RETROSPECTIVE STUDY OF THE INCIDENCE AND TREATMENT OF PRENEOPLASIC CERVICAL LESIONS

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Abstract: *Cervical cancer is the 2nd leading cause of death in women worldwide. The aim of the paper was to evaluate the prevalence of precancerous cervix lesions and their management. The retrospective study was performed over a period of six years. We observed an increased incidence between 26-45 years, coinciding with the peak of female sexual life. 50.81% of patients had abnormal vaginal bleeding,11.35 % presented with modified leucorrhea and 9.72% for abdominal pain. The main procedure performed for this pathology was cold knife conization followed by endocervix curettage in 52.43% cases. Cervical dysplasia has a higher incidence in low/middle income countries because of the lifestyle factors, that includes also the participation in adequate screening programs. These results point out the importance of prevention programs, including vaccination and screening.*

Key words: *cervical dysplasia, cervical cancer, HPV.*

1. Introduction

Cervical cancer is the 2nd leading cause of death in women worldwide. According to the latest reports, Romania holds the first place in Europe regarding mortality due to cervical cancer, with mortality rates 6.3 times higher than the average of the EU countries [8].

Numerous studies concluded that risk factors are: exposure to biological agents (such as Human Papilloma virus, Epstein Barr Virus, HIV1, HCV, Helicobacter pylori) or physical agents (such as ionizing radiation, UV) [5], [24]. *Aleksandrova et al* pointed out in a study from 2014 that cancer has multifactorial causes (environmental and life style factors), the etiology of this disease being associated with genetic anomalies and inherited genetic aberrations (caused by endogenous and exogenous agents) [1].

The main purpose of the cervical screening is to identify patients with asymptomatic disease. The screening programs from the developed countries decreased the incidence of this pathology and the stage of cancer if the disease is diagnosed. The pre-malignant lesions of the cervix are also defined as cervical intraepithelial neoplasia (CIN). It is classified into mild, moderate or severe, described by their depth (CIN 1, 2 or 3). If the cervical intraepithelial neoplasia is not diagnosed and progresses, it develops into squamous neoplasia.

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The main cause of the precancerous lesions of the cervix is Human papillomavirus (HPV). It has more than 100 subtypes and is present in almost 95% of pre-invasive and invasive squamous carcinomas of the cervix [23].

2. Objectives

The aim of the paper was to evaluate the prevalence of precancerous cervix lesions and the treatment used for this pathology in the Clinical Hospital Of Obstetrics and Gynecology „Dr. I.A.Sbârcea" Brasov.

3. Material and Method

The retrospective study was carried out in the Clinical Hospital of Obstetrics and Gynecology „Dr. I.A. Sbârcea" Brasov, conducted over a period of six years. The study included a total of 185 cases diagnosed with precancerous lesions in the period January 2010 to December 2015, admitted in our clinic for surgical interventions.

The diagnosis of precancerous lesions has been triggered by previous examinations performed in the private practice or in the ambulatory of the hospital (Pap smear, HPV genotyping, colposcopy or biopsy). Data was obtained from the medical records (a limitation of the study was the lack of information regarding the additional examinations, this data was not found in the medical records of the hospital). We analyzed the distribution of the precancerous lesions according to the age, sociodemographic characteristics, symptoms, cytological type lesion and treatment performed.

Statistical and graphical data was performed using MS Excel 2016 and MedCalc program.

4. Results

In the studied period, we identified 185 cases diagnosed with precancerous lesions aged between 21 and 80 years (Figure 1). There is an increased incidence between 26-45 years, coinciding with the peak of female sexual life. Lowest risk has had patients under 27 years and over 46 years.
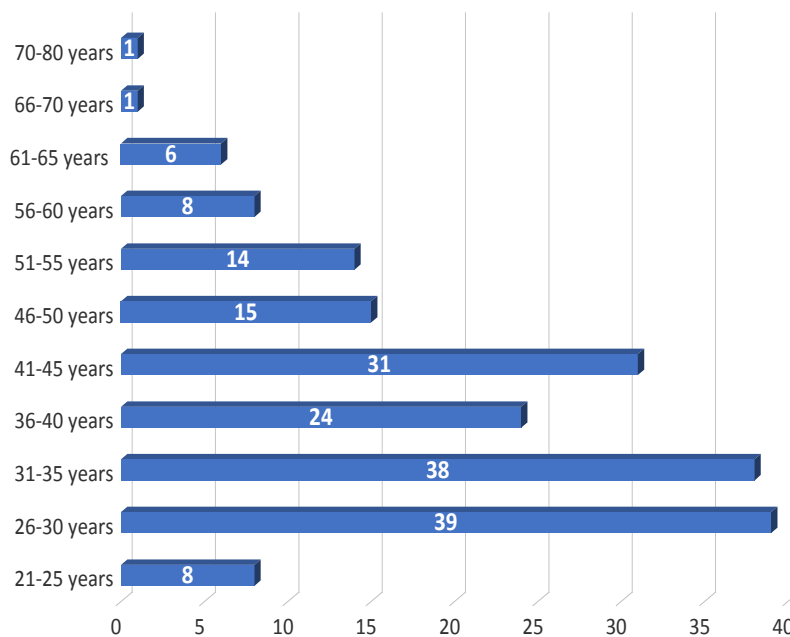

