Management of Endometrial Hyperplasia : A Retrospective Analysis

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Abstract

Objective: To determine the incidence of endometrial hyperplasia and to analyse the management of patients with this disorder.

Method: Retrospective descriptive study at the Department of Obstetrics and Gynecology, Ramathibodi Hospital. The medical records of patients with endometrial hyperplasia from 1990 to 1995 were analysed. Descriptive statistic was used.

Result: Medical records could be obtained in 87 per cent of cases. Incidence of endometrial hyperplasia was 1 per cent of gynecological out-patients and 11 per cent of uterine curettage. Half of the patients had cystic hyperplasia. Main treatment options of patients with cystic hyperplasia were expectant and progestogen therapy. The major treatments of adenomatous hyperplasia were progestogen and hysterectomy. Most patients with atypical hyperplasia underwent hysterectomy. Most of the patients with expectant or hormonal therapy have recurrence of abnormal uterine bleeding.

Conclusion: Endometrial hyperplasia is not uncommon in gynecolgical practice. All gynecologists should be familiar with the pathophysiology and the natural history of this disorder. The unopposed estrogen stimulation should be investigated and corrected. Treatment options should be tailored to individuals according to disease grading, age of the patient and desire of pregnancy. Long-term follow-up until menopause is mandatory to prevent the excessive uterine blood loss and the progression to carcinoma.

Key word : Endometrial Hyperplasia : Management - Retrospective Analysis

Endometrial hyperplasia is an outgrowth of endometrial glands and stroma characterized by a proliferative glandular pattern with varying degrees of architectural and cytologic atypia[1]. It is the result of prolonged unopposed stimulation by estrogen. Apart from the significant uterine bleed-

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ing the serious health hazard of endometrial hyperplasia is the progression to adenocarcinoma[2]. There are also clinical problems associated with the chronic anovulatory state which is a common cause of endometrial hyperplasia[3].

Endometrial hyperplasia is not uncommon in gynecological practice but the exact incidence is infrequently presented. Most patients present with abnormal uterine bleeding and the diagnosis of this disorder is made from the pathological examination of the endometrial tissue. The endometrial pathology varies widely from simple to atypical hyperplasia. The most recent classification purposed by the International Society of Gynecological Pathologists and the World Health Organization depends on its architectural (simple or complex) and cytological (atypical or not atypical) features[4,5]. This classification is more related to the natural history of the disease. In cases with simple hyperplasia the progression to carcinoma is 1 per cent, while in atypical complex hyperplasia 29 per cent of patients subsequently developed cancer[2]. At Ramathibodi Hospital the former classification has been used. Endometrium hyperplasia is divided into cystic, adenomatous and atypical hyperplasia. However, the change towards the recently purposed classification is undergoing.

Several treatment options in women with endometrial hyperplasia are available i.e. expectant, hormonal and surgical treatment[6]. Selection of the appropiate treatment depends on age of the patient, desire for future pregnancy, accurate histological diagnosis, associated pathology as well as the gynecologist and patient's preferences.

The objectives of this study are to determine the incidence of endometrial hyperplasia at Ramathibodi Hospital and to analyse the management and outcome of patients with this disorder.

MATERIAL AND METHOD

The medical records of gynecologic patients with histologically proved endometrial hyperplasia from 1990 to 1995 were retrospectively analysed. The incidence of endometrial hyperplasia was calculated by the number of women attending the out-patient gynecological clinic and the number of uterine curettage from gynecological causes.

To study the outcome of treatment only patients with the follow-up period of more than 1 year after the initial uterine curettage were included.

RESULTS

The medical records were obtained in 558 out of the total 643 patients with endometrial hyperplasia (87%). During the same period there were 56,848 out-patients and 5,546 uterine curettages from gynecologic problems. The incidence of endometrial hyperplasia was about 1 per cent of the total gynecologic out-patients and 11 per cent of patients who underwent uterine curettage.

