Incidence of endometrial carcinoma in patients with endometrial hyperplasia

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Summary

Objective: The purpose of this retrospective study was to establish the risk of developing endometrial adenocarcinoma in patients diagnosed with endometrial hyperplasia.

Material and Methods: The incidence of endometrial hyperplasia and its relation with endometrial adenocarcinoma was evaluated in 1,139 patients who presented with abnormal bleeding between January 2000 and December 2004; D&C was performed in all cases. There were 591 (51.88%) cases of simple endometrial hyperplasia, out of which 110 (18.61% from 51.88%) cases had atypia, 60 (5.26%) cases of complex hyperplasia, out of which 19 (31.66% from 5.26%) had atypia, and the remaining 488 (42.84%) had different forms of mixed hyperplasia.

Results: The incidence of endometrial adenocarcinoma was 3.87% in atypical hyperplasia and 0.81% in other forms, and was related only to cases with atypia in which the incidence was 0.61%.

Conclusions: The most indicated measure to prevent endometrial carcinoma in cases with complex endometria hyperplasia with atypia is hysterectomy, while for other forms of hyperplasia, hormonal treatment is used but only under strict control.

Key words: Endometrial hyperplasia; Atypical hyperplasia; Endometrial carcinoma.

Introduction

Endometrial hyperplasia represents a series of glandular and stromal epithelial proliferating modifications which result in an abnormal architectural and cytological spectrum with simple or complex aspects and with or without the presence of atypia.

Patients were distributed in four specific histological categories of endometrial hyperplasia: simple hyperplasia with or without atypia and complex hyperplasia with or without atypia according to the classification used by the International Society of Gynaecological Pathologists and corresponding to those proposed by Kurman and Kaminsky in 1985 [1].

Endometrial hyperplasia could appear at any age between puberty and menopause but it most frequently appears during fertility in women. It is hard to determine a limit between endometrial bleeding, which has a clinically established organic cause, and to identify dysfunctional uterine hemorrhage. It has been found that even in uterine hemorrhage microlesional modifications can exist which, many times, are hardly identifiable even by histological exam [2].

Whatever the etiology of endometrial bleeding is, it is important to understand if the patient fits into the category of women at high risk for endometrial carcinoma.

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Material and Methods

The purpose of this study was to identify high-risk patients and to determine the incidence of endometrial carcinoma in patients with endometrial hyperplasia and repeated endometrial bleeding.

In the period 2000-2004, 1,139 patients hospitalized in our Clinic of Obstetrical Gynaecology, Craiova were studied retrospectively. They had endometrial bleeding with multiple etiologies, except spontaneous abortion.

The histological exam of the endometrium was performed in the Pathologic Laboratory of the Municipal Hospital of Craiova.

In some cases (34.6%) the histological exam was repeated for the same person, to reevaluate after treatment with progestin after a period of time adapted to the therapeutical protocol used.

The cases were followed according to age and form of hyperplasia in which in the *other forms of hyperplasia* category polypoid and stromal hyperplasia were included, and in the *mixed forms of hyperplasia* category all the cases which presented at least two types of hyperplasia were included.

Results

Recurrence of cases showed the highest frequency of endometrial hyperplasia in the 40-49 age group (628 cases), and the lowest incidence in groups of extreme ages: under 19 years (1 case) and over 60 years (34 cases). Correlating patient ages with endometrial hyperplasia with the cases according to the study period, the highest incidence was in 2003 (Table 1). This high level is problematic and unclear. However asserting that the difference between the number of cases other years of the study was not very big, we can say that the annual rate of endometrial hyperplasia was relatively constant.

Table 1. — *Distribution of cases in age/years.*

Year/Decade of age	<19 years	20-29 years	30-39 years	40-49 years	50-59 years	> 60 years	Total
2000	0	7	38	134	35	8	222
2001	0	7	52	123	49	7	238
2002	0	7	21	100	47	8	183
2003	0	15	43	130	65	3	256
2004	1	6	33	141	51	8	240
Total	1	42	187	628	247	34	1,139
%	0.08	3.68	16.41	55.13	21.68	2.98	100

Table 2. — *Distribution of cases of endometrial hyperplasia/years.*

Year/Form of hyperplasia	Simple endometrial hyperplasia without atypia	Simple endometrial hyperplasia with atypia	Complex endometrial hyperplasia without atypia	Complex endometrial hyperplasia with atypia	Other forms of endometrial hyperplasia	Mixed endometrial hyperplasia	Total
2000	79	42	12	7	35	47	222
2001	89	17	7	5	61	59	238
2002	76	6	7	1	48	45	183
2003	102	24	13	4	62	51	256
2004	135	21	2	2	37	43	240
Total	481	110	41	19	243	245	1,139
%	42.2	9.6	3.5	1.6	21.3	21.5	100

The histologic types of endometrial hyperplasia found are shown in Table 2.

