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REVIEW ARTICLE

Prevention of carcinoma cervix in Bangladesh perspective

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Abstract

Carcinoma cervix is a preventable disease. Etiological factor is known that is human papilloma virus (HPV). Two types of vaccines are available. Cervix is easily accessible allowing screening tests possible. Screening is simple and available. The disease has long premalignant phase that can be detected by screening. Although Pap smear is the gold standard method of screening, visual inspection with acetic acid (VIA) particularly single-visit approach, can be an appropriate alternative in Bangladesh considering our available health care facilities. If abnormal screening results (Pap test,VIA, HPV test), colposcopy and guided biopsy can be taken. Colposcopy can detect cervical intraepithelial neoplasia and early invasive carcinoma. Treatment in pre-invasive and early invasive carcinoma is found to be curative.

Key words: Carcinoma cervix, prevention, Bangladesh perspective.

Introduction

Carcinoma cervix is the commonest female genital malignancy. It is the 3rd common female cancer. An estimated 500000 new cases and 300000 deaths occur annually due to cervical cancer and almost 80% of these cases happen in developing countries & 40% of these deaths occur in South East Asia including India, Pakistan & Bangladesh.[1,2]

Cervical cancer is the 2nd most frequent female cancer and commonest gynecological cancer in Bangladesh. According to World Health Organization report, age standardized incidence of cervical cancer in Bangladesh is 29.4 per one lac women. Mortality from the disease is 17.9 per one lac women.[1]

The objectives of the present review was to find out the answers to the questions who are at high risk in developing cervical cancer, is cervical cancer worth preventing, is there any vaccine available in our country, what are the screening methods available now and which one is the most suitable for our people?

Risk factors for cervical cancer

Human papilloma virus (HPV) is the single most important causative factor. HPV is a double stranded deoxyribonucleic acid (DNA) virus. There are 15 to 20 types of HPV to be associated with cervical carcinoma. About 70% of cervical cancer is caused by HPV16 and 18, 80% cervical cancer by 16, 18, 31, 45 and other high risk HPV strains are: 33, 35, 39, 51, 52, 56, 58, 59, 68, 82.3 About 99.7% of cervical cancer is associated with HPV. HPV acts by initiating changes in cervical cells during the unstable stages of their life cycle and thereby acting as mutagens or co-factor.

Increased frequency of coitus- Smegma

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beneath the prepuce is carcinogenic. Circumcision offers so possible protection and the increased danger is due to poor hygiene. Spermatozoa are carcinogenic, nucleic acid in sperm head acts as mutagen. The sexually active woman is 2 to 4 times more likely to develop cancer of the cervix than the sexually inactive woman.4 Women who have multiple sexual partners and history of sexually transmitted diseases (STDs)/ sexually transmitted infections (STIs) are more prone to develop cancer.

Low socio economic condition- carcinoma cervix is 20 times more common in women with low socio economic condition. Early marriage, poor hygiene, too many and too frequent childbirth acts as contributing factors.[5]

Oral contraceptive pill (OCP)- It favors direct contact of semen with unstable epithelium in young age. OCP also makes epithelium unstable.[5]

Smoking- Cigarette smoking and HPV infection have synergistic effect on development of cervical intraepithelial neoplasia (CIN). Cigarette smoking is associated with 2 fold increase in the relative risk of cervical cancer.

Immunocompromised state- Human immuno-defficiency virus (HIV)/ aquired immuno-defficiency virus (AIDS), diabetes, steroid medication, chemotherapy.

Causes of high prevalence of cervical cancer in Bangladesh

Risk factors like early marriage, multi parity, low socioeconomic condition, poor hygiene are common here. There is no population based screening programme in Bangladesh, facilities of management of positive screening tests are less, there is a scarcity of trained manpower here. Lack of knowledge about cervical cancer and about existing facilities is also responsible.

Cervical cancer prevention

Primary prevention is offered by HPV vaccination and life style modification. Life style modification includes measures to reduce or avoid exposure to HPV and other STIs/STDs, limit number of sex partners, use condoms consistently and correctly during sexual activity, not to smoke cigarette.

HPV vaccination

One can be exposed to HPV for the first time when she is sexually active, from only one infected sexual partner. It is transferred from one person to other through tiny invisible breaks in the skin. Most sexually active women (at least 80%) have been exposed to HPV by age 50 years. So, every sexually active person is at risk for HPV. Women with more than one sex partner and the sex partner(s) have more than one sex partner are at higher risk.

