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Preventive Oncology

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President's Address

Dr. Rishma Dhillon Pai
President FOGSI

Greetings to all !

I am really happy to see that the new newsletter of ICOG is being released. This issue on 'Preventive Oncology' is an excellent update on the new and important aspects of prevention and early diagnosis of cancer.

ICOG the academic wing of FOGSI, under the leadership of Dr. Mala Arora and with the help and support of Dr. S. Shanthakumari and Dr. Sushma Reddy, is working very actively towards promoting all types of academic activities including workshops, articles and net based learning.

I congratulate team ICOG for their interest and efforts towards excellence in the field of education in obstetrics and gynaecology.

Best wishes!

Chairperson's Address

Dr. Mala Arora
Chairperson ICOG
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Esteemed Fellows & members of ICOG

Prevention of gynaecological cancers will improve women's health in the post reproductive years. Fortunately most gynecological cancers are amenable to screening and have curative treatment options if detected early.

Cervical cancer screening is one of the success stories on this century. HPV vaccination of adolescent girls, HPV screening coupled with Liquid based cytological examination and colposcopy allow treatment of cervical cancer in early stages by local ablative techniques. Our challange is to take this to the high risk group i.e those with multiple sexual partners.

Ovarian cancer being silent by nature requires ultrasound screening. However it is only beneficial in the high risk group.

Endometrial cancer can be diagnosed by pipelle biopsy and being hormone dependent can be managed by progesterone therapy in its early stages.

Breast cancer though not the domain of the gynecologist deserves special mention being the commonest cancer with a rising incidence. We as gynecologist need to be teaching women Self breast examination and should perform a Clinical Breast exam at every opportunity. In the high risk group, those with leiomyoma, endometrial hyperplasia and a positive family history we need to perform screening with BRCA gene studies and mammographies between the age of 45-60 years.

So let us give our best contribution to prevent and timely treat gynecological cancers in our patients.

Secretary's Message

Dr. S. Shantha Kumari
Secretary ICOG

Dear Friends

Cancer as a disease has been a cause of significant morbidity and mortality that has been well recognised in the past century. However, the optimistic view from the medical community is that in many aspects, cancer is a preventable disease. This prevention can be done at primary. Secondary and tertiary levels with effective interventions in the potentially "at-risk" groups. Effective risk stratification methods have now been developed to analyse screening and early detection of various gynecological cancers as this is the key to successful treatment of cancer. The role of cytology based screening changed the outlook for cervical cancer from a primary killer to a manageable entity. There have been paradigm shifts in the understanding of surgical preventive methods for women with genetic or familial predisposition to ovarian and breast malignancies.

Apart from effective lifestyle modification to alter the risks of gynecological malignancy, the past few decades have witnesses the roller coaster ride of vaccines intended at preventing cervical cancers. The burden of the disease on the health care system can be drastically reduced if effective prevention methods can alter the incidence and morbidity from cancer.

This issue of the newsletter has addressed all these issues and intends to bring the readers up to date with preventive oncology in Gynecology.

Happy reading!

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Greetings to All!

I am grateful to all of you for appreciating our e-newsletter 'ICOG Campus'. Your feedback gives us direction and helps us to deliver our best. Our next step in direction of female healthcare is **'Preventive Oncology'**.

Cancer is the most dreadful of all the illnesses and preventive oncology includes any measure that is taken to prevent development or progression of malignant process. Cancer prevention occurs at 3 stages: Primary prevention: Before the development of disease by modifying or averting the risk factors; Secondary prevention: Before onset of the clinical symptoms or signs and tertiary prevention: After development of disease by decreasing complications and recurrence of the disease.

The issue stresses on the primary and secondary preventive aspects of cancer ovary and cervix, besides discussing recent guidelines for management of endometrial hyperplasia and an interesting journal scan on latest controversies of HPV vaccine. There is a refreshing segment of brainteasers at the end as always.

I acknowledge the two guest editors for this issue, Dr. Sadhna Gupta and Dr. Sarita Agrawal who are senior members of ICOG governing council.

"Success is the sum of small efforts repeated day in and day out"

-Robert Collier

I would like to wish happy reading to all of you.

REVIEW ARTICLE

Gonadal Health and Screening

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INTRODUCTION

The formation of primordial follicles in female fetuses starts even before their birth; however, it is only at puberty that maturation and reproductive functions of ovaries start. The main functions of the female gonads, i.e., ovaries, are production of ova for reproduction and as primary site of production of estrogen and other related hormones. The problems associated with female gonadal health include alteration in its ovulatory or endocrinological function (PCOD or Premature Ovarian failure), dysgenetic gonads, infections (oopheritis) or the development of ovarian tumors (Non-neoplastic or neoplastic. Despite this wide range of deviations in the health of female gonads, the main concern is the risk of developing a malignant lesion.

MALIGNANT OVARIAN NEOPLASMS: OVARIAN CANCER

Malignant neoplasms of ovary are cause of more deaths than any other female genital tract cancer. Worldwide in 2008, ovarian cancer (OC) was the 7th most common cancer in women, and incidence rates are higher in developed countries more than developing.[1,2] They are in fact a heterogeneous group of malignant tumors that may arise from germ cells, stromal tissue, or epithelial tissue within the ovary. The majority of these malignant lesions (85–90%) are epithelial which are also the most lethal ones. Detection of these epithelial carcinomas has been the focus of screening programs.

WHY IS SCREENING FOR OVARIAN CANCER NECESSARY?

Over two-third of cases of OC are diagnosed when the disease has progressed an advanced stage (Stage III/IV) and involved the peritoneal cavity or other organs. Due to this reason, it continues to claim the lives of a significant proportion of women who are diagnosed with this condition. The reason for this late diagnosis is that symptoms associated with OC are typically nonspecific, and the association is often not recognized until the disease has advanced. The overall 5 years survival rates in this stage are below 40% which is in marked contrast to the 90% 5 years survival in women diagnosed in stage I.

There is therefore need for a screening strategy that can achieve detection sufficiently early in the natural history of OC to reduce mortality and the burden of comorbidity associated with disease treatment in advanced stage.

CHALLENGES IN DEVELOPING STRATEGIES FOR OVARIAN CANCER SCREENING

Firstly, it OC does not have a well- defined precursor lesion which can be diagnosed with readily available diagnostic modalities. So, though screening may be able to detect the disease in early stages it cannot prevent the disease.

Secondly, definitive diagnosis of OC requires surgical excision of the ovary and Fallopian tube. OC has a lifetime risk of 1.38%.[3] For a disease with such low prevalence a screening test with a lower positive predictive value (PPV) will result in more surgeries required per case of cancer to be confirmed. Therefore, a cost-effective screening strategy would require a PPV of minimum 10%, which in turn means a sensitivity of at least 75% and a specificity of more than 99.6%.

Another challenge is developing a screening test that is not only effective, but also reasonably inexpensive as a large number of women need to be screened to detect a single OC.

SCREENING FOR OVARIAN CANCER IN GENERAL POPULATION

Advances in transvaginal sonography (TVS) have helped to detect changes in size and architecture that might precede the development of symptoms. Different morphologic indices have been developed over time in which measurement of ovarian volume, cyst-wall characteristics, presence of septae, and its thickness, presence of solid areas, etc. are used to calculate a risk score for development of malignant disease (morphological index). The sensitivity and specificity of these indices varies between 70–85 and 90–100%, respectively, giving a very low PPV in a low prevalence population. Transvaginal color- flow Doppler to assess the vascularity of the ovarian vessels has not proved useful either. Multimodal screening involving CA-125 and TVS has been experimented within the past but with limited success.

Serum CA-125 and TVS are being evaluated in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOC) in which use of OC algorithms to interpret CA-125 is being utilized for further assessment of the risk. Preliminary results are encouraging; however, the final results are yet to be published.

SCREENING IN HIGH-RISK WOMEN

There are various risk factors for OCs both environmental and genetic; however, positive family history is the most important one. Having a single affected first-degree relative is associated with a 2- to 3-fold increased risk of disease. It is estimated that approximately 22% of the risk of ovarian cancer (ROC) is attributable to heritable factors.

The two important syndromes responsible for most inherited cancers in gynecologic organs are hereditary breast and ovarian cancer syndrome, including site-specific OC syndrome, and hereditary nonpolyposis colon cancer syndrome, also named Lynch syndrome. Other mutations which have been identified in families of OCs are RAD51c, RAD51D, BRIP1, etc.

Retrospective and prospective cohort studies of annual surveillance of such women at high risk for OC using serum CA-125 and TVS, have reported low PPVs, limited sensitivity with a high number of false-positive findings and inability to detect early-stage OC.[4] Bilateral salpingo-oophorectomy appears to be the most effective approach to decrease the ROC and thereby reduce mortality in high- risk women.

