Role of Colposcopy and Cervicography in the Screening and Management of Pre-Cancerous Lesions and Early Invasive Cancer of Uterine Cervix

Seung Jo Kim
Comprehensive Gynaecologic Cancer Center, Bundang CHA General Hospital, Pochon CHA University School of Medicine, Sungnam Sie, Kyonggido, Seoul

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Worldwide, according to statistics, every year, 8,000,000 new cases of cancer are diagnosed and about 5,000,000 people die from the disease, whilst maternal mortality is currently estimated to be around 560,000 deaths per live birth per year, the estimate on death from cervical cancer is also around 450,000 (IARC Scientific Publications 1997)

Out of all cervical cancer cases seen in the world 14% occurs in the developed countries and about 86% occur in developing countries. Whereas we know that cervical cancer is considered to be preventable disease by WHO because it can be diagnosed in its pre-cancerous phase and can be controlled.

1. Basic questions in the screening of cervical cancer.

Screening for cervical cancer is one of the most prevalent and successful public health measure for the prevention of cancer.

In regard of cervical cancer screening, basic questions exist : 1) Does the incidence of cervical cancer justify screening? 2) Does the screening of cervical cancer decrease morbidity or mortality? 3) What is the best method of the screening, 4) Who should be screened for cervical cancer, 5) What is the optimal screening interval? (Canadian Task Force Report, 1976)

2. Problems of cytologic screening as a standard method.

The occurrence of cervical cancer in screened women is increasingly viewed as an avoidable failure.

The traditional approach to cervical cancer screening in Western society is dependent on the use of the Papanicolaou (Pap) smear as an independent test. (Papanicolaou and Traut, 1943).

Despite wide spread clinical acceptance and use of this test, cervical cancer remains a disease of prime importance since reports of cytology sensitivity in detecting cervical neoplasia range from 50% to 98% (Coppleson and Brown 1974) (Koss 1989) Many different approaches such as VIA (visual inspection with acetic acid), liquid base cytology, Thin Prep Pap, HPV-DNA typing and cervicography, have been studied to improve the accuracy of cervical screening. (Kurman & Solomon, 1994; Stafl, 1981, Navratil et al 1958; Tawa et al 1988; Kurman et al 1991; Spitzer et al 1986; Kim 1999; Travers 1990; Hutchinson et al 1994; Williams et al 1998)

Bethesda System in cytology

In 1988, a group of experts met and outlined the "Bethesda" Classification for cervical/vaginal cytology. (National Cancer Institute Workshop 1989). The Bethesda system includes a statement on the adequacy of the test by the cytologist, and attempts to reduce the use of the term "atypia" to only those situations where other diagnosis cannot be rendered. The terminology defines two groups of squamous intraepithelial lesions-low grade (HPV, CIN I, mild dysplasia) and high grade (CIN II or III, moderate dysplasia, severe dysplasia, carcinoma-in-situ) in the Bethesda System. The utility of the classification system is as yet undetermined between different classification systems.

Consequently, the terms and classification used in cytology, colposcopy (cervicography) and histopathology must correspond with each other especially in the precancerous lesions of the uterine cervix. (Table I)

Table I. The correlation of histology, cytology and cervicographic classification

Histological Diagnosis	Normal/benign conditions	BAUS CIN 1	CINI	CIN2	CIN3		Invasive cancer
CIN system							
WHO system	Normal /benign condition	? Not recognized	Mild dysplasia	Moderate dysplasia	Severe dysplasia	CIS	Invasive cancer
Bethesda terminology (cytology)	Normal/benign conditions	ASCUS (including HPV change)	LSIL	HSIL			Invasive cancer
Bethesda terminology (applied to) Histopathology)	Normal/benign Conditions		LSIL (includes HPV changes)	HSIL			Invasive cancer
Cervicography (Kims classification)	Normal/BA		SA	PL	PH		PC

BAUS: basal abnormalities of uncertain significance; CIN: cervical intraepithelial neoplasia; ASCUS: atypical squamous Cells of undetermined significance; LSIL: Low Grade Squamous Intraepithelial Lesion; HSIL: High-Grade Squamous Intraepithelial lesion; HPV: Human Papillomavirus; BA: benign atypical lesion; SA: suspious atypical lesion; PL: Positive-Low Grade CIN; PH: Positive-High Grade CIN; PC: Positive Invasive Cancer; WHO Classification: Papanicolau smear system

3. Adjuncts to cytologic screening

When cytology was introduced, there was an idealistic opinion that regular yearly cytological examinations would completely eliminate cervical cancer. However, this goal was never achieved, even in populations screened practically 100% as was done in British Columbia. The reason for this is the false-negative rate of cytology. The false-negative rate of cytology is difficult to establish, because if cytology is negative and the cervix is not clinically suspicious, nothing else is done. From a mathematical model, Coppleson (1974) calculated that the false-negative rate of a single Pap smear is between 20-44%.

