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Enlightening the Path for Next Generation of Gynaecologists

Dedicated Issue:
Preventive Gynae Oncology

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From the President's Pen

This issue of Monthly Bulletin of AOGD is devoted to "Preventive Oncology". Great strides have been made in prevention of Cancer Cervix: Similar efforts are on for prevention of other Gynaecological Cancers. After reading present issue one will get latest news about prevention of other Cancer.

Happy Holy

Dr Sunesh Kumar
President, AOGD

From the Secretary's Desk

Dear friends,

The AIIMS term for AOGD Secretariat is coming to an end. Keeping with our high standards, we deliver another edition of AOGD bulletin for your perusal. The last Bulletin was on Gynecological Cancers, an important cause of morbidity and mortality in women. We all know prevention is always better, so the current issue is dedicated to "Preventive Gynae Oncology". It is dedicated to cervival cancer screening and HPV vaccine, with contribution from stalworths in the field of gynae oncology.

Hope it will be useful for everyone.

Two CME's on Endoscopy and Infertility were organized by MAMC. A CME on Preeclampsia was organized by Manipal Hospital under Safe Motherhood Committee.

National FOGSI conference on "Women's Reproductive & Sexual Health" was organized by Dr Mala Srivastava and her team on 29th Feb-1st March.

Heartfelt thanks from AIIMS team for your continuous support.

Wish you all very best

Dr Vatsla Dadhwal
Hon. Secretary

Note

Monthly Clinical Meeting

Monthly Clinical Meet is deferred due to immense threat of **Corona Virus**

From the Editor's Desk


Dr Neerja Bhatla **Dr Jyoti Meena**

Guest Editors

Dr J B Sharma

Editor



Dr Reeta Mahey **Dr P Vanamail** **Dr Vidushi Kulshreshtha**

Co-Editors

Dear Colleagues,

We feel encouraged and humbled by the overwhelming response to the bulletins and kind words of appreciation. After the issue on Gynecological cancers, we are bringing out this issue on Preventive Oncology. In many respects, cancer is a preventable disease. Estimates indicate that approximately one half of all cancer cases either arise from modifiable risk factors or can be detected as precursor lesions before the development of disease.

As the saying goes, "An ounce of prevention is worth a pound of cure". Prevention of cancer can take place on several different levels: Primary, Secondary and Tertiary prevention. Cervical cancer is the only type of gynaecological cancer for which there is primary prevention in the form of HPV vaccination as well as secondary prevention by several screening tests. The lack of tests for endometrial and ovarian cancer, which are also common cancers, makes it especially important that the women and doctors both be attuned to the early symptoms and modifiable risk factors of these diseases. The earlier they are detected, the more successfully they can be treated. There is a need to create awareness and to make health services accessible, so that these cancers can be screened and detected early.

In this issue we present articles on recent developments in field of screening and prevention of various gynaecological malignancy with main focus on cervical cancer screening and prevention in keeping with the WHO's Call for Elimination of Cervical Cancer. The role of VIA and cytology in modern era has been illustrated by Dr Vijay Zutshi. The importance of primary HPV testing, co-testing with the FOGSI GCPR charts on HPV testing have been concisely summarised by Dr Neerja Bhatla. The role of single visit approach and the management of screen positive cases is outlined by Dr Seema Singhal. Dr Gauri Gandhi has described screening and prevention of ovarian cancer and Dr Amita Suneja has summarised the management and surveillance of postmenopausal bleeding. The overview of recent update on the HPV vaccination is given by Dr Jyoti Meena and on portable colposcope by Dr Jayashree Natarajan. The latest articles are nicely summarised by Dr Y M Mala in Journal scan. An interesting and stimulating cross word and pictorial quiz has been drafted by Dr Bindiya Gupta. We would like to thank all our authors for their contributions.

Hope you all will find this issue informative and helpful in clinical practice. Do attempt the quiz in the end. Your feedback is always welcome.

The Editorial Team

Role of Cervical Cytology and VIA in the Modern Era

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[1]Professor Consultant, [2]Junior Resident, Department of Obstetrics and Gynaecology, VMMC & Safdarjung Hospital, New Delhi.

Introduction

Cervical cancer is the most commonly encountered genital malignancy in women in India, the second most commonly diagnosed malignancy in women after breast cancer and the third most common cause of death after lung and breast cancer. Current data from GLOBOCAN 2018 indicate that cancer cervix ranks fourth in incidence as well as mortality among female cancers in the world. India accounts for ~20% of the world burden of the disease.

There has been a large decline in the incidence and death rate of cervical cancer in industrialized countries observed during the past few decades. This unfortunately, has not been mirrored by a similar decline in developing nations. In industrialized nations, the age-adjusted incidence of cervical cancer is 10 out of 100,000 per year; however, in developing nations the incidence of the disease can be as high as 40 out of 100,000. The age-standardized incidence and mortality rates in India (ASR) are 14.7/100,000 and 9.2/100,000 women, respectively. By 2030, it is anticipated that at current rates of screening cervical cancer will be responsible for the death of 474,000 women annually with over 95% of these deaths anticipated to occur in low- and middle-income countries (LMICs).

The decline in cervical cancer incidence in developed countries was the result of organised screening programmes based on Pap smear screening. Dr. George Papanicolaou first described the use of cervicovaginal smears in 1928, and by the 1940s it was being utilized as a screening test for cervical cancer. However it was the implementation of national call and recall programmes for three-yearly screening that produced the maximum impact on reduction of cervical cancer incidence and mortality by about 70%, while increasing the incidence of in situ preinvasive lesions. The success of Pap testing for cervical cancer screening despite poor sensitivity was based on the long precancerous phase of cervical cancer of nearly 10-15 years during which lesions could be detected by repeated rounds of screening.

The Pap test has several advantages as a screening tool for cervical cancer including simple procedure to obtain and manage specimens, and high specificity. However, it requires considerable infrastructure, and repeated rounds of screening as the sensitivity of the test is low. Because of these requirements it has not been possible to implement this widely in developing countries.

Liquid based cytology (LBC) was introduced in 1990 to reduce the drawbacks of conventional cytology but it has not shown any significant difference in sensitivity and specificity. The rate of unsatisfactory smear is reduced. Also the same sample can be used for HPV reflex testing and co-testing. Also, other microorganisms such as vaginal trichomonas, vaginal candidiasis, bacterial vaginosis, chlamydia and gonorrhoea can be detected.

Role of Cytology in the Current Scenario:

The discovery that visual inspection with acetic acid (VIA) could be done with similar sensitivity as the Pap led to a change in perspective in developing countries. As per WHO guidelines (2013), if a cytology-based screening programme is in place in any country, it may continue provided the programme meets the quality indicators including training, coverage and follow-up. If finances permit, adding HPV test to it may be considered. If quality assurance criteria are not met, the need to change to another test should be reviewed, e.g., an HPV test (if financially viable) or VIA.

The Federation of Obstetrics and Gynaecological Societies of India (FOGSI) Resource-based GCPR (2018) recommends cytological screening every 3 years from age 25-65 years in high resource setting. At the present time HPV DNA testing has the highest sensitivity. It can additionally be used with Pap smears as co-testing for optimizing diagnosis of high-grade cervical intraepithelial neoplasia (CIN). In this situation, if the Pap report is abnormal e.g., ASCUS, but the HPV test is negative, it will reassure the patient that she does not have significant abnormality. If on the other hand, the HPV test is positive, she can be immediately referred to colposcopy and managed accordingly.

Some experts argue that because HPV testing has greater sensitivity than Pap smear, while the Pap smear has greater specificity, HPV testing should be done first and Pap smear screening should be reserved for reflex testing of those positive for HPV. The potential advantage to this was seen in a Canadian trial that found that HPV testing followed by Pap smear caused

lower referrals for colposcopy than did either alone (1.1% vs 2.9% with only Pap smear or 6.1% with just HPV testing).

Since cytology has a high specificity, the likelihood of finding high grade CIN in women with abnormal Pap smear is very high. This has been the basis of the see-and-treat program in colposcopy clinics. If a woman has HSIL on Pap, and is found to have a significant lesion on colposcopy, e.g., Reid score >3 or Swede score >5, such a patient has a high likelihood of CIN2/3 and can be considered for immediate excision by LEEP with very low risk of over-treatment.

Cytology has an additional advantage that it can be combined with other biomarkers. In women undergoing routine cervical cancer screening, dual staining for cellular proteins p16/Ki-67 outperformed cytology in detecting cervical pre-cancer among HPV positive women. At the same time, dual staining referred fewer women to colposcopy, a secondary screening involving visual inspection of the cervix with magnification dual staining may be option as a triage strategy for women who are HPV positive on primary screening.

Role of Visual inspection with acetic acid (VIA) in cervical cancer screening in modern era:

VIA is a simple test which involves application of freshly prepared 5% acetic acid and observation of acetowhite areas at one minute. Several large studies in India and Africa, led by Dr R Sankaranarayanan and Prof. Lynette Denny demonstrated the comparable sensitivity of VIA with cytology. It offers the distinct advantage over cytology that it can be performed by trained paramedical staff and gives an immediate result which allows treatment in a single visit.

It has been reported that the sensitivity to detect CIN grade 2 or higher is similar for VIA (range 64.5%–89.5%) compared with Papanicolaou test (range 52.6%– 62.3%). The specificity of VIA test (76.4%-84.2%) was found to be lower than HPV testing (80.7%-81.3%) and cytology had highest specificity(76.1%-99.1%). In a study by Sankaranarayanan et al in Ambillikai in Tamil Nadu, a single round of VIA screening by trained nurses led to significant 25% reduction in cervical cancer incidence (hazard ratio 0·75 [95% CI 0·55–0·95]) and a significant 35% reduction in cervical cancer mortality (hazard ratio 0·65 [0·47–0·89]).

Li et al. from China studied 10,269 women for feasibility of VIA / VILI as a primary screening method for cervical lesions in basic resource settings and also concluded that VIA can be used as a primary screening method. Several countries including Bangladesh and Thailand initiated screening programs based on VIA.

Based on the Ambillikai study results, the Tamil Nadu government initiated a District level program of NCD screening including testing for blood pressure, blood sugar, clinical breast examination and VIA. The study showed the feasibility of this strategy and informed the current strategy under the NPCDCS (National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke) for screening of common cancers including oral, breast and cervical cancers. It recommends opportunistic screening using VIA as screening method between 30-59 years of age, once in 5 years. All women of this age group are screened in OPD settings on two prefixed days of the month. Any women found positive on VIA is referred to a District hospital where she undergoes colposcopy and directed biopsy. Women with normal findings are followed up with VIA every 5 yearly till the age of 59 years. A screen-and-treat approach by ablation at the same sitting is encouraged for all lesions that fit the criteria in order to improve compliance *(discussed in the article on Single Visit Approach).*

VIA has been accepted as a method of screening for limited and basic resource countries by both WHO and the American Society for Clinical Oncology (ASCO). WHO has advocated that VIA permits a single-visit approach providing LMICs immediate test results and screen and treat approach. Studies have shown that in developing countries screening women once in their lifetime using VIA at 35 years of age the lifetime risk of cancer can be reduced to 25-36%. With two rounds of screening one at 35 years and another at 40 years further reduces the relative risk by 40%. FOGSI also proposes VIA as the method of screening for low resource settings for the age group 30-65 years. The major limitation of VIA is that it is not an ideal screening method for post-menopausal women where the squamocolumnar junction recedes into the endocervical canal. Also, it is a subjective method and there can be inter observer variation in the detection of abnormal areas. For this purpose, the International Agency for Research on Cancer (IARC) has described the criteria for VIA positive. Continuous monitoring and retraining is essential for quality assurance.

Until a cost-effective HPV test is developed, VIA will be the mainstay of screening in LMICs.

Key Messages:

1. Cytology has low sensitivity but is highly specific. It is suitable, if used in repeated rounds of screening.

2. There is no difference between conventional cytology & LBC in terms of test performance.
3. The main advantage of LBC is the possibility of reflex HPV testing on the same sample.
4. VIA should be used as an extension of gynaecological examination in all women.
5. VIA positive women can be treated in a single visit approach if suitable or referred for further management.

Suggested Readings

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Calendar of Monthly Clinical Meetings 2019-20

Months	Name of the Institute
27th March, 2020	LHMC
24th April, 2020	Apollo Hospital

HPV in Cervical Cancer Screening: Where are we today?

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Introduction

Cervical cancer is the second most common cancer among Indian women. India contributes to one quarter of the global burden with 96,922 incident cases and 60,078 deaths in 2018. Human papillomavirus (HPV) is the main causative agent responsible for 98.7% of all cervical cancers. Cervical cancer is preventable, because it has a long pre-invasive phase and persistent HPV infection to development of cervical cancer takes several years to decades. Thus, provides a long window period to detect and treat infection in pre-invasive stages of the disease. The incidence of this disease is directly related to the available resources and medical infrastructure for population-wide screening and the treatment of identified cancers. The goals of screening programs for cervical cancer include the identification and treatment of true precursors of cervical cancer.

HPV Prevalence

HPV infections are widespread all over the world; however, prevalence and type distribution show some geographical variation. The age-specific HPV prevalence varies in young and advanced age women populations. The lifetime cumulative risk of HPV infection is greater than 80%. Most genital HPV infections are transient, with a persistence rate of less than 10% for infections with high risk HPV, which are associated with pre-invasive and invasive cancer. The natural history from persistent HPV infection to development of cervical cancer takes several years to decades. It thus provides a long window period to detect and treat infection in pre-invasive stages of the disease.

Many studies have been done worldwide on the epidemiology of HPV infection and on oncogenic properties of HPV genotypes. It was found that 10.4% of patients with normal cytology were detected with either high- or low-risk HPV types. Women in less developed countries and those who are younger than 25 years have a higher prevalence, ranging from 15 to 45%, the highest HPV prevalence being in sub-Saharan Africa, Eastern Europe, and Latin America and lowest in Northern America and Western Asia. However, in India the prevalence is lower, ~7%, ranging from 6 to12% in most studies.

Screening Tests for Cervical Cancer

The main modalities used for screening of cervical cancer are cytology, visual inspection with acetic acid (VIA), HPV testing (primary HPV testing or co-testing). (Table1 shows an overview of the screening tests)

Table1: Primary screening methods for cervical cancer

Screening test	Strengths	Limitations
VIA	- Simple and inexpensive - Easily available - Requires brief training - Requires minimal infrastructure - Results are immediately available - Immediate treatment (screen & treat) is feasible	- Require quality control and quality assurance - Interpretation is subjective - Not appropriate for postmenopausal females - Low sensitivity (67.6%), though equivalent to Pap
Cytology	- Proven effectiveness to decrease cervical cancer in repeated rounds of screening - widely accepted - Training and method are well established - Highest specificity (93.5%)	- Require infrastructure - Patients are lost to follow-up - Require transportation - Require quality control and quality assurance - Interpretation relatively subjective - Results are not immediately available, require multiple visits - Less Sensitivity (62.1%)
HPV DNA test	- Relatively simple - Assay result is definitive and endpoint - Requires brief training - High specificity (91.5%) - Self-sampling can be done	- Requires minimal infrastructure - Require quality control and quality assurance - High cost - Results are not immediately available - Require transportation - Less sensitivity (77.8%)

Papanicolaou (Pap) smear or cervical cytology is the conventional method of screening in good resource settings and has been the mainstay of cervical cancer screening for 60 years. However, the major drawback with cytology-based screening is overall low sensitivity 62.2% (50%-91.4%) necessitating frequent rounds of testing, the need for infrastructure and need for quality control, which has prevented its widespread implementation in low-middle income countries. While labs with good sensitivity may continue using this as a screening tool, its high specificity of 93.5%

(85.6%-98.6%) makes it more suitable for a triage test in the present-day scenario.

