

### The quarterly newsletter of Asia Oceania research organization on Genital Infections and Neoplasia - India



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#### From the editor's desk

Dear Readers,

Cervical cancer is a preventable tragedy but it is still continuing to curse young and old, the rich and the poor alike with a devastating experience of untold pain and misery. As the actions are defined by WHO to eliminate cervical cancer, it becomes more important than ever to come together and work for the cause. The awareness about cervical cancer screening and HPV vaccination is increasing across the country among both clinicians and the public. As a result of this increased awareness, more and more screening opportunities are being organized. AOGIN India is in the forefront of spreading the current knowledge/recent advances in the field of cervical cancer prevention. We believe, we must acknowledge the hard work done by our members towards imparting awareness for prevention of cervical cancer. We humbly request the members to share their activities, so that others go through them and get inspired to do the same in whatever way it is possible.

In this issue we have brought an interesting review on Newer markers in cervical cancer screening by Dr Kanika Batra. In journal scan Dr Satinder Kaur and Dr Akansha has highlighted reliability of colposcopy during pregnancy and Dr Jyoti Meena & Dr Arthi Jayraj has contributed some interesting case scenarios in cervical cancer screening during pregnancy.

We hope that the readers would benefit from the various sections in this newsletter. We look forward to a proactive participation of all the members.

Happy reading !!!

**Dr Seema Singhal**



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## Message From the President

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Dr Abraham Peedicayil, Professor and Head Department of Gynae Oncology, CMC Vellore



Dear Colleagues,

Greetings!

This year we will not be having an annual conference as we had decided to do this once in two years at our last general body meeting. However, there regional CMEs being planned in Lucknow, Vellore and Kolkata. I hope that there will be active participation at these meetings. The AOGIN / IPVS meeting in Sydney takes place first week of October and hope to see some of our members there.

Policies at a national and state level to promote primary prevention, primary care, community health and family medicine seem to be neglected over tertiary and quaternary care. The health care industry is concerned only with profits as the bottom line and so who will do the not so profitable work?

We need to understand why women do not seek preventive care, ignore early warning signs and do not comply with our treatment schedules. The issues related to lack of awareness, family dynamics, social stigma, misconceptions and poor health seeking behavior could derail our best vaccination and screening programmes.

Cost-effective strategies, better communication with community leaders and including men to champion women's issues would go a long way to improve the health of our women.

I am happy that many in our organization are doing a great job towards creating awareness and preventing HPV related cancers. Keep it up!

Best wishes,

**Abraham Peedicayil**

# Markers in Cervical Cancer Screening and Diagnosis

Dr Kanika Batra Modi, Gynaecologic Oncologist, Max Institute of Cancer Care, Saket, New Delhi

A declining trend of the incidence and mortality of cervical cancer has been observed in most of the Western countries. This has been possible due to multitude efforts at various levels from changes in the pattern of hygiene and living ways and by the strengthening of screening programme. Since the 1970s, population-wide screening programs were implemented in many Western countries, and this further accelerated the decline in the incidence and mortality of cervical cancer, despite an increasing incidence of precursor lesions over the same time period<sup>1</sup>.

There are major limitations associated with Pap's smear with respect to the lack of objectivity in its interpretation and the lack of reproducibility. This can lead to increase in costs caused by repeated testing and further psychological as well as physical distress.

Due to these limitations of an otherwise very successful concept in cancer prevention, substantial research efforts were undertaken to better understand the molecular events involved in cervical High-Risk and Low-Risk HPV Infections.

Many markers are studied and published in literature right from the Human Papilloma Virus as marker to various proteins which are altered in cell cycle and metastasis. However, only a few are used in clinical practice as p16 and Ki-67 markers. Here a list of markers is discussed with their role in cervical cancer etiopathogenesis and its use in screening and diagnosis.

