Cervical Epithelium in the Adolescent, Its significance in Carcinogenesis

Malcolm Fonseca and Usha. B. Saraiya
Cytology Clinic (AMWI), Cama & Albless Hospital, Mumbai - 1.

Cervical cancer continues to be a major health problem in India. The incidence varies from 20 to 40 per 1,00,000 (AAR) women, as reported by the various cancer registries. In most parts of the developed world this figure has come down to less than 10. Hence, in India, the goal remains to control the disease and decrease the AAR by at least half.

Raigoni Stern (quoted by Miller, 1978), had noticed a century ago, that virgins (Christian Nuns) never developed cancer of the cervix. This probably provoked Rotkin (1967) into doing his classic epidemiologic study on age at first coitus and its relation to cancer cervix. Ever since, investigators have persistently highlighted the significance of coitus during early adolescence in the etiology of cervical carcinoma. Early age at sexual initiation and early age at first childbirth are known and accepted epidemiological factors. Hence it is very important to understand the patho-physiology of the cervical epithelium in the adolescent. Every effort must be made to protect it against known and unknown carcinogens. This is part of Preventive Oncology - a new discipline concerned with cancer prevention.

What is the normal epithelium of the ectocervix during adolescence is a vexed question. Studies show that the epithelial boundaries can vary, from the squamo-columnar (SCJ) being within the endocervical canal to being partly on the vagina, and all of them may be considered normal. The process of metaplasia is constantly occuring within this area, and the entry of foreign nucleic acids, coitally transmitted, into susceptible metaplastic cells, and their subsequent transformation into dysplasic and later malignant cells is one hypothesis of causation of cervical carcinoma. Coitally active adolescents will have, in their life-time a more prolonged exposue to such carcinogens. Such adolescent girls are also more likely to be promiscuous and therefore, exposed to a greater variety of carcinogens. But these facts have not deterred investigators from looking for a particular susceptibility in adolescent cervical epithelium to such carcinogenic stimuli.

This study of the cervix in adolescence is hampered by the fact that studies in normal (non-sexually active) adolescents are difficult since a speculum examination is not good gynaecological practice. Most of the studies of normalcy, hence, are in those adolescent girls who required a speculum examination for medical reasons (D & C, etc) or are done as post-mortem examinations. Adolescents may not be frank and forthcoming on sexual activity for social reasons. The studies by Coppleson & Reed (1975) and Singer (1975) were done in state prisons or institutions where sexually active adolescents were required by law to undergo examinations.

Singer (1975) has divided the adolescent girl population into 3 groups:
1. virginal group
2. sexually active but nulliparous group and,
3. sexually active and parous group.

The transformation zone (TZ) in these 3 groups were then compared with the TZ in adult parous women. A physiological TZ seems to be the most common in all groups. An atypical TZ was more common in the sexually active groups (10-44%) giving credence to the hypothesis of early coitus-induced carcinogenesis, but, was also seen in 12.5% of virgins.

The total area of the TZ is also important. Singer (1976) has also compared the total area of the TZ in virginal v/s sexually active adolescents and found that the TZ of the virginal cervix is significantly larger than that of sexually

active girls. There are very few other equivalent studies, and on the basis of the above study, and a similar subjective impression by other investigators, Singer (1976) feels that the SCJ probably retracts to within the endocervix as an effect of coitus.

The metaplastic process begins, in fact, from the time of menarche. When the menstrual flow passes through the hymen for the first time, the Doderlein's bacilli enter the vagina and cause it to become acidic. Later on, other bacilli invade the vagina. Pixley (1967, 1971) did a study of 64 (36 pre-menarchal and 28 post-menarchal) virginal girls. He classified cervices into 2 types:

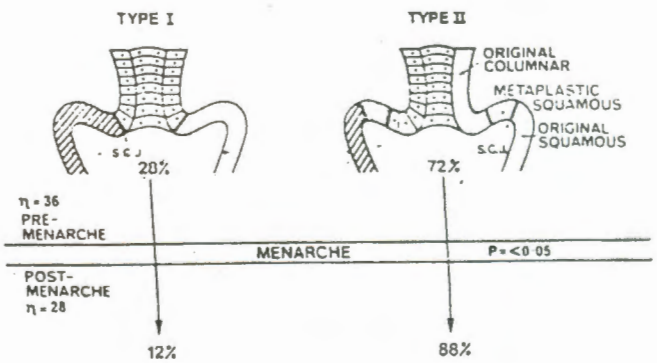
Type 1: SCJ at the external OS
Type 2: SCJ on the ectocervix with variable amounts of original squamous & columnar & metaplastic squamous epithelium on the ectocervix.

Type 2 predominates 3:1 or more in both groups. The post-menarchal girls tend to have a type 2 cervix to a greater extent than pre-menarchal girls. Pixley believes that the newly developing vaginal fluid with its acidic pH provides the stimulus for the formation of metaplastic squamous epithelium.

In regard to atypical TZs in adolescent virgin and non-virgin girls there seem to be some peculiarities. Atypical TZs were seen in 12.5% of virgins, but on histology, most of them turned out to be benign. The colposcopic appearance has been attributed to infiltration and oedema in the cervical stroma. In non-virgins, the incidence of an atypical TZ compares equally with the incidence of atypical TZs in adult women. In this group too, precise correlation between colposcopic and histologic findings was found to be difficult. In Singer's series (1975) only 10% of 63 biopsied cervices with an atypical TZ had dysplasia on histology. Stafl and Mattingly (1974), in this regard, have an interesting caveat stating that light microscopy may not reflect the true biological behaviour of the cell. In concurrence with this caveat are the studies of Jones et al (1967) who have demonstrated aneuploidy, and other investigators who showed dysplastic surface changes by scanning electron microscope in histologically benign epithelium removed from colposcopically atypical TZs.