Fig.1. *Distribution of patients diagnosed with CIN by age*

The sociodemographic characteristics of the study population are summarized in Table 1.

The residence areas were mainly urban (85.25%), possibly due to early presentation to the hospital and because of the multiple risk factors from the environment (food, sexual behavior, smoking).

We also observed that patients with higher levels of education and employed presented earlier at the hospital for screening of cervical cancer.

Sociodemographic characteristics of the study group   Table 1

Residence area	Urban	156	85.25%
	Rural	29	14.75%
Education status	Without studies	1	0.54%
	Less the high school graduated	9	4.86%
	High school	70	37.83%
	Professional school	39	21.08%
	Superior studies	66	35.67%
Occupation	Student	3	1.62%
	Unemployed	51	27.56%
	Employees	131	70.81%

The reasons for presenting to the hospital were also investigated in our study. Half of the patients had abnormal vaginal bleeding (50.81%), 28.10% presented following the screening program results, 11.35% presented with modified leucorrhea and 9.72% for abdominal pain, as showed in figure 2.
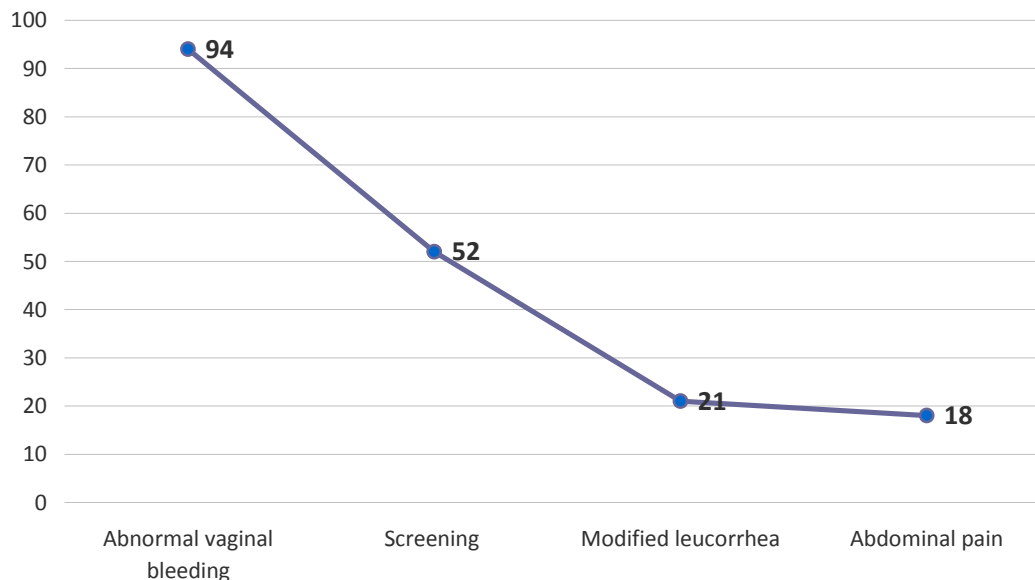

Fig. 2. *Distribution of the patients regarding the symptoms*

144 of patients (78.69%) were diagnosed at the stage of severe dysplasia, the prevalence of moderate (27 cases- 14.75%) and mild dysplasia (12 cases - 6.56%) being lower, mostly because of the delayed appearance of symptoms and the lack of instruction for the cervical cancer screening programs.
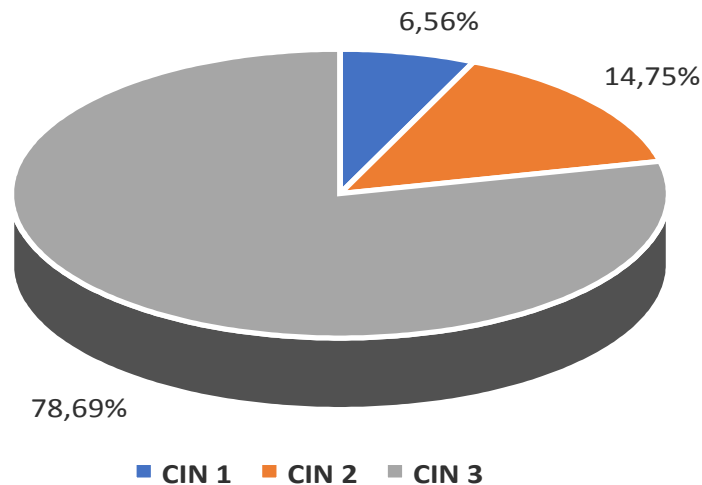