Visual inspection with acetic acid (VIA) is the simplest, cheapest and therefore the preferred mode of screening for low-resource settings. It is the method adopted in operational framework for screening of cervical cancer by the Ministry of Health and Family Welfare (MoHFW), Govt. of India, in the National Programme for Screening of Common Cancers. VIA has a sensitivity of 67.6% (54.8%-90%) which is comparable to Pap, and a specificity of 84.3% (53.3%-91.2%). It has the advantage of being a point of care test with instant results, where a screen-and-treat approach can be implemented. However, its high false positive rate, combined with the need to train and re-train a large work force to maintain quality assurance, and to motivate women for follow-up at secondary level results in a very labour intensive programme with potentially high rates of loss to follow-up.

HPV testing was first used as reflex-testing to triage atypical Pap smears to colposcopy or close follow-up after the ALTS trial in 2003. However, the sensitivity of HPV test is highest 77.8% (45.7-100%) which makes it most suitable for a screening test. Thus, the philosophy of co-testing with HPV and cytology came about. Co-testing can detect 51% more cases of CIN2/3 or invasive cancer than cytology alone. The negative predictive value is high when both test results are negative and this protection lasts for at least 5 years. Thus 5-yearly co-testing was recommended for women aged 30-65 years, and this continues to be the recommendation in several guidelines. However, co-testing detects only marginally fewer cases while increasing the cost substantially. Therefore, in the last two years, there has been a move towards primary HPV screening, using selected approved tests.

Types of HPV tests

HPV cannot be cultured reliably in a laboratory setting; therefore, HPV diagnostics rely on molecular technologies that detect HPV DNA in cervical/vaginal samples. These can be broadly divided into amplified and non-amplified tests. (Table 2)

Amplification tests are mainly used in clinical research and can be done either by amplification of a viral DNA fragment (with or without genotyping) or through mRNA detection. Non-amplification techniques rely on a variety of laboratory-based molecular diagnostic methodologies and include southern blot hybridization, dot blot hybridization and in situ hybridization.

Table 2: Types of HPV tests used for cervical cancer screening (FOGSI GCPR)

HPV test	Technique used	Commercial Name
DNA	Direct Genome detection Amplification Amplification and genotyping of HPV 16/18	Hybrid Capture 2 (HC2) *care*HPV test GP5+/GP6+ bio PCR- EIA Cervista HPV HR Cervista HPV 16/18 Cobas HPV test Xpert HPV Abbott Real time hrHPV assay Papillocheck
RNA	Amplification of E6/7 proteins Monoclonal antibodies	Aptima HPV assay PreTect HPV- Proofer HV AVantage HPV E6 test

High risk HPV detection methods comprise of HPV DNA assays and E6/E7 mRNA assays. HC2 has been the gold standard for cervical cancer screening until 2011-2012 when FDA approved Aptima, Cervista and Cobas HPV assay. The Cobas 4800 HPV test combines in a single assay the identification of pooled 12 hrHPV types as well as genotypes 16 and 18 individually. HPV screening tests that detects HPV DNA have a high NPV but, the PPV is <50% for determination of CIN2+. The addition of E6 and E7 mRNA improves the PPV to 78%. Hybrid capture 2 and G5+/6+ are clinically validated prototype assay as they have shown better performance in lowering the incidence of CIN3+. The clinical sensitivity of an HPV test is an important consideration for the use of this test in screening programs.

Recommendation for screening tests

Several organisations have developed screening algorithms for use of the various screening tests available. However, the recommendations for currently used screening test that shape today's standard of care in cervical cancer screening come from the American College of Obstetricians and Gynaecologists (ACOG), the American Society for Colposcopy and Cervical Pathology (ASCCP) and US preventive Services Task Force (USPSTF). (Table 3)

Table 3: Cervical cancer screening recommendations, ACOG, ASCCP, USPSTF, FOGSI

Test	ACOG (2016)	ASCCP/SGO (2015 interim guidelines)	USPSTF (2018)	FOGSI (2018)
Cytology only	Every 3 years	Every 3 years	Every 3 years	Every 3 years
Co-testing	Every 5 years (30-65yrs)	Every 5 years (30-65yrs)	Every 5 years (30-65yrs)	Every 5 years (30-65 yrs)
HPV testing only	Can consider in women ≥25 yrs every 3 years	Can consider in women ≥25 yrs every 3 years	Every 5 years (30-65 yrs)	Every 5 years (30-65 yrs)

Different Strategies for HPV Testing:

1. Co-testing

Incorporation of HPV testing with cytology has the potential to reduce the incidence and mortality of cervical cancer in women aged 30 years and older. Schiffman et al. investigated the relative performance of each component and found that the first co-test could detect 67.9% cases likely to progress in next 10 years. Only a small fraction, i.e., 3.5% cases of preinvasive and 5.9% cases of invasive disease were detected in women who had HPV−/cytology+ results and were actually benefited by adding cytology to HPV test. In India the majority of women will have infrequent screening and variable methods of HPV testing are being used, hence FOGSI recommends that it may be prudent to use co-testing till one has more data. Figure1 depicts the management based on co-testing results.

2. Primary HPV testing

Primary HPV testing has replaced cytology in the cervical cancer screening programs in various countries including Australia and some parts of Europe. However, it cannot differentiate between persistent and transient infection; therefore, it has 3-4% lower specificity than cytology (at cut-off ASCUS+). It is generally not recommended in women aged 21 to 29 years, as the prevalence of infection in this age group is high and most of the infection does not persist, although Cobas is approved for primary screening over 25 years.

Several studies have studied HPV test as a primary screening test and have shown high sensitivity and negative predictive value of this test. Besides this a negative HPV test provides better reassurance that high-grade lesion is currently absent and thus allows safe prolongation of the screening intervals to 5 years. Wright et al in their study observed the cumulative incidence rate of CIN3 and cancer in HPV negative women >25 years of age as low as 0.34% (95% CI 0.10-0.65), 0.78% (95% CI 0.53-1.09) in cytology negative women and 0.30% (95% CI 0.05-0.62) in co-test negative women. This small decrease in cancer risk associated with co-testing does not make it a cost-effective option.

The specificity and positive predictive value of HPV test is low which can lead to increase in colposcopy referrals. To reduce these referrals it is useful to triage HPV positive women with either cytology or VIA or HPV 16/18 genotyping. Triage positive women may then be referred to colposcopy. Figure 2 depicts FOGSI recommendation of management based on HPV test result.

HPV test is also more sensitive than cytology in post-treatment follow up and leads to earlier diagnosis of persistent or recurrent disease following treatment of CIN.

Role of HPV Genotyping

Genotyping is the process of amplification of a single genotype of HPV by targeting a type-specific DNA sequence. It is indicated in women who are HPV positive and cytology negative, because the risk of

Figure 1: Screening with Co-testing in women aged > 30years (FOGSI GCPR)

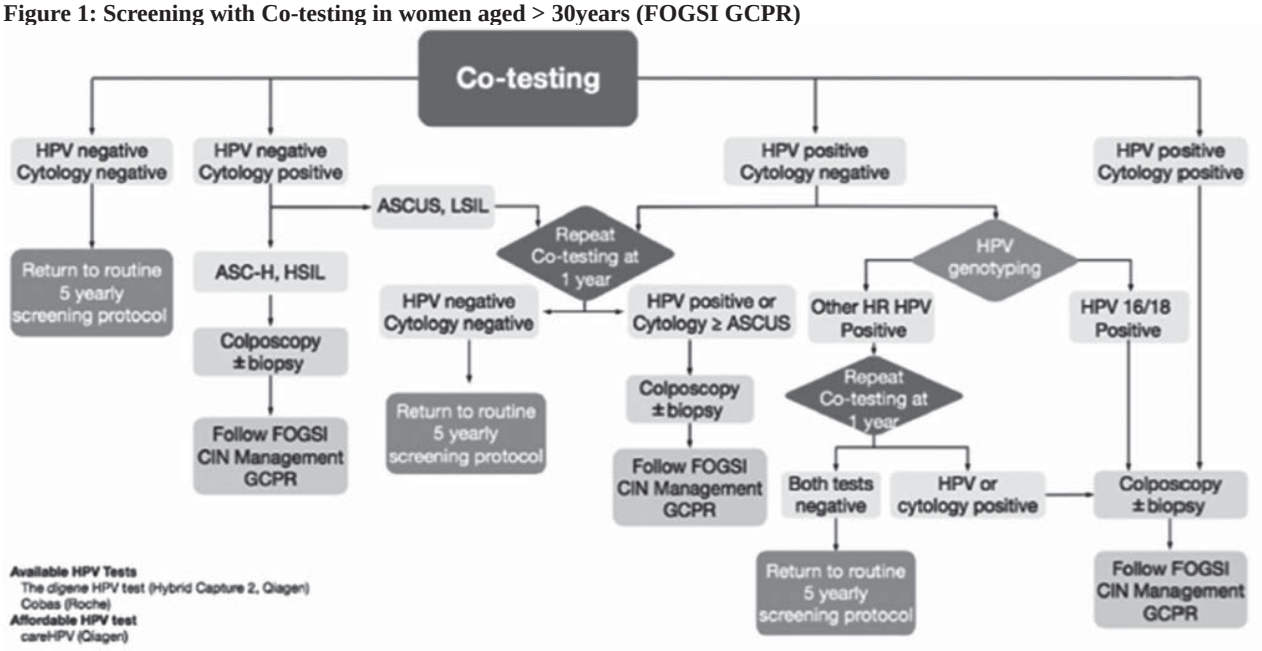
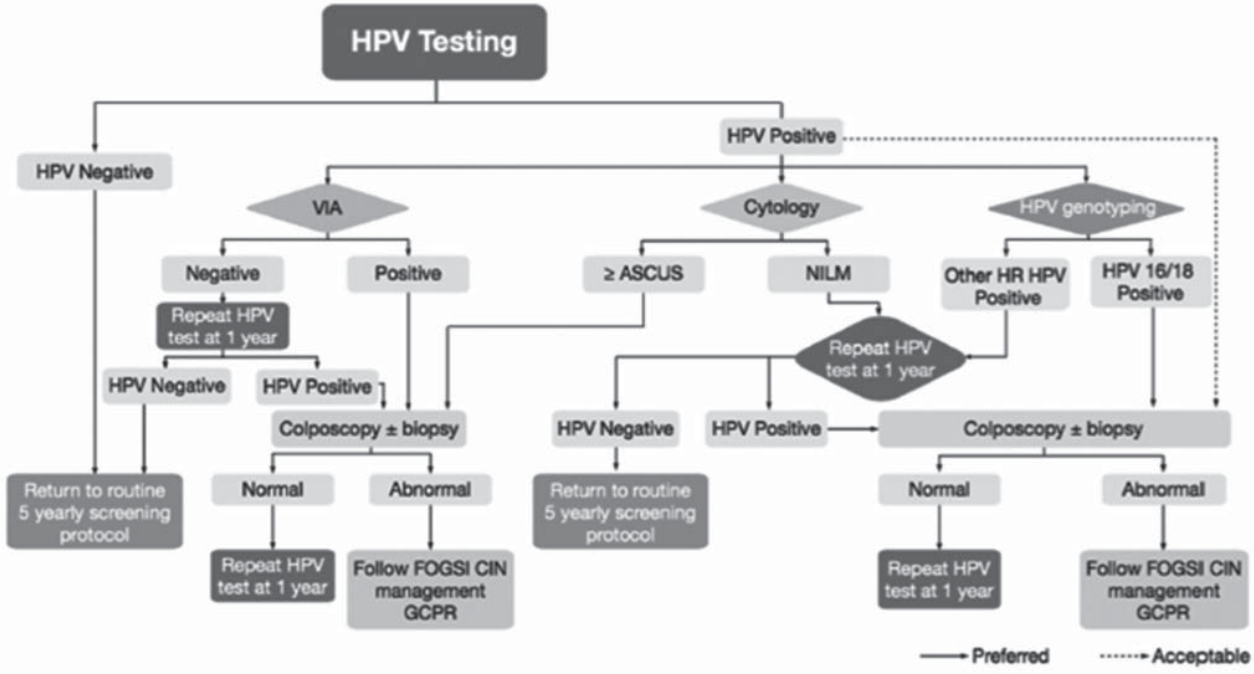


Figure 2: Primary HPV testing in women aged >30 years (FOGSI GCPR)



CIN3+ is genotype dependent and HPV16/18 have a higher rate of persistence and progression.

Self-sampling

The feasibility and acceptability of a screening test is the main deciding factor for success in any screening programme. The possibility of self-sampling for HPV by a woman provides an attractive alternative due to its convenience, less discomfort and anxiety and ease of procedure. It is feasible in remote areas where there is a lack of infrastructure and personnel. The sensitivity of self-collected samples varies between 60 to 90%, with moderate to good agreement. A study by Bhatla et al found that self-sampling for HPV compares favourably with physician-sampling and cytology. The sensitivity and specificity were 82.5%, 93.6% for self-sampling , 87.5%, 93.2% for physician-sampling and 77.5%, 87.3% for cytology, respectively.

A meta-analysis by Yeh etal found greater screening uptake among self-sampling participants compared to control (RR:2.27, 95%CI 1.89-2.71). Using HPV self-sampling methods, especially opt-out methods, increases uptake of cervical cancer screening services.

Conclusion

Cervical cancer screening guidelines have changed dramatically over the last 15 years, following introduction of testing for the 13-14 hrHPV types that cause virtually all cervical cancer and its precursors. HPV testing is the most sensitive method for screening of cervical cancer. Primary HPV testing using standardized tests can be preferred over co-testing with an option of self-sampling to improve coverage.

Suggested Reading:

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Management of CIN and Single Visit Approach

Seema Singhal[1], Swati Mittal[2]
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Worldwide, cervical cancer remains a major public health problem and 85% of the cervical cancer deaths occur in low income countries. The sole reason for this inequity is lack of access to screening and treatment of precancerous lesions in under-resourced areas. Every screening effort should be followed by appropriate treatment for effective cervical cancer prevention. The current article describes the treatment strategies for treatment of cervical intra epithelial lesions (CIN), modalities for treatment and single visit approach (SVA).

Management of Cervical Intraepithelial Neoplasia

The aim of CIN management is to prevent progression of disease while avoiding over-treatment of lesions that might otherwise regress. In women who have been diagnosed with CIN on biopsy which may or may not be colposcopy guided, further management is guided by the preceding cytology and HPV report if available. This is important in the case of low grade CIN (CIN1) where the preceding cytology report can indicate the future CIN3+ risk. A preceding low-grade cytology (ASCUS-LSIL/HPV+) has a five year risk of 3.8% versus 15% with preceding high grade cytology. Thus treatment by ablation or excision is warranted if the abnormality persists for two years. The risk of progression of CIN1 when preceded by ASC-H or HSIL is more than 15%, thus immediate colposcopy examination is advised. 40-58% of CIN2 will regress and only 22% will progress to CIN3; the cumulative incidence of invasive disease in untreated CIN3 is 31% after 10 years. Patients with CIN2/3 with type-I or type-II TZ on colposcopy may be treated by excision or ablation. Risk of invasive cancer is as high as 7% in women with type-III TZ on colposcopy or in recurrent CIN, therefore excisional procedures with either LLETZ/LEEP (Large loop excision of TZ) or cold knife conization are performed and ablation should be avoided in such situation.

