Singapore Med J 1997; Vol 38:11-15

Endometrial Hyperplasia And The Risk Of Endometrial Carcinoma

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ABSTRACT

Objectives: To determine the incidence of endometrial carcinoma in endometrial hyperplasia and try to identify those patients at greatest risk.

Methods: We conducted a retrospective study of 116 patients who had simple, complex or mixed (simple with focal complex) endometrial hyperplasia with or without atypia, from January 1991 to December 1994.

Results: Twenty-nine patients had endometrial hyperplasia with atypia and 87 without atypia. Incidence of endometrial carcinoma was 27.6% in those with atypia; and 3.4% in those without atypia. All were stage I (A or B) adenocarcinomas. Polycystic Ovary Disease and subfertility were found significantly in the cases with cytological atypia; however, they were not significant in the cases with carcinoma. No significant historical differences that could predict carcinoma were found.

Keywords: endometrial hyperplasia, cytological atypia, endometrial carcinoma

INTRODUCTION

'Endometrial hyperplasia' denotes a set of mixed epithelial and stromal proliferations that exhibit a spectrum of architectural and cytological abnormalities ranging from "disordered proliferative" endometrium to proliferations so complex and atypical that they resemble well-differentiated adenocarcinoma[1].

There has been many attempts at classifying endometrial hyperplasia over the years. The newly proposed classification formulated by the International Society of Gynaecological Pathologists (ISGP) under the auspices of the World Health Organisation (WHO) has four categories, corresponding to those proposed by Kurman in 1985[2]: *simple hyperplasia, complex hyperplasia, atypical simple hyperplasia and atypical complex hyperplasia.* In this classification, simple hyperplasia includes lesions with mild and moderate degrees of glandular crowding, complex hyperplasia is reserved for lesions with marked glandular crowding and complexity. In atypical hyperplasia, there is cellular atypia indicated by prominent nucleoli, variation in nuclear size and shape, increased amounts of eosinophilic cytoplasm and coarse or clumped nuclear chromatin[3]. Atypical simple hyperplasia is uncommon due to the natural progression of the lesions from simple hyperplasia to complex hyperplasia to atypia appearing. Carcinoma developed in only 1.6% of patients without atypia compared to 23% of patients with atypia[2].

Endometrial hyperplasia with cytological atypia has been recognised for many years as a cancer precursor[1-11]. Kurman in 1985[2] showed that cytological atypia is the most important feature in identifying a significant frequency of progression to carcinoma. The risk of endometrial carcinoma has been reported to be between 5% and 25% in some centres[2,5,6,8,9].

We are interested in determining the incidence of endometrial carcinoma in cases of endometrial hyperplasia in this centre to determine if these findings could be confirmed and to try to identify those patients at greatest risk of endometrial cancer.

PATIENTS AND METHODS

Patients were selected by screening the database of the histopathological laboratory at Kandang Kerbau Hospital for all cases of simple, complex and mixed (simple with focal complex) endometrial hyperplasia with or without cytological atypia on either endometrial biopsy or curettage between January 1991 and December 1994.

Endometrial lesions prior to June 1993 were classified as cystic or adenomatous endometrial hyperplasia according to the criteria set by Tavassoli and Kraus[8]. Cystic hyperplasia was taken to be simple hyperplasia and adenomatous hyperplasia to be complex hyperplasia. Cystic adenomatous hyperplasia and simple adenomatous hyperplasia were found to be simple with focal complex hyperplasia on review of slides and we would call them mixed hyperplasia in this study. Occasionally, there were diagnoses such as atypical hyperplasia or hyperplasia with atypia without mention of whether it was cystic or adenomatous. For these ambiguous diagnoses, the histology slides were reviewed and re-classified into simple, complex or mixed hyperplasia with or without atypia.

From June 1993, the categorisation of endometrial hyperplasia used in Kandang Kerbau Hospital was according to the ISGP criteria which correspond to those established by Kurman in 1985[2].

Patients with coexisting adenocarcinoma at the time of uterine sampling were excluded from the study.

Medical records of the cases of simple hyperplasia were not reviewed as there were no cases of cytological atypia among these cases and the risk of carcinoma from simple hyperplasia is very low due to the natural progression of the condition. There were 185 cases of complex and mixed hyperplasia with and without cytological atypia. The medical records of these cases were reviewed to obtain historical, operative and pathological data.