## HPV

Human papilloma viruses (HPVs) are DNA viruses having a genome of about 8kb and code for 8-10 genes. The genome of HPV encodes a long control region (LCR), early proteins (E1-E8) and late proteins (L1-L2). Although more than 100 different present, more than 100 different HPV types have been identified. They differ significantly in carcinogenic potential<sup>2</sup>. The oncogenic forms of HPV (including types 16 and 18) are associated with cervical carcinoma and are commonly used for detection.

## E6 & E7 Protein

After the HPV virus integrates in the host genome, it releases these early proteins E6 and E7 which cause immortalization of HPV infected cells by inhibitory effects on p53 and pRb. These early proteins can be detected ImmunoHistoChemistry(IHC). Although, these markers cannot confirm dysplastic change of the host cells and further carcinogenesis. A high expression of these markers suggests integration of high-risk HPV DNA into the host cell genome

and possible immortalization. Even the immortalized cells can be spontaneously cleared without further progression to carcinogenesis<sup>3</sup>.

Increased expression of these markers indicates integration of HR-HPV DNA into host cell genome and probably immortalization of the host cells. However these markers does not confirm dysplastic change of the host cells, their proliferation and hence carcinogenesis. In addition the immortalized cells can be spontaneously cleared without further progress<sup>5</sup>.

## Ki67/MIB-1

Dysplastic cells have an increased turnover of cell cycling. Markers of cell-proliferation can be used as biomarkers for CIN. Ki67 and MIB-1 are markers of proliferation and are expressed in CIN lesions but can also be expressed in basal cells having a proliferative capacity<sup>4</sup>.

## Epidermal Growth Factor Receptor (EGFR)

EGFR is a glycoprotein spanning across the cell membrane with glycoprotein receptor coded by a gene located on chromosome 7 which regulates intracellular signal transmission required for cell growth. Increased expression of HR-HPV E6 is associated with increase in EGFR levels and it's over expression is associated with poor outcomes and can be possibly used for target therapy<sup>5</sup>.

## MYC

MYC is an oncogene, which is overexpressed in preinvasive lesions and cervical cancer cells. The levels are increased with the grade of CIN. So it's detection can be demonstrated using PCR and higher levels are suggestive of high grade of CIN<sup>6</sup>.

## p16

HPV targets regulatory cell cycle proteins, one of which is p16. P16 is an inhibitor of CDKs 4 and 6 and functions for the progress of cell-cycle from G1 to S phase. In high risk HPV infection p16 is over-expressed and can be detected in histology and cytology<sup>7</sup>. Overexpression of p16 is correlated with HPV 16 and 18 and can be detected in both squamous cell and adenocarcinoma<sup>7</sup>.

## Survivin

An independent marker of high-risk HPV type is survivin, a member of the family of human apoptosis inhibitors. It might be an early predictor of cervical carcinogenesis. Some studies have 14 established a linear relationship between the intensity of survivin expression and the grade of CIN<sup>8</sup>.

### **Phosphatase and tensine homologue (PTEN)**

It is an antioncogene is negatively related to survivin expression in CIN and cervical cancer. PTEN expression in squamous cell carcinoma is lower compared with normal cervical epithelium and this can be used as an early marker diagnosis and prognosis of cervical cancer<sup>9,15</sup>.

### **Telomerase**

Fluorescence in situ hybridization (FISH) detection of telomerase RNA amplification is found in cervical dysplasia with varying sensitivity for detection of high-grade CIN and is useful for differentiating between high and low grade lesions<sup>10</sup>.

### **Mini chromosome maintenance (MCM)**

It is a class of proteins of the DNA pre-replication complex and MCM proteins, in particular, MCM5 are useful for detection of cervical dysplasia. The detection of MCM5 expression is seen in both low-grade and high-grade dysplasia.

In addition to MCM-5, others members from the MCM family (MCM2, MCM7, MCM6) have been shown to be potentially useful markers for the detection of CIN. MCM-7 appears to be a specific marker for the detection of high-grade cervical disease using immunochemistry formats<sup>11</sup>.