SERUM CA-125 AS TUMOR MARKER AND RISK OF OVARIAN CANCER ALGORITHM

Measurement of serum CA-125 values in an individual patient over time (rather than a single measurement) appears to improve the estimation of a patient's ROC. A woman with a low baseline followed by a change point where serum CA-125 levels increase significantly higher than the baseline may be detected earlier than when a fixed reference level of 35 U/mL is applied. Conversely, a woman with high yet steady serum CA-125 levels would yield an appropriately negative test result, in contrast to a fixed reference level.

This hypothesis was evaluated in a retrospective study which concluded that the use of an algorithm to assess the trend of serum CA-125 levels had greater sensitivity in detection of cancer in preclinical stages.[5] This algorithm, called ROC, was confirmed to have a reasonably high PPV (19%) in a subsequent prospective pilot study involving more than 13,000 post- menopausal women. Applying formal statistical modeling to serial serum CA-125 data results in a hierarchal "change point" and "flat point" model describing the behavior of serum CA-125 over time in former and latter cases, respectively. This risk calculation is implemented in the form of an algorithm in screening programs by prescribing decisions for each level of risk. Within this algorithm defined as the risk of ovarian cancer algorithm (ROCA), by comparing the change profile of the test samples to these known patterns in health and disease, the algorithm predicts the ROC, which is classed as "normal", "intermediate", or "elevated." "Normal" indicates routine annual screening, "intermediate" indicates a low-level screening intervention, and "elevated" indicates a high-level intervention.

In average-risk postmenopausal population, where serum CA-125 is tested annually, elevated ROCA triggers referral to a TVS directly whereas an intermediate ROCA risk triggers a serum CA-125 test in 3 months, and the risk is recalculated and triaged accordingly. In women at high risk due to a multiple family history of OC or breast cancers, an intermediate ROCA risk triggers referral to TVS, whereas an elevated ROCA risk results in a referral for TVS and a consult from a gynecologist.

The first ROCA trial (1995-2001) screened 14,000 postmenopausal normal provided justification for funding and conducting the next trial.[6]

MAJOR OVARIAN CANCER SCREENING TRIALS

In June 2011, the results of the ovarian arm of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial were published.[7] This trial used a fixed serum CA-125 level of 35 U/L or greater to define abnormality. These results demonstrated no benefit of screening on OC mortality; the overall ratio of surgeries to screen detected cancers was 19.5: 1 and 72% of the screen detected cancers were at late stage.

Retrospective analysis of data from the same study has also shown that longitudinal algorithm and velocity of change of serum CA-125 may well correlate with risk of developing OC.[8]

In the UKCTOCS trial use of algorithm ROCA to interpret CA-125was done, followed by well-defined, centrally coordinated management of screen-detected abnormalities with protocols for intervention based on screening findings. Data from prevalence screen shows that careful monitoring of serum CA-125 levels and ROCA can detect the disease with sufficient sensitivity and specificity (89.4 and 99.8%).[9]

OTHER BIOMARKERS

Overall more than 200 biomarkers are differentially expressed in women with OC compared to healthy volunteers. The most robust of these is human epididymal antigen 4 (HE4). However, none of these has been shown to contribute to the power of serum CA-125 alone though serum HE4 has been shown to complement it in early-stage ovarian carcinomas and in distinguishing malignant from benign tumors.[10]

A retrospective study evaluated 7 proteomic biomarkers (apolipoprotein A1, truncated transthyretin, transferrin, hepcidin, beta-2 microglobulin, connective- tissue activating protein III, and inter-alpha-trypsin inhibitor heavy-chain) in addition to CA-125. It came to the conclusion that the addition of the 7 protein biomarkers to CA-125 did not improve the sensitivity beyond the use of CA-125 levels alone.[11] Their role is yet to be evaluated prospectively in large population-based studies.

CURRENT STATUS OF OVARIAN CANCER SCREENING

General Population:

Recommendations from various societies for general population is that women, especially in premenopausal age, should not be screened for epithelial ovarian cancer (EOC) (Table 1). Presently, there are no screening studies for non-EOC tumors.

Familial Ovarian Cancers

Family history remains the backbone of risk calculation to determine the appropriateness of gene testing and estimate the probability of an inherited susceptibility. The diagnosis of hereditary cancer predisposition often has great predictive value for family members. Generally, it involves first screening for the culprit mutation in the index case and thereafter organ-directed screening for related cancers in screen positive women.

Breast Ovarian cancer syndrome

About 7–18% of unselected cases of carcinoma ovary are related to BRCA1/ BRCA2 mutations. Testing for mutations in individuals with suspected hereditary breast cancer and OC will help in early diagnosis and treatment of other related cancers by appropriate screening in patients who are actually at risk and also offer preventive measures in relatives by screening for the respective mutations and, if found positive for the mutation, then screening for related breast cancer and OCs. However, if genetic testing is unavailable, not affordable or declined, cancer-risk evaluation solely on the basis of the family history is also possible. The following risk factors make an individual suspect for hereditary breast cancer or OC:

- Diagnosed with both breast cancer and OC
- Diagnosed with OC and has a close relative with OC or early-onset breast cancer
- Ashkenazi Jewish origin and diagnosed with either ovarian or early-onset breast cancer
- Bilateral breast cancer, one before age 45 years
- A male patient with breast cancer
- Diagnosed with "triple negative, basal-like" breast cancer phenotype.

Genetic test outperforms other risk estimate and is carried out in peripheral blood sample on DNA extracted from leukocyte nuclei.

Current recommendation: Screening should be started after 35 years of age. Screening 4–6 monthly with serum CA-125 followed by TVS evaluation yearly or when serum CA-125 is elevated is recommended at present.

Hereditary Nonpolyposis Colon Cancer

The National Cancer Institute published its revised recommendations in 2004 for identification of individuals who should receive genetic testing for Lynch syndrome. The recommendations (revised Bethesda guidelines) are as follows:

- Colorectal carcinoma (CRC) diagnosed in a patient less than 50 years old.
- Presence of synchronous or metachronous CRC or other Lynch syndrome- associated tumors, regardless of age
- CRC with high microsatellite instability histology diagnosed in a patient less than 60-year-old
- CRC diagnosed in one or more first-degree relatives with a Lynch syndrome- associated tumor, with one of the cancers being diagnosed at less than 50 years of age
- CRC diagnosed in two or more first-degree or second-degree relatives with Lynch syndrome-associated tumors, regardless of age.

Immunohistochemical staining for the three mismatch repair proteins in the tumor material of suspected cases can be used as a screening test with further confirmatory genetic testing depending on positivity of screening test.

Table 1: Recommendations for Ovarian Cancer Screening by Different Groups

Professional group	Recommendations
US Preventive Services Task Force[12]	Does not recommend routine screening
American Cancer Society[13]	Does not recommend routine screening; possible screening for women with a family history of OC though the benefit of this is not certain
American College of Obstetricians and Gynaecologists[14]	Does not recommend routine screening; suggests evaluation of signs and symptoms of OC
National Comprehensive Cancer Network[15]	Does not recommend routine screening; recommends screening of high-risk women (i.e., those with either a family history of OC or breast cancer or a documented *BRCA* mutation) with transvaginal ultrasonography and CA-125 measurements every 6 months, starting at the age of 35 years, or 5–10 years before the earliest age at diagnosis of OC in relatives

(OC: Ovarian cancer)

CONCLUSION

The search is still on for a cost-effective screening modality for OC. Though the results of UKCTOCS and other trials is reassuring but the final answer will be given only when their results are published. Women at risk of hereditary OCs should be offered some form of surveillance for timely detection of disease.

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The woods are lovely, dark and deep, But I have promises to keep,
And miles to go before I sleep

- Robert Frost

Cervical Cancer Screening - in a Nutshell

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INTRODUCTION

Cervical cancer is the most common female genital cancer in our country but in developed nations like the United States, it ranks at third position because of effective screening programs. Worldwide incidence of cervical cancer is approximately 5,10,000 new cases and 2,88,000 deaths per year. In India, approximately 1,32,000 new cases are diagnosed and 74,000 deaths occur due to cervical cancer. This accounts to nearly one third of the global cervical cancer deaths. Indian women face a 2.5% cumulative lifetime risk and 1.4% cumulative death risk from cervical cancer. At any given time, about 6.6% of women in the general population are estimated to harbor cervical HPV infection. HPV serotypes 16 and 18 account for nearly 76.7% of cervical cancer in India.

Cervical cancer is considered a preventable disease because of its the special characteristics like an identified causative agent (HPV); the prevention available (HPV vaccine); a long pre-invasive state (CIN); effective screening methods (cytology, VIA, HPV DNA); diagnostic methods (colposcopy, biopsy) and treatment options (cryotherapy, LEEP) for the pre-invasive lesions. Screening for early detection of preinvasive disease is a cost-effective measure to reduce the morbidity & mortality associated with cervical cancer as this disease fulfills all the components of Wilson and Jungner classic screening criteria given below:

1. It is an important health problem.
2. There is an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment are available.
4. There is a recognizable latent or early symptomatic stage.
5. There is a suitable test or examination.
6. The test is acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, has been adequately understood.
8. There is an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) is economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding is a continuing process and not a "once and for all" project.