Histopathological findings of the second histological report obtained was defined as second histology. The specimen(s) for this second histological report was obtained, at an interval from the first uterine sampling, from a hysterectomy or an endometrial biopsy by a dilatation and curettage or Pipelle endometrial sampling. The interval between the first and second histological reports was variable due to the different methods of therapy undertaken.

If there was carcinoma, the presence or absence of endometrial hyperplasia, type of endometrial carcinoma, stage and grade of endometrial carcinoma, presence or absence of myometrial invasion and percentage of invasion if present were noted. Staging of endometrial carcinoma

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Table I - Outcome at second histology

	First histological finding	
Outcome at second histology	Atypia	No atypia
Carcinoma	8 (27.6%)	3 (3.4%)
Atypia	10 (34.5%)	8 (9.2%)
No atypia	9 (31.0%)	41 (47.1%)
Normal	2 (6.9%)	35 (40.2%)
Total	29	87

Table II - Characteristics of cases with carcinoma

		Atypia	No atypia
Number of carcinoma		8	3
Grade 1		7	1
Grade 2		1	2
Stage	1A	6	1
	1B	2	2
Myometrial invasion of <50%		2	2
Lymph node involvement		nil	1

Table III - Distribution of historical factors in the study population

Factor		Atypia (29)	No Atypia (87)	P	Carcinoma (11)	No Carcinoma (105)	P
Mean age, years		43.18	44.82	-	45.91	44.24	-
(range)		(23-84)	(24-61)	-	(30-84)	(23-71)	-
Race	- Chinese	22	73	-	10	85	-
	- Malay	3	9	-	1	11	-
	- Indian	4	4	-	0	8	-
	- Others	0	1	-	0	1	-
Obesity	- yes	18	20	-	4	34	-
	- no	3	20	-	2	21	-
	- no data	8	47	-	5	50	-
Gravidity		1.59	2.64	-	1.73	2.45	-
Parity		1.24	2.15	-	1.45	1.97	-
Menopause		2	6	NS	1	7	NS
Hypertension		6	18	NS	4	20	NS
Diabetes		6	8	NS	3	11	NS
Liver disease		0	0	-	0	0	-
Breast cancer		0	2	NS	1	1	NS
PCOD		3	1	0.0478	1	3	NS
Subfertility		8	9	0.0488	3	14	NS
Spon. abortion		3	6	NS	1	8	NS
F/H endom. Ca		0	0	-	0	0	-
F/H breast Ca		0	0	-	0	0	-
F/H GIT Ca		0	0	-	0	0	-
On HRT		0	3	NS	0	3	NS
Using OCP		0	0	-	0	0	-
Tamoxifen		0	1	NS	0	1	NS
Smoking		0	0	-	0	0	-

Entries represent mean values for continuous variables and number of patients for non-continuous variables.
Significance at $P < 0.05$, NS = not significant
PCOD = PolyCystic Ovary Disease
Spon. abortion = spontaneous abortion
F/H = family history
endom. Ca = endometrial carcinoma
GIT Ca = gastrointestinal tract carcinoma
HRT = hormone replacement therapy
OCP = oral contraceptive pills

was according to the International Federation of Gynaecology and Obstetrics(FIGO) staging system.

Data on all patients were analysed for differences between those with and those without atypia and those found to have cancer and those not to have cancer. $\chi 2$ tests were applied to categorical data, with Fisher's exact test used for values <5 in any category.

RESULTS

Of the 185 patients identified with complex or mixed (simple with focal complex) endometrial hyperplasia, 35 had complex hyperplasia with atypia, 118 had complex hyperplasia without atypia, 2 had mixed hyperplasia with atypia and 30 had mixed hyperplasia without atypia.

A total of 116 patients had a second histology for comparison. There were 29 from the group with cytological atypia and 87 from the group without cytological atypia. The outcome at the second histology is presented in Table I. Atypia was not found in the single case of mixed hyperplasia with atypia at second histology.