### **RAS Gene**

The mutant RAS gene converts HPV immortalized keratinocytes into tumorigenesis state. The expression is higher in HSIL and carcinoma compared to normal and LSIL<sup>12</sup>.

### **Topoisomerase II- $\alpha$ (TOP2A)**

Is over expressed in cervical diseases and is established to be a hallmark within high-grade cervical disease and provides the link between infections with oncogenic HPV viral subtypes and the molecular behaviour of cervical disease. Using this approach, MCM-6, MCM-4 and TOP2A have been identified as over expressed genes in CIN.

### **ProExC**

This antibody is a novel biomarker cocktail containing antibodies against topoisomerase II alpha and mini chromosome maintenance 2 proteins. It is a marker which helps distinguish dysplastic and endocervical lesions from the normal metaplastic cells. It can also be in conjunction with morphology and human papillomavirus evaluation for better classification of indeterminate cervical lesions in Papanicolaou smears<sup>13</sup>.

### **p53 and pRB**

There are the targets of HPV oncogenes E6 and E7. Loss of p53 and pRB represents an indirect sign of HPV E6 and E7 expression. Unfortunately this loss is not specific for HPV and is present also in other tumors. In HPV infection a low frequency of p53 and pRB is associated with a higher risk of progression<sup>14</sup>.

### **Methylation**

DNA methylation plays a role in maintaining genomic stability and in the regulation of gene expression. DNA methylation changes are an early event in carcinogenesis and can be seen in precursor lesion of cervical cancers. Three markers (DAPK1, CADM1, and RARB) showed elevated methylation in cervical cancers consistently across studies but at present no methylation marker can be used for cervical cancer<sup>15</sup>.

### **Angiogenetic markers**

The progression of CIN is accompanied by angiogenesis and cell proliferation. Some studies have demonstrated that angiogenetic parameters such as microvessel density and the expression of vascular endothelial growth factor (VEGF) increase with the grade of CIN.

High grade CIN lesions have significantly higher microvessel density and an intense expression of VEGF protein than normal epithelium and low-grade CIN 1 lesions<sup>16</sup>.

### **Cytokeratin (CK)**

Cytokeratins are fundamental markers of epithelial differentiation, which forms cytoskeleton in all eukaryotic cells. Cytokeratins persists even in metastatic tumours where all other identifying features are lost. The normal distribution of cytokeratins are; for ectocervical squamous epithelium and mature squamous epithelium. The studies of various cytokeratins in cervical dysplasia and cancer have given a diversified and inconclusive result<sup>17</sup>.

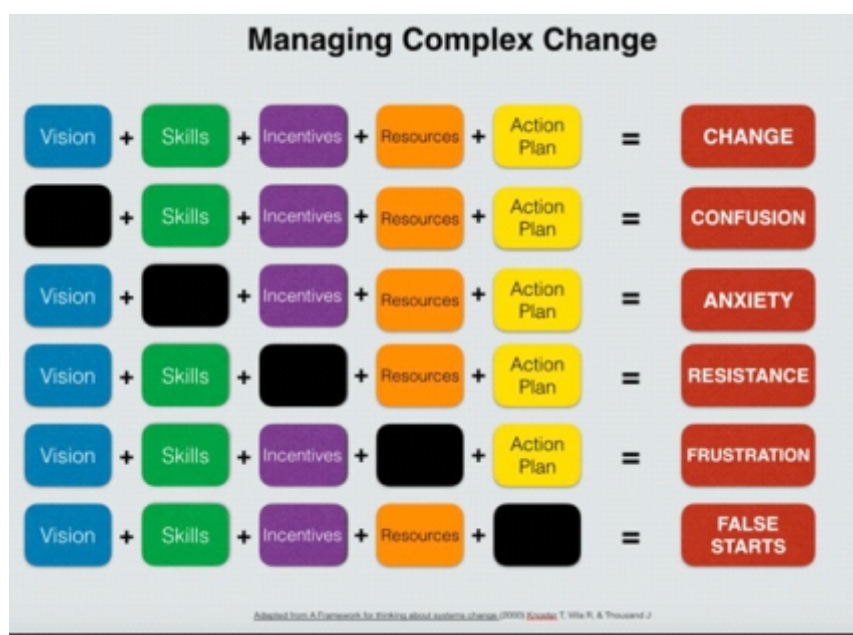
These markers described can be used by themselves or in a combination with each other. Among single markers p16 is commonly used as surrogate marker. Combined / cocktail markers are more useful and informative. Markers can be used to detect dysplastic and malignant cells with High sensitivity and specificity. It gives better understanding of genetics and biology of cervical carcinogenesis. It also helps in developing chemo preventive/ therapeutic strategies and targeted therapy. Further studies are needed for better understanding of the best markers for screening, early diagnosis and therapy.

