



PRECANCEROUS CERVICAL LESIONS: DIAGNOSIS AND TREATMENT

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Abstract

In Armenia more than 1000 women per year are diagnosed as having cervical cancer. However, the number of deaths from cervical cancer has decreased by more than 40% during the last 20 years, and the incidence of cervical cancer is now more than that, for example, breast cancer (41,000 new cases per year). This decrease is directly related to implementation of cervical screening programs.

Cervical Pap smears have been used for many years as a screening method for cervical cancer. This test is an important part of the program for preventing this disease in women in Armenia. The goal of cervical cytology screening is to reduce the incidence of cervical cancer by detecting and treating preinvasive lesions. Screening for cervical cancer with the use of cytology has significant effects on the incidence, morbidity, and mortality from invasive disease by facilitating the eradication of precursor lesions.

The incidence of preinvasive disease of the cervix has been increasing in Armenia over the past decade. It is estimated that approximately 15% of mild to moderate dysplasias progress to invasive cancer if not treated.

Certain predisposing factors of cervical cancer are recognized. Sexual activity seems to be positively correlated with the disease, and sexual intercourse at a relatively early age is a highly significant factor. Cancer of the cervix is 4 times as frequent in women with multiple sexual partners as in other women.

The average age at diagnosis of patients with cervical cancer is 45, but the disease can occur even in the second decade of life and occasionally during pregnancy. Over 95% of patients with early cancer of the cervix can be cured. With present methods of management, about 1000 women in the Armenia die of this disease each year. This could be greatly reduced if cervical cancer was detected early and treated properly.

By screening Pap smear results a physician plays an important role in lowering death rate from cervical cancer. Only then it is possible to choose an adequate treatment method, if a patient has an abnormal Pap smear result. The choice of financially justified tactics of treating a patient with a low degree of atypia (atypical squamous cells of uncertain significance and squamous cell intra-epithelial disorders of low grade) is of particular importance. The next step – a repeated Pap smear for cytological screening or colposcopy – depends on many circumstances.

In this regard, human papilloma viruses (HPV) have got a great deal of attention in recent years. The morphological changes in epithelial cells, which are induced by HPV are frequently seen in cervical intraepithelial neoplasia (CIN).

Today, unfortunately, one-half of women who develop cervical cancer have never been screened. Since dysplasia is, probably, a transitional phase in the pathogenesis of many cervical cancers, and many patients with preinvasive disease are asymptomatic, its early detection is extremely important.

When dysplasia is diagnosed cytologically, steps should be taken to confirm the diagnosis histologically and to determine the extent of the lesion.

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In addition to gross inspection of the cervix, the diagnostic procedures include the Schiller test, colposcopic examination, directed biopsy, endocervical curettage.

If cervical epithelial neoplasia is combined with signs of an inflammatory process, it is necessary to find the etiological factor and conduct the required treatment. However, an inflammatory process with no infectious agent is often observed in cases of invasive carcinoma of the cervix. It is recommended to have an early repeat examination of the patient.

Conclusive diagnosis and management of cervical intraepithelial lesions is based on a combination of consecutive cytology, colposcopy, directed biopsy, and endocervical curettage.

In treating CIN the transitional area between the squamous and columnar epithelia, where the abnormalities are located, must be completely removed. Various treatment modalities are possible. The choice of a particular method will depend on the nature of the lesion, the patient's age, and her wishes concerning maintenance of fertility. We are especially in favor of the technique of loop excision. This method allows achieving good results both diagnostically and therapeutically. The procedure is carried out at outpatient clinics under local anesthesia and using colposcopy, the atypical transformation zone is excised with the help of a diathermic loop. It should be pointed out that, irrespective of the treatment chosen, cytological follow-up is indicated in cases of CIN.

Keywords: LEEP, preinvasive lesions, dysplasia, colposcopy, Pap smear, punch biopsy.

Introduction

Cancer of the cervix is the third most common type of cancer in women after cancer of breast and endometrium. It is believed that in 2006, 2.5 million women will have abnormal Pap smear results, 50,000 of them will have carcinoma and 15700 – invasive cervical cancer. It is expected that 5000 women will die from cervical cancer during this year. The statistical data on these abnormalities and death rates resulting from them are in dramatic contrast in the countries where cytological screening of Pap smears is not done. Every year in different parts of the world 500,000 women develop invasive cervical cancer, which results in death more often than any other oncologic disease except for breast cancer [*Clinical practice guidelines, 2005*].