A) Carcinoma

Incidence of endometrial carcinoma was found to be 27.6% (8 of 29) in those with atypia and 3.4% (3 of 87) in those without atypia. This was statistically significant at P=0.0000629. In the group with no atypia, carcinoma was found to be coexisting with cytological atypia in 2 of the 3 cases. The atypia may have been present at the time of endometrial sampling but was missed due to incomplete sampling. Characteristics of the cases with carcinoma are in Table II. No carcinoma was found for the group of mixed hyperplasia without atypia.

They were all stage 1 (A or B) adenocarcinomas. There were no cases of adenosquamous, clear cell or uterine serous papillary carcinoma. Eight were grade 1 carcinomas and 3 were grade 2 carcinomas. There were no cases of grade 3 carcinoma. Myometrial invasion was present in 36.4% of our cases with carcinoma (2 of 8 and 2 of 3). The only case with lymph node involvement was the case that had 40% myometrial invasion from the group without atypia. This patient received adjuvant radiotherapy.

B) Basic clinical characteristics

Basic clinical characteristics are presented in Table III. The mean age of the 116 patients with endometrial hyperplasia was 44.4 years, mean gravidity was 2.4, mean parity 1.9. Eight patients were postmenopausal. There were 95 Chinese, 12 Malays, 8 Indians and 1 Eurasian among the 116 patients. Twenty-four patients (20.7%) were hypertensive, 14 (12.1%) had diabetes mellitus, 2 (1.7%) had history of breast cancer, 4(3.4%) had polycystic ovary disease, 17 (14.7%) had history of subfertility, 9 (7.8%) had

Table IV - Presenting symptom(s)

Symptom	Atypia	No Atypia	P	Ca	No Ca	P
1) IMB	1	4	NS	0	5	NS
2) PMB	2	7	NS	1	8	NS
3) Menorrhagia	20	48	NS	7	61	NS
4) PCB	1	2	NS	0	3	NS
5) Irreg. menses	6	13	NS	3	16	NS
6) Subfertility	2	7	NS	1	8	NS
7) Others	2	8	NS	1	9	NS

IMB = intermestrual bleeding, PMB = postmenopausal bleeding, PCB = postcoital bleeding, Irreg. menses = irregular menses
Others included 1 case of secondary subfertility, cervical polyp, abdominal distension, lower abdominal pain and backache, recurrent urinary tract infection, secondary amenorrhoea, bleeding while patient was taking tamoxifen and 2 cases of dysmenorrhoea.
Ca = carcinoma
P significant at <0.05.
NS = not significant

spontaneous abortions before, 3 (2.6%) were on hormone replacement therapy and 1 of the patients who had breast cancer was taking tamoxifen. There were no patients with history of liver disease or family history of endometrial, breast or gastrointestinal tract cancer. None was noted to be a smoker and none was noted to be on oral contraceptive pills (assuming that the history taking was complete). We were unable to determine the number of patients who were obese as many of the case records lacked evidence of the patients' weight and height.

Only Polycystic Ovary Disease(PCOD) and subfertility were found to be significant in cases with cytological atypia; however, they are not significant in the cases with carcinoma. There are no significant distinguishing characteristics between those with and without carcinoma.

C) Presenting symptoms and signs

The presenting symptoms of our patients are tabulated in Table IV. Six patients had more than one symptom. The P value was significant at <0.05, hence there was no statistical significance between symptoms for the atypia and no atypia groups and between the carcinoma and no carcinoma groups.

Abnormal uterine bleeding was the commonest presenting symptom in the form of menorrhagia, irregular menses, postmenopausal bleeding, intermenstrual bleeding or postcoital bleeding in descending order. The second commonest presenting symptom was subfertility.

An enlarged uterus was the commonest sign on clinical examination, being present in 72.4% of those with atypia, 55.2% of those without atypia, 69.6% of those found to have carcinoma at second histology and 54.5% of those who did not have carcinoma at second histology.

D) Endometrial sampling methods

The distribution of endometrial sampling methods is shown in Table V.

