Endometrial Cancer: Study of the Precursors Lesions

Layla Abdul Amir  
Ali Hassan Altimimi

College of Medicin - Babylon University -Hilla P.O. Box 473, IRAQ.

Abstract
Carcinoma of the endometrium is one of the most common gynecologic malignancies and its incidence is rising. It typically occurs in elderly patients; approximately 80% are postmenopausal at the time of diagnosis. It has been suggested that endometrial carcinoma can be divided in two distinct types on the basis of their pathogenesis: the more common one—occurring as a result of excess estrogenic stimulation and developing against a background of endometrial hyperplasia. In the present study the nuclear area and shape of epithelial cells were measured in cytological specimens from cases with precursors of endometrial cancer including 15 patients with cystic hyperplasia of the endometrium and 12 patients with adenomatous hyperplasia and compared with 10 patients having endometrial cancer. Only specimens from patients with histological confirmed widespread disease of the endometrium were accepted in the study. The mean nuclear area in cystic hyperplasia was significantly lower than in adenomatous hyperplasia. Results from measurements with the same method in normal and malignant conditions were compared with those from hyperplastic conditions. Cases with precursors of endometrial cancer both cystic and adenomatous hyperplasia differed from normal endometrium but not from malignant conditions. There were no differences in nuclear shape between cases with precursors of endometrial cancer, and cases with malignant conditions.

Introduction
Reports on the ability of modern cytological cell samplers to replace curettage in the assessment of endometrial disorders show both high sensitivity and specificity of the cytological method in the detection of malignant endometrial lesions. [1-6]
Many authors have also reported the cytological detection of hyperplasia of the endometrium. Success in this field is variable as sensitivity varies between 20% and 90% in accuracy tests.[1-7] This may be because of variation in the sampling ability of the different types of instruments used, but may also reflect difficulties in interpretation of sampler material. The nuclei of hyperplastic epithelium from material aspirated from the endometrium are said to be larger than nuclei from normal endometrial epithelium but smaller than those found in malignant conditions[8-10] Irregular shape of the nuclei is said to be characteristic of adenomatous hyperplastic conditions.[11 12] Thus it may be possible with this material to identify a hyperplastic condition by using nuclear size and shape as diagnostic aids. On the other hand, measurements of multiple parameters in histological specimens have shown that nuclear size and shape are of little importance in the discrimination between different conditions of the endometrium.[13] Other investigators have found that in histological specimens nuclear size may be used to predict whether the hyperplasia will proceed to malignancy[14]

Measurements of nuclei in epithelial cells in cytological sampler material have shown that the use of nuclear area as a diagnostic criterion to differentiate between malignant and normal endometrium is of important values. Furthermore, the shape of the nuclei in normal and malignant conditions shows a significant variation.

The diagnostic value of nuclear size and shape in the detection of hyperplasia in cytological sampler material is still an open question. In the present research the morphometric criteria of normal, malignant conditions and precursors of endometrial cancer was studied.

Materials and Methods

Clinical Materials

Cytological material were obtained from specimens taken at colposcopy clinics in the Hilla gynecology hospitals and department of gynecology, Medical College, Babylon University, Babylon ,Iraq between Jan 1996 & June 2004.

The cytological material was available from a study of 62 cases in which cell sampling had been followed by curettage. 15 cases where the curetting showed cystic hyperplasia in all or most of the fragments of endometrium seen in the histological specimen were accepted for inclusion in the cystic hyperplasia group in this study. 12 cases showed adenomatous hyperplasia as a widespread phenomenon in the histological sample. These were accepted in the adenomatous hyperplasia group.

In the group with cystic hyperplasia 9 of the 15 patients were premenopausal. The median age was 46 years (range 30 to 65 years). 6 of the 12 patients with adenomatous hyperplasia were premenopausal. The median age was 51 years (range 45 to 69 years).

