Early detection of endometrial cancer and hyperplasia: a reappraisal

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Summary: It is widely recognized that endometrial carcinoma represents one of the most frequent types of pelvic malignancy in women. Recent improved knowledge about population at risk, the criteria of classification of endometrial hyperplasia, different potential for neoplastic transformation for each type of neoplasia, and asymptomatic latency of the pathology allow some considerations. Endometrial cytology is of basic importance in a mass screening programme due to its low cost, accuracy and feasability. The combination of hysteroscopy and endometrial biopsy is the diagnostic method of choice for symptomatic patients. It permits the elimination of curettage in the diagnostic management in over 95% of cases, with obvious advantages, better diagnostic accuracy and greater convenience for patients and doctors.

Key words: Endometrial Cancer; early detection; screening.

It is widely recognized that endometrial carcinoma represents one of the most frequent types of pelvic malignancy in women ([1]).

During the last twenty years a large increase of the number of new cases has been observed in many USA regions. This tendency began in the 1960s and reached a peak in 1975 ([2, 3]) (Tab. 1).

White women between 50 and 75 years of age living in the more industrialized countries were particularly affected ([1, 4, 5]).

From the epidemiological point of view this malignancy is not very clear ([4, 6]). The absence of national tumor registries, the lack of criteria in the definition of the population at risk, the approximations of the classification criteria and, finally, the absence of a clear clinical screening program and treatment protocols are the main causes of this problem.

POPULATION AT RISK

Exogenous estrogen treatment ([7, 8, 9, 10]) endogenous estrogens ([11, 12]), obesity ([13, 14, 15]), hypertension ([16]) and high-fat diet ([17]) are all considered risk factors for endometrial carcinoma. All of them induce, by different metabolic way, higher levels of free blood estradiol. Estradiol has been shown to have a close link with endometrial proliferation, which means a rise in the mitotic index of this tissue and increase of the possibility of cellular mutation ([11, 12]).

However in 30% of the cases endometrial carcinoma is not a hormone-dependent malignancy and in this type of endometrial malignancy the clinical evolution seems to be more aggressive ([18]).

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Table 1. – *Number of gynecologic neoplasmas in the United States during 1982* *.

Localization	No. of new cases	No. of deaths
Cervix	16,000	7,000
Endometrium	39,000	3,000
Ovary	18,000	11,400
Others	4,400	1,000

* From American Cancer Society: Cancer Facts and Figures, 1981. Used with permission.

CRITERIA OF CLASSIFICATION OF ENDOMETRIAL HYPERPLASIA

The term endometrial hyperplasia (EH) may include many different types of cellular changes ranging from paraphysiological to the frankly pathological forms ([19]). The histopathologic classification has been based on a morphologic or a cytologic evaluation of the lesion. Nowadays, the cytologic appearance of the endometrial pathology aspect has been considered the only way to follow for classifying the endometrial hyperplasia especially those forms that may undergo neoplastic transformation. Two pathogenetic types of endometrial hyperplasia have been described according to the presence of cytological atypias ([20, 21]). Lesions with cytological nuclear atypias have a high potential for neoplastic transformation and they should be considered as precursors of endometrial carcinoma.

CLASSIFICATION OF ENDOMETRIAL CARCINOMA

The classification of endometrial cancer is much less complicated than that of hyperplasia. The grading and histologic typing of endometrial adenocarcinoma provide important information regarding the biological behaviour.

Jones ([22]) reported up to 5 years survival in 81% of well differentiated forms, in 74% of the moderately differentiated forms and in 50% of the undifferentiated forms.

Some reports ([18, 23]) have classified endometrial carcinoma on the basis of the pathogenesis. 1) 70% of the cases, are hormone-dependent and involve relatively young women with histories of anovulation and abnormal bleeding; the lesions are always well differentiated. 2) 30-40% of the cases are not related to the metabolic or endocrine systems; most of them are asymtomatic and they are more common in older women. Morphologically, papillary and undifferentiated types are seen.