Fig. 3. *Distribution of patients diagnosed with CIN lesions by type of lesion*

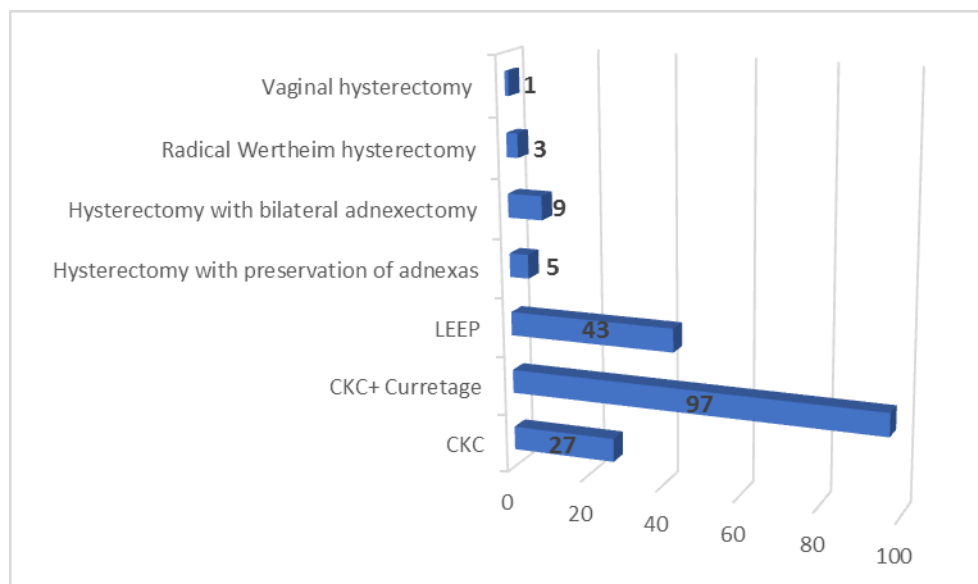The treatment for the patients included in the study is exemplified in figure 4.

Fig. 4. *Treatment applied for patients with CIN*

The choice of surgery was taken according to the clinical examination, the patient's age, the desire to preserve their fertility and the histopathological results of cervical biopsies (where it was the case). There were performed cold knife conization (CKC) in 27 cases (14.59%), CKC followed by endocervical curettage

in 97 cases (52.43%), large loop excision of the transformation zone (LEEP) in 43 cases (23.24%), hysterectomy with preservation of adnexa in 5 cases (2.70%), hysterectomy with bilateral adnexectomy in 9 cases (4.86%), radical Wertheim hysterectomy in 3 cases (1.62%) and vaginal hysterectomy in 1 case (0.54%).

5. Discussions

The infection with high-risk HPV (HR-HPV) is known to be the main cause of cervical premalignant lesions and cervical cancer [25]. Several HR-HPV genotypes are identified, as following: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59and 68 [Munoz, Guan]. World Health Organization (WHO) recommends HPV genotyping, together with the other cervical cancer screening methods if health resources allow in the area [27], because HR-HPV infection is predictive of subsequent risk for developing CIN [7]. Genotyping for HR-HPV can identify women at the greatest risk for developing CIN 3 or worse (CIN3+) and may also warrant a less aggressive management of low-risk HPV lesions [14].

A study of Onuki et al. [22], observed that the 4 most common types in the CIN1 group were HPV16, HPV18, HPV58, and HPV33 and for the CIN2+ group were HPV16, HPV58, HPV52 and HPV33. These results suggest that HPV16 played a major role in developing CIN. Another study proposed several HPV subtypes (HPV16, 18, 31, 33, 35, 52, and 58) as high risk for the progression of cervical lesions [16]. It was observed that compared with CIN2, cervical cancer showed an increased positive rate of HPV16 [11].