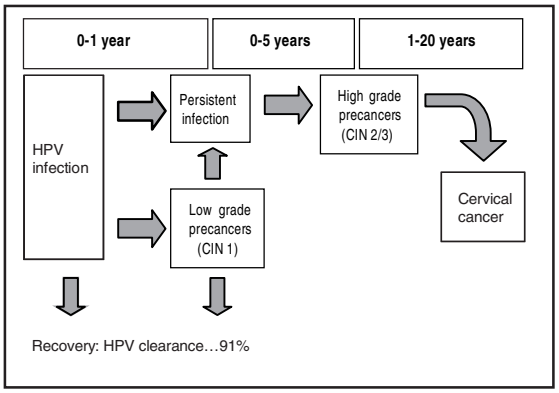

Fig. 1. Human papilloma virus (HPV) infection and cervical cancer. CIN, cervical intraepithelial neoplasia.

Most people get HPV infection, but very few (5%) get cervical cancer. HPV infection goes away on its own. More than 91% resolve without treatment within 2 years (Fig. 1). Sometimes, the HPV infection does not go away after many years. This type is called "persistent". It can lead to cervical cancer.[6]

Most HPV infections are asymptomatic and transient. Abnormal Pap test results are often a sign of HPV. Presence of koilocytes (cells with peri-nuclear halo) is an indication HPV infection.[7] Another effective way of knowing is HPV DNA test can find high-risk HPV types.

Condoms offer some but not total protection from HPV, as they do not cover all of the genital skin but it can definitely reduce the chance of HPV infection if it is used correctly and effectively. However, condoms do protect against other STIs and help to prevent unwanted pregnancy.

HPV vaccine technology
It is an empty shell formed by recombinant biotechnology to mimic the viral 3D shape. It does not contain infectious DNA. It provides both humoral and cellular immunity. It provides neutralizing antibody working locally by preventing attachment of virus to the cervical epithelium.

Candidates for HPV vaccine
The target women group is aged 9-20 years. The vaccine provides highest immunity in sexually unexposed and prevents 80% invasive carcinoma. Complementary catch up group is aged 20-26 years. The vaccine prevents progression. The group under consideration is aged up to 55 years. In this case, the vaccine may help in delay of progression of the disease. Patient may take it if she wishes.[8]

HPV vaccine Cervarix
It is a bivalent vaccine (HPV2). It protects against HPV 16 and 18, appears to offer cross-protection against other HPV sub-type (31, 33, 35, 39, 45, 51 and 52).[9] Injection is given in upper arm intramuscularly at 0, 6 months in 9-14 years and at 0, 1, 6 months in more than 14 years of age. The cost is about Taka 2000 (US$25)/vial.

HPV vaccine Gardasil
It is a quadrivalent vaccine (HPV4). It protects against HPV 6, 11 (75-90% genital warts) and 16, 18 (70% cervical cancer). It is indicated for girls and women 9-26 years of age. It is given at 0, 2 and 6 months. The cost is more than Taka 4000 (US$50)/vial.

Gardasil vs Cervarix
Cervarix appears to induce higher antibody titers against HPV 16 and 18 than Gardasil. Both vaccines appear to offer cross-protection genital warts (HPV types 6, 11). Gardasil has demonstrated vulvar/vaginal cancer protection. Gardasil is approved for use in male.

HPV vaccine safety
The HPV vaccines are safe. Safety is similar to other community-acquired vaccines.[10-12] Some girls have minor side effects such as: pain, redness and swelling at the injection site; however, this is very normal and these symptoms usually go away quickly. Vaccine can be given to lactating women. It can also be given to immune compromised women. Contraindications include acute severe febrile illness, pregnancy and severe allergic reaction after a previous vaccine dose.

HPV Vaccine effectiveness
Both the vaccines provide >90 % protection when given before HPV exposure who have completed all 3 doses.[13] Evidence supports that bivalent vaccine's protection will last for at least 9.4 years and will probably last for life.[14] Need for a booster is being closely monitored. Younger girls build better protection.[15] The vaccine prevents HPV, it does not treat HPV.

Women should continue to receive regular cervical cancer screening (Pap smear) even after vaccination. The vaccine will not protect against all types of genital HPV. If they had been exposed to one or more types prior to vaccination, there is still a risk of cervical abnormalities. Women should continue to practice protective sexual behaviors since the vaccine will not prevent other STDs including HIV/AIDS.