CERVICAL CANCER SCREENING TOOLS

Some screening tests for cervical cancer look at dysplastic changes in epithelial cells (Cervical Cytology), others at morphological changes in cervix due to CIN (VIA, VILI) or at the causative agent, the Human Papilloma Virus DNA (HPV DNA). The Cervical Cytology can be done by Pap Smear or Liquid based Cytology (LBC). Visual Inspection of cervix is done with Acetic acid (VIA) and Lugol's iodine (VILI). HPV DNA can be detected by various techniques like the PCR, hybrid capture etc.

CERVICAL CYTOLOGY

Exfoliative cervical cytology (Pap smear) test has been in place for cervical cancer screening since 1945. This led to a drastic fall in mortality in USA from 14/100,000 in 1940 to 4/100,000 in 2000.

A wooden (Ayre's) spatula is used to take sample from the cervix, a smear is prepared on a glass slide and fixed in 95% alcohol (Figure 1). Sensitivity of Pap test in detecting CIN 2 or CIN 3 ranges from 47% to 62% and the specificity ranges from 65% to 95%. Errors of sampling, fixation, interpretation or follow up may be responsible for missed cases.

Bethesda System is used for reporting the results of Pap smear. It has incorporated the cytopathologic effects of HPV infection (koliocytosis), with mild dysplasia or CINI into a category called Low Grade Squamous Intraepithelial lesions (LSIL). More significant lesions including moderate & severe dysplasia are reported as High Grade Squamous Intraepithelial lesion (HSIL).

LIQUID BASED CYTOLOGY (LBC)-

LBC reduces 70% -90% the rate of unsatisfactory samples encountered with conventional cytology (pap smear). A plastic broom is used to take the cervical sample. Cells are dissolved in liquid medium (Figure

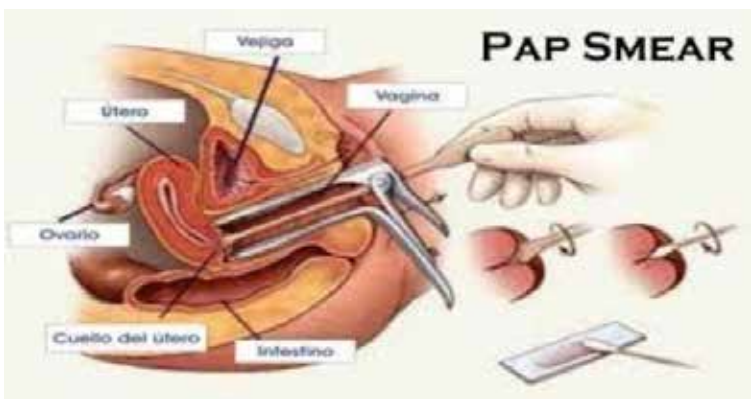

Fig. 1: Pap smear using Ayre's spatula

Fig. 2: Steps of Liquid Based Cytology

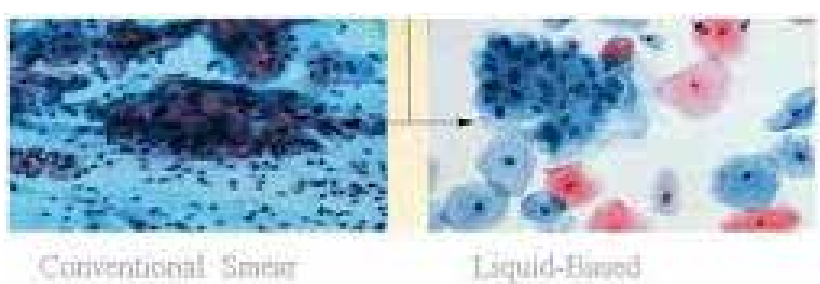

Fig. 3: Difference between a conventional and Liquid-based smear

2). The LBC machine automatically provides a uniform, thin layer of cervical cells on a glass slide after removing the blood mucus and debris. Thus, LBC gives a higher yield of cells and lower incidence of unsatisfactory smears.

VIA & VILI -

These methods detect pre-invasive lesions on the basis of morphological changes developing on the cervix. Both these methods are proven to be cost-effective in low resource setting and for mass screening. Studies done by JHPIEGO (1999) and Cronje et al (2003) found that the diagnostic efficacy is comparable to colposcopy.

Visual Inspection with Acetic acid (VIA): Visual inspection with acetic acid involves naked eye inspection of the cervix in bright light. After removing any vaginal discharge; 3-5 % of acetic acid is applied on the cervix for one minute using a cotton swab stick. Cervix is then re-examined to look for any acetowhite areas. Presence of an acetowhite area indicates a VIA positive test (Figures 4 & 5).

An acetowhite area is an opaque white patch that develops due to difference in precancerous cell structure, rate of absorption and protein coagulation after application of acetic acid. The reversible coagulation of intracellular proteins (nuclear proteins & cytokeratins), resulting in noticeable opacity & a decrease in the reddish hue imparted by sub-epithelial vasculature produces acetowhite areas. The cervical tissue with intraepithelial neoplasia (CIN) undergoes maximal coagulation due to higher content of nuclear protein. Larger, thicker, and more opaque lesions with a clear margin suggest more severe disease.

Aceto-whitening is not specific to cervical cancer and it may be seen in other conditions like immature squamous metaplasia, leukoplakia, condyloma and Inflamed, regenerating cervical epithelium. For differentiation, the acetowhite epithelium in CIN & early invasive cancer is more dense, thick and opaque with well-defined margins. The changes appear quickly and persist longer than one minute whereas immature metaplastic cells are translucent white, without well-defined margins & take longer time to appear & quick to disappear. Sensitivity of VIA is 89.5 % and its specificity is 91.2%.

Visual inspection with Lugol's Iodine (VILI) - Visual inspection of cervix with Lugol's iodine, also known as Schiller's test is performed with 10% Lugol's iodine. Lugols iodine may be prepared by dissolving 10 g potassium iodide in 100 ml of distilled water and adding 5 g **iodine** crystals, while shaking. The solution can be filtered and stored in a tightly stoppered brown bottle.

VILI is commonly used as an adjunct with VIA, has a higher sensitivity (100%) but lower specificity (52.6%). Normal squamous epithelium (both native and mature metaplastic cells) contain stores of glycogen that give a mahogany brown or nearly black stain on application of 10% Lugol's iodine solution. In contrast, dysplastic cells do not contain glycogen and remain mustard yellow (Figure 6). Thus, presence of iodine negative areas on cervix indicates a positive VILI test and suggests the presence of CIN which can be confirmed by a biopsy from this area.

HIGH RISK HPV DNA TESTING-

Since more than 75 % of cervical cancer is caused by high risk HPV types 16 and 18, HPV DNA test is used for cervical cancer screening. HPV DNA can be detected in a cervical broom sample, the same as used for liquid based cytology.

Various methods of HPV detection include PCR and hybrid capture techniques. HPV test can be done as **Reflex test** where

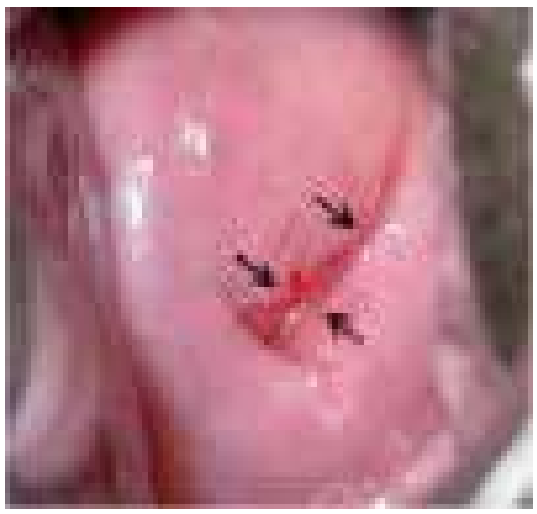

Fig. 4: VIA negative: No acetowhite area seen. Note the advancing edges of squamous metaplasia in anterior and posterior lips (arrows).

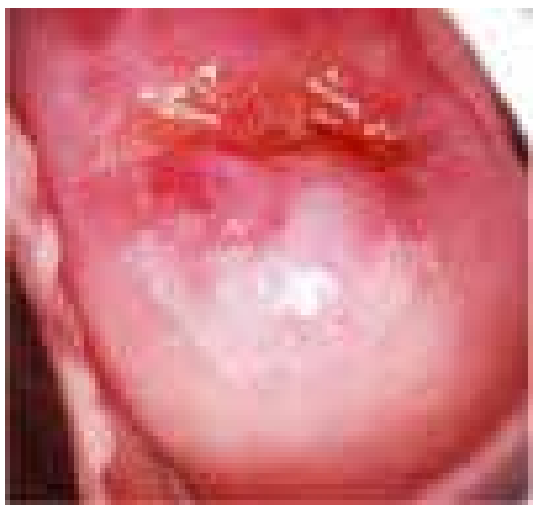

Fig. 5: VIA positive: well-defined, opaque acetowhite area, regular margins, in lower lip, abutting the squamocolumnar junction, which is fully visible.