Seventy five per cent (419 cases) had more than one year follow-up period and were included for further analysis. The range of follow-up period was one to five years.

The indication for uterine curettage in all women was abnormal uterine bleeding. The age of patients varied from 18 to 79 years. Most women were in the reproductive period. Only 37 cases (7.5%) were post-menopause.

About half of the patients had cystic hyperplasia. Adenomatous and atypical hyperplasia were found in 139 and 33 cases, respectively (Table 1).

Cystic hyperplasia

The management of women with cystic hyperplasia is shown in Table 2. Among 247 patients, 47 cases had undergone hysterectomy due

Table. 1 Histological diagnosis.

Histology	Number	%
Cystic hyperplasia	247	58.9
Adenomatous hyperplasia	139	33.2
Atypical hyperplasia	33	7.9
Total	419	100.0

Table. 2 The management of women with cystic hyperplasia.

Treatment	Number	%
Expectant	50	20.2
Cyclic progestogen for 6 cycles	136	55.1
Continuous cyclic progestogen	14	5.7
Hysterectomy	47	19.0
Total	247	100.0

to associated pathology mainly uterine fibroids. Fifty patients received no treatment while the other 150 patients had been treated with cyclic progestogen for 6 consecutive cycles. Fourteen patients received cyclic progestogen until menopause. The commonly used progestogens in this institution were norethisterone (Primolut N, Schering) and medroxyprogesterone acetate(Provera, Upjohn). The dose was 10 mg daily for 10-14 days each month.

During the follow-up period of 50 patients who received no treatment, 34 cases(68%) developed abnormal uterine bleeding. In these women, 18 cases received cyclic progestogen treatment and the other 16 patients had repeated uterine curettage. The histology was normal endometrium in 7 cases and endometrial hyperplasia in 9 cases. (cystic 4, adenomatous 3, atypical 2). Two cases with atypical hyperplasia underwent hysterectomy and the endometrial histology showed adenomatous hyperplasia. Thus, about 10 per cent women with cystic hyperplasia on expectant treatment progressed to adenomatous or atypical hyperplasia but none developed carcinoma.

Forty-seven patients (19%) with cystic hyperplasia had a hysterectomy perfomed within two months after initial curettage. The endometrium from hysterectomized specimens were normal in 29 cases (62%), cystic hyperplasia in 14 cases (30%) and adenomatous hyperplasia in 4 cases (8%).

Cyclic progestogen was given for 6 consecutive cycles in 136 patients. It is not our policy to repeat uterine curettage after the hormonal treatment in this group, however, periodic follow-up was practiced. During the follow-up period, 65 patients (48%) had regular periods. Seventy one cases (52%) had abnormal uterine bleeding and 49 patients underwent uterine curettage. Normal endometrium, cystic, adenomatous and atypical hyperplasia was observed in 24, 18, 5 and 2 patients, respectively. Therefore, in the hormonal treatment group,18 out of 136 cases (13.2%) still had cystic hyperplasia and 7 cases (5.1%) progressed to a more severe degree of abnormalities.

Twenty three patients in this group had a hysterectomy performed later. Uterine fibroids and ovarian tumors were the associated pathology in 8 and 2 cases, respectively. Hysterectomized specimens revealed normal endometrium in 15 patients, cystic hyperplasia in 7 patients and adenomatous hyperplasia in one patient. No endometrial carcinoma was observed.

In 14 premenopausal women, cyclic progestogen was administered till no withdrawal bleed occurred. Duration of the treatment ranged from 6 to 60 months with a mean of 29 months. Regular period was observed in all cases until menopause. At the end of this study 11 women had already reached menopausal state.

Adenomatous hyperplasia

Among 139 women with adenomatous hyperplasia, hysterectomy was performed in 68 cases (48.9%). Fifty seven cases (41.0%) received progestogen treatment while the other 14 cases (10.1%) were under expectant therapy (Table 3).