By screening for early detection, diagnosis and treatment of pre-invasive and early invasive stages of cervical cancer. Cervical cancer is the easiest female cancer to prevent through screening. Screening is the search for the disease, such as cancer, in people without symptoms. Screening can detect treatable, precancerous lesions before they progress to cancer. There is 75% reduction in cervical cancer in countries with adequate screening.[16]

Situation in Bangladesh

To gain success in screening in cervical cancer 80% of the population has to be screened. Currently, 32 million women are aged between 30 and 60 years and less than 0.4% are screened annually with a Pap smear. In Bangladesh, cancer related deaths will increase from 7.5% in 2005 to 13% in 2030 if measures are not taken.

Screening methods
Pap smear
It is the gold standard method for cervical cancer screening. Cells are collected from the surface of the cervix by a doctor or trained person. These cells are then checked under a microscope for any abnormalities. If abnormal (or precancerous) cells are found, they can be treated before they turn into

cancer. One may feel a little uncomfortable, but the test is quick. There may have some spotting (light bleeding) afterward.

One will schedule the Pap test when she is not having a menstrual period, does not have sex for 2 days before the test, does not use any per-vaginal medications for 2 days before the test. First Pap test should be done no later than age 21 or 3 years after marriage. Between age 21-64 years Pap test should be done in every 3 years if results are normal. Between age 31-64 years if Pap test are HPV test are done together the screening interval can be increased in every 5 years. One can stop doing Pap test at age of 65 or older if 2 consecutive results are normal for the previous 10 years.[17]

Drawbacks of Pap smear

There are some drawbacks such as delayed result, need of strict quality control, trained person, histopathologist and sophisticated instrument, and screening of large population is not possible.

Next step after getting abnormal Pap tests

The test should be repeated for follow up. HPV DNA test, colposcopy and biopsy and colposcopy and endocervical curett can be done.

Visual inspection of cervix by acetic acid (VIA)

The VIA is an opportunistic screening program that is provided through the existing healthcare infrastructure in Bangladesh. VIA is adopted as national cervical cancer screening programme in Bangladesh from 2004. People attending the healthcare centers like MCWCs, DHs, MCHs, BSMMU, UHFWCs and UHCs, UPHCCs and NGOs can get VIA facilities. VIA is considered as an alternative to Pap test in a low resource countries like Bangladesh.[18]

The target population for VIA screening is apparently healthy, married women aged 30 years and above or 10 years after marriage and it has to be done 3 yearly upto 50 years.

VIA is not performed during menstrual cycle, during treatment with vaginal pessary and in postmenopausal women. VIA is avoided when suspicious mass is seen. Acetic acid application is then avoided and patient is referred for further evaluation. VIA can be performed easily in any clinical setting with an examination table, good light source/ torch, sterile gloves, Cusco's speculum, cotton swabs, acetic acid in dilution 3-5 %. It is not a painful procedure, only slight discomfort may be reported. It is an outdoor procedure without requiring any analgesia and anesthesia.

Acetic acid dissolves mucus, induces intracellular dehydration and causes coagulation of protein. As a result, cells with increased nuclear/cytoplasmic ratio, nuclear density, and chromosomal aneuploidy become opaque to produce aceto-white area- the test is positive. It is a sharp, distinct aceto white lesion with dense and definite raised or non raised margin, close to squamocolumner junction in transformation zone. All VIA-positive women are referred with a pink referral card for colposcopy. Women with negative VIA are given blue card and are advised to come back after 3 years.

Strengths of VIA

It is simple with easy-to-learn approach, low start-up and sustaining costs. Many types of health care providers can perform the procedure. No special skill or training is required. Immediate result can be observed in only one visit. VIA screening can be integrated into primary health care services. It is very useful for mass screening and it has excellent sensitivity.

Limitations of VIA

It has moderate specificity. There is a need for developing standard training methods and quality assurance measures. It is less accurate among post-menopausal women.

Single visit approach (SVA)

in this approach trained doctors using VIA screen women. If the test is positive, biopsy should be taken and when eligible, women are directly treated with cryotherapy or loop electrosurgical excision procedure (LEEP) (Fig. 2). Follow up after 6 months is needed. When carcinoma cervix is suspected or diagnosed women should be referred.

Advantages of SVA includes- treatment is also given in same visit, no need of repeated visit, no risk of missing patient during follow up, psychological trauma can be avoided. It is cost effective.[19] It decreases burden on health care facility.

