus 31.6 %, p = 0.005) and the mode of delivery did not affect cervical cytological changes and HPV infection (p=0.140).

Conclusion: The high regression rate suggests that in the absence of invasive disease, definite management of abnormal cervical cytology can be carried out in the postpartum period.

EFFECTOFPREGNANCYANDMODEOFDELIVERYONHPVINFECTIONANDONCERVICALCYTOLOGICALCHANGES

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I. Background

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 and most sexually active women will be infected with HPV at least once during their lifetime, with the majority of infections cleared within two 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 a short time, has been associated with higher risk for cervical intra-epithelial neoplasia, compared to women without a history of HPV infection [10, 11]. After initial infection, HPV clearance is very frequent in the first six months, with rates of 50-70% per follow-up year [12, 13].

Physiological changes in immunity and other biological parameters (for example, 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]. The aim of this study is to find out how pregnancy affects the cervical cytological changes and the natural history of HPV infection.

II. Materials and Methods

A prospective study was carried out in Nanjing Maternity and Child Health Care Hospital from January 2015 to December 2017.

The inclusion criteria were as follows;

- Adults aged 18 to 30 years with given consent
- Pregnancy in the first 24 weeks
- Females:

i. with positive TCT (Thin prep cytology test) and HPV positive
ii. having only one partner
iii. who do not smoke and do not indulge in alcohol or substance abuse.

The exclusion criteria were as follows;

- All immunosuppressed patients
- Patients who are or were known cases of cervical carcinoma
- Patients who had previous surgeries of the cervix

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- Females who are known to be HPV positive and positive cervical cytology before pregnancy

All women up to 24 weeks of gestation attending the antenatal clinic for the first time in their pregnancy had TCT done. Here, after insertion of a vaginal speculum, we used plastic broom to collect material from the endocervix and this was then immediately distributed in a buffer solution by shaking the broom vigorously. The samples were then transported to the Molecular Biology. Those with positive cytological changes, that is positive PAPS smear, were asked in their next review to do the hybrid capture test 2 for HPV testing. These patients were seen as per the normal ANC review and no treatment was given for HPV positivity. However, after delivery, all those patients who were positive (ASCUS+HPV positive) were asked to repeat the TCT and the hybrid capture test 2 to know their status postpartum .The mode of delivery included both normal vaginal delivery and Caesarian section (Cs). We repeated the tests after a minimum of six weeks, that is the puerperium, when all the hormone levels and physiological changes during pregnancy return back to normal. During the same period of study, we followed a control group of 57 patients from the gynecological department with initial positive PAP smear(ASCUS-atypical squamous cell of undetermined significance) and positive hybrid capture test 2(HPV positive). The mean period for the repeat tests for both pregnant and nonpregnant patients was 40 weeks. In this study, regression was defined as those cases where the first cervical cytology and HPV test was positive but became negative after the second test. Persistence were those cases in which both the first and the second tests were positive. Progression were those cases which worsened on the second test based on the cytological findings.

We used SPSS 19.0 statistical software for statistical analyses. p-values of <0.05 were considered statistically significant. The impact of pregnancy and the mode of delivery on regression persistence and progression were assessed using the Chi-squared test. Binary logistic regression analysis was performed to calculate odds ratios and 95% confidence interval.

III. Results

Within this study period, a total of 114 patients with proven cytological changes and HPV infections were included in the analysis. Among them, 57 were pregnant and 57 who were nonpregnant served as the control group. As far as the effect of the mode of delivery is concerned, as shown in table 1, where the vaginal delivery rate was 75.4%, the regression rate was 65.1%. For the Cs group, the regression rate was 42.9%. Based on the p-value which was 0.140, that is >0.05, we did not find any significant difference between the effect of Cs and vaginal delivery on regression of HPV and its cytological changes. On the other hand, as shown in table 2, in the group of pregnant women, the overall regression rate was 59.6%, which was higher than the regression rate in the control group that is 31.6%. Based on the chi-squared test, the p-value was 0.005 which is statistically significant and supports the fact that pregnancy affects the regression (that is a higher regression rate postpartum) of cervical HPV infection and its associated cytological changes.

Table 1: Comparison of effect of mode of delivery on HPV infection

Mode of delivery	Persistence	Regression	X^2	P
Cs	8	6	2.174	0.140
Vaginal delivery	15	28		

Table 2: Comparison of effect of pregnancy on HPV infection

	Persistence	Progression	Regression	X^2	P
Pregnant	23	0	34	10.78	0.005
Non-pregnant	36	3	18		

Table 3: Characteristics associated with all the 114 pregnant and non-pregnant patients (multivariable analysis)