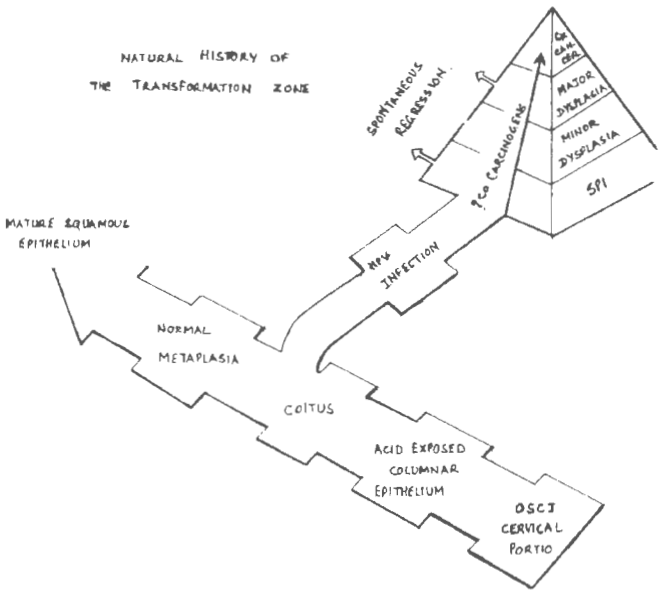
Massad and Anoina (1996) report on 62 adolescents girls who were under the age of 16 and from a low-income group. All had abnormal cytology and were referred for colposcopy. Twenty one % had biopsies showing atypia and koilocytosis and 21% had dysplasia (CIN II). There was no case of CIN III or invasive cancer. Unfortunately, 66% of the girls failed to comply with suveillance.

The natural history of the transformation is discussed by Reid et al in 1984. The young adolescent has original SCJ on the ectocervix. The columner epithelium is thus exposed to the acid of the vaginal epithelium. Due to the trauma of coitus, this columnar epithelium undergoes normal metaplasia and then mature squamous epithelium. The SCJ then returns to its normal site at the external os. If however, at this tender juncture, in addition to coitus, the epithelium suffers an HPV infection, the growth goes off at a tangent and may lead to various grades of dysplasia and even carcinoma (Fig. 1). Human Papilloma Virus infection is implicated in the development of cervical cancer. This infection can be diagnosed by cytology. The smears show large cells with a vacuolated cytoplasm and a large bland nucleus. These cells are



Type 1: SCJ at the external OS
Type II: SCJ on the ectocervix with variable amounts of original squamous & columner & metaplastic squamous epithelium on the ectocervix.

Significance of HPV Infection in the transformation Zone of the Adolescent Girl.
(Reid, Fu, Herschmann 1984)



1. OSCJ - Original Squamo - Columnar Junction
2. SPI - Subclinical Papilloma Virus Infection

called koilocytes. There are also clusters of small cells with an orangeophilic cytoplasm and dark, small nuclei called dyskeratocytes. The presence of one or both types of these cells suggests an HPV infection. Further confirmation with colposcopy and histology are mandatory. Cervical cancer rarely occurs in young girls. Hence routine screening of adolescent girls is not necessary. However, girls who are exposed to multiple partners, who have sexually transmitted diseases and who are used to smoking or tobacco chewing constitute a high risk group. These girls need to be checked periodically for precursors of cervical cancer.

Significance of age at marriage : Age at sexual initiation plays an important role in carcinogenesis. Rotkin (1967) has stated that sexual initiation before the age of 17 years was the most significant factor in all the studies reviewed by him. Saraiya and Lulla (1983) analysed the age at marriage in 3 groups of women - cancer, dysplasia and controls. In this study, 60% of cancer patients were married before the age of 17 years and only 26% after that age. As opposed to that, 35% of controls and 31% of the dysplasia group were married before the age of 17, and 46.5% of controls and 47.6% of the dysplasia group were married after that age. These figures were statistically significant. In India, child marriages are still common although the official age for marriage has been raised to 18. Strict adherence to this law will have an impact on the occurrence of cervical cancer.

Nutritional Requirements of the Epithelium:

To maintain the integrity of the epithelium certain minerals and vitamins are required. Folic acid, Vit A and its precursors β-carotene, Vit C & E in adequate amounts will lead to healthy cell growth and division. Anaemia adversely affects the body's immune system. Regular dietary intake of leafy green vegetables and dairy products will suffice. However, those who are deficient need supplementation with Vit A,C,E & Folic acid. The deficiencies of these also lead to carcinogenesis. Addition of these nutrients to diet is called chemo-prevention of cancer. (Ananth 1997).

Young adolescents are often found to be in a poor nutritional state. It may be due to poverty, lack of health education or poor eating habits. Due attention needs to be paid to correction of anaemia and avitaminosis.

In conclusion, the understanding of the patho-physiology of the cervical epithelium of the adolescent is necessary to counteract and prevent the process of carcinogenesis. If the curtain has to come down on invasive cervical cancer, we must begin with the care of the adolescent girl.

Sexual activity and marriage should be delayed till the age of 18 years. Child birth should be delayed till the age of 20 years as mature squamous metaplasia would occur by then. Nutrition should be adequate. Absence of anaemia with adequate intake of Vit A, C and E should be a part of health education for all young girls. Adequate facilities for sexual and menstrual hygiene need to be emphasised. Early detection and prompt treatment of lower genital tract infection will go a long way in maintaining a healthy epithelium. For all this to happen

in the coming century, we must learn to value the girl child.

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