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## The Lighter Facet



## Article 1

## Reliability of Colposcopy in Pregnancy

Ciavattini A, Serri M, Di Giuseppe J, Liverani CA, Fallani MG, Tsioglou D, Papiccio M, Carpini GD, Pieralli A, Clemente N, Sopracordevole F. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2018 Oct 1;229:76-81

**Objective:** To investigate the reliability of colposcopy during pregnancy and to evaluate the concordance between colposcopic patterns and histopathological findings during pregnancy.

**Material and Methods:** It is a multicenter observational study involving pregnant women who attended various institutions from January 2013 to December 2017. Patients were retrospectively analyzed in an observational cohort study. During the study period, 88 women were diagnosed with an abnormal PAP smear during pregnancy and subsequently underwent a colposcopy. For the present analysis, only 69 pregnant women who underwent a colposcopy-guided biopsy and fulfilled the inclusion and exclusion criteria were considered. The biopsies were performed only on areas with abnormal colposcopic findings and random biopsies were not performed. The study population was divided into two subgroups based on the gestational age at the moment of the colposcopic evaluation: women with a gestational age  $\leq$  20 week were compared to women with a gestational age  $>$  20 week. The colpo-histopathological concordance was evaluated in these two subgroups.

**Results:** Among the 69 women, 45 women (65.2%) had "major cytological abnormalities" while the remaining 24 women (34.8%) had "lesser cytological abnormalities".

Fourteen women (20.3%) showed "grade I abnormal colposcopic findings", 52 (75.4%) showed "grade II abnormal colposcopic findings" and the remaining 3 women (4.3%) had a "suspicious for invasion" colposcopy. The histopathological diagnosis showed 2 negative biopsies, 12 (17.4%) cases of CIN1, 50 (72.5%) cases of CIN2 and 5 (7.2%) cases of invasive cervical cancer. An overall "colpo-histopathological concordance" of 68.1%, with a colposcopic overestimation and underestimation rate of 14.5% and 17.4%, respectively was found. The "cyto histopathological concordance" appeared to be similar the "colpo-histopathological concordance" (71% vs 68.1%). A better reliability of colposcopy in women in the firsts two trimesters and in particular in women  $\leq$  20 weeks pregnant was found (Cohen's weighted kappa: 0.65). In the whole study cohort, we found a moderate agreement between cytology and histo-pathological analysis performed during pregnancy.

**Conclusions:** When performed by gynecologists with expertise, colposcopy is a reliable diagnostic tool, even during pregnancy. The high specificity of colposcopy in pregnancy for the diagnosis of invasive carcinoma allows to select with reasonable certainty patients to be subjected to diagnostic excision in case of suspected colposcopic invasion (low rate of false positives). Whenever possible, a colposcopic evaluation during the first half of pregnancy is preferable.