The most dependable and best diagnostic methods for detection of cervical cancer may, of course, be direct inspection of the transformation zone of the cervix with the naked eye, collection of cytologic material, HPV-DNA test, colposcopy and colposcopy-guided biopsy. These combination methods are, however, individually based. On the other hand, the population based diagnostic method, at present, is the cytologic smear as a single method with adjunctive cervicography or HPV-DNA test.

There is a well established causal link between HPV and all grades of CIN and invasive cervical cancer (Richard 1998). The technology for HPV detection is still evolving, with continuing optimization of type spectrum, sensitivity, specificity, and ease of use.

Numerous strategies such as neural network, thin-layer slide preparation, and immunostaining with antibodies against the DNA regulatory proteins, Cdc6 and Mcm5

have been described to improve the detection efficiency for dysplastic cells in Pap smears.

In literature (Navratil et al 1958; Tawa et al 1988; Kurman et al 1991; Spitzer et al 1986; Kim 1999; Kim and Namkoong 1997), reporters of the colposcopy and the cervicography demonstrated that by combination of both cytology and colposcopy or cervicography, it is possible to increase the accuracy of cervical cancer detection to almost 100%.

4. Colposcopic assessment of uterine cervix

The colposcope is a microscope designed to allow examination of the cervix with magnification ranging between 5- and 40- fold. It was invented by Hinselmann (1954), like others in his time, felt the need to diagnose cancer of the cervix in its earliest possible form, and thought that if the cervix could be magnified with the use of an optical instrument, cancer would become visible at its earliest stage, as either a small ulcer or a small exophytic lesion. Cervical cytology and colposcopy were complementary to each other, and Hinselmann (1954) stated that "the man who thinks that cytology is better than colposcopy, or that colposcopy is better than cytology, is a fool who knows nothing of either".

Transformation zone of the uterine cervix: Definition of transformation zone: the area of cervix bounded caudally by the original squamocolumnar junction, and cephalically by highest point that squamous metaplasia reaches.

Ideally, SCJ is situated at the external os, and squamous epithelium lines the ectocervix, and columnar epithelium lines the canal.

Deviation from the ideal anatomy of the cervix is the starting point of a chain of events that lead to invasive squamous cell carcinoma.

Squamous metaplasia: Vaginal higher acidity than endocervical environment in reproductive age cause squamous metaplasia from columnar epithelium mature and fully differentiated epithelial cells cannot change into another type of epithelium. The first sign of squamous metaplasia in endocervix is beginning of fusion of endocervical villi through the reserve cell hyperplasia.

Coppleson (1974) and Reid and Scalzi (1985) described as follows the three stages of metaplasia that may be colposcopically recognizable (Kim et al 1997)

1. stage I there is loss of translucency of the columnar epithelial villi, with each individual villus assuming a ground-glass appearance
2. stage II the grape like configuration disappears as successive villi are fused and their intervening spaces filled in.
3. stage III the villous configuration is lost, and the new surface takes on the appearance of a decreasingly translucent vascular area, following fusion of the villi, the end result is normal squamous epithelium

Colposcopic terminology and nomenclature: New nomenclature: New nomenclature for colposcopy (Table II) was proposed by the Nomenclature Committee of the International Federation for Cervical Pathology and Colposcopy, 7th World Congress of Cervical Pathology and Colposcopy, Rome, May 13-17, 1990 after report of the committee on terminology. The original colposcopic terminology developed by Hinselmann (1954) over 50 years ago was cumbersome, confusing and did not reflect new concepts of the natural history of cervical neoplasia. The old colposcopic terminology was one of the major obstacles in the further progress of colposcopy.

Table II. Colposcopy Terminology proposed by the Nomenclature Committee of the international Federation for Cervical Pathology and Colposcopy. 7th world Congress of Cervical Pathology and Colposcopy, Rome, May 13-17, 1990.

A) normal colposcopic findings
- Original squamous epithelium
- Columnar epithelium
- Normal transformation zone

B) abnormal colposcopic findings
1. within the transformation zone
   - Acetowhite epithelium
     - Flat
     - Micropaillary or microconvoluted
   - Punctation
   - Mosaic
- Keratosis (leukoplakia)
- Iodine Negative

Atypical vessels

2. outside the transformation zone (e.g. ectocervix, vagina)
   acetowhite epithelium
      flat
      micropapillary or microconvoluted
   Punctation
   Mosaic
   Keratosis (leukoplakia)
   Iodine negative
   Atypical vessels

C) colposcopically suspect invasive carcinoma

D) unsatisfactory colposcopy
   Squamocolumnar junction not visible
   Severe inflammation or severe atrophy
   Cervix not visible

E) miscellaneous findings
   Non acetowhite micropapillary surface
   Exophytic condyloma
   Inflammation
   Atrophy
      Ulcer
      Other

4-1. Colposcopic appearance of normal cervix

The colposcopist must be aware of the following easily observable characteristic features of normal and abnormal cervical epithelium, as described by Kolstad;

1. vascular pattern
2. intercapillary distance
3. color tone relative to the junction of normal and abnormal tissue
4. surface contour
5. sharp line of demarcation between different tissues

4-2. Colposcopic appearance of cervical intraepithelial neoplasia

Acetowhite change: Epithelium that turns white after application of acetic acid (3-5%) is called acetowhite epithelium. The application of acetic acid coagulates the proteins of the nucleus and cytoplasm and makes the proteins opaque and white. Dysplastic cells contain large amounts of chromatin (protein), therefore they are those most affected.