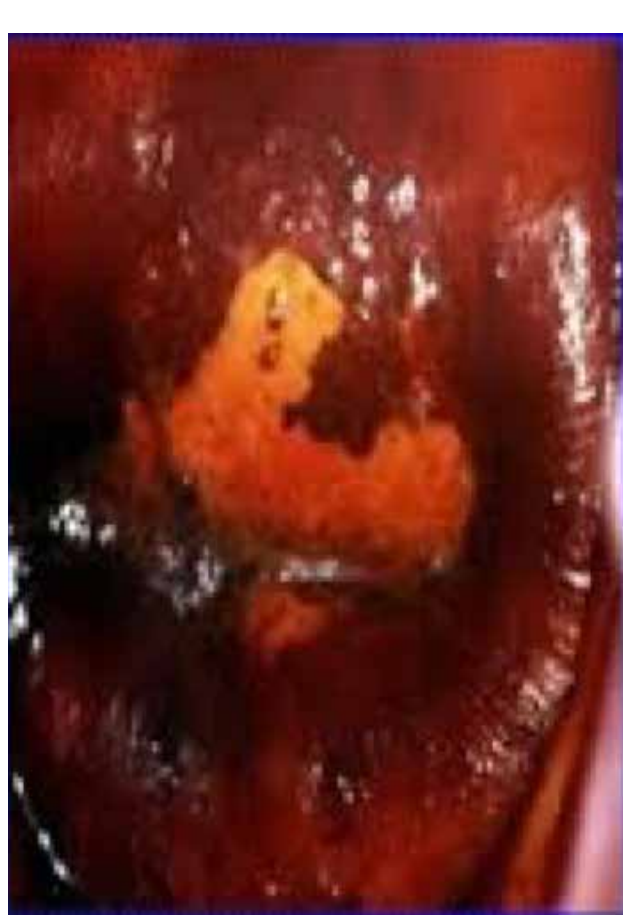

Fig. 6: VILI positive- well-defined area, canary yellow; transformation zone VILI negative- Mahogany brown

Fig. 7: HPV self- test kit

Fig. 8: Gynocular

HPV DNA testing is done following abnormal cytology report (ASCUS or higher). It can also be used as a **Co test** where HPV testing and cytology are done simultaneously and management decision is based on combined report. ASCCP & NCCN GUIDELINES recommend HPV co-testing every 5 years for women above 30 years.

HPV SELF SAMPLING –

Women can now take the cervical sample themselves for HPV test. The hesitation that keeps them away from cervical cancer screening is allayed. These tests though costly are now available in India (Figure 7).

COLPOSCOPY AND CERVICAL BIOPSY –

They are the **diagnostic tests** for cervical cancer. Several scoring systems have been used for stratification of the lesion seen via colposcope under magnified view. The commonly used Reid's index is now being replaced with Swede's score. Diagnosis of preinvasive disease is made by colposcopy, VIA or VILI guided biopsy. For an obvious lesion/growth seen with naked eye, direct biopsy should be taken using a punch biopsy forceps or wedge resection with scissors. **Gynocular** - This is a hand held portable colposcope with an attached smart phone. It is being evaluated as a screening tool for screening of Cervical cancer (Figure 8).

GUIDELINES FOR CERVICAL CANCER SCREENING (ACOG, ACS & ASCCP)

When to start screening- Start screening for cervical cancer at the age of 21 regardless of the age of onset of sexual activity. Women <21 years should not be screened regardless of age at sexual initiation and other behavior-related risk factors (Level A evidence). Screening is to continue as per guidelines in women who have been vaccinated with HPV Vaccine. ***Methods for cervical cancer screening*** - **Cervical Cytology** may be done with Pap smear or LBC every 3 yearly. If **HPV co-test** is used for screening, it needs to be started at 30 years of age and repeated every 5 years. As per **ASCCP (2015) and SGO (2015)** guidelines, HPV DNA test may also be used as a Primary screening test from 25 years of age and needs to be repeated every 3 years. **When to stop screening** –It may be stopped in women aged above 65 years with adequate negative prior screening*(Level A evidence). Those with a history of CIN2, CIN3, or AIS should continue routine age- based screening for at least 20 years (Level B evidence).

WHO Screen & Treat recommendations (2013) are mainly aimed at community screening programs across the globe. WHO states that screening test should be chosen according to the facilities available. HPV DNA test alone or with VIA may be used in high resource setting while VIA is good enough for low resource setting like ours. The guidelines recommend treatment of VIA positive lesions with cryotherapy or LEEP depending upon the eligibility so as to avoid the loss to follow up seen in the traditional process of diagnostic confirmation with colposcopy and biopsy. The Screen and treat approach does involve some overtreatment yet the overall benefit has been found to be more than that risk due to high efficacy, mass coverage, minimal complications seen in various studies.

National Cancer Control program of India (2006) recommends screening of women aged 30-59 years by VIA at PHC level to be repeated every 5 years if negative. Screen positive women should be referred to district hospital where a repeat VIA, Pap smear, Colposcopy should be done with Punch biopsy if needed. CIN diagnosed on colposcopy should be treated with Cryotherapy/ LEEP. If HPE does not show CIN, Pap and colposcopy should be repeated after 1 year at District Hospital. Woman should be referred to medical college or Regional Cancer Centre if cervical biopsy shows **malignancy**. This recommendation, though ten years old, still holds good today. Yet modifications are needed in view of availability of high risk HPV DNA tests.

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Endometrial Hyperplasia Management: Current Guidelines

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INTRODUCTION

Endometrial hyperplasia is defined as an irregular proliferation of endometrial glands along with an increase in gland to stroma ratio. Endometrial hyperplasia develops in those conditions when estrogen, unopposed by progesterone, stimulates endometrial cell growth. The growth of endometrial lining occurs and it does not shed and this leads to endometrial hyperplasia.

Risk factors for endometrial hyperplasia are:

- Obesity
- Anovulation – associated with PCOS or infertility
- Estrogen secreting ovarian tumors
- Drug induced endometrial stimulation for example tamoxifen
- Age>35 years with abnormal uterine bleeding
- Early menarche, late menopause
- Cigarette smoking
- Family history of cancer endometrium, ovary or colon
- Nulliparity

WHO 2014 classifies endometrial hyperplasia as: Hyperplasia with atypia & Hyperplasia without atypia. According to WHO 1994 classification system endometrial hyperplasia was divided into four categories based on histological features like glandular/stroma architectural pattern and presence or absence of cytological atypia. The classification was simple hyperplasia without atypia, simple atypical hyperplasia, complex hyperplasia without atypia, complex atypical hyperplasia.

ACOG 2015 and RCOG 2016 favor the use of WHO 2014 classification system and it also simplifies interpretation and management. Women with endometrial hyperplasia without atypia usually respond to progestin therapy vis-à-vis those with nuclear atypia.

CLINICAL PRESENTATION

- Heavy menstrual bleeding
- Frequent menstrual cycles
- Postmenopausal bleeding

Diagnosis of endometrial hyperplasia is based on histological diagnosis by endometrial biopsy. Endometrial biopsy is an outpatient department procedure which can be obtained by endometrial biopsy curette, pipelle, or vabra aspirator. Transvaginal ultrasonography may be done to know the endometrial thickness. When endometrial thickness is increased, endometrial hyperplasia can be suspected in premenopausal (>12mm) and postmenopausal women (>4mm) Transvaginal ultrasonography can detect irregular endometrial proliferation or abnormal double layer which may provide a reason to perform endometrial biopsy in postmenopausal women. Role of ultrasonography in premenopausal women is restricted to identifying structural abnormalities. Role of hysteroscopy comes when there is focal hyperplasia on ultrasonography. Direct visualization of endometrial cavity and guided biopsy are the added advantages of hysteroscopy. CT and MRI are not recommended in diagnosis of endometrial hyperplasia (grade B recommendation). Several biomarkers associated with endometrial hyperplasia have been investigated but none of them predicts disease or prognosis accurately. Potentially useful markers could be PTEN, BCL-2, BAX but more research is needed in this area.

MANAGEMENT OF ENDOMETRIAL HYPERPLASIA WITHOUT ATYPIA

Risk of endometrial cancer (endometriod type) in women with endometrial hyperplasia without atypia is less than 5% over 20 years (level 2 evidence). There can be two options for management

- One is observation alone with follow up endometrial biopsies to ensure disease regression.
- Other option is treatment with progestins which has higher disease regression rate compared to observation.