## Article 2

## Diagnostic Utility of HPV16 E6 mRNA or E7 mRNA Quantitative Expression for Cervical Cells of Patients with Dysplasia and Carcinoma

Wu MZ, Li WN, Cha N, Tian LX, Zhang YI, Wu X, Guo KJ, Wu GP. Cell transplantation. 2018 Jul 30;0963689718788521

**Background:** Current human papillomavirus (HPV) 16 DNA testing has high sensitivity (97.6%) but low specificity (17%), while mRNA testing (qualitative) improves the specificity. However, both techniques are not able to discriminate between transient and persistent infections. The primary objective of this study was to apply qRT-PCR to quantitatively detect the mRNAs of E6 and E7 in HPV16-positive and negative cervical epithelial cells and determine the possibility of this technique to overcome the disadvantages of current HPV DNA and HPV mRNA testing.

**Materials and Methods:** This study was conducted in China

Medical University from June to October 2015. A total of 87 patients with an average age of 42.4 years (23 to 77 years) with HPV 16 positive cervical brush cytology were taken as cases. An additional 31 randomly selected patients without HPV16 were included in the study and used as a control group. Residual materials from cytology specimen were used for E6 and E7 mRNA qRT-PCR analysis. Total RNA was extracted from cells using TRIzol Reagent and RNeasy RNA isolation kit. The qRT-PCR was performed using SYBERGreenMaster Mix on a 7900HT Fast Real-Time PCR system (Applied Biosystems). All HPV16-positive women were examined by colposcopy and underwent cervical

biopsy. Biopsy samples were obtained within 4 weeks after the initial HPV DNA tests. The histological biopsy results were categorized into four general groups: benign (including no pathologic alteration and benign or reactive changes), LSIL (CIN1), and HSIL (including CIN2/CIN3, squamous cell carcinoma in situ, and/or involving glands).

**Results:** The expression levels of both E6 and E7 mRNA were significantly increased in HPV16-positive patients relative to HPV16-negative patients ( $p < 0.01$ ). The 87 HPV16-positive patients were further divided into four groups: invasive carcinoma, HSIL, LSIL, and benign according the histological diagnosis. The expression levels of E6 mRNA were significantly increased in invasive carcinoma compared with HSIL ( $p < 0.01$ ), and in HSIL compared with LSIL ( $p < 0.01$ ). There were no significant changes between LSIL and benign groups ( $p = 0.97$ ). The expression levels of E7 mRNA were not significantly different among invasive cancer, HSIL, and LSIL

groups, but there was a significant increase in the invasive cancer and HSIL groups when they were compared with the benign group individually ( $p < 0.05$ ). We followed up a total of 57 patients for 1 year and divided them into two groups: the persistent infection group (18 patients) and transient infection group (39 patients). The expression levels of both E6 and E7 mRNA were significantly increased in the persistent infection group relative to the transient infection group ( $p < 0.01$ ). The follow-up results showed that 10 patients with LSIL and 29 patients with benign lesions had a natural outcome in transient infection group after 1 year.

**Conclusion:** The quantitative detection of the expression levels of E6 mRNA in cervical brushing cells may not only be used as an ancillary tool to cytological diagnosis of cervical neoplasia, but may also help to determine the severity of the lesions and the triage of transient infection.

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## Forthcoming Events

CME on Diagnostic Dilemmas in Gynae  
Oncology under the aegis of  
AOGIN India will be organized on 30th September 2018 at  
Hotel Clarks Awadh Lucknow.

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CME on cervical cancer prevention on 3rd November 2018  
organized by  
"Department of Gynecologic Oncology, CMC Vellore"

## Preinvasive Lesions in Pregnancy

Dr Jyoti Meena\*, Dr Aarthi S. Jayraj\*\*

\* Assistant Professor, Department of Obstetrics & Gynecology, All India Institute of Medical Sciences, New Delhi

\*\*Mch resident Gynae Oncology, Department of Obstetrics & Gynecology, AIIMS, New Delhi

(Image courtesy- Dr Neerja Bhatla and Dr Surabhi Sudhakaran)

### Case 1

Mrs X a 32-year-old G2P1L1 at 16 weeks POG presented to ANC with c/o excessive discharge per vaginum. On per speculum examination cervix was hyperemic with copious frothy discharge and bled on touch.