It has been estimated that about 2% of all women over age 40 will develop cervical cancer [*Per-noll M. et al., 2001*]. Based on the age-specific incidence rate, cervical premalignancy appears to be a disorder of the woman in the years after the menopause [*Rigoni-Stern D., 1998*].

Nonetheless, it is also found regularly in women in the fertile years of life. The apparently increased incidence of carcinoma of the cervix in young women emphasizes the necessity for all sexually active women to take form of cytological examination of the endo- and ectocervix. Carcinoma of the cervix is an example of a premalignancy

for which screening at an early stage can find patients at risk, for which proper treatment can be often instituted.

Dysplasia literally means disordered growth or development. In the cervix, this term is applied to abnormal zones, in which only a part of thickness of the squamous epithelium has been replaced by abnormal cells [*Young L., Rickinson A., 2004*].

Cervical neoplasia is presumed to be a continuum, from dysplasia to carcinoma *in situ* to invasive carcinoma. For this reason, screening for cervical cancer with the use of exfoliative cytology (Pap smear) can have significant effects on the incidence, morbidity, and mortality from invasive disease by facilitating the eradication of precursor lesions [*Walker P., 2005*].

A single negative Pap smear may decrease the risk of developing cervical cancer by 45%, and nine negative smears during a lifetime decreases the risk by as much as 99%. Using a mathematical model, it was indicated that in women 35 to 64 years of age, screening intervals of 1.5 and 3 years reduced the incidence of invasive cervical cancer by 64%, 84%, and 91% respectively [*Lambrou N. et al., 1999*].

For higher quality of screening one should follow precisely the method of taking a Pap smear and know the terminology of cervical cytology [*Giannopoulos T. et al., 2005*].

Compared to the time when cytological testing

of Pap smears was established as screening method, the death rate from cervical cancer dropped by 70% [Clinical practice guidelines, 2005].

Cervical diagnosis is done to determine qualitative and quantitative cell composition in the smear-print, smear-scraping or aspirate from the cervical canal [Rusakevich P., 1998].

In standard colposcopic testing for cytological study material is taken from the surface of the ectocervix and endocervix. It is necessary to include cells from all suspicious areas, including the transition area between columnar and squamous epithelium [Majewski S, Jablonska S., 2002]. Whilst there is strong evidence that HPV is the principal aetiological agent in cervical neoplasia, some other sexually transmitted agents may either contribute or protect against cervical carcinogenesis, such as the herpes virus family (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human immunodeficiency virus (HIV) or Chlamydia trachomatis (CT). Epidemiological studies suggest that HSV may have a role in cervical neoplasia, but there is no clear supportive experimental evidence [Grainge M. et al., 2005].

Evidence supports the significant role of HPV infection in the etiology of cervical neoplasia. HPV types 16, 18, 31, 45, 51-53, and 56 are associated with invasive carcinoma. HPV DNA (predominantly types 16, 18, and 31) has been isolated from 80 to 100% of cervical carcinomas. The changes in epithelial cells which are induced by HPV are frequently seen in CIN [Meisels A., 1999].

Various HPV subtypes can be distinguished and each is associated with certain lesions. Subtypes 16 and 18 appear to be associated more with CIN and cervical carcinoma. Oncogenic factors (e.g., HPV) induce maturation and growth disturbances in the transitional area between the squamous and columnar epithelia of the cervix uteri, the squamocolumnar junction [Evers J., Heireman M. 2000]. Cervical cancer and its precursors have been associated with several epidemiologic variables: young age at first coitus (under 20 years); multiple sexual partners, young age at first pregnancy, high parity, divorce, lower socioeconomic status, smoking, STIs, abortions [Burghardt E., 1987].

Clinical symptoms of microinvasive carcinoma are nonexistent or non-specific and, therefore, are of no assistance in making the diagnosis [Campbell K., 2006].

Therapy for preinvasive disease is usually curative and prevents the subsequent development of invasive cancer [Pernoll M. et al., 2001].

The most important tasks in managing patients with cervical dysplasia are to rule out invasion and to determine the extent and distribution of the lesion [Pharoah P., 2005].