P = 0.086 when the method of endometrial sampling was compared between the atypia and no atypia groups;

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Table V - Method of endometrial sampling

	Atypia	No Atypia	Carcinoma	No Carcinoma
Pipelle	0	2 (2.3%)	1 (9.1%)	1 (1.0%)
D+C	16 (55.2%)	64 (73.6%)	7 (63.6%)	73 (69.5%)
D+C, hysteroscopy	13 (44.8%)	21(24.1%)	3 (27.3%)	31 (29.5%)

D+C = Dilatation and Curettage

Table VI - Treatment

	Atypia	No Atypia	Carcinoma	No Carcinoma
Conservative	5	23	1	27
Surgical	24	64	10	78
(P before op)	(25.0%)	(26.6%)	(50.0%)	(23.1%)

P = progesterone

Table VII - Outcome after conservative treatment with progesterone followed by repeat endometrial sampling by D+C or Pipelle

	First histological finding	
Outcome at second histology after treatment with progesterone	No Atypia	Atypia
Normal	17 (73.9%)	1 (20.0%)
No Atypia	4 (17.4%)	2 (40.0%)
Atypia	2 (8.7%)	1 (20.0%)
Carcinoma	0	1 (20.0%)
Total	23	5

and P = 0.727 when compared between the carcinoma and no carcinoma groups. P was significant at <0.05, hence the difference between the methods of endometrial sampling was not statistically significant.

P = 0.07 when dilatation and curettage(D+C) and D+C, hysteroscopy were compared for atypia and no atypia groups; and P = 0.727 for carcinoma and no carcinoma groups. P was significant at <0.05, hence the difference between the methods of endometrial sampling was not statistically significant.

E) Treatment

Treatment is usually guided by the age of the patient, her interest in child-bearing, refusal for surgery and degree of atypia of the hyperplasia. The types of treatment that the patients received are shown in Table VI. Conservative implies treatment with progesterone, then D+C or Pipelle endometrial sampling was repeated. Surgical treatment includes total hysterectomy with or without bilateral salpingo-oophorectomy, laparoscopically assisted vaginal hysterectomy (LAVH) and conventional vaginal hysterectomy. The patient may or may not have treatment with progesterone while awaiting surgery.

Progesterone treatment has been noted to be highly effective for hyperplasia without atypia. The outcome of our patients who were treated conservatively with progesterone is shown in Table VII.

The endometrium of 73.9% of patients who did not have atypia treated with progesterone became normal. We are unable to comment on the effectiveness of treating patients who had atypia with progesterone as our numbers were too few.

The time to the second histology was 1 to 20 months for the group who were treated conservatively and 1 week to 24 months for the group treated surgically. When the time to surgical treatment is prolonged, it was due to the patient initially refusing surgical treatment or the patient had defaulted and then returned for surgery, or as in 1 case, the patient was medically unfit for surgery and time was

required to resolve her medical problems. Of the 11 cases with carcinoma, 7 cases were found to have carcinoma at the second histology within 3 months of the first endometrial sampling. For these cases, carcinoma was probably already present when the first endometrial sampling was carried out, but was missed due to incomplete sampling.

DISCUSSION

The relationship between endometrial hyperplasia and endometrial adenocarcinoma has been suggested by numerous investigators over the years. Endometrial hyperplasia have been thought to be precursors of endometrial carcinoma because of an observed increase in the frequency of endometrial cancer in women with endometrial hyperplasia followed-up for a long period of time and the coexistence of adenocarcinoma and atypical endometrial hyperplasia in the same endometrium[11]. Kurman in 1985[2] showed that cytological atypia is the most important feature in identifying a significant frequency of progression to carcinoma. He noted in his study that carcinoma developed in 1% of the cases with simple hyperplasia, 3% of those with complex hyperplasia, 8% of those with simple atypical hyperplasia and 29% of those with complex atypical hyperplasia[2]. Recently, Janicek & Rosenshein[13] reported a 43% incidence of coexistent endometrial carcinoma in patients undergoing hysterectomy for atypical endometrial hyperplasia and Widra et al[14] reported a 50% incidence of endometrial carcinoma in patients with atypical endometrial hyperplasia.

In our study, adenocarcinoma of the endometrium was found in 27.6% of the cases with atypia. This rate is similar to the incidence reported by other publications[2,5,8,9]. However, in the group with no atypia, 3.4% of the cases were found to have endometrial carcinoma and adenocarcinoma was found to be coexisting with cytological atypia in 2 of the 3 cases. This rate is higher than Kurman's in 1985[2] and departs from the findings of Hunter[12] and Widra[14], both of whom did not find any carcinoma in their cases with no cytological atypia. One explanation for the discrepancy between our study and theirs may be that in our cases, the atypia may have been present at the time of endometrial sampling but was missed due to incomplete endometrial sampling. Another reason may be that atypia was not recognised by an inexperienced pathologist. The interpretation of atypia also varies with different pathologists.