In women ≤ 30 years the probability of regression is higher and 70% of CIN2 lesions would regress. Therefore, conservative management is preferred and treatment is advisable when CIN2 persists for over 24 months. The management of CIN depending on the severity is depicted in Fig.1 and 2.

Fig 1: Management algorithm showing management of CIN 1on histology (FOGSIGCPR)

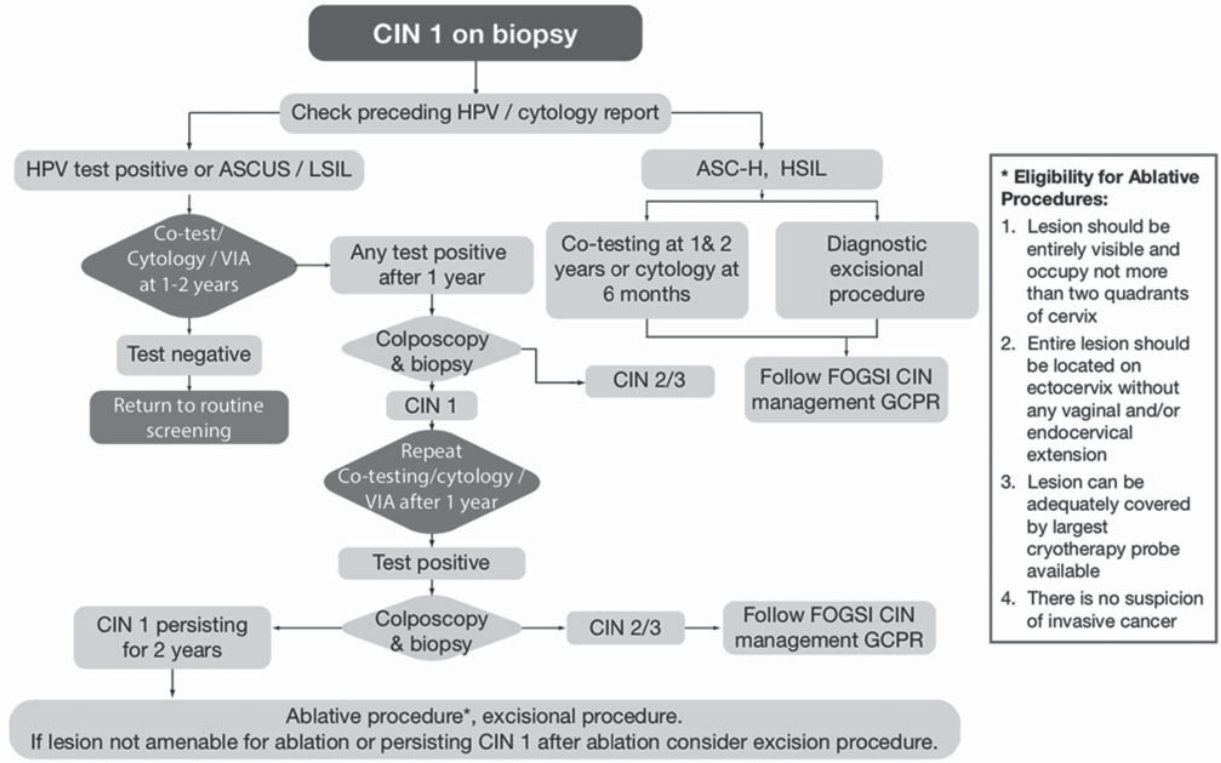
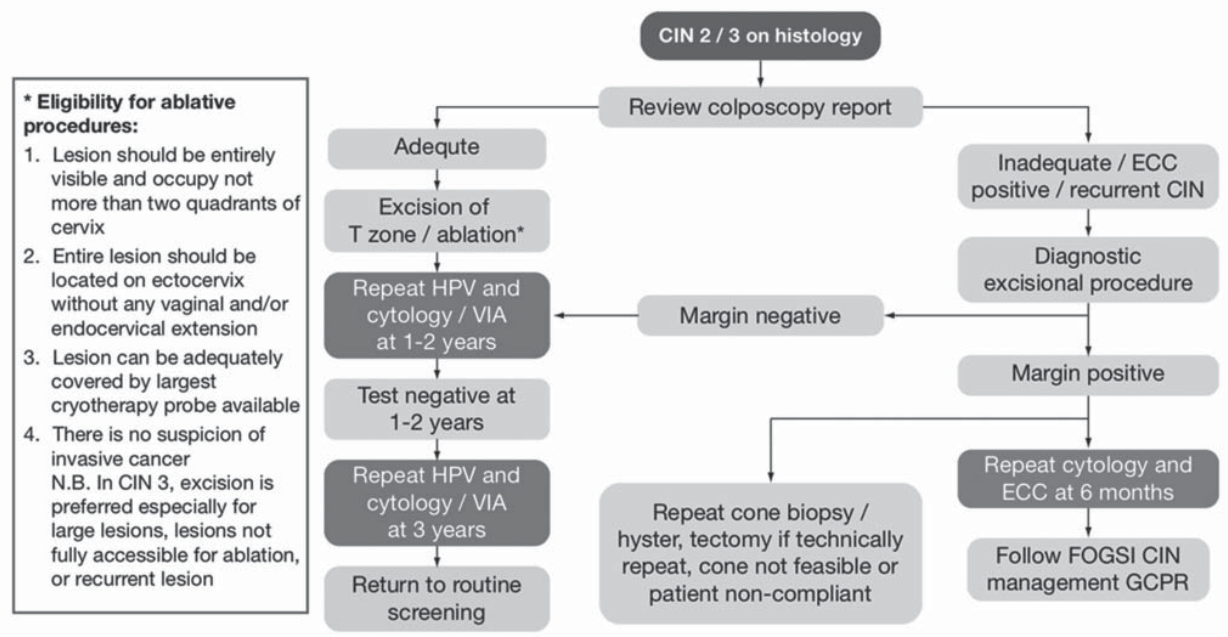


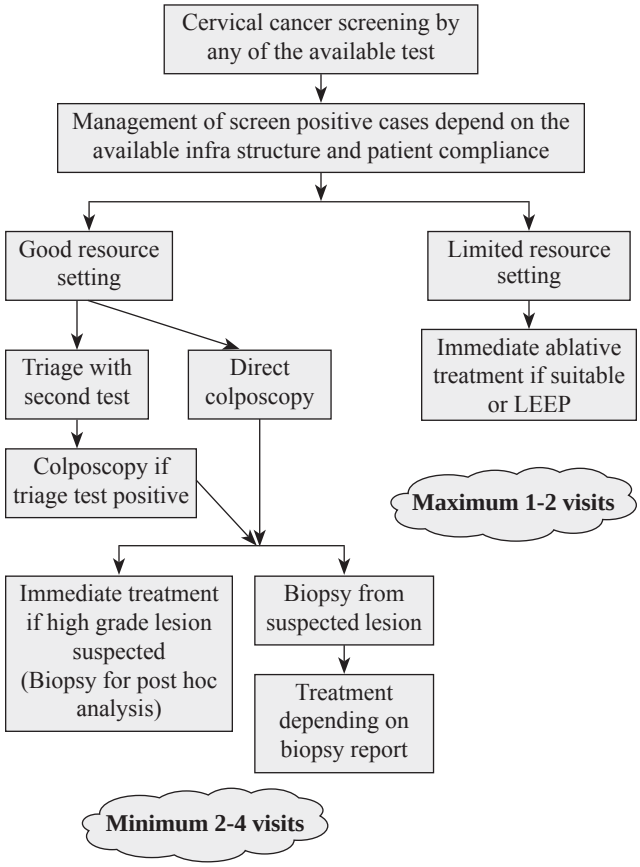
Fig 2: Management algorithm showing management of CIN 2/3 on histology (FOGSIGCPR)



Single visit approach (SVA)

Traditionally, a 3-step approach is followed for cervical cancer screening and management of pre-invasive lesions of cervix: *(i)* ***Screening*** with available modality (either Pap smear or HPV or co-test or VIA); *(ii)* ***Colposcopy*** of abnormal screening result cases and directed biopsy if indicated; and *(iii)* ***Treatment*** of lesions. These multiple visits are associated with a high rate of loss to follow up and increased costs for poor women. Women also suffer from anxiety while awaiting the test results. Hence, a feasible and sustainable model for screening and treatment of pre-invasive lesions of cervix was very much needed to successfully implement the population-based cervical cancer screening. A strategy consisting of screening and providing treatment at the same visit is the most efficient, feasible and cost-effective strategy (Fig 3). In one study from Congo, patients underwent a combination of VIA, VILI, and colposcopy with or without loop electrosurgical excision procedure (LEEP). 644 women were screened and CIN was present in 15 (2.33%), squamous cell carcinoma (SCC) in 6 (0.93%) and non-neoplastic cervicitis was identified in 11 (1.71%) cases. This study concluded that the SVA is feasible in reducing cervical cancer morbidity and mortality. Singla et al evaluated SVA for the management of CIN using VIA and LEEP; 450 women were screened and treated. Patients with modified Reid score >3 underwent LEEP at the same visit. The detection rates of VIA, VILI and cytology were 20, 22.2 and 22.2 per 1000 women, respectively for CIN2+ lesion. The overtreatment rate was 12.5% and the efficacy of LEEP was 81.3% with no major complications.

Fig 3: Chart showing summary of management options for screen positive cases. Screening and treatment can be completed in a single visit (SVA) if there is point of care screening test (VIA or *care*HPV) and lesion is suitable for ablation



Usually SVA links VIA with an offer of immediate treatment or referral, as indicated. However, with the introduction of low-cost point of care HPV tests, HPV test can also be linked with immediate treatment. Biopsy can be taken for the visualized abnormality before treating the lesion for post-hoc analysis. The SVA is implemented by either of the two modalities depending on the infrastructure and available expertise and the suggested criteria is depicted in Fig 4.

Fig 4: Summary of criteria for SVA

See and Treat	Screen and Treat
In Colposcopy	*In Public Health Programs*
Patient referred with abnormal cytology report	VIA detects abnormal lesion
Colposcopy scoring indicates a high grade lesion	Criteria for ablation fulfilled
Simultaneous treatment done - excision or ablation	Treat immediately, with or without biopsy
Low probility of over-treatment because high specificity of cytology	Lower probability of over-treatment in high prevalence areas
Post-hoc analysis of biopsy report/excision specimen	Post-hoc analysis is possible if biopsy was taken

Treatment Modalities for Screen Positive Cases:

There are two modalities available to provide treatment of screen positive woman during SVA; ablation and excision.

Ablation Methods to Treat Screen Positive Cases

The ablation is performed on outpatient basis. No anaesthesia is required and patient can go home after completion of procedure. It can be done using See and treat or screen and treat approach. Before performing ablation on the cytology/HPV positive women, either colposcopy should be done or 3-5% acetic acid should be applied on the cervix for 1 minute to ensure that the criteria for ablative treatment are fulfilled.

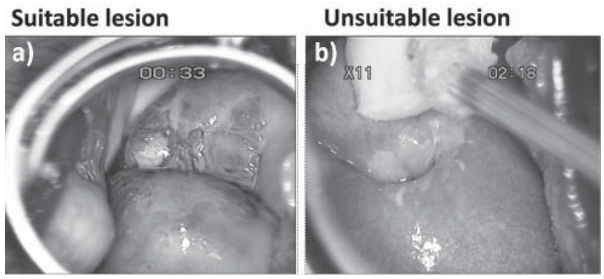
Eligibility criteria for ablative procedure: (Fig 5)

1. Type 1 TZ
2. The lesion should not extend into endocervical canal or vagina.
3. The lesion should not occupy more than 75% of TZ.
4. The probe should be able to cover the lesion in its entirety
5. No suspicion of invasive or glandular disease
6. Woman should not be pregnant

Pre-requisites

1. Informed consent
2. Privacy of woman should be respected
3. Should fulfill the eligibility criteria

Fig 5: a) shows a VIA positive lesion suitable for ablation, **b)** The VIA positive lesion extending into endocervix and occupying all quadrants of cervix and thus is unsuitable for ablation



Cryotherapy

This procedure utilizes the refrigerant property of nitrous oxide (N_2O) or carbon dioxide (CO_2) gas. The gas is passed through a nozzle to the tip of a metallic probe that is applied on the transformation zone of the cervix. (fig 6) The temperature of the cervical epithelium underlying the probe is reduced to −20°C, which in turn crystalizes the intracellular water and coagulates the cellular protein. The epithelium of the transformation zone undergoes cryonecrosis and is replaced by mature normal squamous epithelium over the next few months. A meta-analysis reported cure rate of 92% for CIN 2 lesions and 85% for CIN 3 lesions. The major advantage of cryotherapy over LLETZ is that the former is associated with fewer major complications including haemorrhage, and future adverse obstetric outcomes including preterm births but the recurrence rates after treatment of CIN 2+ lesions was higher compared with LEEP. WHO recommends cryotherapy as a simple, safe, and effective method of treating CIN, especially in resource-limited settings. Chumworathayi et al. from Thailand evaluated the visibility of squamocolumnar junction after cryotherapy during SVA after VIA screening. Repeat VIA was done after 1 year and it was observed that the SCJ was visible to the colposcopist in 91.7% (594/648) of the women. Among 42 women assessed as abnormal by the nurses, colposcopic findings were abnormal in 83.3% (35/42), with one low-grade squamous intraepithelial lesion, two high-grade squamous intraepithelial lesion (HSIL), and one adenocarcinoma confirmed later by biopsy. On the other hand in VIA negative women colposcopy was abnormal in only 23.4% cases. Hence, it was concluded that VIA was still a feasible option to screen women after ablation during SVA.

Method

The probe is applied to the cervix ensuring that it does not touch the vagina. The machine is switched on and

the gas is allowed to flow for 3 minutes, during which period a nice ball of ice forms on the probe extending to the cervix. The gas flow is turned off for 5 minutes to thaw the cervix and the ice melts. The gas is again turned on to freeze the cervix for another 3 minutes. This double freeze technique is reliable and reduces the risk of recurrence. The main limitation of cryotherapy is logistics and availability of gas and transportation of heavy cylinders. Recent portable versions (CryoPen and CryoPop) are available in the market that do not need refrigerant gas.

Thermal ablation / Thermocoagulation

Thermal ablation uses heat to coagulate the cervical epithelium at the TZ. The epithelium sloughs off and the underlying stroma and the crypts are desiccated by dry heat. The thermal ablation unit consist of a probe that is heated to 1000C and is kept in contact with cervix for 20-45 seconds.(fig 7) The procedure is simple, causes minimal pain, does not require any anaesthesia, has very low complication rates and is feasible in very basic settings. Duncan et al treated 1628 biopsy proven suitable CIN 3 lesions with thermal ablation and followed them for 10 years. They reported the 1 year and 5 year response rates as good as 95% and 92% respectively.

