International Journal of Advanced Research and Development
ISSN: 2455-4030, Impact Factor: RJIF 5.24
www.advancedjournal.com
Volume 2; Issue 2; March 2017; Page No. 24-27

Evaluation of oral contraceptives in development of premalignant cervix lesions

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Abstract
Background: Cervical cancer (CC) is among the most prevalent carcinomas, it is related to infection with human papillomavirus (HPV). In literature there are conflicting data on the use of oral contraceptives (COC) as a risk factor for the development of CC. Based on the data above, this study aimed at analyzing the results of cytopathology (CP) and pathological (AP) analysis and their association with the use of COC.
Methods: 153 patients were asked about the use of COC. Afterwards, the results of the questions were compared to CP and AP examinations.
Results: The use of COC, especially in periods longer than three months, is associated with increased frequency of low and high grade squamous intraepithelial lesion in CP and AP exams, which is most apparently influent in the age group 25-45 years.
Conclusion: Present data suggest that the use of COC for more than three months may represent a risk factor for the emergence of cervical cancer precursor lesions.

Keywords: Cervical intraepithelial neoplasia, oral contraceptives, human papillomavirus

1. Introduction

Cervical cancer (CC) is among the most common cancers affecting women's health, ranking second among the most prevalent cancers [1]. It is known that CC is associated with persistent infection with oncogenic types of HPV (Human Papillomavirus). HPV infection is associated with proliferative malignant or benign lesions [2].

Low-grade and high-grade squamous intraepithelial lesion (LSIL and HSIL) can be diagnosed by different methods, such as Pap smears and histopathology biopsy of the cervix by directed colposcopy. Studies indicate that the biopsy histopathology shows greater sensitivity and specificity. Papanicolaou test, also called Pap smear or cytopathology tests, is unquestionably important for a prognosis of precancerous lesions. In fact, getting a Pap smear periodically can prevent, through early treatment, for example, a low-grade lesion to evolve into a high-grade lesion or even into an invasive carcinoma [3].

HPV is a necessary factor for developing cervical, vulvar and rarely penis and anus cancer. However, studies state that there are predisposing factors to worsening or onset of a neoplastic process in the cervix, for example, the use of oral contraceptives (COC) [4, 5]. There are several forms of CC treatment, but it is important to note that early diagnosis and identification of predisposing factors allow a less invasive treatment and satisfactory results [6].

The high rate of spontaneous regression of HPV infection and only evolution of some cases to malignant transformation, suggest that viral infection alone does not trigger the aggravation of the disease. Other variables are involved in this aggravation process, such as irradiation, smoking and hormones. Among the hormonal factors the use of COC stands out, which is added to the risk of developing CC [4].

Both triphasic COC and its lower dosage versions are associated with increased transcription of HPV types. The use of COC for more than five years increases the risk of high-grade squamous intraepithelial lesion development. COC may be an important factor in the pathogenesis of CC if the use occurs before the full development of the female genital tract, that is, before the age of 17. Literature data also shows that the risk for developing cervical adenocarcinoma in situ is also increased for women with long oral anticoagulation (more than 12 years) [4].

Epidemiological studies showed a strong suspicion regarding the use of oral hormonal contraceptives and an increased risk of cervical cancer. A study published in 2002 revealed COC to be a cofactor for CC predisposition [7]. Corroborating these data, a survey conducted by IARC (International Agency is Research on Cancer) in eight countries, including Brazil, showed that COC can act as an important co-factor in the risk of CC development in women tested positive for HPV. It is known that HPV is responsive to in vitro steroid use, which interferes with the activity of viral oncogenes by stimulating it [4, 8].

However, there is still great controversy on the relation between the use of COC and CC. Other studies in the area observed differently: women using COC had lower CC risks [9, 10].

Thus, the aim of this study is to investigate the possible relation between the use of COC and the results from AP and

CP tests. This study is based on cytological findings which stood out in the cytological and anatomopathological analyses in patients treated at a laboratory of cytology and pathological anatomy.