In 68 women who had hysterectomized, associated uterine fibroids and ovarian tumors were found in 30 cases (44%). The results of histological examination of the endometrium are shown in Table 4.

In 57 cases with hormonal treatment all but two received six consecutive cycles of oral progestogen. The dose and duration of progestogen treatment were the same as in patients with cystic hyperplasia. Two cases had cyclic progestogen until

Table. 3 The management of women with adenomatous hyperplasia.

Treatment	Number	%
Expectant	14	10.1
Cyclic progestogen for 6 cycles	55	39.6
Continuous cyclic progestogen	2	1.4
Hysterectomy	68	48.9
Total	139	100.0

Table. 4 Endometrial histology in hysterectomized specimens of women with adenomatous hyperplasia.

Endometrium	Number	%
Normal	39	57
Cystic hyperplasia	12	18
Adenomatous hyperplasia	15	22
Atypical hyperplasia	2	3
Total	68	100

menopause. After the hormonal treatment 32 women had repeated uterine curettage to assess the efficacy of progestogen (Table 5). The hislotogic examinations revealed normal endometrium in 28 cases (87.5%), cystic hyperplasia in 1 case and persistent adenomatous hyperplasia in 3 cases (9.5%). Hysterectomy was performed in the latter 3 patients. Normal endometrium, cystic hyperplasia and adenomatous hyperplasia were observed in each patient. Two patients aged 45 and 49 years who were treated with cyclic progestogen up to menopause had regular periods until no withdrawal bleeding appeared.

Fourteen patients received no treatment after uterine curettage. Abnormal uterine bleeding recurred in 11 cases (79%). Repeated uterine curettage was done in all but one case who had a hysterectomy. The histologic examinations were normal except one case which was cystic hyperplasia. In patients who underwent hysterectomy the endometrium showed adenomatous hyperplasia.

Table. 5 Efficacy of cyclic progestogen treatment in women with adenomatous hyperplasia.

Endometrial histology after 6 cycles of progestogen	Number	%
Normal	28	87.5
Cystic hyperplasia	1	3.1
Adenomatous hyperplasia	3	9.4
Total	32	100.0

Table. 6 The management of women with atypical hyperplasia.

Treatment	Number	%
No treatment	1	3.0
Cyclic progestogen	5	15.2
Hysterectomy	27	81.8
Total	33	100.0

Table. 7 Endometrial histology in hysterectomized specimen of women with atypical hyperplasia.

Endometrial histology	Number	%
Normal	11	40.8
Cystic hyperplasia	4	14.8
Adenomatous hyperplasia	7	25.9
Atypical hyperplasia	3	11.1
Adenocarcinoma *in situ*	1	3.7
Invasive adenocarcinoma	1	3.7
Total	27	100.0

Atypical hyperplasia

Most women (27 out of 33 cases) with atypical hyperplasia had a hysterectomy performed (Table 6). The results of histological diagnosis are shown in Table 7. Two women (7.4%) with atypical hyperplasia diagnosed by uterine curettage had coexisting endometrial adenocarcinoma. Both patients were postmenopausal, obese and had hypertension. Five women who desired future pregnancy were treated with 15 mg of norethisterone daily for 14 days each month for 6 consecutive cycles. Repeated uterine curettage after the hormonal treatment revealed normal endometrium in all cases.

One patient incidentally received no treatment. Five months later abnormal vaginal bleeding recurred and uterine curettage was done. Endometrium pathology showed no evidence of hyperplasia.

DISCUSSION

This study on the management of endometrial hyperplasia by its design has several limitations. However, the retrospective assessments of the day-to-day clinical practices usually form the basis of future analytical studies which often lead to the improvement of patients' care.

From this study it appears that endometrial hyperplasia is not an uncommon problem in gynecological practice. One per cent of all gynecological out-patients and 11 per cent of uterine curettages had endometrial hyperplasia. All gynecologists should, therefore, be familiar with this clinical problem and able to manage such patients.