Benefits

1. The unit is portable and is available as both electrically operated and rechargeable battery operated versions.
2. The probe can be applied on the cervix multiple types. Up to 5 overlapping applications can be made to treat the large transformation zones.

Complications

1. The treated women may have a watery vaginal discharge that may last up to 2-3 weeks

Excisional procedures

There are two known excisional procedures; LEEP and cold knife conization. While LEEP can be done on OPD basis, conization requires general anaesthesia and is usually not used for SVA.

LEEP (Loop electrosurgical excision procedure) / LLETZ (Large loop excision of transformation zone)

LEEP/LLETZ is a very effective technique for treating all grades of CIN irrespective of size or location of the lesion. A thin tungsten or steel wire loop electrode powered by an electrosurgical unit is driven through the TZ to excise a cone-shaped sample

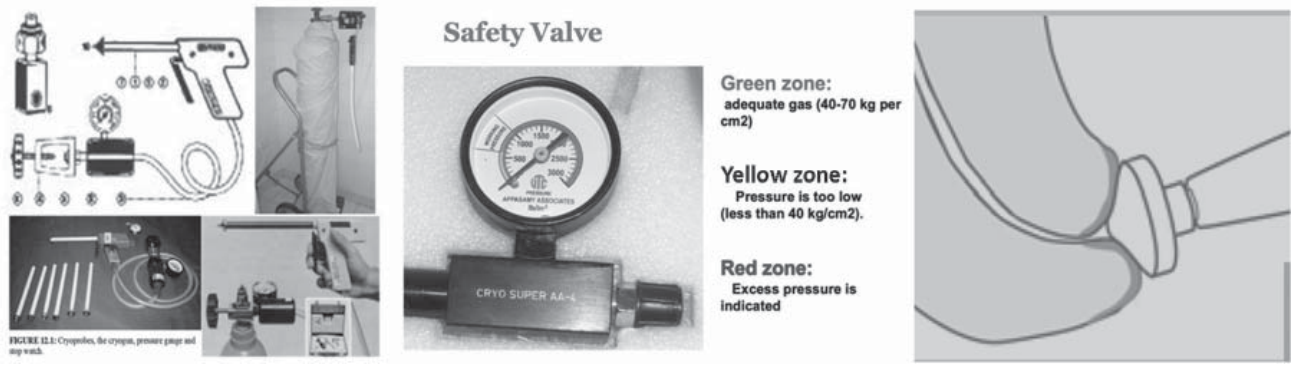


Fig 6: Showing equipment used for cryotherapy and application of cryoprobe over the cervix.

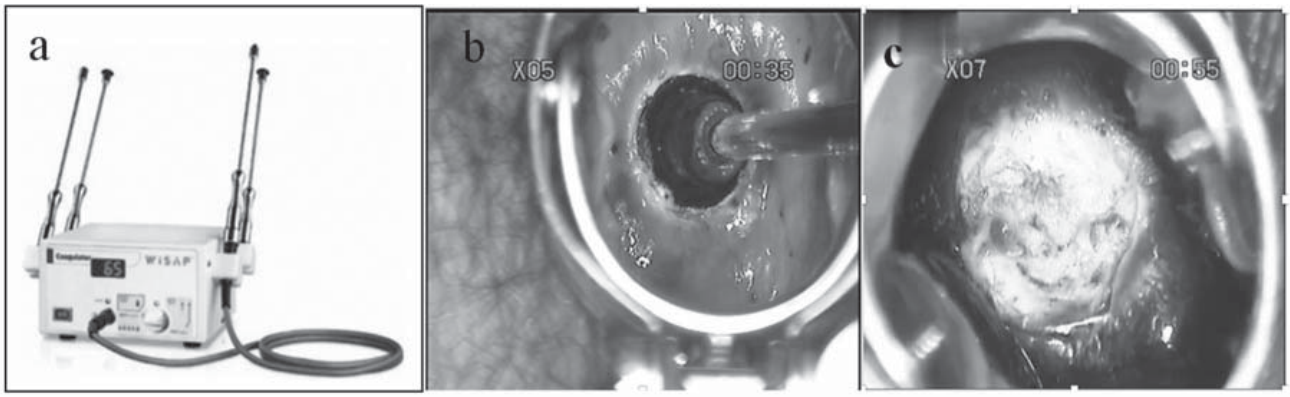


Fig 7: A: Thermal ablation unit, **B:** Thermal ablation probe in contact with TZ, **C:** Appearance of cervix after application.

from the cervix. (Fig 8) It can be done on OPD basis but requires local anaesthesia. It has an added benefit of providing specimen for histology. The length of excision depends on the type of transformation zone. For a type I TZ an 8 mm long cone and for a type III TZ a 15-20 mm cone may be required The chance of adverse pregnancy events increases with the length of the cone excised. The cure rates are high reaching up to 90%. Complications have been reported in 7%-10% of treated women and 50%-70% of these complications were intraoperative or postoperative bleeding, the majority of which could be easily controlled.

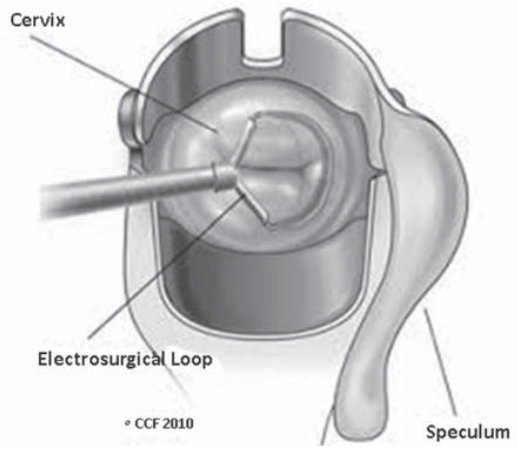


Fig 8: Large loop excision of TZ using loop electrode

Cold knife conization (CKC)

Cervical conization with a scalpel is an excisional method generally reserved for treating AIS and microinvasive carcinoma. (Fig 9) CKC avoids the thermal artefact of LLETZ, thus allowing better histopathologic assessment of cone margins. The major disadvantages of CKC are that the procedure has to be performed under regional or general anaesthesia for which hospitalization will be necessary and complications such as primary and secondary haemorrhage and adverse pregnancy events are higher than with LLETZ.

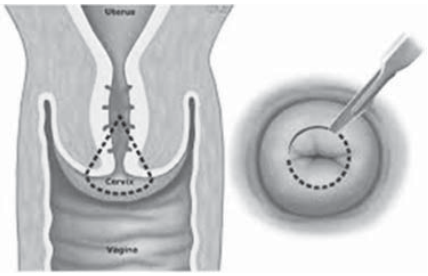


Fig 9 : Cold knife conization

Follow up after treatment

After the procedure woman should be advised to abstain for 4 weeks and should refrain from using vaginal tampons or douche. She may feel mild cramps and clear vaginal discharge for six weeks. However, she should be advised to report to facility if she experiences fever, bleeding or pain. WHO recommends that the first follow-up should take place at 1 year after treatment and routine screening can follow with a 3-5 year interval when there is no evidence of disease. Women with histology confirmed CIN 3 or AIS are recommended to have yearly follow-ups for 3 consecutive years, and if negative they are advised to resume routine screening. Methods of follow-up may include any of the screening tests or colposcopy depending on the facilities available. High- risk HPV testing is commonly used as a "test of cure" to distinguish between women with residual disease and those without. The absolute risk of residual CIN 2+ was 74.4% (95% CI: 64.0-82.6) when the HPV test was positive vs only 0.8% ([95% CI: 0.15-4.6]; P o 0.001) with a negative HPV test.

Conclusion

For effective cervical cancer screening efforts, it is essential to follow standardized treatment protocols for screen positive cases. Implementation of the "screen and treat" approach for detecting and treating pre-cancerous and cancerous cervical lesions is an effective option for LMICs for cervical cancer prevention. However, community awareness, mobilization, proper training of providers to conduct VIA, colposcopy and LEEP, referral and follow-up should be ensured.

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Role of AI in Cervical Cancer Screening

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Introduction

A field of science and engineering associated with the computational understanding of intelligent behaviour and with the creation of artefacts that exhibit of such behaviour is called as artificial intelligence. Aristotle, an ancient Greek philosopher and scientist had formalised 'right thinking' (logic) through his syllogisms (a three part deductive reasoning). Most of the development in the field of artificial intelligence has been based on his work. These early studies on the operation of mind helped to establish contemporary logical thinking. Artificial intelligent systems are programs which help computers to function in the ways, that make people seem intelligent. Turing test is defined as intelligent behaviour in a computer and the ability to achieve human-level performance in cognitive tasks. Many researchers in the last century, have explored the potential applications of intelligent techniques in almost all fields of medical science. The first application of AI technology in the field of surgery was investigated by Gunn in 1976, when he explored the possibility of diagnosing acute abdominal pain with computer analysis. The last three decades have seen a major surge in the interest in medical AI.

The challenges of including AI in modern medicine is acquiring, analysing and applying the large amount of knowledge necessary to solve complex clinical problems and set up of programmes for the same. The development of medical artificial intelligence has been related to the development of AI programs intended to help the clinician in the formulation of a diagnosis, making of therapeutic decisions and prediction of outcome. They are designed to support healthcare workers in their everyday duties, assisting with tasks that rely on the manipulation of data and knowledge. Such systems include Artificial neural networks (ANNs), fuzzy expert systems, evolutionary computation and hybrid intelligent systems.

Artificial Neural Networks (ANNs)

The computational analytical tools that are inspired by the biological nervous systems are called ANNs. These consist of networks of highly interconnected computer processors called 'neurons' which are capable of performing parallel computations for data processing and knowledge representation. They can analyse from historical examples, non-linear data, can handle imprecise information and generalise enabling application of the model to independent data. This made them a useful analytical tool in medical science. The first artificial neuron was invented by McCulloch and Pitts in 1943 using binary threshold functions. This process took a major leap when Frank Rosenblatt who was a psychologist, developed the Perceptron in 1958 as a practical model. There are many variations of the basic Perceptron network but the most popular model has been multilayer feed forward Perceptron. Baxt developed a neural network model which could accurately diagnose acute myocardial infarction. His work was latter prospectively validated with similar accuracy. Since then, ANNs have been applied in almost every field of medicine.

Genetic Algorithms

Almost four decades ago, the idea of applying the biological principle of natural evolution to artificial systems have been introduced. But most progress in this aspect has occurred only in the past few years. Evolutionary algorithms or evolutionary computation are a group of domains such as genetic algorithms, evolution strategies, evolutionary programming, and genetic programming. These algorithms are used commonly in the present era and have been successfully applied to numerous problems from different domains, including optimization, automatic programming, machine learning, economics, medicine, ecology, population genetics, and hardware design. an iterative procedure that involves a population of individuals, each one represented by a finite string of symbols, known as the genome, encoding a possible solution in a given problem space is called genetic algorithm. This space is called search space and it includes all possible solutions to the problem at hand. They are commonly applicable to spaces which are too large to be exhaustively searched. The symbol alphabet used is often binary, though this has been extended in recent years to include character-based encodings, real-valued encodings, tree representations, and other representations. The standard genetic algorithm proceeds as follows: an initial population of individuals is generated at random or heuristically. Every evolutionary step, known as a generation, the individuals in the current population are decoded and evaluated according to some predefined quality

criterion, referred to as the fitness, or fitness function. To form a new population (the next generation), individuals are selected according to their fitness. There are many selection procedures that are currently in use such as fitness-proportionate selection, where individuals are selected with a probability proportional to their relative fitness. This ensures that the expected number of times an individual is chosen is approximately proportional to its relative performance in the population. Thus, high-fitness individuals stand a better chance of 'reproducing', while low-fitness ones are more likely to disappear. Selection alone cannot introduce any new individuals into the population. These are generated by genetically inspired operators, out of which the most well-known are crossover and mutation. Crossover is performed with probability p_c between two selected individuals, called parents, by exchanging parts of their genomes (i.e. encodings) to form two new individuals, called offspring. So, substrings are exchanged after a randomly selected crossover point. This operator tends to enable the evolutionary process to move toward 'promising' regions of the search space. The mutation operator is introduced to prevent premature convergence to local optima by randomly sampling new points in the search space. It is carried out by flipping bits at random, with some (usually small) probability p_m. Genetic algorithms are stochastic iterative processes that are not guaranteed to converge. The termination condition may be specified as some fixed, maximal number of generations or as the attainment of an acceptable fitness level.

Fuzzy Expert Systems

Fuzzy logic is the science of reasoning, thinking and inference that recognises and uses the real world phenomenon – that everything is a matter of degree. Instead of assuming everything is black or white (conventional logic), fuzzy logic is that in reality, most things would fall somewhere in between, which is varying shades of grey. This was proposed by Lofti Zadeh who is an engineer by profession. It uses continuous set membership from 0 to 1 in contrast to Boolean or conventional logic which uses sharp distinctions, i.e. 0 for false and 1 for true. Medical science cannot be an all or none phenomenon. It is a continuous domain and most of that data is inherently imprecise. Fuzzy logic is a data handling methodology that permits ambiguity and hence is particularly suited to medical applications. It captures and uses the concept of fuzziness in a computationally effective manner. Zadeh proposed in 1969 that: 'the most likely area of application for this theory lies in medical diagnostics and, to a lesser extent, in the description of biological systems'. Fuzzy expert systems comprises of a series of 'if – then' rules for modelling. The techniques of fuzzy logic have been explored in many medical applications. Schneider et al. proved that fuzzy logic performed better than multiple logistic regression analysis in diagnosing lung cancer using tumour marker profiles. This application of fuzzy logic has been explored in the diagnosis of many medical and surgical conditions such as acute leukaemia, breast and pancreatic cancer. This was also used to predict survival rate in patients with breast cancer. Fuzzy controllers have been designed for the administration of vasodilators to control blood pressure in the peri-operative period, for the administration of anaesthetics in the operation theatre.

Role of AI in Cervical Cancer Screening

Visual inspection with acetic acid (VIA) is being currently used in rural areas and low resource settings by health care workers. In this, 5% acetic acid will be applied to the cervix and aceto- whitening of the cervix, if noted, is considered VIA +ve. Such patients are referred to higher centres for further evaluation and management. But this method is not accurate, so there are false negative and false positive cases. The sensitivity and specificity of VIA for CIN2+ is 73.2% and 86.7% respectively. So, this method needed improvement.

Here comes automated visual evaluation(AVE) to improve accuracy. In this, the CDS (clinical decision support) AI machine learning algorithm currently deployed on the EVA System can evaluate an input of an image of a cervix captured during a colposcopy and output a risk assessment whether high risk or low risk. Referral to higher centre and biopsies can be taken according to the risk stratification. Here, health care workers can use only a cell phone camera or similar camera for cervical treatment. Same steps similar to VIA are used, but instead of naked eye inspection, a camera is used to click the pictures and a result will be given with an inbuilt AI system. This technique needs only minimal training and equipment. The sensitivity of screening for this method is around 94%. Overall, the algorithm developed was better than all standard screening methods.

