

Cervical cytology in adolescence

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Summary

The prevalence of cervical intraepithelial neoplasia in young women is increasing worldwide. Frequency of the abnormal Papanicolaou smears was examined in sexually active young females aged 13 to 19 years. The smears were reported as within normal limits or with benign cellular changes due to inflammation in 96.2% of cases. The cytological changes were related in 2.5% of cases of HPV infection, in 1.0% of cases to CIN I and in 0.3% of cases to CIN II. These results show a frequency of 3.8% of abnormal smears.

Key words: Cervix; Papanicolaou smear; Adolescence.

Introduction

Although cervical dysplasia and carcinoma have been considered disorders of middle-aged women, the prevalence of cervical intraepithelial neoplasia (CIN) in young women is increasing worldwide.

The prevalence of cervical precancerous lesions has increased by more than 60% in the past 15 years, and the mean age of maximal incidence has steadily dropped so that young women in their teens or early 20s are frequently seen with pre-invasive cervical cancer [1, 2].

There are two widely accepted behavioral risk factors for Pap smear abnormalities: young age at first coitus and multiple sexual partners. Of the two, early age of first intercourse appears to be the more significant risk factor [3]. The significance of early age at first coitus is thought to be related to the biologic changes that occur in the cervix during puberty. The adolescent cervix appears to be especially vulnerable to the initiation of carcinogenesis. The increased mitotic activity present during normal physiologic growth of the cervix during puberty increases susceptibility to carcinogenesis [4]. Adolescents have a preponderance of metaplastic and columnar cells on the ectocervix, which may make it especially vulnerable to human papillomavirus, other sexually transmitted agents and subsequent neoplastic change [3, 5].

The relation between number of sexual partners and cervical carcinoma addressed to adolescents exclusively has not been studied.

This risk factor is particularly relevant for adolescents, as adolescence is a time when much sexual experimentation occurs. It was found that in women with confirmed diagnosis of CIN III, those with seven or more partners had a six-fold increased risk of developing cervical carcinoma compared with women with one or no partner [6]. Generally the increase in sexual activity among teenagers and the rising frequency of sexually transmitted diseases among adolescents have been considered as predisposing agents.

Other risk factors have received attention, but their role in cervical neoplasia is more controversial; notably oral contraceptive use, smoking and low socioeconomic status. These factors may potentially have a latent effect on cervical carcinogenesis in older women. Behavioral and biologic risk factors, the human papillomavirus and the possible role of the human immunodeficiency virus may play a role in the increasing prevalence of cytological abnormalities in teens. Smoking has been associated to cervical cancer but this effect of smoking may require a latent period and thus may not be manifest in adolescents [7].

Despite the rarity of cervical carcinoma in teenagers, with the establishment of cytology as an important diagnostic tool, reports began to appear in the literature on cytology in teenagers.

The purpose of this paper is to present our experience with cervical cytology in teenagers.

Materials and Methods

During the period 1988-1994 2,453 symptomatic teenagers (aged up to 19 years) were examined at the Division of Pediatric and Adolescent Gynecology of the Department of Obstetrics and Gynecology, University of Crete and Department of Pathology, University Hospital, Heraklion.

In all cases of infection a therapy was prescribed and re-examination was performed. Smears were classified as normal (negative) or abnormal. Inconclusive smears were further categorized as those containing cells suggestive of mild, moderate or severe cervical dysplasia.

The term "cytological abnormality" refers to any Papanicolaou smear result which is more severe than inflammation (i.e. atypia, koilocytosis, cervical intraepithelial neoplasia).

The prevalence of human papillomavirus (HPV) type was detected by using HPV DNA assays that are considerably more sensitive and that are able to detect a wider spectrum of HPV types. With the use of the polymerase chain reaction (PCR) technique, viral DNA has been detected in cervical smears from adolescents with evidence of low grade squamous lesions (HPV and/or CIN).

Results

Abnormal cervical cytology has been found in substantial number of adolescents between the age of 13 and 19. The smears were reported as within normal limits or with benign cellular changes due to inflammation in 2,360 cases. The cytological changes were related in 61 cases to HPV infection, in 25 cases to CIN I (encompassing HPV) and in seven cases to CIN II (encompassing HPV) (Table 1). The frequency of the abnormal smears according to the age of these young women are shown in table 2. There is no agreement on the timing and sequence of follow-up procedures for HPV infection. Colposcopy is usually needed for further evaluation of atypia.

In all cases of abnormal smears a colposcopy was performed and most of the smears were established histologically. Re-examination after three years was recommended for all those who had normal smears.

The typing of the virus revealed a higher prevalence of HPV 16 in 36% of cases, HPV 11 in 13%, HPV 18 in 10%, HPV 33 in 3.2%, HPV 16 and HPV 11 in 6.5% while 31.3% of cases were found negative for HPV DNA (Table 3).