The ability to locate and precisely define the size and distribution of the intraepithelial lesion by colposcopy in most patients has allowed a more conservative approach to the disease. For conservative forms of management, the entire transformation zone must be visible and accessibly to the method [Gilyazutdinova Z. et al., 2002].

Colposcopy after a cervical smear shows any kind of squamous intraepithelial lesion on the cervix. Colposcopy is inadequate to evaluate disease in the endocervical canal [Burghardt E. et al., 2008].

Materials and Methods

From 2001, in Armenian-American Wellness Center cervical cytology screening was done in 10365 women. Preinvasive lesions were established for 1564 patients. For reporting on cervicovaginal cytologic diagnoses we used the Bethesda system, which divides cervical lesions into two basic categories: low-grade squamous intraepithelial lesions (LSILs) and high-grade squamous intraepithelial lesions (HSILs). Our investigations showed: 705 women (45%) had LSIL-s (CIN I) (Figure 1).

HSIL-s (includes moderate and severe dysplasia) were detected in 859 patients (55%). The study showed that progression of LSIL to invasive disease occurs over 10 to 26 months. In our retrospective study of 705 women, whose first smear suggested CIN-I at colposcopy and biopsy 61% of lesions were found regressed to normal spontaneously, 22% had persisted as CIN I, and 17% progressed to CIN II.

The age range of the investigated women was from 22 to 73 years; 5100 women were of reproductive age; 2960 women – in menopausal age;

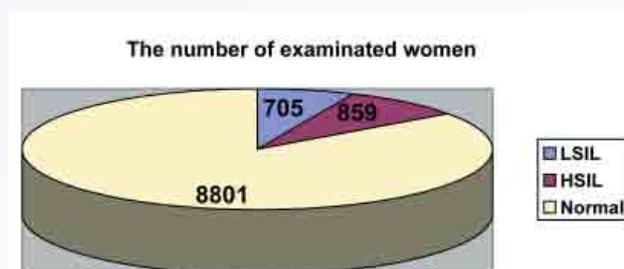


Figure 1. The number of examined women

2305 women – in postmenopausal age. A number of studies indicate that mostly cervical dysplasia occurred in females the age of 22 and above, with a peak incidence in the age group from 27 to 38 years. Cervical premalignant disease is relatively rare before the age of 20

About 25% of women with abnormal Pap smear result (LSILs) had leukocytes in the smear and various microflora as well. The fourth degree indicates absence of normal flora in the vagina; instead, there is a large amount of microbes: streptococci, staphylococci, intestinal sticks. The pH of the vaginal canal is in this case alkaline (> 7.2). If specific infections such as chlamydiosis or gonorrhoea, and vaginitis caused by candida, trichomonas or gardnerella were identified, the treatment with antibiotics was appropriate. Women with a diagnosis of CIN-I associated with severe inflammation were re-evaluated, preferably after 2 to 3 month (Figure 2 and 3).

HPV (16 and 18 types) was detected in 80 to 90% of precancerous cervical lesions. Recent studies documented a stronger link between cervical carcinoma and the HPV. Testing for HPV helps to identify high- and low- risk patients.

Preinvasive disease (dysplasia and carcinoma *in situ*) does not produce symptoms. The discharge frequently seen in preinvasive disease is most often due to accompanying infection. Clinical findings of precancerous cervical lesions are non-specific and, therefore, are of no assistance in making the diagnosis.

Patients with cervical preinvasive disease have a normal general physical examination.

The most common complains of the patients were: Vaginal discharge – in 594 women (37.9%); Postcoital bleedings - 296 women (18.9%); Abnormal



Figure 2. HSIL: sheet of parabasal and basal cells with enlarged and hyperchromatic nuclei and irregular nuclear outlines.