The most common presentation of patients with endometrial hyperplasia is menstrual disturbances. All patterns of menstrual disorders were observed i.e. metrorrhagia, menorrhagia, oligomenorrhea and amenorrhea.

Theoretically, endometrial hyperplasia does not occur in women with a regular ovulatory cycle. Therefore, routine screening of the general population as in the case of cervical cancer is not benefi-

cial. The definite diagnosis of endometrial hyperplasia could be made only by the histologic examination of the endometrium. Women with high risk of developing endometrial hyperplasia such as prolonged unopposed estrogen stimulation should have uterine curettage or endometrial biopsy. Ultrasound examination of the uterus although non-invasive has limited value and can not be used for the diagnosis of this disorder[6].

The most common type of hyperplasia in this study was cystic hyperplasia (equivalent to simple hyperplasia in the new classification). Since the risk of progression to invasive carcinoma is very low the treatment of this disorder should be conservative either expectant or hormonal therapy. In this study, no patient with cystic hyperplasia after conservative treatment progressed to endometrial carcinoma. However, about 10 per cent of cases in the expectant group and at least 5 per cent of the hormonal group turned to more severe degree of hyperplasia. The other health problem in these patients is abnormal uterine bleeding. About 68 per cent of the expectant group and 52 per cent of the hormonal group had recurrent bleeding. For these reasons all patients with cystic hyperplasia should have long-term periodic follow-up. Should abnormal vaginal bleeding recur, hormonal treatment must be instituted to prevent excessive blood loss and progression to more serious problems. To prevent recurrent uterine bleeding the cause of unopposed estrogen stimulation should be identified and corrected. In most cases, however, the causes are not obvious. Long-term treatment and follow-up are, therefore, needed.

It is believed that benign endometrial hyperplasia can be resolved with curettage[7] but the observation from this study is that the curettage may not be an effective treatment of cystic hyperplasia in most cases. Its therapeutic aspect may only be to lessen the uterine bleeding. This surgical procedure may not remove all hyperplastic endometrium and does not alter the cause of endometrial hyperplasia. The abnormal growth of endometrium will remain or recur shortly after the curettage. In this study, the hysterectomized specimens after uterine curettage revealed 38 per cent of endometrial hyperplasia.

For patients with adenomatous hyperplasia, the treatment may be either hormonal or surgical depending on the patient's age, reproductive wish, menopausal status, general medical health and patients' compliance. Expectant therapy is not recommended since the disease may progress to more serious disorders and most patients will suffer from abnormal uterine bleeding.

Medical treatment is considered in young patients who still desire pregnancy. Progestogen is usually effective for the treatment of endometrial hyperplasia without atypia[8]. However, a previous study showed failure to respond to medroxyprogesterone acetate in 16 per cent of cases[9]. In this study 12.5 per cent of patients had persistent endometrial hyperplasia at the completion of cyclic progestogen therapy. Uterine curettage after the course of progestogen treatments is, therefore, necessary to ensure the reversal of hyperplasia. The medical failure may be due to an inadequate dose and duration of progestogen as well as patients' compliance. Continuous progestogen therapy may be more reliable in patients with poor compliance[8,10].

Besides the reversal of endometrial hyperplasia prevention of unopposed estrogen stimulation should be carried out. Ovulation induction should be started in those who want to become pregnant.

It is a common clinical practice to withhold medical treatment after 6 months of progestogen. However, the periodic follow-up is still necessary. In this study, more than half of the patients who completed the course of progestogen therapy had recurrent abnormal uterine bleeding during the follow-up period and required treatment again. In perimenopausal women, cyclic progestogen may be given until no bleeding occurs[10]. In this case, patients will have regular cycles up to menopause. This strategy may reduce patient's anxiety regarding abnormal uterine bleeding and the need of repeated uterine curettage to reassess the disease.