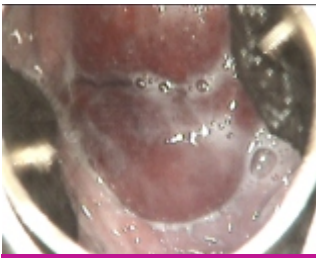


Figure 1

She was subjected to cervical cytology and HPV test (HPV DNA positive)

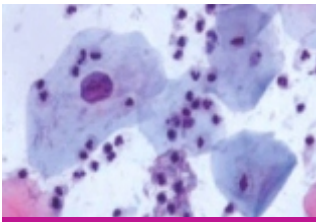


Figure 2

1a. What is your interpretation?

She was subjected to colposcopy examination, which revealed following findings.

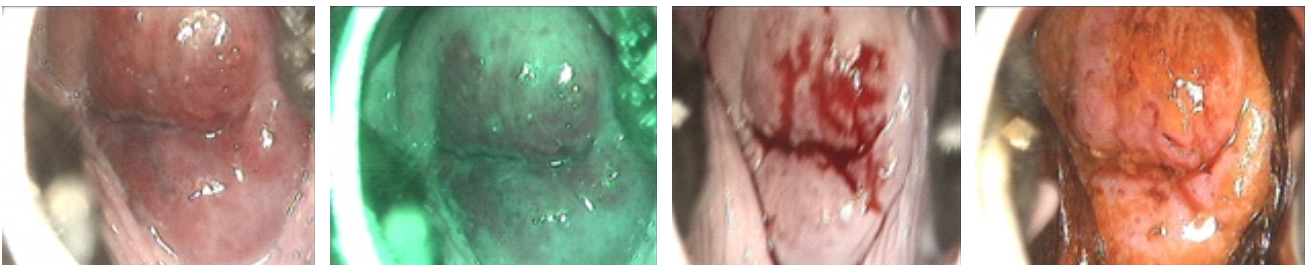


Figure 3

1b. What is your interpretation and further management?

## Case 2

Mrs Y, a 28-year-old G2P1L0 at 20 weeks period of gestation came to OPD with c/o postcoital bleeding. Her gynecological examination was unremarkable except for blood on the gloved fingers on per vaginal examination.



Figure 4

She further underwent a Pap cytology and HPV test (HPV DNA positive)

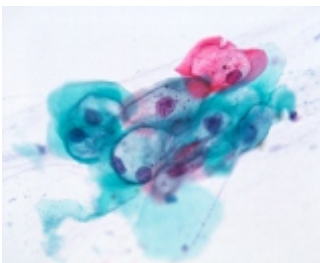


Figure 5

2a. What is your interpretation?

She underwent a colposcopy examination.

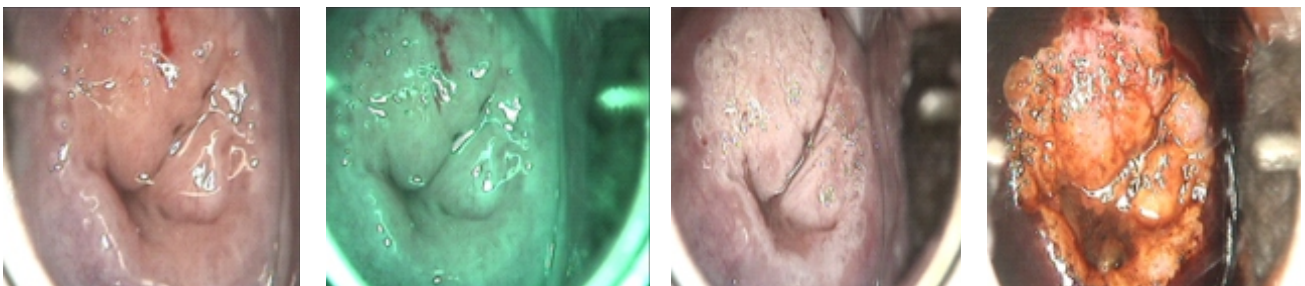


Figure 3

She underwent colposcopic guided cervical biopsy and histology revealed following finding:

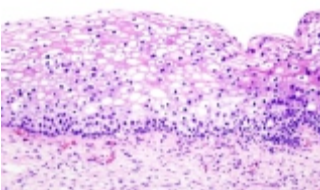


Figure 7

2b. What is your interpretation?