Application in Diagnosis

ANNs have been used in the clinical diagnosis, image analysis in radiology and histopathology, data

interpretation in intensive care setting and waveform analysis. A neural network derived classification algorithm was developed by Stamey et al called Prost Asure Index which can classify prostates as benign or malignant. This model had a diagnostic accuracy of 90%, sensitivity of 81% and specificity of 92%. There are other surgically relevant diagnostic applications of ANNs such as abdominal pain and appendicitis, retained common bile duct stones, glaucoma and back pain. ANNs have also been used in diagnosing cytological and histological specimens. PAPNET, a computerised automated screening system based on neural networks was developed to assist the cytologist in cervical screening and is one of the few ANN models which was promoted commercially. Breast, gastric, thyroid, oral epithelial cells, urothelial cells, pleural and peritoneal effusion cytology were also subjected to analysis by neural networks with varying success rate. In radiology, it is possible to use both human observations and direct digitised images as inputs to the networks. ANNs have been used to interpret plain radiographs, ultrasound, CT, MRI, and radioisotope scans. ANNs pattern recognition ability has been used to analyse various wave forms including the interpretation of ECGs to diagnose myocardial infarction, atrial fibrillation, and ventricular arrythmias. Analysis of electro-enchalograms (EEG) by neural networks has led to its application in the diagnosis of epilepsy and sleep disorders. They have also been trained to analyse electromyographic (EMG) and Doppler ultrasound wave forms as well as haemodynamic patterns in intensive care patients.

Application in Prognostication

Prognostication is extremely important in planning appropriate treatment strategies and follow-up. Accurate identification of high-risk patients may facilitate targeted aggressive adjuvant therapy which may help cure the disease and prolong survival. ANNs with their ability to exploit non-linear relations between variables are particularly suitable to analyse complex cancer data. It has been demonstrated that neural networks can predict survival in patients with breast and colorectal cancer. ANNs have also shown to perform better than consultant colorectal surgeons in predicting outcome in patients with colorectal cancer. The authors of this paper have demonstrated the generalisability of ANNs, once trained on a particular data, the networks were able to predict outcome for patients from an independent institution without retraining. ANNs have also been used to predict outcome in lung and prostate cancers. They have been applied to predict outcome in intensive care unit and have performed better than APACHE II severity of illness scoring system.

Hybrid Intelligent Systems

Each AI technique has its own strengths and weaknesses. Neural networks are mainly concerned with learning, fuzzy logic with imprecision and evolutionary computation with search and optimisation. The advantages of these technologies can be combined together to produce hybrid intelligent systems which can work in a complementary manner. Their synergy allows a hybrid system to accommodate common sense, extract knowledge from raw data, use human-like reasoning mechanisms, deal with uncertainty and imprecision, and learn to adapt to a rapidly changing and unknown environment. There are many different hybrid systems available and the popular ones are ANNs for designing fuzzy systems, fuzzy systems for designing ANNs, and Genetic Algorithms for automatically training and generating neural network architectures. Once again, the application of hybrid intelligent systems has been explored in many diverse clinical scenarios. Some examples include breast cancer diagnosis, analysis of microcalcification on digital mammograms, diagnosis of coronary artery stenosis, assessment of myocardial viability, and control of the depth of anaesthesia.

Conclusion

There are a large variety of novel data management tools that have become available over the past decade. They vary in their suitability to a given task, the degree to which the achieved solution is understandable (transparent or opaque), and the ease of configurability. There are many different AI techniques available which are capable of solving a variety of clinical problems. However, in spite of earlier optimism, medical AI technology has not been embraced with enthusiasm. One reason for this is the attitude of the clinicians towards technology being used in the decision-making process. Paradoxically, there is no qualm in accepting the biochemical results generated from an auto-analyser or images produced by magnetic resonance imaging. However, it is the obligation of researchers active in this field to produce evidence that these techniques work on a practical level. The need to undertake more randomised controlled studies to prove the efficacy of AI systems in medicine is, therefore, vital. There is compelling evidence that medical AI can play a vital role in assisting the clinician to deliver health care efficiently

in the 21st century. There is little doubt that these techniques will serve to enhance and complement the 'medical intelligence' of the future clinician.

Suggested Readings

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Forthcoming Events

- International Hysteroscopy Congress on 18th & 19th March 2020 at Cairo, Egypt under the aegis of Endoscopy committee, Contact : Dr Richa Sharma
- FOGSI FORCE PG training programme on 21st & 22nd March, 2020 at AIIMS under the aegis of AOGD.
- VagSurgiCon 2020, State of the Art Live Vaginal Surgery Workshop: Basics to Advances on 21st & 22nd March, 2020 at Sant Parmanand Hospital by Society of Vaginal Surgeons, Delhi
- CME on "Symposium On Endometriosis" on 22nd March, 2020 at auditorium, Max Super Speciality Hospital, Saket under the aegis of Endometriosis Committee of AOGD.
- Next Monthly Clinical Meeting on 27th March, 2020 (4:00-5:00 pm) at Lady Hardinge Medial College (LHMC).

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- Monthly Clinical Meeting on 17th January, 2020 at Dr Ram Manohar Lohia Hospital, New Delhi.



- CME on 'Preeclampsia-an update' on 19th February, 2020 at Manipal Hospital Safe Motherhood Committee of AOGD.



- National FOGSI Conference -"Women's Reproductive & Sexual Health" on 29th February - 1st March, 2020 at The Lalit, New Delhi by Sir Ganga Ram Hospital under the aegis of FOGSI & AOGD

- Monthly Clinical Meeting on 6th March, 2020 at UCMS & GTB Hospital, New Delhi.

I.F.C.P.C

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Eliminating Cervical Cancer-Call for Action

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17th World Congress for Cervical Pathology and Colposcopy

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- Eliminating Cervical Cancer - The Landscape Science and Politics
- The Biology of Cervical Premalignancy and Malignancy: The Transformation Zone
- Screening and Vaccination
- Clinical Challenges
- Multi-zonal disease
- IFCPC session- Terminology and Training
- New Technologies and Artifical Intelligence
- Patient Advocacy

PRE-CONGRESS WORKSHOPS

Wednesday, 30 September 2020

- Training the Trainer
- Vulva with Hands-on Module
- Screen 'n' Treat

Thursday, 1 October 2020

- Comprehensive Colposcopy Course & Hands-on LEEP
- Cytopathology & HPV
- Surgical Options for CIN & Cervical Cancer (Live Surgery)
- Vulvar Reconstructive Surgery

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2. HPV Testing and HPV Vaccination
3. Cervical Cancer Screening
4. Management of CIN
5. Quality Assurance
6. Cervical Cancer
7. Public Health
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Portable Colposcopes - Evolution and Expectations

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Introduction

Colposcopy is an integral part of cervical cancer screening and management. Once a screening test, whether Pap smear, HPV test or VIA, has been found to be positive, the next step is confirmation of disease status. Colposcopy is used in triage of screen positive women to detect lesions, estimate severity and guide the biopsy. This has been a challenge as the previous equipment was bulky and expensive, and hence it was not possible to equip every primary and secondary care facility. Moreover there is a need for trained manpower for this procedure. Referral to district and tertiary hospitals results in loss to follow up. New innovations have resulted in the development of portable colposcopes which can overcome these barriers. Health care workers can be trained to take and transmit images. Artificial intelligence may be integrated into these devices to allow treatment in a single visit approach.

History of Colposcope

The colposcope was introduced by Hans Hinselmann (Germany) in 1925 and is now in common use for magnified stereoscopic examination of the cervix, vagina, and vulva. Hinselmann mounted a binocular, Leitz dissection microscope on a tripod with a built-in light. He mounted the device on a mobile stand allowing to move the device to focus the cervix. Though the peer group in his time appreciated the equipment, they found it difficult to use due to the poor adjustment and required skills. With successive improvement in different methods to identify cervical lesions by colposcopy, the utilisation of the device improved.

Colposcopy developmental steps	Researcher (year)
Schillers test	Walter Schiller, 1928
Application of acetic acid	Hans Hinselmann, 1938
Concept of using green filter	Helmut Kraatz & W.Stoeckel, 1939

Newer developments in the image-based screening of cervix:

i) **Digital imaging colposcopy –** includes digital techniques to predict histological grade.

ii) **DySIS** -uses proprietary dynamic spectral imaging technology, helps to identify the severity of abnormality and guide in selection of biopsy site.

iii) **Zedscan** - uses electrical impedance spectrometry to diagnose the histological grade

iv) **LuViva** - uses multimodal hyperspectroscopy (MHS), provides a real time objective result without the need for a tissue biopsy.

v) **NIRIS imaging system** - uses a technique called optical coherence tomography, visualizes tissue microstructure similar to ultrasound to a depth of 1.6 mm and a spatial resolution nearing the resolution of histopathology.

vi) **LUMA TM cervical imaging system** - is a combination of fluorescence, reflectance and spectroscopy intrinsic to in-vivo tissues that should allow it to be used as an adjunct to colposcopy for detection of high-grade CIN.

Newer developments in digital technologies have revolutionized communication technologies. These advancements from basic colposcopy techniques have brought new insights and furthered the colposcopy experience but they are still not affordable for the LMICs especially in public sector health services. The desired features from a portable device are automated light source, automated focusing or simpler technology to use, battery operated not requiring electricity, portable, cost-effective, and image quality comparable to standard-of-care colposcope. The newer portable devices developed with this vision are discussed below.

AV Magnivisualizer:

AV Magnivisualiser was developed by National Institute of Cancer Prevention and Research (NICPR) Noida, India (Figure 1). The Magnivisualizer is a portable, battery operated device, and easy to handle. This is used for visual inspection with acetic acid under magnification (VIAM).

Though VIAM does not improve the test performance of VIA, the availability of a hand-held battery operated good light source is beneficial in field settings.

AVIscope™

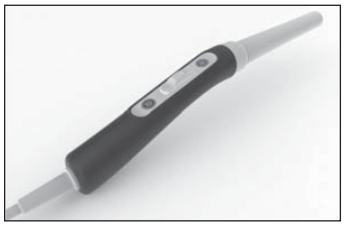
As an alternative to VIA, a low cost, hand held monocular, battery operated device with 4x magnification, green light option and smaller in size was devised by Program for Appropriate Technology in Health (PATH) (AviScope; O'Ryan Industries, Vancouver, WA, USA) (Figure 2). Advantages over the colposcope were portability, durability, non-reliance on a ready source of mains electricity, ease of repair and maintenance.

Gynocular

Gynocular is a portable colposcopic device, weighing 420 g and 10cm in length. This device provide 3x, 8x and 12x magnifications. It has inbuilt green filter and LED light. (Figure 4)

It has the advantage of being portable and lower price than standard premium colposcopes, it helps in faster and efficient examinations. The device combined with a software and a smart phone, makes it possible to register demographic data and clinical examination findings. It is battery driven, hence can be used in rural areas in the absence of electricity. The mobile phone adapter helps to turn Gynocular into a video colposcope. The battery lasts at least 2 hours of continuous use. The Gynocular has a triage to diagnose (T2D) cloud-based software, which is a clinical record software to use together with Gynocular for a structured colposcopic examination with integrated image documentation stored in cloud-based storage space. This can be used in mobile phone, laptop or stationary desktop.

Pocket colposcope



Ramanujam et al from the Department of Biomedical Engineering, Duke University USA, have developed a novel, low cost Point of Care digital Colposcope (Pocket Colposcope). The Pocket Colposcope is shaped like a transvaginal transducer and can be inserted and positioned such that it is 30–40 mm away from the cervix, providing image with better clarity comparable to standard colposcopes. The need for high-end optics and high-resolution cameras used in state of the art colposcopes, was obviated by the reduced working distance. In their study, the Pocket Colposcope had comparable optical characteristics when compared to commercially available colposcopes. The device has US FDA approval. In vitro and pilot in vivo imaging results are promising capturing comparable quality images to standard colposcopesfollowed by treatment during the same visit or a subsequent visit with cryotherapy if a suspicious lesion is found. Implementation of these guidelines is hampered by a lack of: trained health workers, reliable technology, and access to screening facilities. A low cost ultra-portable Point of Care Tampon based digital colposcope (POCkeT Colposcope.(Figure 5)

The transvaginal colposcope will reduce the expertise needed by the operator to image the cervix and thus can be used more seamlessly at the community health setting. The hand-held colposcope when placed at the vagina for image capture, provide automatic illumination, auto focus and magnification.

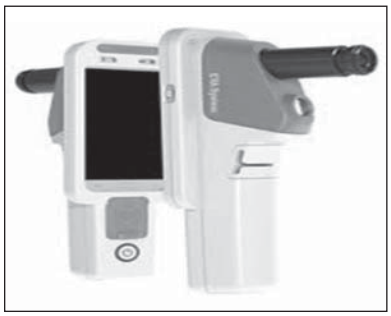
The images captured can be displayed in a smartphone or tablet or laptop. The images can be stored and transmitted to a remote site thus making the interface between community health and tertiary treatment facilities more streamlined. Transvaginal colposcope can provide both white light and green images like standard colposcopes. In the studies conducted at AIIMS, Pocket colposcope performed comparable to digital video colposcope.

FemiCam

FemiCam is a smart camera designed to document or visualize in the form of images from the examination of cervical cancer innovated in Indonesia with

technology from South Korea (Figure 6). Ocviyanti et al (2018) studied the clients perspective about VIA with images, and found that the patients had more understanding about the test, operator was able to explain the test and results easily and clearly which had the potential to motivate the women for regular screening.

MobileODT



MobileODT developed by EVA System is similar to Gynocular in that it consists of mobile phone attached to the lens to magnify the cervix, and it has software for image capture and relay (Figure 7). It was shown to improve workflow and documentation in screening camps, and the experience was found to be more positive than VIA for both patients and providers. This device has been shown to be useful in hospital-based screening and camp-based screening.

Smart Scope

Smartscope is a transvaginal colposcope with telemedicine facility developed by Periwinkle technologies, Pune, India (Figure 8). It has incorporated artificial intelligence into the device, it provides results with comparison. It will be of an advantage when screening women in areas where trained manpower are less. It can help in training the health worker also.

The Way Forward in Colposcopy

In the modern era, communications have improved enabling even remote places to be contacted with the newer mobile and internet facilities at a lesser cost. This digital revolution can be used for cervical cancer prevention. The newer devices have incorporated the features required for better image, storage and transmission. Health workers at the last mile facilities can be trained in image capture and transmission to permit remote advice from specialists on management and referral. Algorithms based on stored images incorporating artificial intelligence can guide the diagnosis of preinvasive lesions.

In a further step forward, a self-examining system called Callascope, for speculum free imaging is being designed by Duke University, USA, which is under the phase of preclinical testing. With teaching videos, Callascope will enable a woman to capture image of her cervix and send the images to physician.

Conclusion

Portable colposcopes have the advantage of portability, good performance and convenience which brings new hope in cervical cancer screening. Newer insights into designing and training will improve coverage in remote areas.