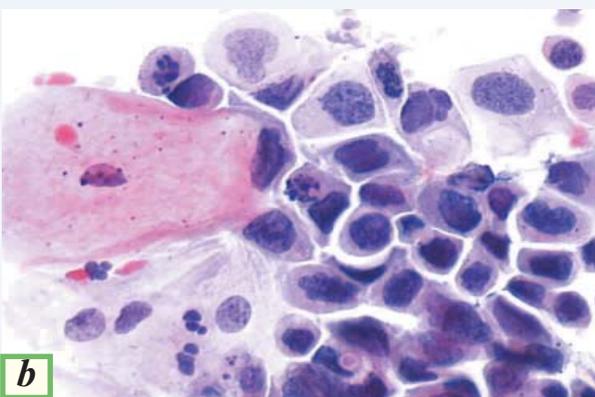
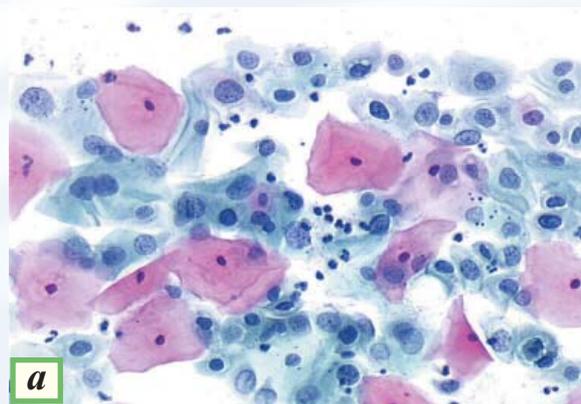


Figure 3a. HSIL: parabasal and basal cells with enlarged and hyperchromatic nuclei and irregular nuclear outlines. Note the abundance of spindle cells.

Figure 3b. Detail of Figure 3a.

menstrual bleeding or intermenstrual spotting – 329 women (21%); Postmenopausal bleeding – 312 women (20%); Pain in lower abdomen – 375 patients (24%).

Among women with the preinvasive disease 391 (25%) were asymptomatic.

The management of cervical intraepithelial lesions was based on a combination of cytology, colposcopy, directed biopsy and endocervical curettage.

Colposcopy examination data: Normal transformation zone in 560 women (35.8%); Abnormal transformation zone in 792 women (50.6%) (Figure 5); White epithelium and iodine negative areas – 999 (63. 8%) (Figure 4); Mosaicism or coarse punctuate pattern of the surface capillaries – 813 (52%) (Figure 6);

If the colposcopic examination was satisfactory colposcopically directed biopsy was done taken from the worst area(s), together with an endocervical curettage(ECC). When colposcopy was inadequate to evaluate disease in the endocervical canal in that cases we performed endocervical curettage (ECC).

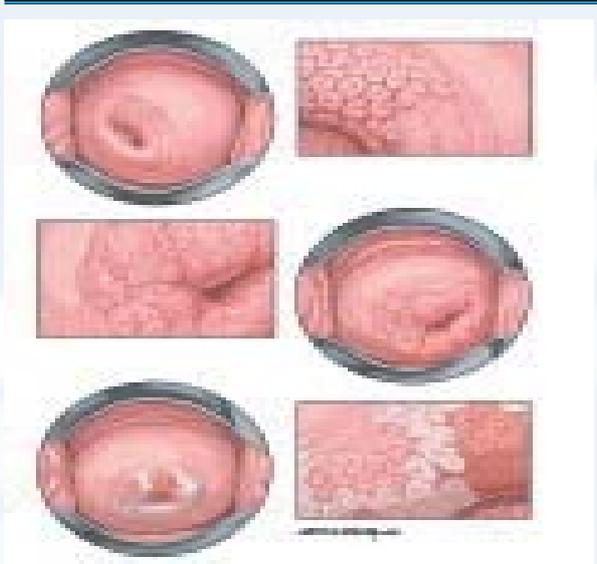


Figure 4. White epithelium on the cervix, mosaic changes on the transformation zone.

For patients with a preinvasive lesion that was confirmed cytologically and completely visualized colposcopically the invasion has been ruled out: Loop electrosurgical excision procedure (LEEP) of the transformation zone was performed.

Finally, diagnosis and treatment of cervical intraepithelial lesions were based on consecutive cytology, colposcopy, directed biopsy, and endocervical curettage.

For treatment of cervical preinvasive lesions at the Armenian-American Wellness Center, we performed LEEP. The procedure was done on an outpatient basis under local anesthesia using local infiltration of 1% lidocaine, with or without epi-



Figure 5. Colposcopy of the cervix with abnormal transformation zone and mosaicism.

nephrine; the use of vasoconstrictor was helpful in decreasing the bleeding.