Simple endometrial hyperplasia without atypia had cytological modifications with a slow augmentation of the rapport with the nucleus/cytoplasm and abundant stroma (Figure 1).

Complex endometrial hyperplasia without atypia presented an extended glandular proliferation with discrete intraluminal proliferation (Figure 2) and a strong augmentation of the rapport with the nucleus/cytoplasm.

Complex endometrial hyperplasia with atypia was manifested by intense glandular proliferation with pluristratified glandular epithelium, lower stroma and a hypercromatic nucleus with irregular contours (Figure 3). In the other forms of endometrial hyperplasia, zones of complex endometrial hyperplasia were present with or without atypia, as well as zones of complex endometrial hyperplasia with atypia alongside adenocarcinoma (Figure 4).

The incidence of endometrial carcinoma was significantly lower than the incidence cited in the literature. We found endometrial adenocarcinoma in one case of simple endometrial hyperplasia with atypia, in four cases of patients who presented complex endometrial hyperplasia with atypia and in two cases with mixed forms of endometrial hyperplasia.

The diagnosis of adenocarcinoma in the case of simple endometrial hyperplasia with atypia was predicted after a second histological exam was performed after 12 months, a period in which the patient followed treatment with progesterone.

For the other six cases, the diagnosis was established at the first histological exam and followed by an adequate surgical course.

As for a correlation between bleeding and the presence of atypia and endometrial adenocarcinoma, we found that the symptoms guiding the patient to the doctor were not significant for the appearance - especially of one of the forms of endometrial hyperplasia or endometrial adenocarcinoma (postmenopausal bleeding, vaginal bleeding, endometrial polyps, irregular menses). What is important is that there were enough symptoms present to determine that the patient should be examined.

Discussion

Naturally the principal relation which was investigated was the relation between endometrial hyperplasia and endometrial adenocarcinoma, a possibility that has been suggested by multiple studies [3-5]. Endometrial hyperplasia has been suspected of being a precursor stage of endometrial adenocarcinoma, discovering zones with adenocarcinoma and hyperplasia with atypia at the level of the endometrium [6].

Simple endometrial hyperplasia with atypia (swiss-cheese hyperplasia) presents the lowest risk for endometrial adenocarcinoma and is considered the least dangerous [7, 8]. Complex endometrial hyperplasia without atypia (medium adenomatosis hyperplasia) has a risk of leading to endometrial adenocarcinoma of 1-4%, but is not considered as a preneoplastic form. Usually, this form responds to progestin therapy.

At the time when atypia appears the situation is comparable to cases of cervical dysplasia because those atypical cells are not neoplastic, but have a big posibility of becoming so. Therefore, the patient has a risk of developing endometrial adenocarcinoma during her life, but does not have any certainity. Thus, it is much better to consider complex endometrial hyperplasia with atypia as endometrial intraepithelial neoplasia (EIN), and to identify atypia at the histological exam. Thus, we recommend D&C in the majority of suspicious cases, even if some authors have shown that the risk is low enough to not identify adenocarcinoma by using hysteroscopic resection [9].

In our case series the frequency of endometrial adenocarcinoma was very low, appearing only in cases of endometrial hyperplasia with atypia (4.2%). Thus early surgical intervention was carried out with progesterone therapy being reserved for cases of endometrial hyperplasia without atypia, depending on the age of patient, but without making concessions when the situation required hysterectomy. We have discovered that when the option of the patient is for progesterone treatment and not for a surgical intervention in severe forms of atypia only 20% of cases respond to this treatment. Nonetheless, after a surgical intervention is carried out in these patients, we find endometrial carcinoma in 25-40% of cases undetected at the previous biopsy. Complex endometrial hyperplasia with atypia necessitates hysterectomy whenever fertility is not a priority [10].