3. Methods

Patients treated at a cytology and pathology private laboratory and at a public service clinic were invited to participate in the study. Cytopathology tests and / or cervical biopsy were performed and patients agreed to sign the Informed Consent Form. These patients were asked about their COC use.

Data on the use of contraceptive methods were obtained from a questionnaire, which was previously used in other studies and adapted by the researchers for this study. Cytological and pathological examinations were performed in a cytology and pathological anatomy laboratory, which followed the standard methodology for its analyses.

For statistical analysis, data were analyzed and processed using SPSS - Windows, 20.0, chi-square test. The ethics committee in research and advice number 635.090 approved this study.

4. Results

The study included 153 women with a mean age of 34.6 years, of these, 27 patients (17.6%) aged below 25 years, 101 patients (66%) aged between 25 and 45 years, and 25 patients (16.3%) over the age of 45 years. As to education, most patients had incomplete undergraduate education (27.5%), followed by the ones who finished high school (20.3%).

Participants were treated in public and private laboratories in the city of Caxias do Sul (Brazil). 129 patients (84.3%) were treated at a private laboratory and 24 (15.7%) were treated at a public one.

Regarding the use of COC, 107 patients (69.9%) took ACO, 71.2% took COC for more than 3 months and 28.8% took ACO for less than 3 months. Patients who took 34 different brands of COC, in which the most frequent compound was ethinyl estradiol, found in the compositions of different brands.

Regarding the use of COC, most of HSIL and LSIL are in patients who take the medication, but this association was not significant (p=0,08) (FIGURE 1). When relating CP results with time of use of COC, it also shows a higher frequency of HSIL and LSIL in patients taking COC for more than three months. However, we cannot observe a significant difference between data.

For patients younger than 25 or older than 45, there was no significant association between the use of COC and CP test results in each group.

As for patients from 25 to 45 years of age, there was a higher frequency of LSIL (66.7%) in patients taking COC for over 3 months compared to patients not taking COC for over 3 months. This is a statistically significant difference (p<0,05), indicating that the use of COC may be related to the higher prevalence of lesions in the cervix linked to cervical cancer.

Figure 1: Frequency of cytopathology tests results related to the use of oral contraceptives (COC) (#p=0,08).

When we relate the use of COC to the AP exam results, no significant difference is observed. However, a higher prevalence of injuries like LSIL (26.8%) and HSIL (12.2%) was seen in patients who take COC. Comparing the time of OAC use with the AP results, we can observe a statistically significant association (p <0.05) in which patients who took ACO for more than 3 months had more LSIL (73.3%) and HSIL (80%) if compared to those who did not take COC for more than 3 months, 26.7% and 20% respectively (FIGURE 2). Thus, focusing on the possible contribution of using COC for the development of injuries related to cervical cancer.

Stratification of the samples according to age, patients younger than 25 and older than 45, showed no significant association between the use of COC and AP test results in each group.

In patients aged 25 to 45, a significant difference associated with the use of COC and the results of AP (p <0.05) has been found, indicating that this age group seems to be more associated with the COC effects in the epithelium of the cervix.

Figure 2: Frequency results of anatomopathological examination related to the time of use of oral contraceptives (COC). (*p <0,05)

Therefore, the data above suggest that the use of COC, especially in periods longer than three months, is associated with higher frequency of HSIL and LSIL in CP and AP exams, which influenced mostly the 25-45 age group.

When analyzed separately, the type of hormone used and the results of CP and AP, no significant association was observed.

Discussion

Different HPV epidemiological data are shown in literature, this variation is the result of different levels of development of the countries and different population surveyed profiles. Prevalence of 10% of HPV-DNA in the world population was observed in meta-analysis [11, 12].