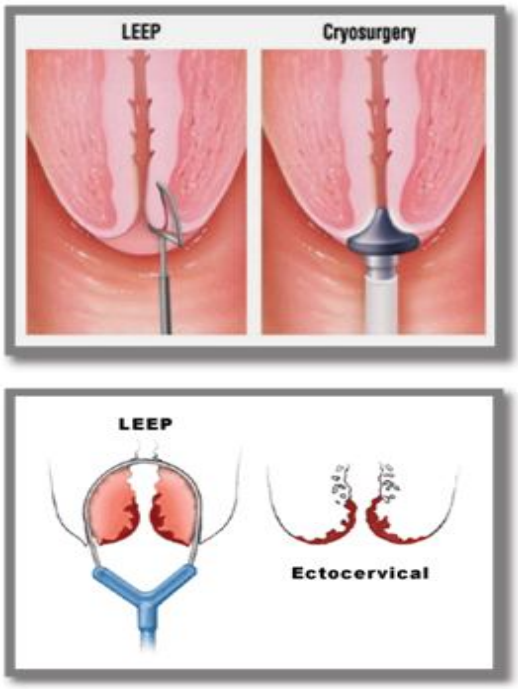

Fig. 2. Treatment options of cervical intraepithelial neoplasia.

Disadvantages- there is chance of over treatment, carcinoma cervix may be missed, actual grade of CIN whether I/II/III is not known, done by nurses so procedure success depends on their judgment. In spite of these disadvantages, in a low resource setting like Bangladesh, where incidence of cervical cancer is high, SVA at community level by trained paramedical person can help to decrease the incidence of cervical cancer.

HPV DNA test in cervical cancer screening
It is the most sensitive screening test with negative predictive value of 99%.[20] It is not recognized as population based screening as it is a costly, time consuming and technically difficult method.

It is done in combination with a Pap test in women at the age of 30 and older. If it is done along with Pap test, screening interval can be increased up to 5 years. Is also done in patients with minimally abnormal cervical smear (AS-CUS) in patients age >30 years. It has no role in women with LSIL or HSIL.[21]

Interpretation of the test
If positive- only then Colposcopy is done to reduce the need for unnecessary Colposcopy. If negative- there is a need to repeat Pap smear after 1 year. If smear abnormal, HPV positive but Colposcopy normal- then there is a need to repeat both tests after 6-12 months and again to repeat Colposcopy if both are abnormal.

Role of Colposcopy in cervical cancer screening
It is a triage or back up tool for screening but alone not considered as sufficient tool for screening, as alone it has low sensitivity and positive predictive value.[22] It is an optical instrument that can detect changes in the cellular pattern and vascularity of the covering epithelium of cervix and vagina under magnification. It is said to be satisfactory when transformation zone is visualized. When colposcopic findings are positive, guided biopsy is also taken and sent for histopathology.

Indications of Colposcopy are abnormal cervical cytology smear, positive VIA, positive HPV testing, clinically abnormal or suspicious looking cervix and unexplained intermenstrual or post coital bleeding.[23,24] Contraindications include presence of active bleeding, an obvious growth of the cervix and any deep ulceration in cervix.

Colposcopy facilities are available in Bangabandhu Sheikh Mujib Medical University (BSMMU) and in all government medical college hospitals. BSMMU acts as central coordinator, a training centre (to train family welfare visitors, nurses and doctors), a primary screening and referral centre.

CIN after hysterectomy

In 2%-3% of patients with high-grade CIN, the disease extends to the vaginal vault.[25] If vaginal cuff is not carefully excised in these patients, neoplastic epithelium may be sutured into the vaginal vault. High grade vaginal intraepithelial neoplasm occurs in 1-7% on the patients who have undergone hysterectomy to treat CIN. The patients should have vault cytology and colposcopy at 6 months and at 12 months of hysterectomy. If normal findings thereafter, she should be screened by vaginal vault cytology on an annual basis.[26]

Conclusion

Carcinoma cervix is a preventable disease. Etiological factor is known that is HPV and two types of vaccines are available. Cervix is

easily accessible allowing screening tests possible. Screening is simple and available. The disease has long premalignant phase that can be detected by screening. Although Pap smear is the gold standard method of screening, VIA particularly SVA, can be an appropriate alternative in Bangladesh considering our available health care facilities. If abnormal screening results (Pap test, VIA, HPV test), colposcopy and guided biopsy can be taken. Colposcopy can detect CIN and early invasive carcinoma. Treatment in pre-invasive and early invasive carcinoma is found to be curative.

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