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HPV Vaccination : Newer perspectives

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Introduction

It has been more than a decade since the first HPV vaccines were licensed and introduced in number of countries all over the world. These were targeted against HPV 16/18, the two main types of oncogenic HPV that contribute to 70% of the cervical cancer burden globally and over 80% in India. Subsequently a nonavalent vaccine has also been licensed, which targets HPV 6/11/16/18/31/33/45/52/58, but this has not yet been marketed in India. HPV vaccine now occupies an important position in the armamentarium of vaccines, yet remains underutilized. The number of national HPV vaccination programs has increased steadily; as of June 2019, nearly 100 countries (49%) have introduced HPV vaccines in the national immunization programmes or in part of the countries. Currently, an estimated 30% of girls aged 9-14 years globally live in countries that have introduced the HPV vaccine.

Still, there is great variability across the globe in terms of HPV vaccine supply, vaccination policies and accompanying barriers to the implementation and/or sustainability of programs. Although, there is a decline in cervical cancer incidence with a falling rate of 1–2% per year, it still remains a cancer with a high burden in India. Mortality rates are higher due to lack of awareness leading to late diagnosis as the majority of women seek help only after they become symptomatic or at an advanced stage. Screening of asymptomatic patients is <5% even in well-organized health care programs. Awareness and health-seeking practices have been shown to be poor in most developing countries including India, thus necessitating the need for proper awareness and vaccination program.

Current Status of HPV Vaccination

Since the introduction of the HPV vaccine in 2006, rates of HPV infections have started to decline in countries that introduced it in the national program. According to a recent systematic review and meta-analysis by Drolet et al (2019) the prevalence of HPV 16 and 18 decreased significantly by 83% among girls aged 13-19 years and by 66% among women aged 20-24 years after 5-8 years of vaccination. The study also showed significant herd immunity among unvaccinated boys and girls. Multicohort vaccination and high vaccination coverage led to a greater and faster direct impact and herd effects. With several countries now switching to two-dose schedules, gender-neutral vaccination and with introduction of the nonavalent vaccine, these results should be considered within the rapidly changing landscape of HPV vaccination. Cervical cancer screening and HPV vaccination programmes have been well implemented in most of the high-income countries. However, coverage remains low in low middle-income countries (LMICs).

In 2018, the Director-General of WHO announced a call to action for the elimination of cervical cancer which is considered as a public health problem. Studies conducted in different countries have shown promising results. In Scotland, a substantial reduction in pre-invasive cervical disease has been found in girls who were aged 12–13 years when vaccinated with the bivalent HPV vaccine and it has shown clinically relevant herd protection in girls who had not been vaccinated. These results are similar to those reported earlier from Australia, one of the first countries to introduce HPV vaccination for girls in 2006, including a catch-up program for women up to the age of 26 years. Studies from Denmark and Sweden have also reported a decline of >70% in prevalence of CIN 2 or worse lesions following quadrivalent HPV vaccination of young girls. Australia was one of the first countries to introduce HPV vaccination of boys and since December 2018 has changed to screening of women aged 25-70 years with HPV testing 5 yearly. It is likely to reduce the annual cervical cancer incidence to <6 cases per 100 000 women by 2020 and < 4 per 100 000 (the goal of the WHO Cervical Cancer Elimination Initiative) by 2028 if the country maintains its current level of coverage of HPV vaccination and screening.

HPV Vaccines

Currently, three HPV vaccine are available: GSK's Cervarix (bHPV), using the proprietary AS04 adjuvant, and Merck's Gardasil (qHPV) and Gardasil 9 (HPV9), both using aluminium adjuvant. Current available evidence suggests that the three licensed HPV vaccines have relatively similar effectiveness in preventing cervical cancer. The bivalent and quadrivalent HPV vaccines are commercially available in India and approved by the Drug Controller General of India (DCGI) for use.

In addition to providing protection against the HPV types included in these vaccines, the vaccines have

been found to provide cross-protection against a few additional HPV types that can cause cancer. The vaccines do not prevent other sexually transmitted diseases, nor do they treat existing HPV infections or HPV-related diseases.

Target Age Group

WHO recommends that the primary target population for HPV vaccination are girls aged 9-14 years, prior to becoming sexually active. The Indian Academy of Pediatrics Committee on Immunization (IAPCOI) recommends offering HPV vaccine to all females who can afford the vaccine. However, vaccination of secondary target population, i.e., females older than 14 years of age is recommended only if it is feasible, affordable, cost-effective and does not divert resources from vaccination of primary target population.

As of 2017, the WHO recommended countries vaccinate a multi-age cohort of 9-14 years old in the first year of introduction and then continue with routine immunization of 9 year old in the second year to accelerate impact. In the context of the supply constraint, SAGE recommended that countries that already have HPV vaccine on the national schedule employ alternative strategies until the supply allows equitable access in all countries. These strategies include pausing vaccinations in boys, older girls (>15 years), and multi-age cohorts; or adopting an extended interval between doses. New and forthcoming evidence on the potential for a single-dose vaccination schedule could help alleviate future supply issues and accelerate new introductions.

Dosage Schedule

WHO in 2014 revised the recommendations of HPV vaccination from a three-dose schedule to two doses, administered at an interval of at least six months, for the bHPV and qHPV vaccines for girls aged 9 to 14 years old. This recommendation was based on the evidence of non-inferior antibody responses in adolescents girls aged 9 to 14 years compared with those for whom efficacy was demonstrated in clinical trials with a three-dose schedule. WHO guidelines allow for dosing flexibility for the second dose as early as five months and upto 15 months after first-dose in the two-dose schedule. According to the recommendation, girls aged ≥15 years or immunocompromised, should continue to receive three-dose schedule.

Barriers in HPV Vaccination Programs

A number of factors have influenced the slower introduction of HPV vaccines in LMIC. These include the initial cost of the vaccines and a delay in provision of financial mechanisms to support countries in obtaining the vaccine. HPV vaccine supply also poses a challenge. The supply currently available to LMICs is insufficient to meet demand in 2020 and 2021, leaving them unable to scale-up HPV vaccination programs as per WHO recommendations. The most prominent factor affecting current HPV vaccines for public health worldwide is their high cost.

The sustained financial commitment for the cost of vaccine procurement and vaccine delivery in LMICs has been a key factor in their governments' hesitancy to introduce HPV vaccine in national immunisation program. Thus, various approaches have been suggested to make the HPV vaccine more affordable for LMIC, including integrating vaccination into existing adolescent or school-health programs, reducing the vaccine dose and production of cheaper vaccines which are in pipeline and will be introduced in market in near future.

Future Directions

Emerging evidence from observational studies suggests that even a single-dose of HPV vaccine may protect against HPV infection. The results of observational studies done in Costa Rica and India on single dose HPV vaccine efficacy in prevention of targeted HPV infections are particularly consistent in showing high level of prevention of vaccine-targeted HPV infection. A dose-reduction recommendation to a single-dose regimen could potentially reduce the costs of vaccine supply and delivery, since different delivery strategies might be available for a single-dose schedule. Similarly, the ongoing evaluation of IARC study for HPV vaccination two-dose schedule in girls aged 15-18 years, if proved effective will not only ease the logistics but will also reduce the financial cost of catch-up vaccination of girls aged 15-18 years.

Future projected introductions are from China and India. Three products are currently in advanced clinical development: two bHPV vaccines from Innovax and Shanghai Zerun Biotech, both in phase III, and one qHPV4 vaccine from Serum Institute of India has successfully completed phase II trial for efficacy and safety of HPV vaccine in male and female aged 9-26 years.

Conclusion

Combination of an efficient cervical cancer screening programmes and HPV vaccination will be highly propitious for the elimination of cervical cancer as a

public health problem, as well is also important for prevention and early detection of cervical cancer worldwide. The feasibility of introducing widespread HPV vaccination in India and other low-income and middle- income countries will substantially increase when either the Indian or the Chinese HPV vaccine is found to be effective and affordable; is available for prescription and public health use; and when the single dose is shown to be effective in protecting against vaccine-targeted HPV infections and cervical neoplasia.

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Answer: February Issue

Crossword

Across

1. Swede
2. ECOG
3. Piver
4. Cytoreductive
5. Querleu
6. MMR

Down

7. HIPEC
8. Wertheim
9. VAIN
10. Cervix

Pictorial Quiz

Figure 1: Picture shows Clitoromegaly. Probable diagnosis is Sex cord stromal tumor.

Figure 2: Slide suggestive of HSIL. Patient needs diagnostic excisional procedure.

Figure 3: Uterus didelphys with Ovarian mass

Ovarian Cancer Prevention

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Introduction

Worldwide there are 3, 00,000 new cases of Ovarian Cancer and 1, 85,000 ovarian cancer related deaths annually. Although 5 years survival in stage 1 and 2 is 80-85%, unfortunately most cases (75%) are diagnosed in advanced stages 3 and 4 in whom 5 years survival is only 25%. Therefore, the overall 5 years survival falls to less than 45%.

Thus, attempts have been made to screen for Ovarian Cancer and make an early diagnosis of this malignancy. Screening for Ovarian Cancer starts with history to identify high risk vs average risk women.

Risk Factors for Ovarian Cancer

The strongest risk for ovarian cancer is family history of breast and ovarian cancer. 10-15% of ovarian cancers are due to genetic predisposition and up to 20% of high grade serous ovarian carcinomas are due to genetic causes. Therefore, National Comprehensive Cancer Network (NCCN) recommends genetic testing for all ovarian cancer.

Other risk factors are older age, nulliparity, smoking, alcohol, obesity and long-term use of hormone replacement therapy (HRT). HRT users have a 20% higher risk than never users. Smoking increases the risk for mucinous tumors more than other histopathology.

Average Risk Women

The lifetime probability of developing ovarian cancer is 1.5% in average risk women. Thus, ovarian cancer is a low prevalence disease but since mortality is high due to late diagnosis, attempts have been made to screen and diagnose the disease at an early stage.

Factors protective against Ovarian Cancer

Certain factors that decrease the risk of ovarian malignancy are following: -

- Pregnancy
- Birth Control Pills (These decrease the risk by 35-50% after use of five years)
- Fallopian tube ligation (Decrease the risk by 30%)
- Salpingectomy (Decrease the risk by 60%)
- Breast Feeding (Decrease the risk 40%)
- Hysterectomy (Decrease the risk 40-50%)

Symptoms of Ovarian Cancer

Early ovarian cancer has no specific symptoms. The most common symptoms associated with ovarian cancer are abdominal bloating, increased abdominal size, pelvic pain, abdominal pain, feeling full quickly, and difficulty eating. Urinary symptoms are also frequently present. When these symptoms occur for more than 12 days per month and are of new onset, then ovarian cancer should be considered as a possibility. However ovarian cancer symptom complex has been found to have a very low specificity and low positive predictive value.

Benefit of Screening

The potential benefit of screening is the ability to reduce mortality due to ovarian cancer. 5 year survival with ovarian cancer is < 45 percent and with distant metastasis. However, to reduce mortality, a screening program would need to detect ovarian cancer at an early stage, because with current treatment methods, ovarian cancer mortality is closely related to stage at diagnosis.

Screening methods that have been studied are: -

CA 125 (Cancer Antigen)

TVS (Trans Vaginal Sonography)

Multimodal testing with a combination CA125 and TVS

Cancer antigen 125 (CA 125)

CA 125 is a tumor associated antigen used to monitor patients with ovarian carcinoma. Two randomized trials have used CA125 either alone or sequentially with TVS for multimodal screening. The value that is considered significant is above 35 units/ml. Annual CA125 alone lacks specificity and has a low positive predictive value. This is because it is raised in several benign gynecological and non-gynecological conditions like benign ovarian, endometriosis, liver cirrhosis, pelvic inflammatory disease, uterine fibroids etc. It is raised in 1% of healthy women and it also varies with normal menstrual cycle, age and smoking status.

Even in postmenopausal women single CA 125 value has a low positive predictive value of around 3%. The change in CA125 level overtime maybe more helpful than a single value.

Transvaginal ultrasound (TVUS)

The sensitivity of TVUS ranges from 80 to 100 percent in women with clinically detected ovarian cancer and is in part observer-dependent in several prospective screening studies and specificity ranges from 94-99%. The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO trial) included women in the age group of 55-74 years and performed 6 annual screens of CA125 and 4 annual screens of TVS. They found that this did not reduce mortality due to ovarian cancer. In this trial 75% ovarian cancers detected due to CA125 were in advanced stages (3 and 4).

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) evaluated longitudinal CA 125 measurements which uses serial measurements and the Risk of Ovarian Cancer Algorithm (ROCA), irrespective of absolute single value. The UKCTOCS multi modal screen incorporated two stage approach with ROCA as the primary screen and TVS as secondary screen based on results of the ROCA. For primary ovarian cancer the sensitivity of this multi modal screening was 75% with a positive predictive value of only 2.8 - 5.3%. For every woman found to have ovarian cancer, 10 women had surgery for benign conditions. After a median follow up of 11 years, it was found that there was no mortality reduction in the screened group vs not screened group. TVS has been used alone as well in combination as a screening method.

Harms of Screening

Because ovarian cancer has a low prevalence, the rate of false-positive results will be high unless a screening program has a high specificity. With a high false-positive rate, poor positive predictive value of screening tests many women would be subjected to unnecessary surgical treatment.

Role of Opportunistic Salpingectomy in Average Risk Women

In women with BRCA 1 and 2 (Breast Cancer Susceptibility Genes) undergoing Risk Reducing Salpingo-Oophorectomy (rrSO), it was found that 8% had associated serous tubal intra epithelial cancer (STIC) and that 60% of ovarian cancers also have associated STIC. It is thus believed that a subset of epithelial ovarian cancer originates in the fallopian tubes.ACOG have also acknowledged opportunistic salpingectomy as a means to reduce epithelial ovarian cancer.

High Risk women

Genetic Testing

Approximately 20% of ovarian cancers particularly high-grade serous cancers are due to inherited mutations, and in 65-80% the genetic aberration is the BRCA mutation.[18] There are other gene mutations associated with ovarian cancer including Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC). The other moderate risk genes that affect ovarian cancer include BRIPI, MSH6, RAD15C.[18] Therefore NCCN recommends genetic screening for all ovarian cancers.

The risk of ovarian cancer with Breast Cancer Susceptibility Genes 1 (BRCA1) is about 44%, Breast Cancer Susceptibility Genes 2 (BRCA2) is about 17-20% and in Lynch syndrome 8-10%. These women have ovarian cancer at a younger age than the general population. Women with Lynch syndrome have non-serous epithelial ovarian tumours while the ones with BRCA mutation tend to have high grade serous tumors.

Indications for Genetic Testing

1. Women with family or personal history of breast, ovarian or colon cancer should be screened. A family history is considered essential to identify women with potential hereditary ovarian cancer (Familial Cancer Syndromes).
2. Personal history of breast cancer at <45 years (5-fold increase of ovarian cancer)
3. Personal history of triple negative breast cancer <60 years.
4. Two breast cancer primary tumours
5. Personal history of colon cancer
6. Family history of ovarian cancer, breast, colon cancer or male breast cancer, metastatic prostatic cancer and exocrine pancreatic cancer
7. The family or patient is known to have a hereditary cancer syndrome (eg. BRCA1, BRCA2, Lynch syndrome, or others)
8. Ashkenazi Jewish descent

Risk reducing Salpingo-Oophorectomy (rrSO)

In women with diagnosed genetic cancer syndromes rrSO decreases the risk of ovarian cancer by 80%. It is important to note that not all women with these mutations develop cancer and some of them might be subjected to unnecessary overtreatment.