DIAGNOSIS OF ENDOMETRIAL HYPERPLASIA AND CARCINOMA

In over 90% of cases the first symptom of endometrial neoplasia is abnormal uterine bleeding. The evaluation of this symptom is stricly correlated with the early diagnosis of endometrial pathology. New methods and techniques have been reported to evaluate the patient and so facilitate diagnosis.

1. – NON INVASIVE TECHNIQUES

A) - Ultrasonography;
B) - Cervical and vaginal cytology;
C) - Endometrial cytology.

A) ULTRASONOGRAPHY

Ultrasonographic evaluation of endometrial tissue could be helpful in the evaluation of the phases of the endometrial cycle or in the differentiation of the different stages in woman's life ([24, 25]).

The endometrium looks like a linear image during the follicular phase and a bulky echogenic image in the luteal phase. The endometrium cannot be observed by ultrasound during puberty and after menopause. Increased echogenicity of the en-

dometrial image can be revealed in cases of hyperplasia, polyps, submucous myoma or adenocarcinoma. The observation suggests that sonography may be paticularly valuable in the assessment of endometrial pathology.

A recent study ([25]) reports the use of ultrasound in asymptomatic patients at risk for endometrial pathology. Results were compared with hysteroscopic and biopsy examinations. The accuracy of ultrasound in revealing endometrial pathology was approximatively 87%.

B) CERVICAL AND VAGINAL CYTOLOGY

It is widely recognized that cervico-vaginal cytology cannot be considered a technique for diagnosing endometrial cancer. However in 50-60% of symptomatic patients a carefully evaluated Papanicolau smear reveals the presence of abnormal endouterine cells ([26]).

C) ENDOMETRIAL CYTOLOGY

Several technique have been utilized to obtain an endometrial sample directly from the uterine cavity. Some reports attest a very high accuracy of the cytologic method depending on the method adopted ([27, 28]), but this approach has not been widely used in clinical practice probably because it is much more difficult to interpret than cervical cytology.

Washing, aspiration or brushing are the main methods used. They provide excelent results, they are well tolerated and the costs are low.

However, the specificity and sensitivity of the cytologic evaluation are so low that they cannot be applied to a symptomatic case, where histological techniques seem to be more reliable.

In conclusion endometrial cytology appears to have an important role only in the screening of asymptomatic patients at risk for endometrial neoplasia. This statement looks valid both for its efficiency and for its very low cost ([29]).

2. – INVASIVE TECHNIQUES

A) - Hysteroscopy;
B) - Endometrial biopsy;
C) - Dilatation and Curettage (D & C).

A) HYSTEROSCOPY

In the early 1980s, with the introdution of small endoscopes (less than 4-5 mm outer diameter), hysteroscopy became an office procedure. Moreover, the use of CO_2 as a distension medium in the uterine cavity (with rigid safegards on the delivery mechanism) has been of great help, as it allows clearer vision with an extremely simple technique ([30]). It is now possibile to perform a comprehensive endoscopy examination of the uterine cavity as an office procedure without using any type of anethetic or dilatation of the cervical canal. Obviously, the indications for this examination have increased considerably.

A major advance in the evolution of hysteroscopy is the microcolpohysterescope designed by Hamou ([5]). This apparatus has four magnifications, 1X, 20X, 60X and 150X: The first two are generally used for panoramic view, while the latter two are used for microscopic observation. Hysteroscopy allows the clinician to visualize lesions compatible with endometrial hyperplasia and to select patients for endometrial biopsy. Unfortunately, it is not possible to find a corresponding hysteroscopic picture for every histologic aspect of endometrial hyperplasia. Therefore we have developed a classification of endometrial hyperplastic lesions which can be applied both in clinical and endoscopic practice. It is based on histologic and hy-

steroscopic features, always bearing in mind, however, the natural history of these lesions.

Low-risk endometrial hyperplasia (EH): from a hysteroscopic point of view, these cases often present a picture similar to that of normal glandular endometrium. The plasticity of the mucosa makes it possible to asses its thickness by means of simple pressure on the endoscope. The cystic form often shows a particular hysteroscopic picture of glandular orifices with real cystic formations approximately one millimeter in diameter.