The measurements were performed with a light microscope, as described previously[7,8]. The nuclear circumference was measured, with recordings made at x400 magnification. A morphometric measurement was used to assay the length of the circumference, the area of the nucleus (in mm²), and the shape of the nucleus, expressed as a form factor. A circle has the form factor 1.0. Random measurements—that is, measurements of epithelial nuclei as they presented on screening of the slide regardless of subjective assessment—were performed in all cases.

The measurements that described previously were used in the current study to measure normal endometrial epithelium and cells from well and moderately differentiated endometrial carcinomas for comparison with
hyperplastic and other precursors conditions.
The same methods were used throughout. The statistical methods used were Student's t test and the $\chi^2$ test. Level of significance was set at $p < 0.05$.

**Results**
Endometrial hyperplasia is most seen during the perimenopausal period. However, it was also encountered in younger patients. Some of these develop as the result of estrogenic stimulation. The distinction between an extreme case of hyperplasia (Fig 1, 2) and a well-differentiated adenocarcinoma is very difficult, largely because of the fact that endometrial hyperplasia and carcinoma represent different points in a disease continuum at the morphologic, and cytodynamic levels. Microscopic features favoring carcinoma (Fig 3, 4) include marked pleomorphism with loss of polarity, complex ramification of disorderly arranged glands, extensive papillary formations, confluent glandular pattern with a solid or cribriform appearance, and desmoplastic stroma.

The mean nuclear area (MNA) in cystic hyperplasia was $45 \pm 10$ $\mu m^2$ and for adenomatous hyperplasia $62 \pm 11$ $\mu m^2$. This difference is statistically significant ($p < 0.01$). Using the $\chi^2$ test a MNA of 60 $\mu m^2$ gave the greatest discrimination between cystic and adenomatous hyperplasia. Nine of 10 cases (90%) were placed correctly in the cystic and three of four (75%) correctly in the adenomatous group ($\chi^2 = 5.92, p = 0.01$).

Cases with low MNA values tended to have low standard deviations (SD) while cases with high values showed greater variation in SD, but occasional cases with high values showed low SDs. The variation coefficient for the cystic hyperplasia group was $17\% \pm 4$ and for the adenomatous hyperplasia group $20\% \pm 11$.

The range of MNA values was from 25 to 90 $\mu m^2$ in cystic hyperplasia. Only one of the cases showed uniformity in the recordings. This case had low MNA values compared with the others. Most of the recordings in cystic hyperplasia were between 30 and 60 $\mu m^2$, but one case showed values from 50 to 95 $\mu m^2$.

In adenomatous hyperplasia the scatter had a different pattern, with most of the recordings higher than 50 $\mu m^2$, but one case showed recordings between 39 and 54 $\mu m^2$.

The nuclei were round or nearly round in both cystic and adenomatous hyperplasia. Mean form factor was 0.97 $\pm 0.02$ and 0.94 $\pm 0.04$ respectively; the range of values of both conditions was the same (0.84-1.0).

The MNA for normal epithelium was $38 \pm 9$ $\mu m^2$ and for malignant conditions $57 \pm 16$ $\mu m^2$. In cystic hyperplasia MNA was different from that of normal endometrium ($p < 0.05$), but not from that of malignant cases. The analysis of the results indicates that if the range in each case is taken into consideration, recordings from cystic hyperplasia could be similar to recordings from malignant cases. In adenomatous hyperplasia recordings were located among the upper half of the malignant recordings. Again the scatter shows that almost identical recordings could be made from a case showing adenomatous hyperplasia and a case showing a malignant condition.

At least a quarter of the recordings of MNA fall between 40 and 60 $\mu m^2$ in each condition of the endometrium, and in malignant conditions as much as half (Table 1). An MNA of 40 $\mu m^2$ gives a nuclear diameter of 5.2 mm, 60 $\mu m^2$ a diameter of 6.2 $\mu m$. 
Table 1 Range of mean nuclear areas (MNA) in the different endometrial conditions expressed as a percentage of the total number in each group.