Progestin treatment is indicated in those women who fail to regress following observation alone and in symptomatic women with AUB. LNG IUS is the first line treatment compared with oral progestin (grade A recommendation). It has a higher disease regression rate with a more favorable bleeding profile and associated with fewer adverse effects. LNG IUS contains 52 mg of levonorgestrel and delivers 20 μg/day and is replaced every 5 years. LNG IUS delivers high dose progesterone to endometrium with minimum side effects. Menstrual irregularities are common with the use of LNG IUS with 50% patients achieving amenorrhea within 6 months of insertion.

Cyclic progestins are less effective in regressing endometrial hyperplasia without atypia compared to LNG IUS and continuous oral progestin (grade A recommendation). Continuous progestogens should be used (medroxy-progesterone acetate 10-20 mg/day or norethisterone 10-15 mg/day for women who decline LNG-IUS (grade B recommendation). Progestins are usually well tolerated by patients with few adverse effects like nausea, weight gain, breast tenderness and headache. Prolonged progestin therapy is usually given in the form of medroxy progesterone acetate or LNG IUS. The median time of return of fertility in women using DMPA injection is six months and therefore not suitable for fertility preserving management. LNG IUS has less residual effects and oral progestins have least residual effect on endometrium. Histological regression is achieved when treatment with oral progestin or LNG IUS is given for minimum of six months in patients with endometrial hyperplasia without atypia. If patient does not want to conceive she should be encouraged to use LNG IUS for five years as it reduces risk of relapse. Endometrial biopsy is done at six monthly intervals. At least two consecutive negative endometrial biopsies should be obtained. Women should be advised to follow up if any episode of abnormal bleeding occurs as it may indicate relapse.

In women who have a higher risk of relapse six monthly biopsies are recommended till two negative biopsies and further follow up should be considered with annual endometrial biopsies.

Hysterectomy is not considered as a first line management for hyperplasia without atypia and progestogen therapy may induce histological and symptomatic regression in majority of women.

Hysterectomy is indicated in women who do not want to preserve fertility when:

- Hyperplasia without atypia progresses to hyperplasia with atypia during follow up
- There is no histological regression despite 12 months of treatment
- There is relapse of endometrial hyperplasia even after completing progestogen therapy
- There is persistence of bleeding symptoms
- Women declines to undergo endometrial surveillance or comply with medical treatment.

When surgical treatment is offered to postmenopausal women it should include total abdominal hysterectomy with bilateral salpingo-oophorectomy. In premenopausal women decision of bilateral salpingo-oophorectomy should be individualized. Bilateral salpingectomy should be offered to all as it may reduce risk of ovarian malignancy. Endometrial ablation is not recommended for treatment of endometrial hyperplasia because complete and persistent endometrial ablation cannot be ensured. Intrauterine adhesion formation may preclude future endometrial histological surveillance. Supracervical hysterectomy and morcellation are the unacceptable options for endometrial hyperplasia.

MANAGEMENT OF ENDOMETRIAL HYPERPLASIA WITH ATYPIA

Risk of endometrial cancer in women with atypical hyperplasia is as high as 28% over 20 years. Because of this increased risk of cancer endometrium women should be offered total abdominal hysterectomy with bilateral salpingo-oophorectomy (grade B recommendation). A laparoscopic approach is better than abdominal approach as it has shorter hospital stay, early recovery, less post-operative pain and other complications. There is no benefit from frozen section during surgery or pelvic lymphadenectomy. Intra operative frozen section is not a reliable indicator of final pathology and it will not change further management. Pelvic lymphadenectomy is not indicated because it will increase operative time and can increase surgical morbidity also. Around 43% cases have been diagnosed as endometrial cancer in final histopathology report but all were early endometrial cancers with low risk of lymphovascular disease.

Similar to surgical management of endometrial hyperplasia without atypia postmenopausal women should be offered total abdominal hysterectomy with bilateral salpingo-oophorectomy. In premenopausal women decision of bilateral salpingo-oophorectomy should be individualized. Bilateral salpingectomy should be offered to all as it may reduce risk of ovarian malignancy. Endometrial ablation is not recommended for treatment of endometrial hyperplasia with atypia.

Women who want to preserve fertility should be counseled about risks of subsequent endometrial cancer. Co-existent endometrial and ovarian cancer should be ruled out. First line treatment with the LNG IUS should be recommended (grade B recommendation). Oral progestogens can be prescribed as second best alternative. When fertility is not required, she should undergo total abdominal hysterectomy as there are higher chances of relapse.

Follow up of patients desiring fertility sparing treatment should be at 3 monthly intervals. Once two negative biopsies are obtained, further follow up should be at 6 to 12 monthly intervals until hysterectomy is done. During follow up detailed history and examination of patient should also be done.

Women who opt for fertility sparing approach of management should have at least one negative biopsy sample before conception. Regression of endometrial hyperplasia is required before ART as it is associated with higher pregnancy rates (grade B recommendation). Assisted reproductive techniques should be offered to the patient as they have better conception rates compared to natural cycles. It is also associated with higher live birth rates and less chances of relapse of endometrial hyperplasia.

HORMONE REPLACEMENT THERAPY AND ENDOMETRIAL HYPERPLASIA

Systemic estrogen only hormone therapy should not be given in postmenopausal women who are not hysterectomized (grade A recommendation). All women taking HRT should be counseled to report in case of vaginal bleeding that is unscheduled. Women with endometrial hyperplasia on sequential HRT should be counseled to take continuous progesterone intake in form of LNG IUS or continuous combined HRT preparation (grade B recommendation). Stopping sequential HRT may be sufficient to induce regression of endometrial hyperplasia.

TAMOXIFEN WITH ENDOMETRIAL HYPERPLASIA

Tamoxifen is selective estrogen modulator which is used as adjuvant treatment for breast cancer. It inhibits proliferation of breast cancer but has agonist action on endometrium leading to endometrial polyps and hyperplasia. Routine use of LNG IUS in women taking tamoxifen is not recommended. Also women on Tamoxifen may have a thick endometrium which is due to subendometrial edema. Women on tamoxifen who are asymptomatic do not need endometrial biopsies. Endometrial biopsy is only done if women presents with bleeding

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"Excellence is a continuous process and not an accident."

- Former President A. P. J. Abdul Kalam

Let's strive to follow this great man's footsteps.
We are committed to achieve a better tomorrow.

Colposcopic Visualisation of Normal and Abnormal Cervix

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INTRODUCTION

The role of colposcopy to accurately identify the precancerous lesions of cervix is more crucial after introduction of non cytological screening tests like visual inspection on acetic acid (VIA) and human papillomavirus(HPV) test.[1,2] Colposcope facilitates diagnosis of the abnormalities by allowing magnified vision of the surface of the cervix under good illumination,[3] along with prominent stromal blood vessels with red free filter, thus serves as an important diagnostic aid in detection and management of cervical neoplasias.

INDICATIONS FOR COLPOSCOPY

1. Cervical Pap smear cytology ASC-H or worse. Women with cytology diagnosis of ASCUS can also be referred for colposcopy directly
2. Women positive on cervical cancer screening tests i.e visual screening tests and oncogenic HPV DNA/mRNA tests
3. Cervix is grossly suspicious of malignancy
4. Women complaining of irregular bleeding P/V, post-menopausal bleeding P/V or persistent and foul smelling discharge P/V
5. Treatment of cervical pre cancers under colposcopic guidance

COLPOSCOPIC FEATURES OF NORMAL CERVIX

To maintain uniformity, International Federation of Cervical Pathology and Colposcopy (IFCPC) has published a terminology classification in 2011.[4] The IFCPC 2011 colposcopic terminology is useful in documentation of colpo findings more accurately.

Another classification called SWEDE Score is also available with a scoring system between 0 to 10 based on colposcopy findings.[5] Figures 1, 2 & 3 show various colposcopic views of normal cervix.