A study from 2014 of *Moga et al.* [18] pointed out that 60.8% of the women with precancerous lesions presented HPV infections and in 28.64% of these cases it

was identified an HR-HPV type. They concluded that the increased incidence of HR-HPV genotypes in cervical intraepithelial lesions most be an alarm sign, and the women who are HR-HPV positive have to be included in a more frequent follow up.

In our study, cervical intraepithelial neoplasia is identified with a higher frequency at women between 26-40 years old, the results being similar to the research of *Mosuro et al* [19]. It is well known that the chances of a woman to develop dysplasia increases with the age, therefore the age is an important predictor factor. In the same study, the authors concluded that mean age for cervical dysplasia and carcinoma *in situ* varies from 34.7 to 38.6 years respectively 39.6 to 43.5 years. The results of *Babarinsa et al.* showed an increase incidence of cervical precancerous lesions particularly among women above 30 years of age [2].

Several studies conducted in the past 30 years have indicated that cervical dysplasia and cervical cancer risk is influenced by the sexual behavior: age at first sexual intercourse or the number of sexual partners, smoking (because of the carcinogenic action of cigarette) [6], the number of births[13]. It was demonstrated a linear trend in the association between parity and cervical dysplasia risk because of the lack of screening and because the high parity and deficient diets of women in developing countries can contribute to the increased incidence rates of cervical dysplasia and cancer [20].

Diet is also very important, *Moga et al.* concluded in a review study from 2016 that a high intake of foods containing polyphenols may reduce the risk of cervical dysplasia and neoplasia [17]. The results from studies that used diet recall methods have been corroborated with laboratory samples that were assaying the dietary constituents in plasma. Beside the

reproductive factors, it is possible that diet may influence the various incidence rates in cervical dysplasia and cervical cancer between different areas [4].

Low grade dysplasia is usually asymptomatic and it manifest only when the disease advances, the common complaints in cervical intraepithelial dysplasia being postmenopausal, intermenstrual and postcoital bleeding per according to the study of *Gupta et al.* from 2013 [12]. In our study also, in 50.81% of cases the main cause of the gynecological exam was the postcoital and postmenopausal bleeding.

The management options for CIN grade 1 varies widely across different countries, ranging from simple observation to excisional therapies [15]. Usually, patients with persistent LSIL should be treated with ablative therapies. In case of CIN grade 2 or 3, the management guides are well established and recommend biopsy with/without endocervical curettage [3]. To exclude the invasive disease, cold-knife conization or electroconization should be performed in all patients with confirmed HSIL.

The goal of treating cervical dysplasia is to eliminate the abnormal cells before they have a chance to progress to invasive carcinoma [10]. The treatment depends on the extent of the lesion, but also on factors such as the age of the patient, her desire to preserve fertility and the presence of other medical conditions. In the surgical treatment of cervical intraepithelial neoplasia, it is important to obtain clear margins, particularly clear deep margins. Effective treatment of cervical dysplasia and careful subsequent follow-up are essential to prevent progression of cervical intraepithelial neoplasia to cervical cancer [20]. In our study, 52.43% from the cases were treated by cold knife conization followed by endocervical curettage.

Recognizing that human papilloma virus infection is the main cause of cervical dysplasia has created new research fronts in primary and secondary prevention of this disease [9]. Health promotion strategies geared at a change in the sexual behavior, targeting all STDs. In developing countries, where the incidence of cervical lesions is high, the vaccination against HPV may have greatest value.

The screening programs have been successful in developed countries, but in developing countries these programs lack coverage, accessibility, effectiveness and acceptability. Altering some of the known risk factors such as age at first sexual contact, parity and health-care have showed general improvement in the socioeconomic status and educational level of the population, with positive effect on the risk of cervical dysplasia and cancer [26].

The high prevalence of CIN 3 from our study may be attributed to the patients lack of information on the detection of precancerous cervical lesions and their progression to cervical cancer. This lack of information is an important impediment regarding the participation in the screening programs for cervical cancer. Along with the current Pap smear screening, due to known implication of the HPV infection in precancerous lesions and cervical cancer, HPV genotyping should be integrated into screening.

The study limitation was the lack of information regarding the previous additional examinations (HPV genotyping, colposcopy, biopsy) performed to the patients with cervical intraepithelial neoplasia admitted in our clinic, due the fact that these were not attached in the medical registries.

6. Conclusion

A social class disparity in cervical dysplasia rates is consistently found, but it seems to be more pronounced in low/middle income countries because of the lifestyle factors, that includes also the participation in adequate screening programs. These results point out the importance of prevention programs, including vaccination and screening (ADN HPV genotyping). Effective treatment of cervical dysplasia and careful subsequent follow-up are essential to prevent progression of cervical intraepithelial neoplasia to cervical cancer.

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