No carcinoma was found for the group of mixed hyperplasia without atypia. This could represent the natural progression of endometrial hyperplasia, with simple hyperplasia progressing to simple with focal complex hyperplasia to complex hyperplasia. Atypia was not found in the single case of mixed hyperplasia with atypia at second histology. The atypia could have resolved with conservative treatment.

All our adenocarcinomas were stage 1 (A or B), of grade 1 or 2 and this finding is similar to those by Kurman in 1985[2], Hunter[12], Janicek[13] and Widra[14] although a small percentage of their patients had carcinoma of a higher stage or grade. Myometrial invasion was present in 36.4% of our cases with carcinoma. This is lower than that found by Hunter in 1994[12] where nearly half of endometrial cancers detected exhibited myometrial invasion and one of his cases had extrauterine metastases.

There was significant presence of history of polycystic ovary disease and subfertility in the group with atypia when compared with the group with no atypia. However, we were unable to determine any historical factors predictive of carcinoma or reproduce the well-documented historical risk factors among our patients with atypia and cancer [2,6,8,12,14-19]. This was probably due to the small sample size. This shows the difficulty faced by clinicians in attempting to differentiate those patients who are likely to have endometrial carcinoma from those likely to benefit from medical therapy.

Abnormal uterine bleeding was the commonest presenting symptom and the second commonest presenting symptom was subfertility. This is consistent with previous documentation[1-3,6-8,20]. However, these findings were not found to be statistically significant in our study. The finding of an enlarged uterus was the commonest sign and this is consistent with the documentation in the textbooks[1,3].

The distribution of endometrial sampling methods were similar in the two respective groups and no differences were found in the diagnostic accuracy of these methods. Hysteroscopy was not more helpful. This was also shown by Widra in 1995[14].

In our study, 73.9% of patients who had endometrial hyperplasia without atypia were cured with treatment with progesterone. This is consistent with the outcome reported by several authors. Progesterone treatment has been noted to be highly effective for hyperplasia without atypia, however, about 25% were unresponsive[2,5]. We are, unable to comment on the effectiveness of treating patients who had atypia with progesterone as our numbers were too few. However, all the authors advocate a complete curettage to exclude more severe changes elsewhere in the endometrium if a hysterectomy is not warranted.

Our data supports early surgical intervention with hysterectomy for patients with atypical endometrial hyperplasia whenever fertility is not a priority because the carcinoma found were all stage 1 and mainly grade 1 adenocarcinomas (with <50% myometrial invasion), they have a good prognosis with excellent survival without adjuvant therapy. All hysterectomy specimens for cases of atypical endometrial hyperplasia should be inspected carefully at the time of surgery and if presence of myometrial invasion is confirmed by frozen section, complete staging can be performed. Hysterectomy for atypical hyperplasia was also recommended by many other authors[2,5,7-9,14]. "Hysterectomy ends whatever dangers the endometrium can mount"[8].

Medical treatment with progesterone for patients with atypical hyperplasia is not recommended, unless there are medical problems which make the patient unfit for surgery, because of the high risk of cancer and it is not proven to be effective.

CONCLUSION

Because of the high incidence of endometrial carcinoma coexisting with atypical endometrial hyperplasia, it is recommended that patients with atypical endometrial hyperplasia have surgery as early as possible. Those who are managed medically for any reason should be evaluated regularly with a dilatation and curettage. Patients who are fit for surgery but refuse should be persuaded further with full explanation of the problem and emphasis on the risk of carcinoma.

ACKNOWLEDGMENTS

We would like to express our appreciation to the Departments of Reproductive Medicine and Maternal-Fetal Medicine at Kandang Kerbau Hospital for allowing us to use data from their patients in this study without which this study would not have been successful.

We would also like to thank the judges and organising committee of the 4th Annual KKH Scientific Meeting for awarding us the Best Poster Award.

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