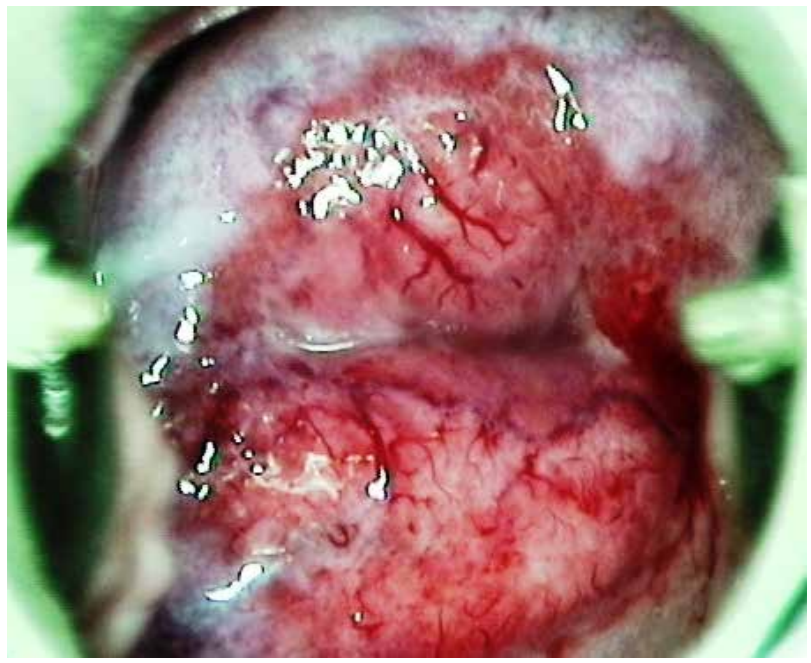

Fig. 2: Normal branching blood vessels viewed through green filter

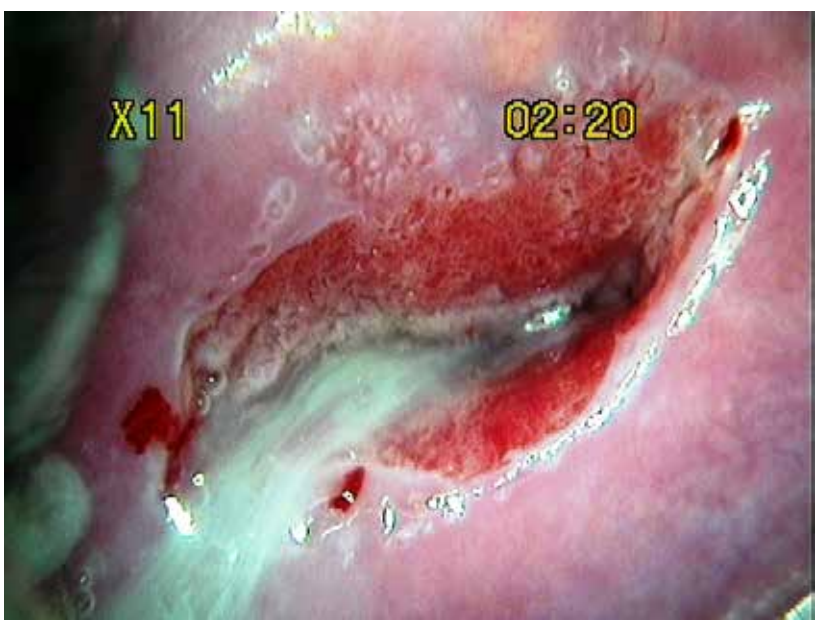

Fig. 1: Features of Transformation Zone: Nabothian follicles, crypt openings, islands of columnar epithelium, squamous metaplasia

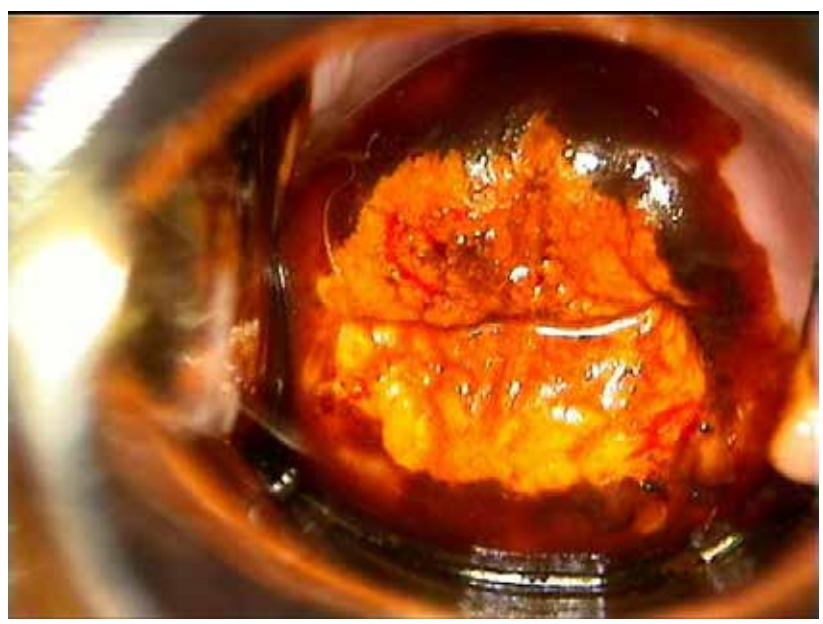

Fig. 3: After application of lugol's iodine: normal mahogany brown stain of glycophilic squamous epithelium, no iodine staining of columnar epithelium.

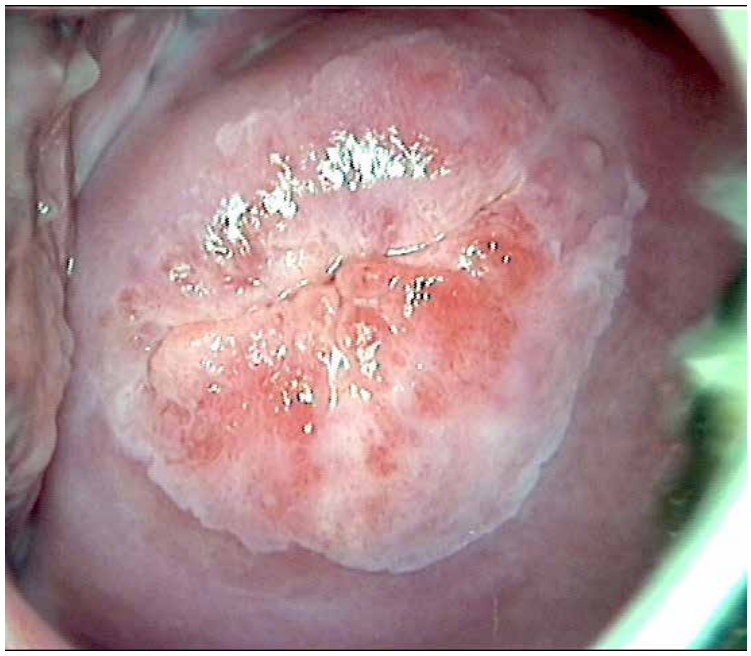

Fig. 4: CIN 1: Thin acetowhite epithelium with well-defined margin

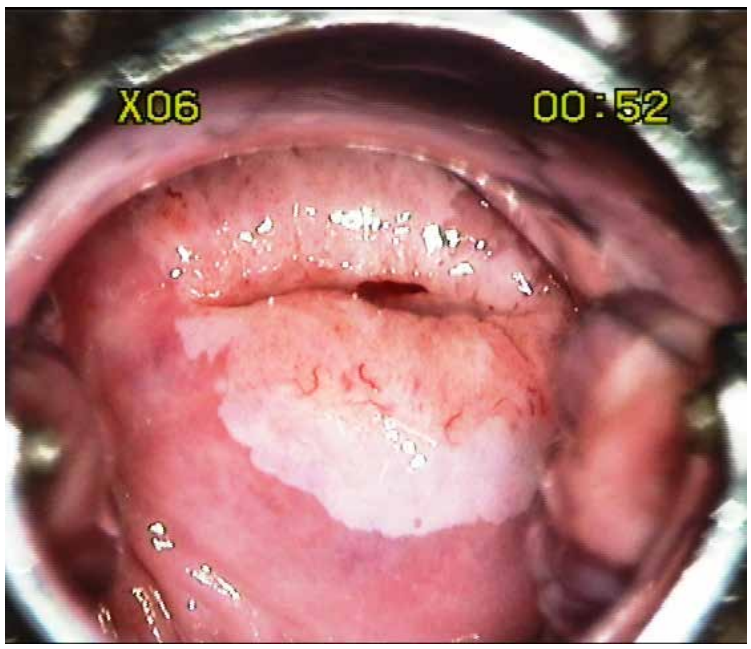

Fig. 5: CIN 2 Lesions: Dense aceto white lesion arising from squamo-columnar junction within the transformation zone