High-risk endometrial hyperplasia (EIN): the hysteroscopic and histologic aspects of this condition are more comparable to preneoplastic lesions or neoplastic lesions. In this situation, the hysteroscopic picture is also extremely varied; there are very clear architectural distorsions. Polypoid aspects are often present and vascularization is clearly atypical.

In a previous study, we tried the diagnostic accuracy of the hysteroscopic pictures alone compared to the histologic results ([31]). The hysteroscopic diagnosis of EH in 98 patients agreed completely with histology in 70%. In 17% there had been a false identification as EH. In contrast, among twelve patients with the hysteroscopic diagnosis of EIN, there was histologic confirmation in 11 instance (92%), while in one case the histology showed hypo-atrophic endometrium. Hysteroscopy has proved to be extremely reliable for the diagnosis of endometrial neoplasia ([9]). The endoscopic pictures are so obvius and clear that they are hardly ever confused with other lesions. In its initial stage, adenocarcinoma shows a germinative picture, with irregular, polylobular, friable excrescenses which are partly necrotic or bleeding, vascularization is also irregular or anarchic. Regarding the accuracy of this investigation in detecting endometrial cancer, in a previous study ([31]), hysteroscopic confirmation was obtained in 94% of 17 patients with a proved histologic diagnosis of endometrial neoplasia.

In summary, although the diagnostic accuracy of hysteroscopy is extremely high, it should not be considered a diagnostic technique « per se », but rather as an examination to be used together with endometrial biopsy. In our opinion, hysteroscopy represents the ideal technique for the examination of women over the age of 45 who complain of any degree of abnormal bleeding. Its application, in association with endometrial biopsy when necessary, is particularly useful for the early detection of adenocarcinoma and for a correct diagnostic interpretation of all other forms of pathology which cause abnormal bleeding.

B) ENDOMETRIAL BIOPSY

Endometrial biopsy, like an office procedure without cervical dilatation and anesthesia, has been developed by reaching an optimal biopsy device.

Many instruments have been developed, trying to evaluate their usefulness on the basis of the quality of endometrial samples obtained ([30, 32, 33]).

By means of these devices it is possible to obtain different endometrial samples for both cytological-histological studies ([33, 34, 35]). The results show that histological endometrial evaluation has a very high accuracy ranging from 87 to 100% ([36, 37]).

Endometrial biopsy, offering an accurate histopatologic diagnosis, represents a well-known optimal techniques: however, on the other hand because of its blind approach to the endometrial cavity, it does not permit either sampling of focal lesions or directed biopsies.

In conclusion this approach looks very good for mass screening study, but by itself it cannot be used as a unique diagnostic approach.

C) DILATATION AND CURETTAGE (D & C)

At present D & C is probably the most commonly performed gynecologic operation due its double function of providing diagnosis and therapy at the same time ([38]).

Many studies have evaluated this technique on the basis of its safety, quality of the sampling, diagnostic accuracy, discomfort experience and therapeutic value.

Adequate sampling is reported in 77 to 84% of cases ([39, 40]). Lower figures have been reported in some cases such as in menopausal women or of atrophic endometrium.

When used by itself D & C misses focal endometrial lesions in more than 10% of the cases.

In 1984 Lerner ([41]) reported that the sensitivity of D & C appears to be only 20% with a predictive value in positive case of only 50%.

For a long time D & C was also considered a therapeutic approach. The higher incidence of renewed bleeding after the initial reduction observed in the months immediately following the intervention, shows how the misunderstanding arose ([42]).

Finally, D & C it is not a very satisfactory technique because its accuracy is relative and it prevides only an occasional and temporary therapeutic effect.

CONCLUSIONS

Some concepts may be derived from this report:

1) Endometrial carcinoma is becoming more frequent.

2) Ultrasound permits a diagnostic assessment of the endometrium. It appears able to identify the patients who require further diagnostic investigation.

3) Endometrial cytology is of basic importance in a mass screening program.

4) The combination of hysteroscopy and endometrial biopsy is the diagnostic method of choice for symptomatic patients. It permits the elimination of curettage in the diagnostic management in over 95% of cases, with obvious advantages; better diagnostic accuracy, and greater convenience for patients and doctor.

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