Vascular pattern of abnormal epithelium

Punctation: punctation refers to dilated capillaries terminating on the surface, which appear from the ends as a collection of dots. When these vessels occur in a well-demarcated area of acetowhite epithelium, they indicate an abnormal epithelium-most often CIN.

Mosaic: Terminal capillaries surrounding roughly circular or polygonal-shaped blocks of acetowhite epithelium crowded together are called mosaic because their appearance is similar to mosaic tile.

Atypical Vessels: These are terminal vessels which are easily seen by the colposcopist. Typically, they are irregular in size, shape, course and arrangement, and the intercapillary distance is significantly greater than that which is found in normal epithelium. There is no particular pattern, the vessels being arranged in a totally haphazard way.

Intercapillary distance

This is the distance between vessels or space encompassed by the mosaic vessels. In normal squamous epithelium, the maximal intercapillary distance of the hairpin and network capillaries varies, but is approximately 50-200 m with an average of 100 m. On the other hand, the maximal intercapillary distance increases as the lesion becomes more severe, i.e. in CIN 1, the average intercapillary distance is often 450-500m.

Colour tone: color tone may change as a result of the increasing vascularity, surface epithelial necrosis, and in some cases, production of keratin. The color tone is a yellow-orange rather then the expected pink of intact squamous epithelium or the red of the endocervical epithelium.

Surface contour: The surface of a lesion can be described as smooth and even, or irregular. For

example, normal squamous epithelium has a smooth surface, while columnar epithelium is easily recognized by its typical grape-like or villous appearance. In abnormal cases, the surface epithelium ulcerates as the cells lose intercellular cohesiveness secondary to the loss of desmosomes. Irregular contour also may occur because of a papillary characteristic of the lesion. This findings sometimes can be confused with a human papillomavirus papillary growth on the cervix and for that reason, biopsies should be performed on all papillary cervical growths.

Line of demarcation

The borderline or line of demarcation between normal and abnormal squamous epithelium is usually sharp, due to the changes in colour that is present in the abnormal epithelium. In contrast, the line of demarcation between normal squamous epithelium and inflammatory lesion is more diffuse. Also, almost always a sharp line of demarcation will be seen between normal squamous and normal columnar epithelium, particularly after application of acetic acid.

Leucoplakia

Leukoplakia is seen less commonly on the cervix than acetowhite epithelium and the vascular abnormalities are detailed above. Normal original or mature metaplastic squamous epithelium of the cervix does not have a layer of keratin on the surface, but in some circumstances keratosis occurs and leucoplakia is seen at colposcopy. An area of leukoplakia is white before acetic acid is applied and does not change in colour after application. It is usually seen as one or more raised plaques which may coalesce as the area becomes larger. The outline of the area is usually irregular.

4-3. Colposcopic features of invasive carcinoma

In many instance, the disease will be clinically unsuspected and will be recognized for the first time when the patient is referred for coposcopy following an abnormal cervical smear.

Even where the cervix is macroscopically normal, wide intercapillary distance, the presence of atypical vessels and an irregular surface, often with ulceration, will alert the colposcopist to the possibility of invasive disease.

4-4. Colposcopy as an adjunct to cytologic screening

In 1956, Navratil (1958) from Graz, demonstrated that both cytology and colposcopy have some false-negative results; however by combination of both methods, it is possible to increase the accuracy of cervical cancer detection to almost 100%. This data was confirmed by Limburg (1958), Coppleson (1974) and others (Kim and Namkoong 1997); however, colposcopy screening still was never used on a larger scale. There are two reasons for this. First, the colposcope is an expensive instrument and it is not possible to equip every examination room with a colposcope. Second, and even more importantly is that there are not enough experts well trained in colposcopy. To overcome these problems a new instrument, cervicograph was introduced in 1981. (Stafl 1981) The colposcopic examination demands special training and a fairly expensive device, and is subjected to inter-or-intra-observer's bias with respect to interpretation.

5. Cervicography as an adjunct to screening of cervical cancer*

Cervicography was developed by Stafl in 1981 and provides a refinement to the approach to screening and could also be used as an intermediary triage for the atypical and negative Pap smear.

Cervicography was patented by the Medical College of Wisconsin (MCW) and is marketed by National Testing Laboraties (NTL) in United States and Cancer Screen Laboratory (CSL) in Korea (Kim 1997) (Coppleson et al 1986) (Lee & Kim 2000). This new method for detection of cervical disease provides a refinement to the approach to screening and could also be used as an intermediary triage for the atypical Pap smear. (Campion et al 1986; Ferris et al 1993). The most important aspect of the quality assurance mechanisms in cervicography, is the skill and expertise