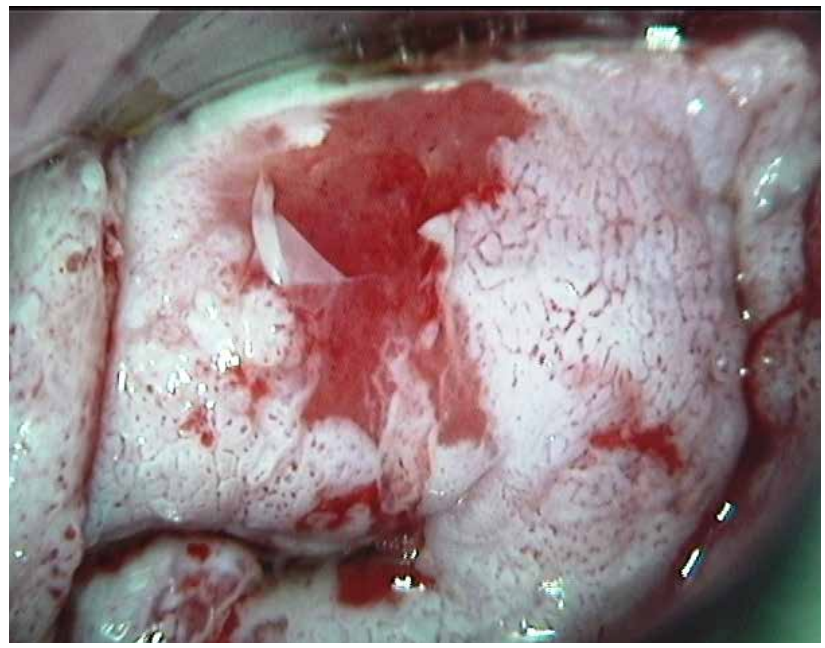

Fig. 6: Coarse mosaics with erosion in a case of CIN3

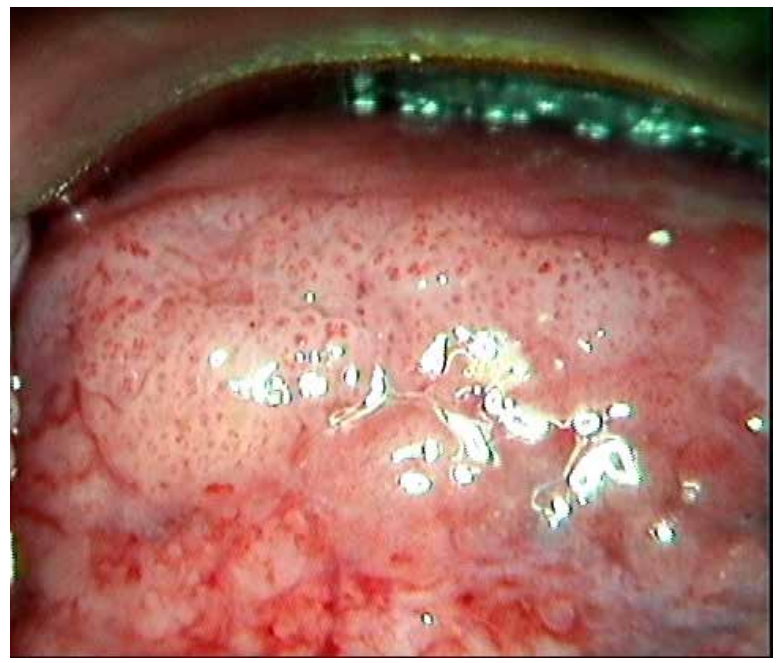

Fig. 7: Surface irregularity with vascular abnormalities suspicion of invasive disease

COLPOSCOPIC FEATURES OF CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN) LESIONS

The detection of CIN lesions by colposcopy involves recognising the following characteristics: colour tone, rapidity of aceto-whitening, margin of the lesion, surface characteristics, abnormal vessel pattern and iodine non uptake by CIN lesions (Figures 4,5,6,7).

CONCLUSION

Colposcopy helps to confirm the diagnosis, localize the lesion and direct the biopsy from the most significant part of the abnormality. The major limitations of colposcopy is that the test is subjective, which makes it liable to interpretation error and the it has limited capability to assess endocervical lesions. With the advancements in medical technology, the role of colposcopy in detection and management of female genital pre cancers is becoming more relevant in day to day practice of modern medicine.

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1. **Human papillomavirus vaccine efficacy in the prevention of anogenital warts: systematic review and meta-analysis.**

   Tejada RA, Vargas KG**,** Benites-Zapata V**,** Mezones-Holguín E**,** Bolaños-Díaz R**,** Hernandez AV**.**

   Salud Publica Mex. 2017 Jan-Feb;59(1):84-94.

Objective: To review evidence on the efficacy of HPV vaccines in the prevention of non-cancer lesions (anogenital warts [AGW], recurrent laryngeal papillomatosis and oral papillomatosis).

Materials and Methods: We conducted a systematic review of randomized trials. We performed random effect models and effects were reported as relative risks (RR) and their confidence intervals (95%CI) following both intention to treat (ITT) and per protocol (PP) analyses.

Results: We included six studies (n=27 078). One study was rated as high risk of bias. One study could not be included in the meta-analysis because it provided combined results. We found that quadrivalent vaccinereduced the risk of AGW by 62% (RR: 0.38, 95%CI:0.32-0.45, I2:0%) in the ITT analysis and by 95% (RR: 0.05, 95%CI:0.01-0.25, I2:66%) in the PP analysis. Subgroup analyses of studies in women or with low-risk of bias provided similar results.

Conclusion: HPV quadrivalent vaccine is efficacious in preventing AGW in men and women.

2. **Evaluation of Type Replacement Following HPV16/18 Vaccination: Pooled Analysis of Two Randomized Trials.**

   Tota JE, Struyf F, Merikukka M, Gonzalez P, Kreimer AR, Bi D, Castellsagué X, de Carvalho NS, Garland SM, Harper DM, Karkada N, Peters K, Pope WA, Porras C, Quint W, Rodriguez AC, Schiffman M, Schussler J, Skinner SR, Teixeira JC, Hildesheim A, Lehtinen M; Costa Rica Vaccine Trial and the PATRICIA study groups.

   J Natl Cancer Inst. 2017 Jan 28;109(7). pii: djw300

Background: Current HPV vaccines do not protect against all oncogenic HPV types. Following vaccination, type replacement may occur, especially if different HPV types competitively interact during natural infection. Because of their common route of transmission, it is difficult to assess type interactions in observational studies. Our aim was to evaluate type replacement in the setting of HPV vaccine randomized controlled trials (RCTs).

Methods: Data were pooled from the Costa Rica Vaccine Trial (CVT; NCT00128661) and PATRICIA trial (NCT001226810)-two large-scale, double-blind RCTs of the HPV-16/18 AS04-adjuvanted vaccine-to compare cumulative incidence of non-protected HPV infections across trial arms after four years. Negative rate difference estimates (rate in control minus vaccine arm) were interpreted as evidence of replacement if the associated 95% confidence interval excluded zero. All statistical tests were two-sided.

RESULTS: After applying relevant exclusion criteria, 21596 women were included in our analysis (HPV arm = 10750; control arm = 10846). Incidence rates (per 1000 infection-years) were lower in the HPV arm than in the control arm for grouped nonprotected oncogenic types (rate difference = 1.6, 95% confidence interval [CI] = 0.9 to 2.3) and oncogenic/nononcogenic types (rate difference = 0.2, 95% CI = -0.3 to 0.7). Focusing on individual HPV types separately, no deleterious effect was observed. In contrast, a statistically significant protective effect (positive rate difference and 95% CI excluded zero) was observed against oncogenic HPV types 35, 52, 58, and 68/73, as well as nononcogenic types 6 and 70.

Conclusion: HPV type replacement does not occur among vaccinated individuals within four years and is unlikely to occur in vaccinated population.

3. **Knowledge, attitude & practice on human papillomavirus vaccination: A cross-sectional study among healthcare providers.**

   Chawla PC, Chawla A, Chaudhary S

   Indian J Med Res. 2016 Nov;144(5):741-749.

Background & Objectives: Cervical cancer is a major health problem and a leading cause of death among women in India. Of all the associated risk factors, high-risk human papillomavirus (HPV) infections being the principal aetiologic agent, two HPV vaccines are in use for the control of cervical cancer. The present study was undertaken to explore the knowledge, attitude and practice (KAP) on HPV vaccination among the healthcare providers in India.

Methods: A cross-sectional study was conducted among 590 healthcare professionals from 232 hospitals and 80 PHCs of nine districts of Delhi-NCR (National Capital Region). A total of 590 (526 female, 64 male) healthcare providers were surveyed.

Results: Only 47 per cent of respondents recommended young women to get vaccinated against HPV. Majority of respondents (81%) were found to be aware about the existence of vaccines for cervical cancer prevention. District-wise, highest (88.3%) awareness about the existence of vaccines against HPV was reported from Gautam Budh Nagar and lowest (64%) in Faridabad. Although 86 per cent of

gynaecologists were aware about the names of HPV vaccines available in the market, only 27 per cent of paramedical staff had this knowledge. There was a significant difference between the respondents from government and private sectors regarding their awareness about HPV vaccines. Lack of awareness about the principal cause, risk factors and symptoms for cervical cancer and HPV vaccination was significantly (P< 0.05) reported in the respondents from paramedical staff category.

Conclusion: The findings reinforce continued medical education of healthcare providers, particularly those from the government sector on HPV vaccination for cervical cancer prevention. Public education is also pertinent for a successful HPV vaccination program in the country.