2c. What will be your management plan?

### Case 3

A 34- year old G3 P0+0+2+0 at 23 weeks POG came in ANC OPD with % blood mixed discharge per vaginum 3 days back. O/E mild pallor +, vitals within normal limits, P/A-Uterus 22 weeks, non-tender. She was subjected to a sonographic examination that showed a single live intrauterine fetus with placenta not low lying, no retroplacental clot, cervical length of 3.5 cm and internal os closed. On local examination, cervix was hyperemic and congested as shown in figure



Figure 8

The patient underwent a cervical cytology and HPV test which was s/o ASC-H and positive HPV DNA. she was subjected to a colposcopy, findings as shown below.

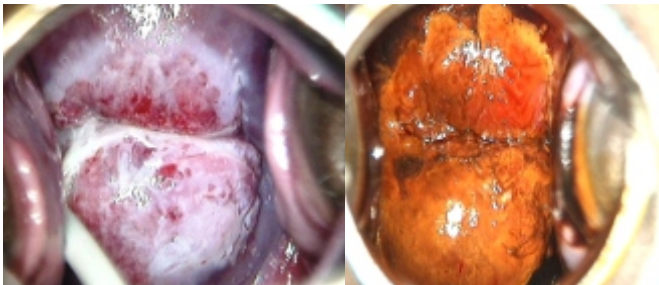


Figure 9

#### 3a. What is your interpretation?

Colposcopic guided biopsy was taken from the dense acetowhite and iodine negative areas of the cervix. Histopathological report was s/o CIN3 with no evidence of invasion.

#### 3b. How will you manage this patient?

Answers on..P11

## Answers

**1a.** Cervical cytology shows Atypical squamous cells of undetermined significance (ASCUS).

**1b.** The colposcopic examination showed irregular milky aceto-white area and were iodine negative. There were no abnormal vessels. The SWEDE score was calculated to be 4, which was s/o low grade lesion in the cervix. So, the patient should be observed throughout pregnancy and colposcopy can be repeated 6 weeks postpartum.

**2a.** Cervical cytology shows LSIL with HPV changes: koilocytic changes, superficial or intermediate squamous cells with large and irregular nuclei and perinuclear halo.

**2b.** The cervical biopsy specimen shows mild dysplasia and dysplastic cells are confined to basal 1/3rd of the epithelium s/o CIN1.

**2c.** The patient does not require any further treatment as CIN1 does not progress to invasive cancer during the course of pregnancy and rate of regression in postpartum period is high. Repeat co-testing test at 12 months.

**3a.** There is dense white acetowhite area with sharp margins and cuffed crypt opening on posterior lip and faint acetowhite area with diffuse margin on anterior lip (pregnancy induced decidual changes), vessels are absent, lesion is >15mm with distinct yellow iodine negative area SWEDE score is 9.

**3b.** Repeat colposcopy is acceptable during pregnancy but no more frequently than every 12 weeks. Repeat biopsy should be performed only if the lesion has a worsening colposcopic appearance or cytology is suggestive of invasive disease. The rate of progression from high-grade intraepithelial neoplasia to invasive carcinoma during pregnancy is estimated to be 0.4%. It is also acceptable to re-evaluate patient with cytology and colposcopy after 6 weeks postpartum as sometimes apparently high-grade lesions in pregnancy may resolve after delivery.

Ref: Stonehocker, J. Cervical Cancer Screening in Pregnancy. *Obstetrics and Gynecology Clinics of North America* 2013; 40(2):269–82.

“The Only way to do great work is to love what you Do.  
If you haven’t found it yet, Keep looking.  
Don’t Settle”

*Steve Jobs*