<table>
<thead>
<tr>
<th>Endometrial condition</th>
<th>MNA &lt; 40 µm²</th>
<th>40 µm² &lt; MNA &lt; 60µm²</th>
<th>MNA &gt; 60µm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal endometrium</td>
<td>70</td>
<td>26</td>
<td>4</td>
</tr>
<tr>
<td>Cystic hyperplasia</td>
<td>30</td>
<td>57</td>
<td>1</td>
</tr>
<tr>
<td>Adenomatous hyperplasia</td>
<td>10</td>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>15</td>
<td>50</td>
<td>3</td>
</tr>
</tbody>
</table>

Discussion
The cytological samples from patients with cystic and adenomatous hyperplasia of the endometrium used in this study were highly selected. Only patients showing hyperplasia in large areas of the endometrium on histology were accepted for study. This was to ensure that hyperplasia could be expected in most of the structures in the sampler material. Since morphological criteria which differentiate clearly between normal and hyperplastic conditions in sampler material are not available, the recordings had to be made under random conditions. Hence, it was important to make sure that the smears were as representative as possible.

As in previous studies [9,16-22] the MNA values in hyperplastic epithelium fell between those of normal and malignant conditions. The present study also confirms that the MNA is lower in cystic than in adenomatous hyperplasia. [9,23-25] The scatter in the MNA values related to SD indicates that the size of the nuclei in normal endometrium and cystic hyperplasia varies in the same way. Contrary to previous reports no differences were found in nuclear shape in the various conditions of the endometrium. The values in adenomatous hyperplasia differed from both normal endometrium and cystic hyperplasia showing a constantly large MNA value from recording to recording in a given sample and the same tendency in all four cases. Judged on the basis of nuclear size and shape, the condition is similar to malignancy. The group is small, however, and firm conclusions cannot be drawn from the present data. Previous data from measurements on endometrial cells in endocervical aspirates have shown a significant difference in the MNA of cells from cases of adenomatous hyperplasia and well differentiated carcinoma of the endometrium.[9,26] This may reflect a difference in size between structures in exfoliated cells versus mechanically removed, rapidly fixed cells. No morphometric data from smaller material suitable for comparison with the study have been found in the published work. Measurements of nuclear area in normal, hyperplastic, and malignant conditions show that between 40 and 60µm² one will find 25% of the normal, 60% of the cystic hyperplasia, 25% of the adenomatous hyperplasia, and 50% of the malignant cases. This area corresponds to a range in nuclear diameter of 5.2 to 6.2 µm. It is questionable whether we would be able to recognize a colony of cells with nuclei of 5 µm diameters with a variation coefficient of 17% from a colony of cells with nuclear diameter 6 µm and variation coefficient of 21%, especially
if the two colonies cannot be examined in the same microscopic field. Thus it seems that the observed differences in nuclear size between normal, hyperplastic, and malignant conditions, were significant and it could be of practical use in differentiation between the various conditions.

**Conclusion**

The gynecological cytological sampler technique is intended for the investigation of a group of patients with an incidence of carcinoma of 1 to 10% (depending on the clinical criteria for the use of the sampler). It is thus important not only to be able to detect the malignant cases but also to use diagnostic criteria which give an acceptable degree of alarm. The use of nuclear size will, on the basis of the present work, create a constantly stressed situation as so many of the examined cases will have nuclei within the limits found in malignancy. Thus its use as a diagnostic criterion may be of great value in the predicting outcome of endometrial precursor’s lesions.

**References**

10. Ng ABP. Gynecol Oncol, 1974, 2, 162.
Figure 1: The uterus opened to reveal large fronds in the endometrial cavity as a result of hyperplasia.

Figure 2: Endometrial cytology from a case of endometrial hyperplasia (Original magnification x400).
Figure 3 Cytology of endometrial carcinoma (Original magnification x 500).

Figure 4 The cellular component of endometrial adenocarcinoma shows markedly atypical cytologic features (Original magnification x250).