The American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology recommend that rrSO should be done between the age 35-40 years when childbearing is complete. The age for rrSO may be younger based

on age of onset within the family. In BRCA2 carriers rrSO can be delayed to between 40-45 years as these cancers appear slightly later.

For women with a *BRCA1/2* pathogenic variant, it is recommended to perform risk-reducing bilateral salpingo-oophorectomy between age 35 and 40 for *BRCA1* carriers and between 40 and 45 for *BRCA2* carriers, when childbearing is complete, rather than screening.

Screening in Carriers not Undergoing rrSO

Ovarian cancer screening options recommended are: an annual pelvic examination, transvaginal ultrasound (TVUS), and cancer antigen 125 (CA 125) every 6 to 12 months, starting at age 30 to 35 or 5 to 10 years prior to the earliest age of first diagnosis of Lynch-associated cancer of any kind in the family.

The ultrasound is preferably performed on days 1 to 10 of menstrual cycle, while CA 125 is best assessed after day 5 of menstrual cycle. However, there is lack of high-quality data to confirm these recommendations, and patients may reasonably opt to avoid these screening procedures.

Screening studies on high risk women are largely limited to observational studies and have found that most cancers are detected in advanced stages.

However, United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS) reported that high risk women who were screened for 3.2 years by TVS and CA125 and adhered to the screening schedule were likely to be detected at earlier stages.

Conclusion

Ovarian cancer has a high mortality due to late diagnosis. However, in average risk women it is a low prevalence disease and screening in asymptomatic women is not recommended. No screening strategy has been shown to reduce mortality and all screening strategies are associated with a high false positive rate and a risk of harm from unnecessary intervention. In average risk women opportunistic salpingectomy may have a potential role in prevention of ovarian cancers.

High risk women can be identified by personal and family history of hereditary cancer syndromes. About 10-20% of ovarian cancers are caused due to hereditary causes. Genetic testing is recommended for all women with high grade ovarian cancer. Past, personal and family history of cancer is essential to identify high risk women who need to undergo genetic evaluation.

Those with hereditary cancer syndrome like BRCA1, BRCA2 and HNPCC will benefit from risk reducing salpingo-oophorectomy. Risk reducing salpingo-oophorectomy (rrSO) reduces risk by 80% in these women.

Screening may be offered to high risk women but there is no data to prove a reduction in morbidity and mortality in the population.

Suggested Readings

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Management of Postmenopausal Bleeding

Amita Suneja[1], Bhavya Prasad[2]
[1]Dir Professor & HOD, [2]Senior Resident, Department of Obstetrics & Gynaecology, UCMS & GTB Hospital, New Delhi

An episode of bleeding 12 months after the last menstrual period is considered as post-menopausal bleeding (PMB) and is encountered in 4-11% of postmenopausal women.

Patients with postmenopausal bleeding have a 10-15% risk of developing endometrial cancer. On the contrary, 80-90% patients of endometrial cancer present with abnormal bleeding. Thus, an expeditious approach is required for evaluation of such patients, to rule out precancerous and cancerous lesions of the endometrium. Yet other extra-uterine causes may be the reason for PMB arising from the vulva, vagina, cervix, fallopian tube. Bleeding may emerge from extra genital sites including urethra, bladder, rectum and bowel.

> Although the most common cause of PMB is atrophy of vagina and endometrium, prompt evaluation for endometrial cancer is justified in all postmenopausal women with abnormal uterine bleeding.

Clinical evaluation

Comprehensive history and examination should include:

- Duration of symptoms
- HRT use
- Recurrence of PMB
- Risk factors for endometrial pathology -diabetes, hypertension, obesity and family history of colon, uterine and ovarian cancer.

  The risk of endometrial cancer in the setting of postmenopausal bleeding increase with increasing age after menopause. Age more than 55 years, history of recurrent bleeding episodes, and bleeding volume exceeding 5 pads per day are significantly associated with endometrial cancer.

  Entire lower genital tract should be examined and Pap smear taken to rule out non-endometrial causes.

Trans-vaginal Ultrasonography (TVUS)

Trans-vaginal ultrasonography can be used as the first modality for the assessment of PMB. In postmenopausal women the mean endometrial thickness is much less compared to premenopausal women and the risk of having malignant pathology increases with increasing endometrial thickness (ET).

TVUS should be performed before attempting endometrial sampling as it may affect the appearance of the endometrium. If already attempted, TVUS should preferably be performed after two weeks for a reliable reporting of ET.

While reporting, note should be made of:

- Endometrial thickness (ET): measured as the maximum anterior and posterior thickness of the endometrial echo in the sagittal plane near the fundus. Several multicenter trials have confirmed that endometrial thickness of 4mm or less in postmenopausal women safely excludes endometrial cancer, as this cutoff has greater than 99% negative predictive value of endometrial cancer.
- Suspected polyps
- Uterine size
- Adnexal morphology
- Presence of fibroids
- Presence of free fluid

Persistent bleeding should prompt additional evaluation in the form of endometrial sampling.

Limitations: Reliable ET measurement may become difficult in patients with obesity, co-existing leiomyomas, adenomyosis or previous uterine surgeries. In case of fibroids, endometrial sampling with Pipelle may be attempted and further referred for hysteroscopy, if a definitive diagnosis is not made. In cases where the ET is not visualized in absence of fibroids, endometrial pathology (especially Type II endometrial cancer) may cause the endometrium to become isoechoic to myometrium and is an indication of endometrial sampling.

Endometrial fluid: fluid may be visualized between the endometrial layers in both symptomatic and asymptomatic women. With the presence of endometrial fluid, the ET is measured by subtracting the antero-posterior diameter of the fluid from the full thickness of the endometrial echo. Studies show that

presence of sonolucent fluid with the ET measuring < 3mm safely rules out malignancy. Contrarily, findings like ET being more than the threshold or if the fluid is echogenic, should prompt immediate further investigation, including histologic evaluation.

What should be done if thickened ET is found incidentally on TVUS in asymptomatic women?

These women do not require endometrial biopsy unless the ET >11mm. Also, presence of endometrial fluid is not an indication of biopsy in asymptomatic women.

Saline infusion sonography (SIS)

SIS appears superior to TVUS in identifying intra-uterine lesions, particularly delineation of endometrial polyps in postmenopausal women.

However, studies have shown that even though the feasibility of SIS is high, the procedure is better in premenopausal women as compared to postmenopausal and thus biopsy and hysteroscopy remain the diagnosis of choice.

Histologic Evaluation of Endometrium

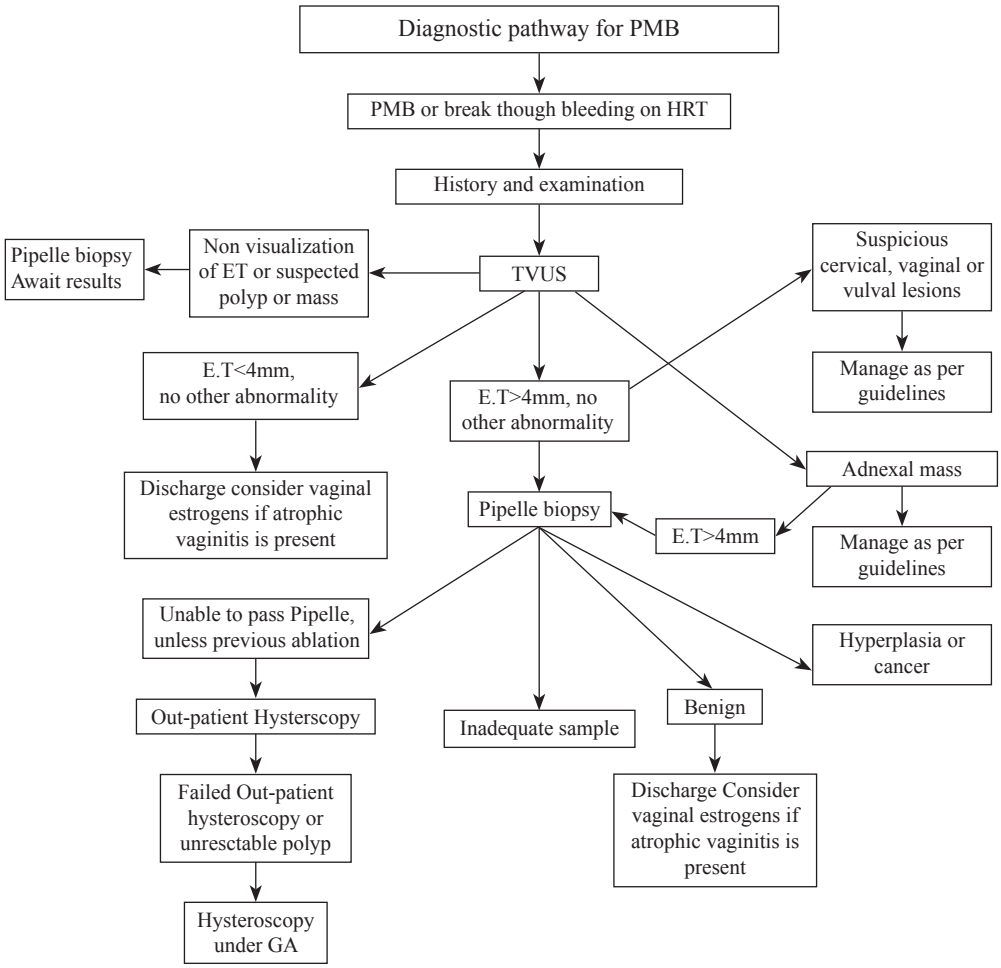
Indications for endometrial sampling:

- ET4mm
- ET not visualized
- Persistent PMB regardless of ET (no need for further assessment if the Pipelle report has been negative in the last 6 months)
- Suspicious polyp or mass on TVUS regardless of ET
- ET3mm with endometrial fluid in the endometrial cavity

Endometrial sampling devices: different meta-analysis have shown that both the Pipelle device and the Vabra device are highly sensitive techniques for the detection of endometrial cancer with the detection rates of 99.6% and 97.1% respectively.

Insufficient Sampling

The sample obtained thus may sometimes be inadequate and hinder histologic evaluation. In such cases the clinician may face the dilemma of further proceeding with more invasive procedures or to rely on



negative result. Studies have shown that the clinician may confidently reassure women with inadequate sample if the hysteroscopic and sonographic evidence support endometrial atrophy. So, it may be acceptable to reassure women and discharge them if they have insufficient sampling and ET <4, without subjecting them to hysteroscopy and curettage.

Hysteroscopy

It is always better to obtain the result of endometrial sampling, as negative result may obviate the need for hysteroscopy.

Indications for hysteroscopy include:

- Unable to pass Pipelle sampler
- Suspected polyp
- Inadequate visualization of the endometrium
- Recurrent PMB (defined as 2 visits to OPD with 2 benign Pipelle biopsy more than 6 months apart in the last 2 years

Studies have shown hysteroscopy to be a better than TVUS and endometrial biopsy for the evaluation of structural lesions. Hysteroscopy has both good diagnostic accuracy and patient acceptability when diagnosing polyps or leiomyomas. However, hysteroscopic visualization alone may not be accurate in identifying atypical hyperplasia and cancer and need backup in the form of antecedent or concurrent endometrial sampling by suction or sharp curettage.

> If endometrial polyp is suspected on TVUS, then Pipelle biopsy should be done at the first instance. Once malignancy is ruled out, woman can then be taken up for hysteroscopy

Hormone Replacement Therapy

The relative risk of developing endometrial cancer with unopposed estrogen is approximately 5 times compared to non-users, which declines with the addition of cyclic or continuous progestins. Studies show that women on continuous, combined estrogen-progestin regimens provide better protection against endometrial cancer, and thus annual TVUS and/or endometrial sampling may be justified in oestrogen users exposed intermittently to progestin treatment.

Endometrial assessment is required in scenarios of abnormal bleeding episodes:

- For sequential regimens: heavy or prolonged bleeding at the end of progesterone phase, or bleeding occurring at any time (break through bleeding).
- For continuous combined regimens: after the first 6 months of treatment or after amenorrhea has been established.

Tamoxifen and PMB

Tamoxifen with its weak estrogenic effect causes 3 to 6 times increase in the incidence of endometrial cancer. Most women on tamoxifen who develop endometrial cancer present with vaginal bleeding, and such patients should be promptly evaluated. Long-term tamoxifen users are associated with higher rate of mixed mesodermal tumors and sarcomas of the endometrium. Debate revolves around the surveillance of these women. Studies show that periodic investigations are not cost effective, and so PMB should be the main trigger for further investigations.

Transvaginal US endometrial thickness requiring biopsy in women with postmenopausal bleeding receiving hormone replacement therapy or tamoxifen has been suggested as >8 mm however, second school of thought suggests that cut off should be 4 or 5 mm, not 8 mm. Every case needs to be individualized & it's better to err on safer side.

High risk group: Hereditary Nonpolyposis Colonic Cancer

Women with HNPCC (Lynch syndrome) are found to have increased risk of endometrial and ovarian cancer (up to 60% and 24% respectively). Women who have completed family and carry an MLH1, MSH2, EPCAM, PMS2 or MSH6 mutation may consider the option of total abdominal hysterectomy and/or bilateral salpingo-oophorectomy for risk reduction. No routine screening methods have yet been identified for the gynecologic cancer in women with these pathologic genetic variations. Yearly endometrial sampling may be offered but benefits are not certain. Routine TVUS and CA -125 are not recommended due to their poor sensitivity and specificity, although these tests may be helpful in some patients.

Delayed Menopause

Natural menopause age of Indian women is 46.2 ± 4.9 years. When it occurs 2 SD later than the average age of menopause (55 years in Indian population) it is labelled as delayed or late menopause. Late menopause is associated with better quality of life

however, there is increased risk of breast, ovarian and endometrial malignancy. There is no consensus on the surveillance policy in this group however, Women should undergo complete evaluation by Pap smear, annual mammogram, TVS and endometrial sampling if indicated.

Suggested Reading

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Journal Scan

Y M Mala
Professor, Department of Obstetrics & Gynaecology, Maulana Azad Medical College, New Delhi

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Inhibition of midkine by metformin can contribute to its anticancer effects in malignancies: A proposal mechanism of action of metformin in context of endometrial cancer prevention and therapy

Karadeniz Z, Aynacıoglu AS, Bilir A, Tuna MY

Metformin is widely used in the treatment of type II diabetes mellitus (T2DM) & has been the focus of interest as a potential therapeutic agent for certain types of malignancies, including gynecological cancers [i.e. endometrial cancer (EC)]. Although the exact mechanism behind the potential anticancer activity of metformin is still not completely understood, certain studies have suggested that different effects on cell functions, such as inhibition of cell migration, apoptosis and tumor cell proliferation, are involved in its preventive and therapeutic effects in certain types of malignancies, including EC. In contrast, midkine (MK), a heparin-binding growth factor and cytokine, which induces carcinogenesis and chemoresistance, promotes the development and progression of many malignant tumours by increasing diverse cell functions such as cell proliferation, cell survival and anti-apoptotic activities via mainly the activation of phosphatidyl inositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways. The same pathways are also subject to certain therapeutic effects of metformin. MK and metformin appear to have opposite effects in various biological processes such as apoptosis, cell proliferation, cell survival, cell migration, and angiogenesis. It seems likely that almost all the pathways and cell functions, which play important roles in malignancies, are inhibited by metformin and activated by MK. Given the opposite relationship between the actions of metformin and MK, metformin may act like a novel MK inhibitor in some malignancies.