Indications for Loop electrosurgical excision procedure (LEEP) were: cytological or colposcopic suspicion, if CIN2 or worse (including micro-invasion); Persistent CIN1 if the likelihood of follow-up is low or when the patient requests treatment; A transformation zone, which is fully visible and fully confined to the cervix; A suspicion of a glandular intraepithelial abnormality; A disparity between the cytological and colposcopic diagnosis.

The following were contraindications for LEEP: pregnancy; apparent invasive carcinoma of the cervix; a bleeding disorder; acute or active inflammation of the cervix, endometrium, fallopian tube, ovary, or peritoneum; “positive” endocervical curettage or lesion in which the endocervical limit cannot be visualized colposcopically; less than 3 month postpartum.

Results and discussion.

Studies indicate that cervical dysplasia mostly occurred in females aged 22 and older, with a peak incidence in the age group from 27 to 38 years. Cervical premalignant disease is relatively rare before the age of 20.

By screening Pap smear results a physician plays an important role in lowering death rate from cervical cancer. Cervical cytology screening is to reduce the incidence of cervical cancer by detecting and treating preinvasive lesions.

Immediate colposcopic assessment after a cer-



Figure 6. Punctuate pattern of the surface capillaries, CIN 2.

vical smear shows any kind of squamous intraepithelial lesion and routine colposcopy decreases the problem of noncompliance.

After colposcopy, when it was inadequate to evaluate disease in the endocervical canal, we performed endocervical curettage, as part of the colposcopic assessment of patients with abnormal Pap smear findings. ECC helped to evaluate the endocervical canal and to exclude the diagnoses of invasive carcinoma, unsuspected adenocarcinoma *in situ* (AIS), and invasive adenocarcinoma.

Loop excision of the transformation zone has been used for cervical intraepithelial neoplasia as a conservative method of treatment.

Our investigations and literature data show that the LEEP has not any complications for further pregnancies and deliveries, procedures were performed independent from the patient's age and gravidity. The excision is a painless procedure, and removing the specimen in one piece is preferable and should be performed right after menstruation. After LEEP no scar and deformation of the cervix are observed and it can be performed even for nulliparous women. The most complications from the operation are: bleeding, inflammation, stenosis, structures, and recurrent CIN-I, CIN-II, or CIN-III. In our investigation we had bleeding and discomfort short-term sequelae of LEEP in 2 cases, inflammation in 1 case; only 1 woman had recurrent CIN-I. There were no cases of cervical canal stenosis. The morbidity rates associated with LEEP are very low. The success rate is greater than 90%.

The advantages of LEEP method are relatively painless, minimal or no blood loss; it is an inexpensive and outpatient procedure and has no appreciable effect on childbearing capacity.

The major side effect is a rather copious vaginal discharge that persists for several weeks. LEEP has minimal scarring, has no cervical stenosis or cervical incompetence.

Retrospective studies suggest that women who are successfully followed by cytology do not have an increased risk of cervical cancer if a biopsy is performed when cytologic abnormalities persist. It is paramount that patients managed in this modality be considered reliable for follow-up. If the follow-up smears show persistent dysplasia, colposcopy and directed biopsy are indicated. After three consecutive negative Pap smear results that are satisfactory for evaluation, the patient can be returned to a routine screening protocol.

Conclusion

In patients who are monitored using repeat Pap tests, compliance is a key component of successful management. The Pap tests should be repeated every 3-4 months for 1 year until three consecutive negative (and adequate) Pap smear results have been returned, at which point the patient can revert to routine screening protocols.