Table 1. — Incidence of normal and abnormal smears

| Year | No of cases | Normal smear | Abnormal smear | | |
|-------|-------------|--------------|----------------|-------------|--------------|
| | | | CIN I | CIN II | HPV |
| 1988 | 220 | 212 | 3 | 2 | 3 |
| 1989 | 297 | 286 | 3 | 1 | 7 |
| 1990 | 385 | 371 | 4 | 1 | 9 |
| 1991 | 441 | 425 | 4 | 2 | 10 |
| 1992 | 446 | 431 | 3 | 1 | 11 |
| 1993 | 320 | 306 | 4 | 0 | 10 |
| 1994 | 344 | 329 | 4 | 0 | 11 |
| Total | 2453 | 2360 | 25 (1.0%) | 7 (0.3%) | 61 (2.5%) |

Table 2. — Incidence of abnormal smears correlated to age

| Age | No of cases | Normal smear | Abnormal smear | | |
|-------|-------------|--------------|----------------|-------------|--------------|
| | | | CIN I | CIN II | HPV |
| 13 | 6 | 5 | 0 | 0 | 1 |
| 14 | 12 | 11 | 0 | 0 | 1 |
| 15 | 18 | 16 | 0 | 0 | 2 |
| 16 | 242 | 234 | 2 | 0 | 6 |
| 17 | 563 | 547 | 4 | 1 | 11 |
| 18 | 659 | 636 | 7 | 2 | 14 |
| 19 | 953 | 911 | 12 | 4 | 26 |
| Total | 2453 | 2360 | 25 (1.0%) | 7 (0.3%) | 61 (2.5%) |

Table 3. — Type and prevalence of HPV

| Type | % |
|-------------------|------|
| HPV 11 | 13 |
| HPV 16 | 36 |
| HPV 18 | 10 |
| HPV 33 | 3.2 |
| HPV 16 & 11 | 6.5 |
| None of the above | 31.3 |

Discussion

Despite the fact that invasive carcinoma of the uterus is exceedingly rare in women under the age of 20, the dramatical increase of sexual activity in the last decades has transposed the age of preventive control with the Pap test towards the left. The reports in the literature testify that the prevalence of intraepithelial neoplasias and HPV infection in young women up to 19 years of age has increased in recent years.

Many epidemiological factors come into play, influencing this increase. Cervical HPV infections often quickly lead to low-grade squamous intraepithelial lesions (mildly abnormal Pap smears, including the diagnoses of koilocytotic atypia and CIN I). HPV infections and their associated lesions are extremely common among young, sexually active women. The infections are typically resolved spontaneously even at the molecular level within months to a few years. Uncommonly, HPV infections and/or low-grade lesions persist and progress to high-grade lesions. The risk factors for progression in women with and without preceding low-grade lesions are mainly unknown, but seem to include HPV type and intensity, cell-mediated immunity, and reproductive factors like parity and oral contraceptive use. Nutritional factors or co-infection with other pathogens may also be subtly involved at this apparently critical etiologic step between common low-grade and uncommon high-grade intraepithelial lesions. The importance of etiologic co-factors like smoking, however, may vary substantially by region.

The commencement of sexual relations, at an early age (under the age of 15), is one of the main epidemiological factors for carcinogenesis, because the cervix in adolescence is vulnerable due to the immaturity of the zone of metaplasia on the one hand and the increased mitotic activity in the range of the still-growing female organism on the other. The large number of sexual partners appears to be strongly correlated with the development of cervical cancer. It has been found that women with 2-5 partners have a probability 3-4 times higher of presenting with dysplasia of the cervix as compared to those women with only one partner.

Smoking does not seem to have such a strong correlation in adolescence because the oncogenic risk is linked to long-term exposure of the woman to nicotine. It is known that high concentrations of nicotine and cotinine in the cervical mucosa of women with in situ cancer have been found [7-10].

The contraceptive pill does not have a direct correlation; nevertheless it has an indirect correlation due to the laxity in sexual activity. Use of barrier methods, due to their direct influence on the cervix, are under discussion. However, it seems that they protect the cervix [11-13]. There is a theoretical risk of accelerated cervical dysplasia and the cervical cap and the diaphragm are contraindicated in the presence of an abnormal Pap smear or lower genital tract infection. This makes barrier methods, besides higher failure rates, a less than perfect choice for most teenagers.

Variations in the prevalence of HPV types in cervical lesions have been found and attributed to geographical differences, heterogeneity of HPV replication within lesions sampled, or variability in the sensitivity of the assays employed [14]. In recent years, it seems that HPV plays a great role, particularly certain types [16-18-31-33], in the appearance of intraepithelial injuries and probably invasive carcinoma as well, and in the injury to the cervical mucosa. In sexually active adolescents examined, 48-51% were found HPV positive in their positive Pap test and only 3-13% were negative. However, in women who have been affected by HPV, only a small number develop intraepithelial neoplasias or carcinoma (Ca) because other factors as well come into play in order to result in carcinogenesis (immunological system of the woman, smoking). In general, the prevalence of HPV in sexually active, adolescent girls ranges from 15%-38% [15-18].