Conclusion

Metformin which inhibits all the pathways and cell functions that are activated by MK, may be a promising candidate agent for the inhibition of MK. Therefore, we propose that metformin may functionate like a novel MKI, with important therapeutic implications for EC and other various cancers.

Comments

The current effective treatment strategies of EC are limited, it is urgent to develop novel agents for improving the outcomes of EC. MK is involved in the development and progression of many human cancers, including EC. Therefore, clarifying the possible relationship between metformin and MK may provide improvements in cancer therapy and possibly other various diseases in which MK is over expressed. Endometrial cancer is the most common gynecological cancer worldwide with rising incidence. It is related to obesity and a rise in metabolic syndrome, which is the risk factor for the development of hyperestrogenic and hyperinsulinemic states. Metformin, a biguanide drug can be a promising drug for cancer prevention and also may play a role in fertility sparing treatment of endometrial cancer.

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Risk-reducing early salpingectomy and delayed oophorectomy as a two-staged alternative for primary prevention of ovarian cancer in women at increased risk

F Gaba, J Piek, U Menon, R Manchandaa

Introduction - Ovarian cancer (OC) is one of the leading cause of death from gynecological malignancies. High-penetrance (e.g. BRCA1/BRCA2) and moderate penetrance (e.g. RAD51C/RAD51D/BRIP1) gene mutations account for most of the known hereditary risk of OC. At least 10% of women with epithelial OC

carry these germline mutations. BRCA1/BRCA2 carriers have a 17–44% risk of OC and 65–72% risk of breast cancer (BC), whereas RAD51C/ RAD51D/BRIP1 carriers have a 6–11% risk of OC. Primary surgical prevention in the form of risk-reducing salpingo-oophorectomy (RRSO) remains the most effective option and gold standard for OC risk reduction. The role of RRSO for primary surgical prevention has expanded to include not just BRCA1/BRCA2 carriers but also women at intermediate risk (≥4–5% lifetime-risk of OC). Risk-reducing salpingo-oophorectomy reduces OC risk by 80–96%. Premenopausal RRSO leads to premature surgical menopause, which has detrimental long-term health consequences. A 3.03% absolute increased risk of cardiovascular mortality has been reported with premenopausal oophorectomy without HRT. Following initial observations in BRCA mutation carriers, there is now broad acceptance of the role of the fallopian tube in the etiopathogenesis of epithelial OC.

The acceptance of a central role for the fallopian tube in OC etiopathogenesis, coupled with the detrimental health sequelae of premature menopause, has led to the attractive proposal of a two-step alternative OC surgical prevention strategy in premenopausal women at increased (high or intermediate) OC risk who have completed their family but decline or wish to delay RRSO. It involves early salpingectomy (ES) as the first step, followed by delayed oophorectomy (DO) after menopause. RRESDO has the advantage of providing a level of risk reduction whilst conserving ovarian function and avoiding negative side effects or health consequences of premature menopause.

Conclusion

The main reason for undergoing RRESDO reported by women at high risk of OC and by health professionals is the ability to obtain some OC risk reduction whilst avoiding the detrimental consequences of early menopause.

Comments

Risk reducing early salpingectomy and delayed oopherectomy (RRESDO) can be an alternative for women who have completed their family and prefer to decline or delay premenopausal oophorectomy. Counselling should be performed regarding the advantages and disadvantages of both and an informed consent should be taken from the patient.

Clinical Proceedings of AOGD Clinical Meeting held at UCMS & GTB Hospital, New Delhi on 28th February, 2020

Myocutaneous Flap to fill the Gap in Vulval Cancer: A Case Report

Rashmi, Sunita S, Amita S, Abha S, Kiran G, Pankaj G, Dhirender S

Vulval cancer being a rare gynecological malignancy, many dilemmas and controversies remain during management of such cases. Radical surgeries are associated with severe post operative morbidity due to wound related complications increasing the hospital stay and delaying adjuvant therapies. A case is discussed where wound complications were avoided with use of flaps.

Case Report: A 58 year old post menopausal lady presented with a large ulcerative growth on right side of vulva and palpable right inguinal lymph node. After biopsy it was diagnosed to be moderately differentiated Squamous cell carcinoma with positive lymphnode. Triple Incision Modified radical vulvectomy with bilateral inguino-femoral lymphadenectomy with Sartorius transposition was done. There was no post operative complication. On histopathology it was Keratinizing Squamous cell carcinoma vulva Grade 2, with tumour free margin of 7.8mm, and single lymph node metastasis of ≥5mm. She was advised adjuvant radiotherapy, but was lost to follow up.

Five month later she presented again with an ulcerative lesion in the right groin. It was diagnosed to be isolated recurrence of Ca vulva. She was managed with wide excision of the lesion with reconstruction of groin wound with Vertical Rectus AbdominusMyocutaneous (VRAM) Flap. Grafted wound and the donor site, both healed well without any complications. Patient was referred for adjuvant radiotherapy. Histopathology confirmed it to be Skin bridge recurrence.

Discussion: Skin bridge recurrences are rare and occur in modified radical vulvectomies with separate groin incisions. Surgical excision of recurrences leave large wounds which need reconstructive surgeries for management. VRAM Flap is a very versatile flap which can be used for reconstruction in genital malignancies.

Purpura Fulminans-A dreaded manifestation of sepsis

Saloni Kamboj, Sandhya Jain, Kanika Kalra, Shalini Rajaram, Seema Prakash, Bindiya Gupta, Anshuja Singla, Bhanupriya

Purpura Fulminans (PF) is an acute, often fatal, rare thrombotic disorder which manifests as blood spots, bruising and discolouration of the skin resulting from coagulation in small blood vessels within the skin and rapidly leads to skin necrosis and disseminated intravascular coagulation. Four cases of PF have come to GTB Hospital in last 4 months with almost similar clinical profile, sepsis being the most common cause.

Case Report: A 30 years old P3L3 presented to Gynae emergency on post-natal day 8 of an uneventful vaginal delivery in a peripheral hospital. She had chief complaints of high grade fever, multiple episode loose stools and cough with expectoration for last three days. She also gave a history of bluish discoloration of right ankle which was rapidly progressive and involved all limbs, abdomen and perineum. She had no significant past history. On examination, she was disoriented and febrile; her blood pressure was 94/70 mm Hg, pulse rate of 120 per minute and respiratory rate was 24 per minute. She was icteric, however no pallor or edema was observed. Chest had bilateral coarse crepts. There were purpural patches present on all the four limbs. Investigations revealed a high TLC, low Platelet, deranged KFT and LFT. Coagulation profile was abnormal and FDP and D-Dimer were markedly elevated. On running a sepsis screen on her, E-coli was found to be present in HVS culture. A diagnosis of puerperal sepsis with multiple organ dysfunction syndrome and Purpura Fulminans was made. A multi-disciplinary approach was followed in consultation with Dermatology, Surgery, Burns and Plastics department. She was managed on broad spectrum intra- venous anti-biotics, analgesics. Blood products were given along with supportive treatment for end organ damage. She recovered but however developed dry gangrene of both distal feet and one digit of her left hand for which she chose auto-amputation.

A rare and deceptive case of pheochromocytoma in pregnancy: A case report

Chaudhary S, Singh S, Singh A, Guleria K, Raizada N, Gupta S

Pheochromocytoma in pregnancy is a rare entity with prevalence of 1 in 54,000 pregnancies. Undiagnosed and untreated pheochromocytoma can lead to life threatening complications for both mother and fetus. It is notorious to masquerade severe preeclampsia.

Case report: A 19yr old primigravida presented to gynae casualty at 29wks gestation with severe headaches, blurring of vision, bleeding per-vaginum with BP of 200/130mmHg. Provisional diagnosis of severe preeclampsia with impending eclampsia and abruptioplacentae was made and patient started on anti eclamptic and antihypertensive treatment with simultaneous induction of labour. An Em LSCS was done due to failed induction. She continued to have persistent HTN despite 3 antihypertensives and developed cardiomyopathy on post day 9. USG KUB done subsequently clinched the diagnosis of adrenal tumor (pheochromocytoma) which was confirmed on CECT. Patient underwent adrenelectomy after preoperative optimisation. She became normotensive and her symptoms improved dramatically in post-operative period and is currently on close follow up.

Timely diagnosis and management of pheochromocytoma in pregnancy, though very challenging, can make a remarkable difference to maternal and fetal morbidity and mortality.

Stillbirths at GTBH: An overview

Richa Aggarwal, Vandana Mohan, Amita Suneja, Shalini Rajaram, Kiran Guleria

Background: Stillbirth account for 2.6 million deaths annually, making this a critical public health problem. India with 5,92,100 stillbirths accounts for 22.6% of the global burden.

Objective: To determine the stillbirth rate at Guru Teg Bahadur Hospital, Delhi, to analyze the epidemiological profile of cases and the etiological factors of stillbirths.

Materials and method: As a part of WHO- SEARO Stillbirth project, records of the women with stillbirths between June 2017 and December 2019 were retrieved and analyzed.

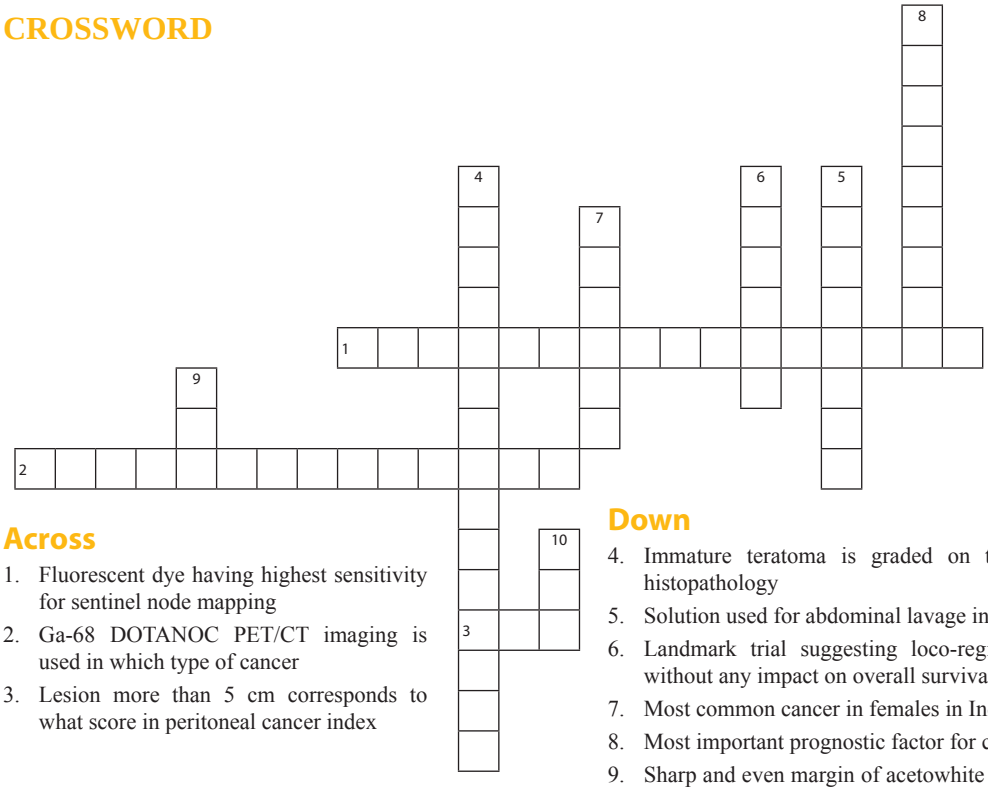
Results: Out of the total 50,461 deliveries, 1,824 were stillborn, a stillbirth rate of **36.15 per 1000 births**. 48% of these were referred as stillbirth, 29% were unbooked and rest 23% registered at GTBH. Most of the women belonged to age group of 21-30 years.54% were illiterate. Most of the women were multiparous. 20.6% of the women had history of previous abortions and 6.5% had previous stillbirths. About 43.3% of them weighed less than 1.5 kg. Over half of the stillbirths were macerated (58.3%). The cause of stillbirth remained unexplained in 528 cases (29%). The major causes were hypertension (23%), fetal growth restriction (12%), abruption (10%) and labour complications (9%). Hypertension, labour complications and unexplained causes were more common among the unbooked cases. Birth defects were present in 63 cases (3.4%), with most common being CNS anomalies.

Conclusion: Stillbirth rate is high at GTBH, mainly due to referred cases. Major causes amenable to interventions are hypertension, fetal growth restriction, infections and labour complications. Better antenatal and intranatal care is required to reduce the stillbirth rate.

The Maze of Knowledge

Sarita Sharma[1], Bindiya Gupta[2]
[1]M.Ch. Gynae Oncology, All India Institute of Medical Sciences, New Delhi, [2]Associate Professor, UCMS and GTB Hospital, New Delhi

CROSSWORD



Across

1. Fluorescent dye having highest sensitivity for sentinel node mapping
2. Ga-68 DOTANOC PET/CT imaging is used in which type of cancer
3. Lesion more than 5 cm corresponds to what score in peritoneal cancer index

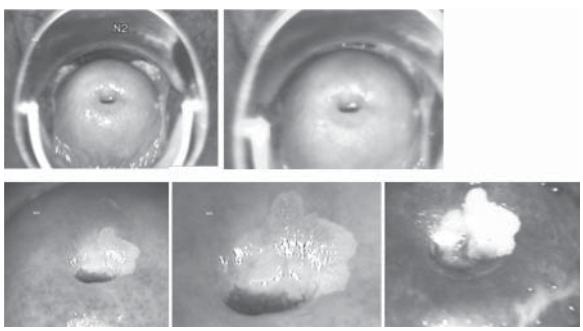
Down

4. Immature teratoma is graded on the basis of what elements on histopathology
5. Solution used for abdominal lavage in Pseudomyxoma peritonei
6. Landmark trial suggesting loco-regional control from adjuvant RT without any impact on overall survival in carcinoma endometrium
7. Most common cancer in females in India
8. Most important prognostic factor for carcinoma cervix
9. Sharp and even margin of acetowhite lesion on colposcopy corresponds to swede score
10. Commonest gene mutation in high grade serous cancer

Pictorial Quiz

Bindiya Gupta[1], Shalini Rajaram[2]
[1]Associate Professor, [2]Director Professor, UCMS and GTB Hospital, New Delhi

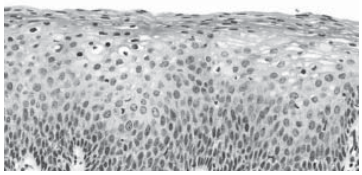
Case 1



Q1. Comment on transformation zone.

Q2. Calculate Swede score.

Case 2



Q1. What is the HPE diagnosis?

Q2. What is the appropriate treatment and follow up?

Q3. Patient gets pregnant after 7 months of treatment, suggest the follow up in pregnancy?

Watsapp your answers to **9211656757.**
Names of first three correct entries will be mentioned in the next issue

Refer page 32 for previous answer key.

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A scientific solution for all vaginal problems

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Syrup — Iron + Zinc + Vit. B complex

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Tablet — Norethisterone - 5

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