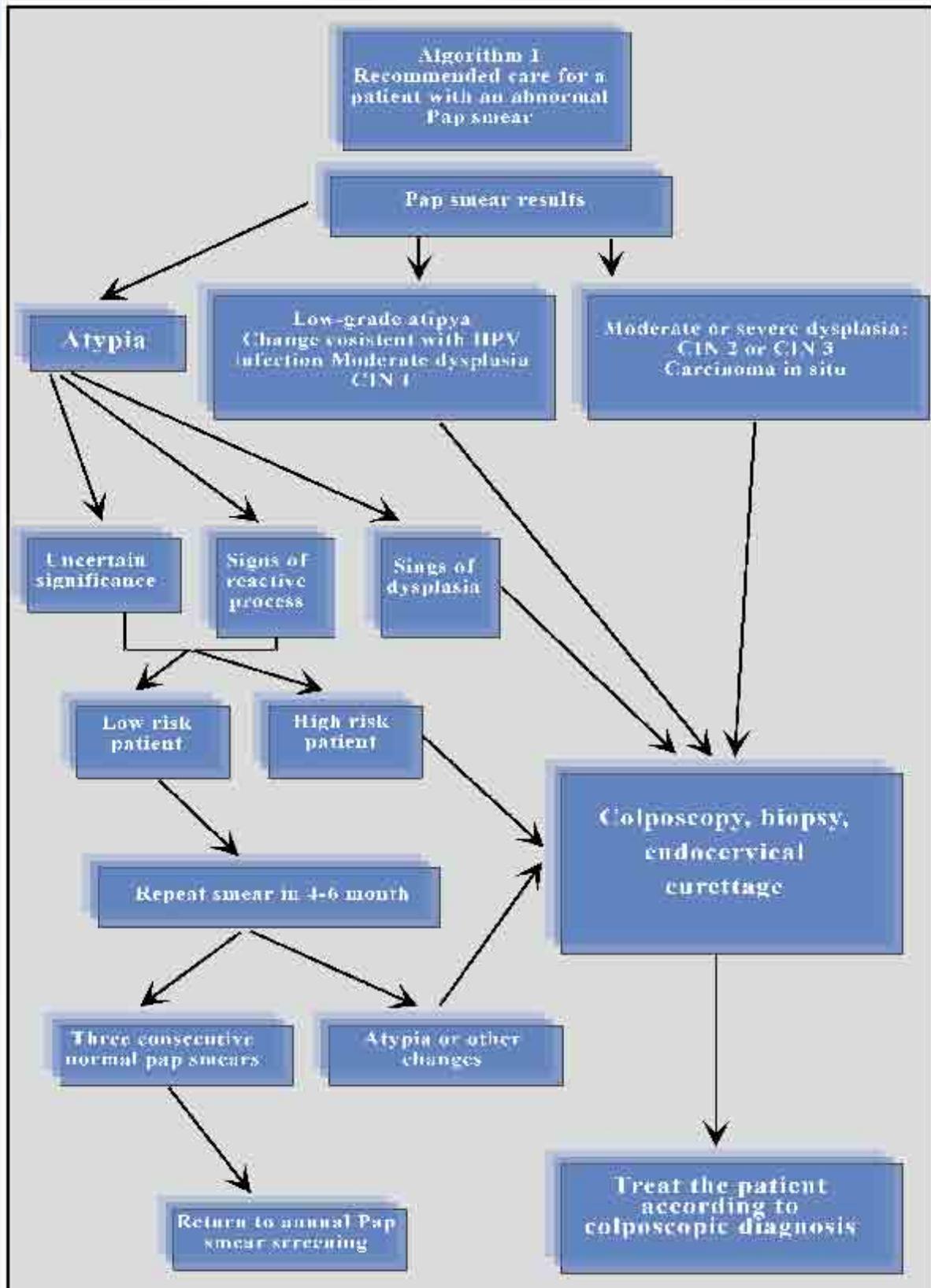
Atypical changes in the transformation zone initiate a cervical intraepithelial neoplasia (CIN), which is the preinvasive phase of cervical cancer. CIN I (mild dysplasia) may gradually progress to moderate dysplasia (CIN II), and to severe dysplasia and carcinoma *in situ* (CIN III). This process is not always continuously progressive and may remain in an earlier phase or regress entirely.

Thus, the management, diagnosis, and method of treatment of cervical intraepithelial lesions are based on a combination of consecutive findings of cytology, colposcopy, directed biopsy and endocervical curettage. For conservative forms of management, the entire transformation zone must be visible and accessible to the method.

Loop Electrosurgical Excision Procedure (LEEP) is the effective, more acceptable and save surgical method of treatment for different stages cervical dysplasia with a minimal complications, either during the procedure, or in postoperative period. LEEP promotes to early and hardy recovery with no side effects for further pregnancy and delivery.

Scheme.

Algorithm for evaluation of patients with an abnormal Pap smear and grossly normal-appearing cervix.



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