The simultaneous increase in Pap smear abnormalities and HIV seroprevalence in female adolescents suggests the need for investigation of a possible relationship of these entities.

Abnormal, cervical cytology has been found in a number of sexually active women between the age of 13 and 19. Careful evaluation and cytologic surveillance is proposed for these young women. In adolescence there is a cervical dysplasia and HPV problem for which the extent and frequency can be verified. The progress in medical research may show in the future the relation between some viruses (HPV, HSV₂) and cervical carcinogenesis.

Because of the extremely small number of invasive carcinomas discovered, the validity of extensive screening programs in young women has been questioned. The detection of intraepithelial neoplasia is important and clearly justifies the time and expense involved in routine screening. Our findings strongly confirm the advisability of obtaining cervicovaginal smears on all sexually active gynecologic and obstetric teenage patients.

It is concluded that young women should be submitted to a Pap test, at regular intervals, after commencement of their sexual relations, not less than every two years, in order to timely observe possible pre-cancerous conditions, and be subjected to treatment (because they can actually be treated) before the appearance of a cancer of the cervix uteri. Also prophylactic measures should be taken during sexual intercourse because HPV, which has been incriminated in the development of Ca, as well as for the pre-cancerous conditions is contracted pre-eminently by sexual relations.

References

- [1] Roberts A.: "Cervical cytology in England and Wales 1965-80". *Health. Trends*, 1982, 14, 41.
- [2] Haddad N., Hussein I., Livingstone J., Smart G.: "Colposcopy in teenagers". *BMJ*, 1988, 297, 29.
- [3] Royce C.: "Abnormal cervical cytology in adolescents: a literature review". *J. Adolesc. health. Care*, 1992, 13, 643.
- [4] Edibirl A.: "Cervical intraepithelial neoplasia: the role of age at first coitus in its etiology". *J. Reprod. Med.*, 1990, 35, 256.
- [5] Mitchell H., Medley G.: "Age and time trends in the prevalence of cervical intraepithelial neoplasia on Papanicolaou smear tests, 1970-1988". *Med. J. Aust.*, 1990, 152, 252.
- [6] Brock K., Berry G., Brinton L.: "Sexual, reproductive and contraceptive risk factors for carcinoma in situ of the uterine cervix in Sydney". *Med. J. Austr.*, 1989, 150, 125.
- [7] Winkelstein W.: "Smoking and cervical cancer-current status: a review". *Am. J. Epidemiol.*, 1990, 131, 945.
- [8] Rosenfeld W.: "Sexually transmitted diseases in adolescents: update 1991". *Pediatr. Ann.*, 1991, 20, 303.
- [9] Leslie-Harwit B., Meheus A.: "Sexually transmitted disease in young people: the importance of health education". *Sexually Transm. Dis.*, 1989, 16, 15.
- [10] Brooks-Gunn J., Furstenberg F. F.: "Adolescent sexual behavior". *Am. Psychol.*, 1989, 44, 249.
- [11] Parazzini F., Negri E., La Vecchia C., Fedele L.: "Barrier methods of contraception and the risk of cervical neoplasia". *Contraception*, 1989, 40, 519.
- [12] Learmouth G., Durcan C., Beck J.: "The changing incidence of cervical intra-epithelial neoplasia". *S. Afr. Med. J.*, 1990, 16, 637.
- [13] Schwartz S., Weiss N.: "Increased incidence of adenocarcinoma of the cervix in young women in the United States". *Am. J. Epidemiol.*, 1986, 124, 1045.
- [14] Arends M. J., Donaldson Y. K., Duvall E., Wyllie A. H., Bird C. C.: "HPV in full thickness cervical biopsies: high prevalence in CIN 2 and CIN 3 detected by a sensitive PCR method". *J. Pathol.*, 1991, 165, 301.
- [15] Ley C., Bauer H., Reingold A.: "Determinations of genital human papillomavirus infection in young women". *J. Natl. Cancer Inst.*, 1991, 83, 997.
- [16] Mosciki A., Palefsky J., Gonzales J., Schoolnik G.: "Human papillomavirus infection in sexually active adolescent females: prevalence and risk factors". *Pediatr. Res.*, 1990, 28, 507.
- [17] Rosenfeld W., Vermund S., Wentz S., Burk R.: "High prevalence rate of human papillomavirus infection and association with abnormal Pap smears in sexually active adolescents". *Am. J. Dis. Child.*, 1989, 143, 1443.
- [18] Centers for Disease Control. "Sexual behavior among high school students-United States, 1990". *MMWR*, 1992, 40, 885.

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