4. **The clinical and economic benefits of school-based quadrivalent HPV vaccination in Singapore.**

   Tay SK, Hsu TY, Shcheprov A, Walia A, Kulkarni AS.

   Int J Gynaecol Obstet. 2017 May;137(2):129-137.

Objective: To investigate the clinical and economic impacts of school-based administration of the quadrivalent HPV vaccine.

Methods: A retrospective health-economic analysis was conducted using data collected in Singapore between 2004 and 2005. A dynamic transmission model was adapted for universal vaccination that provided 80% coverage among students aged 11-12 years. Strategy 1 involved only girls, with a 5-year catch-up vaccination to provide 50% coverage among those aged 13-17 years. Strategy 2 included both girls and boys with no catch-up vaccination. Outcomes included the predicted incidence of HPV-related disease over 100 years.

Results: Current coverage was assumed to be 5%. Strategy 1 would reduce cervical intraepithelial neoplasia grade 1 (CIN1) by 63.8%, cervical intraepithelial neoplasia grade 2-3 (CIN2-3) by 62.9%, cervical cancer by 50.9%, and genital warts by 78.0% (female individuals) and 73.6% (male individuals). Strategy 2 would reduce CIN1 by 64.0%, CIN2-3 by 63.1%, cervical cancer by 50.7%, and genital warts by 79.9% (female individuals) and 80.1% (male individuals). The incremental cost-effectiveness ratio was S$12 464 for strategy 1 and $27 837 for Strategy 2. These values decreased to $7477 and $22 574, respectively, if a two-dose regimen was adapted.

Conclusion: School-based quadrivalent HPV vaccination offered clinical and economic benefits, and is cost-effective in Singapore.

5. **The impact of human papillomavirus type on colposcopy performance in women offered HPV immunization in a catch-up vaccine programme: a two-centre observational study.**

   Munro A, Gillespie C, Cotton S, Busby-Earle C, Kavanagh K, Cuschieri K, Cubie H, Robertson C, Smart L, Pollock K, Moore C, Palmer T, Cruickshank ME

   BJOG. 2017 Jan 19. doi: 10.1111/1471-0528.14563

Objective: To determine whether human papillomavirus (HPV) immunization has affected the prevalence of HPV genotypes and colposcopic features of cervical intraepithelial neoplasia (CIN) in young women referred for colposcopy.

Design: A two-centre observational study including vaccinated and unvaccinated women.

Setting: Colposcopy clinics serving two health regions in Scotland, UK.

Population: A total of 361 women aged 20-25 years attending colposcopy following an abnormal cervical cytology result at routine cervical screening.

Methods: Cervical samples were obtained from women for HPV DNA genotyping and mRNA E6/E7 expression of HPV 16, 18, 31, 33, and 45. Demographic data, cytology, and histology results and colposcopic features were recorded. Chi-square analysis was conducted to identify associations between vaccine status, HPV genotypes, and colposcopic features.

Main Outcome Measures: Colposcopic features, HPV genotypes, mRNA expression, and cervical histology.

Results: The prevalence of HPV 16 was significantly lower in the vaccinated group (8.6%) compared with the unvaccinated group (46.7%) (P = 0.001). The number of cases of CIN2+ was significantly lower in women who had been vaccinated (P = 0.006). The HPV vaccine did not have a statistically significant effect on commonly recognised colposcopic features, but there was a slight reduction in the positive predictive value (PPV) of colposcopy for CIN2+, from 74% (unvaccinated) to 66.7% (vaccinated).

Conclusions: In this group of young women with abnormal cytology referred to colposcopy, HPV vaccination via a catch-up programme reduced the prevalence of CIN2+ and HPV 16 infection. The reduced PPV of colposcopy for the detection of CIN2+ in women who have been vaccinated is at the lower acceptable level of the UK national cervical screening programme guidelines.

6. **Spotlight on the 9-valent HPV vaccine.**

   Lopalco PL

   Drug Des Devel Ther. 2016 Dec 20;11: 35-44.

Abstract: Starting in 2006, vaccination against human papillomavirus (HPV) has been progressively implemented in most developed countries. Two vaccines have been successfully used, a bivalent vaccine targeting HPV-related cancers (b HPV) and a quadrivalent vaccine (q HPV) targeting both HPV-related cancers and genital warts. Between December 2014 and June 2015, a new nonavalent HPV vaccine (9vHPV) was granted marketing authorization in the USA and Europe. The 9vHPV was developed from the qHPV and includes five additional HPV types that should increase the level of protection toward HPV-related cancers. Efficacy and/or immunogenicity of 9vHPV has been assessed in eight clinical studies. The 9vHPV vaccine induced a very robust immune response against all vaccine types, with seroconversion rates close to 100%. The safety profile of 9vHPV is comparable to that of q HPV. Local reactions, especially swelling, have been more frequently reported after 9vHPV than q HPV, and this slightly increases when the 9vHPV is co-administered with other vaccines. The additional coverage offered by the 9vHPV may prevent a significant proportion of HPV-related cancers (variable between 8% and 18%) depending on the local distribution of high-risk HPV types in the population. It is impossible, at present, to anticipate the actual impact of the wide use of the 9vHPV in comparison with the b HPV or the q HPV, since it depends on many variables including duration of protection, potential cross-protection toward non-vaccine types, and herd immunity effect.

Brain Teasers

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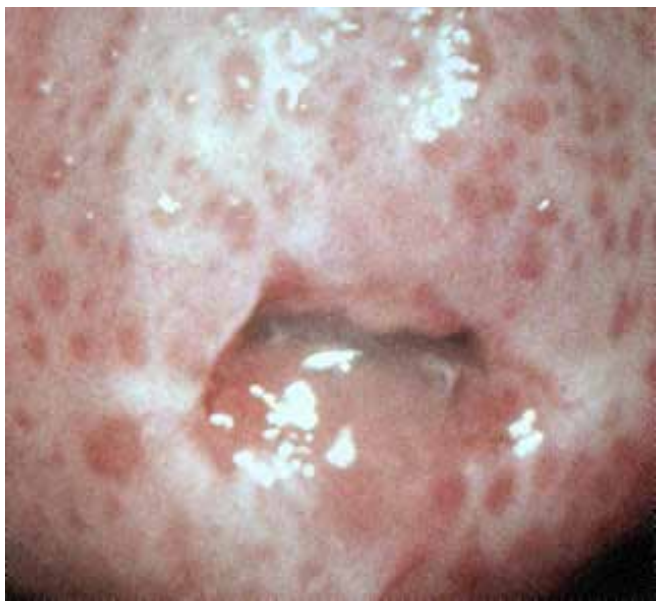
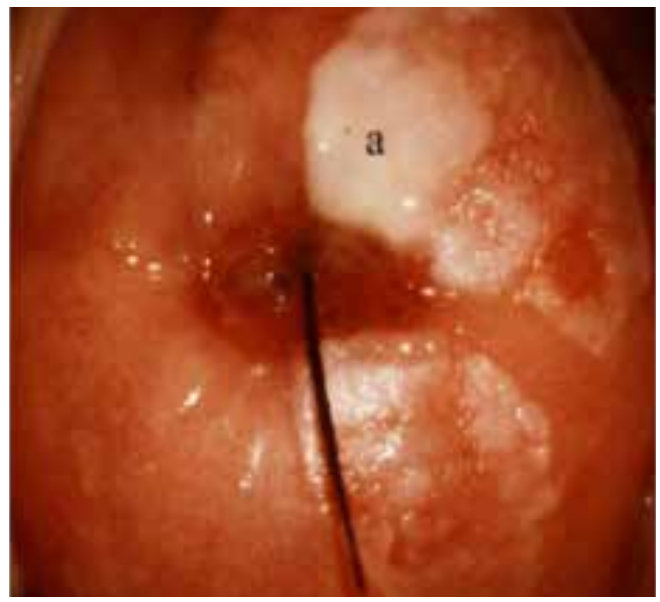
Q. 1. Identify the colposcopic appearance and name the condition in which this occurs



Q. 2. In colposcopy the following feature was seen after application of normal saline. What is the likely diagnosis?



Q. 3. Which of the following, regarding the management of H-SIL, is correct:

a. Regular follow-up of H-SIL is preferred management for women who wishes to retain fertility

b. Cryotherapy is not the method of choice for HSIL

c. Knife Cone is the best method of treatment

d. Management depends on HPV genotype

Q. 4. In which case of CIN I, you will not offer expectant treatment?

Q. 5. The risk at birth of having ovarian cancer at some point of time in a women lifetime is ……..

ANSWERS TO BRAIN TEASERS – APRIL ISSUE

1. Sacrococcygeal Teratoma
2. Fetal Biomagnet (Fetal Magnetocardiography.)
3. Twin twin transfusion syndrome
4. Fetal Doppler Echocardiography
5. a. Highest risk – increased nuchal skin fold thickness
   b. Lowest risk – Echogenic intracardiac focus / Choroid plexus cyst