ig. 1

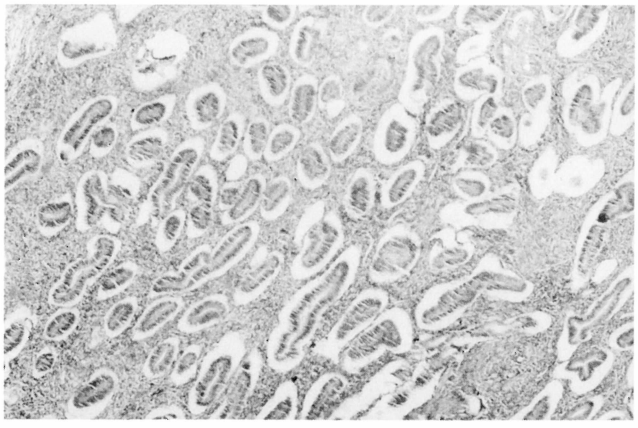
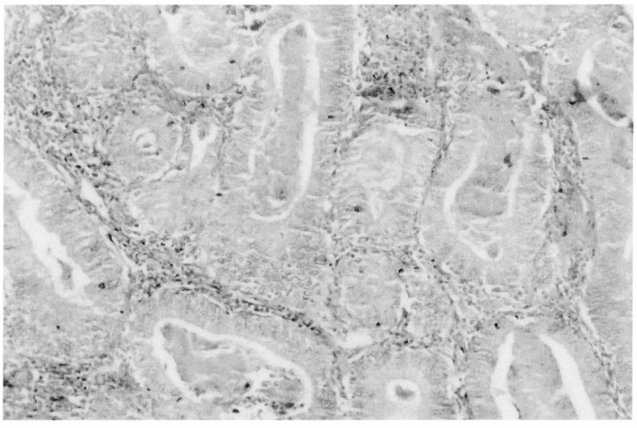


Fig. 2



g. 3

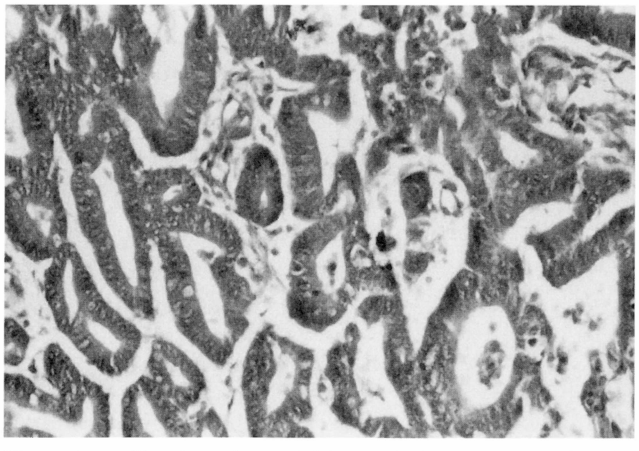


Fig. 4

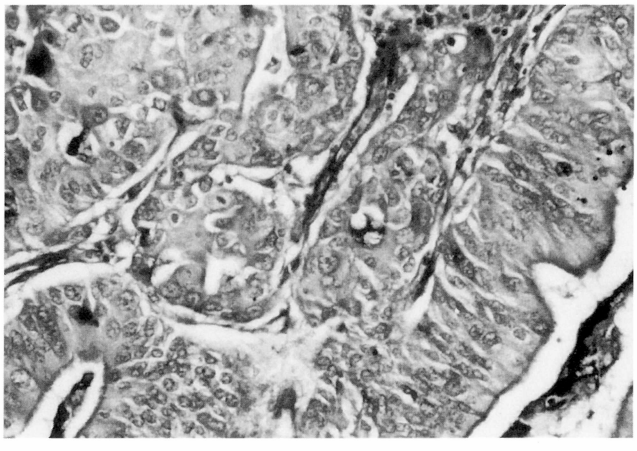


Figure 1. — Simple endometrial hyperplasia without atypia (giemsa).
Figure 2. — Complex endometrial hyperplasia without atypia (gömori trichome).
Figure 3. — Complex endometrial hyperplasia with atypia (hematoxylin eosin).
Figure 4. — Complex endometrial hyperplasia with atypia and areas of adenosquamous adenocarcinoma (hematoxylin eosin).

Conclusions

Due to the high risk of endometrial adenocarcinoma which coexists with endometrial hyperplasia with atypia, the best medical indication is hysterectomy. If, for some reason, the patient refuses or cannot undergo an immediate surgical intervention, they have to be correctly looked after during the entire progesterone treatment with periodic biopsies and when possible a surgical intervention as soon as possible.

Abnormal bleeding is the first symptom of hyperplasia of the endometrium. If patients are correctly informed about the risk it represents, many endometrial carcinomas or preneoplastic states could be avoided.

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