Variables	OR	OR 95% CI	
		Low	Up
Regression	1		
Persistence	0.395	0.186	0.839

IV. Discussion

The present study revealed high spontaneous regression in pregnant women. No cases of progression to higher grades cytological changes or invasive disease during the postpartum follow up period was found. These data support the opinion that once invasive disease can be excluded by colposcopy and CGB, definitive therapy in pregnant women can be deferred until after delivery. The initial obstetrical consultation provides an excellent opportunity to detect patients with abnormal PAP smears [15, 16, 17]. Historically, women with high-grade CIN were treated by cone biopsy during pregnancy [18, 19, 20]. Several studies reported that cone biopsy in pregnancy is associated with an impaired pregnancy outcome [21, 22]. Other reports showed that loop electrosurgical excision procedures are safe during pregnancy with a miscarriage rate <1 % [23]. Due to the low rates of progression during pregnancy, it is nowadays accepted that most patients may safely undergo expectant management if an invasive disease has been ruled out [24, 25]. Within the last decades, several authors studied the natural history of HPV diagnosed during

pregnancy with different outcomes, shown in table 4. The present study reports a significantly high postpartum regression rate of HPV in the group of pregnant patients that is 59.6%. The high regression rate is in accordance with recent previous studies, which report regression rates between 37 and 74 % for pregnant women at the time of postpartum follow up [26, 27, 28, 29, 30, 31, 32].

Table 4: Studies with reported outcomes

Author	Regression (%)
Lurain [32]	77.4
Yost [26]	69.3
Vlahos [27]	61.6
Paraskevaides [28]	37.5
Serati [31]	47.3

Many theories to explain these high regression rates can be found in the recent literature and among them most commonly the ones discussed below. Possible biological mechanisms for this could be that the raised levels of estrogen and progesterone during pregnancy which bring 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 squamocolumnar 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 [33]. These hormones also alter the local immune microenvironment of the cervix and sensitize 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 [34].

Estradiol and progesterone influence the APC (antigen-presenting cell) functions of DC, with estradiol suppressing APC function, which may be due to decreased recruitment of DC or due to hormone-induced TGF- production that maintains DC in an immature state [35]. Moreover, in the transformation zone, estradiol has a high rate of conversion to 16 alpha hydroxyestrone [36, 37] 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 [38- 40]. 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 [37, 41]. Thus, it is hypothesized that both HPV and estradiol enhance the effects of each other, either directly through functional EREs (Estrogen responsive elements) in the viral genome or indirectly encourage uncontrolled cellular proliferation, thus enhancing malignant proliferation [42]. This synergistic combination of estrogen and HPV is the strongest factor in such carcinogenic transformations [38, 43-46]. Also, estrogen has a mitogenic activity which can be amplified by viral oncogenes [47]. 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 [48]. Moreover, estrogen inhibits the oxidative stress-induced apoptosis in keratinocytes by promoting expression of the anti-apoptotic protein Bcl-2 [49]. It can also induce direct DNA damage via its catechol metabolites [50] and HPV infection has shown to considerably increase the formation of these potentially carcinogenic estrogen metabolites [36]. Also, there is increasing evidence that estrogen has the property to influence the immune system by acting on the cytokine production [51]. 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 [52]

Progesterone has also been shown to act on cytokine production to affect the immune system [51]. It increases the production of IkB, an inhibitor of NF-kB [53] and has an inhibitory effect on GMCSF secretion [54]. The immunosuppression 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 [33, 55, 56]. Researchers 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 E 6 and E 7 reading frames that cooperates with activated ras oncogene to transform primary cells [57]. 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 [58]. E6 and E7 oncoproteins bind to p53 and Rb, respectively, and surpass the host defense system [59-61]. In pregnancy, the elevated progesterone level increases HPV gene expression, giving rise to larger numbers of viral copy and multiplication of virus-transformed cells [62]. 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 [63].

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 [64]. E2 and E7 proteins can induce apoptosis in transformed cells [65] and progesterone and estrogen increase the levels of E2 and E7-induced apoptosis [66]. However, with the loss of E2 in HPV infection, cell proliferation might increase [64]. Also, in the absence of E2, these hormones have been found to be a possible risk factor for cervical carcinogenesis by altering HPV gene expression [67]. Other authors speculated that the performance of multiple cervical biopsies in the antepartum evaluation could give the appearance of spontaneous regression [30]. Alternatively, other studies suggested a correlation between CIN course (cervical intraepithelial neoplasia) and mode of delivery and found a higher rate of regression of cervical dysplasia in association with vaginal delivery compared with cesarean section (67 versus 13 %) [30, 68]. A possible mechanism for this finding may be the loss of the dysplastic cervical epithelium during cervical ripening and the passage of the fetus through the birth canal [28, 69]. Other studies have not reported any differences in regression rates among patients who delivered vaginally or by cesarean section [26, 70], which is also the case in the present study.

Limitations of this study include

1. The limited number of cases.
2. The limited data on specific HPV subtypes have to be recognized as a limitation of the study.
3. Also, in the group of pregnant women we did not categorize the patients according to age. This can be a limitation as the females aged less than 24 years are known to be more often infected with HPV while at the same time they are known to clear the infection more spontaneously.
4. Inter-observer variability of TCT and HPV test results.

V. Conclusion

This study supports the fact that a conservative management of HPV infection in pregnancy is safe since it reports high regression rates and no progression after delivery. However, this mode of management of HPV infection during pregnancy is valid as long as an invasive disease is ruled out.

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