HPV can be related to benign and malignant lesions. Among the benign there are warts, which are very common in viral infections, with estimated incidence of 7% to 10% among European population and 1% among US population. In immune compromised patients and in renal transplant recipients this number increases from 50 to 100 times, reaching more than 90% after 15 years of transplantation. Warts can occur at any age, and its incidence increases during school age, peaking in adolescence and young adults [13].

Epidemiological studies have revealed a strong suspicion between the use of oral hormonal contraceptives and an increased risk of cervical cancer. In a study that examined oral contraceptive, HPV and cervical cancer, results showed high risk (3 times higher) of developing cancer in situ [12].

There are many explanatory hypotheses. It seems that exogenous female steroids would act on the HPV genome, triggering stimuli on the process of cervical carcinogenesis. Literature discards any possibility of contraceptive facilitating HPV infection. In literature it is observed evidence that the continued use of COC is a risk factor for development of cervical neoplasia. Marks et al. (2011) [14] suggest that estrogen and progesterone hormones are responsible for immune suppression, thereby facilitating the action of HPV on the cervix.

The influence of COC on the epithelium of the cervix and its relationship with HPV has been pointed out in some studies. When analyzing the prevalence of high-risk HPV in the cervix over women taking and not taking COC, a higher risk in women who take COC continuously was observed [15]. Literature data also revealed that discontinuing the use of

COC reduces the relative risk for developing cervical cancer. Interestingly, we also observed that COC users have a decrease in other genital tract malignancies, such as ovarian and endometrial cancer [16].

A possible mechanism to explain the associations between the use of COC and the risk of CC is that estrogens and progestogens interact with hormone receptors, which are present in cervical tissue and influence HPV infection. COC enhances the expression of HPV 16 E6 and E7 oncogenes stimulating the degradation of p53 tumor suppressor genes [17].

In a report by WHO (1985) [18] the use of COCs for extended time may increase the risk of invasive cancer. Harris et al (1980) [19] also observed a relative risk in the value of 2.1 to carcinoma in situ and dysplastic lesions in patients using COC for over 10 years.

The present results demonstrate that the effects of the use of COC are time dependent. Negrini et al. (1990) [20] showed, by examination, COC as a risk factor for cytological abnormalities of the cervix. 1964 women showed that the use of COC is not related to the risk of LSIL, but it was associated with a high risk of HSIL, which increases with the increase of the duration of COC use (relative risk = 4.6, 95% CI = 1.1 to 18.1 for > 5 years use).

The action mechanism involved in the development of cervical cancer under the influence of hormones and HPV is not well understood. Literature data suggest that estrogen acts as a cofactor with HPV in the development of cervical cancer. This action occurs in the squamous epithelium and cervix via epigenetic mechanisms [21].

Another study investigated the effects of estrogen and progesterone in HPV-infected cells, showing that the presence of these hormones did not change the expression of E6 and E7 proteins, which are produced by HPV infection and responsible for malignant transformation of cells of the cervix. However, changes were noted in epithelial cell proliferation, suggesting that hormones may have permissive role in both growth and development of cervical cancer [22].

In a recent study, Roura et al. (2016) [12] evidenced that several hormonal factors are risk factors for cervical carcinogenesis. In addition, Roura et al. suggest that adherence to current cervical cancer screening guidelines should minimize the increased risk of CC associated with these hormonal risk factors. Another suggested mechanism of action is 16 alpha-hydroxylation of estrogen, which allegedly increases the transcription of HPV high risk. This action is observed for continuous users of COC.

Based on the data presented, it is suggested that the use of COC is a contributing factor to the development of precursor lesions of cervical cancer. The mechanism of action is still not clear in literature, thus more studies aimed at clarifying the mechanisms involved in this process are needed.

Data from this study suggest that the use of COC for more than three months may represent a risk factor for the development of cervical cancer precursor lesions, especially in women aged between 25 and 45 years old. There was no association observed between the type of COC and different types of cervix lesions.

Acknowledgments

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Authors declare no conflicts of interest.

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