Surgical treatment for women with adenomatous hyperplasia should be considered in women who have completed their family, failure to medical treatment, unable to have regular follow-up, and coexisting pelvic pathology. In this study, 68 out of 139 patients (49%) had a hysterectomy as the primary treatment within two months after uterine curettage. In 43 per cent of the cases endometrial hyperplasia still existed. Therefore, uterine curettage is not an effective treatment for adenomatous hyperplasia.

Women with atypical hyperplasia are at risk of developing endometrial carcinoma. These patients were found to have coexisting endometrial carcinoma in 7-25 per cent of cases[2]. In the pre-

sent study, endometrial adenocarcinoma in hysterectomized specimens was found in 7.4 per cent of women with atypical hyperplasia. Therefore, surgical treatment must be primarily considered. Hormonal treatment may be practiced only in young patients who wish future pregnancy. In this case cyclic progestogen for 6-12 months should be given followed by uterine curettage to ensure the reversal of hyperplasia. All five patients with atypical hyperplasia in this study responded well to the hormonal treatment. Previous study, however, revealed only 50 per cent response to progestogen treatment[11]. In cases with hormonal failure and in those who could not have adequate follow-up, hysterectomy should be performed.

In patients with concurrent medical conditions that preclude the surgical treatment, long-term cyclic progestogen therapy may be considered to prevent the recurrence of the disease.

In conclusion, this study assessed the management of endometrial hysperplasia at Ramathibodi Hospital. It is evidenced that this disorder is not uncommon in gynecological practice. The pathophysiology and the natural history of this abnormality should be known by all practicing gynecologists. Women with abnormal uterine bleeding who are at risk of developing this condition should have endometrial investigation. Uterine curettage remains the standard diagnostic method. Adequate endometrial sampling and careful pathological examination are very important. Treatment options include expectant, hormonal and surgical therapy depending on histopathology, women's age, and desire of pregnancy. Long-term follow-up until menopause is mandatory in all patients undergoing expectant or hormonal treatment. Prevention of this disorder is possible by identification of patients at risk and early intervention.

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การรักษาภาวะเยื่อบุโพรงมดลูกหนาตัว : การวิเคราะห์ย้อนหลัง

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วัตถุประสงค์ : เพื่อหาอุบัติการของภาวะเยื่อบุโพรงมดลูกหนาตัว และการดูแลรักษาผู้ป่วยที่เป็นโรคนี้

วิธีการ : การศึกษาย้อนหลัง ในผู้ป่วยที่มีภาวะเยื่อบุโพรงมดลูกหนาตัวที่ได้รับการรักษาในโรงพยาบาลรามาธิบดี ระหว่างปี พ.ศ. 2533 ถึง 2538

ผลการศึกษา : พบอุบัติการของภาวะเยื่อบุโพรงมดลูกหนาตัวร้อยละ 1 ของผู้ป่วยนอกทางนรีเวช และร้อยละ 11 ของการขูดมดลูกทางนรีเวช ครึ่งหนึ่งมีภาวะ cystic hyperplasia ซึ่งการรักษาส่วนใหญ่ทำโดยการสังเกตอาการหรือการให้ฮอร์โมน สำหรับ adenomatous hyperplasia จะรักษาโดยการให้โปรเจสโตเจนหรือผ่าตัดมดลูกออก ส่วนผู้ป่วยที่มีภาวะ atypical hyperplasia ทำการรักษาโดยการตัดมดลูก ผู้ป่วยส่วนมากที่ได้รับการรักษาด้วยการสังเกตอาการและฮอร์โมน มักมีอาการเลือดออกผิดปกติอีก

สรุป : ภาวะเยื่อบุโพรงมดลูกหนาตัวพบได้บ่อย สูตินรีแพทย์ทุกคนควรจะศึกษาและทำความเข้าใจเกี่ยวกับพยาธิสรีรวิทยาและการดำเนินของโรคนี้ การรักษาผู้ป่วยควรพิจารณาเป็นราย ๆ ไปตามความรุนแรงของพยาธิสภาพ อายุผู้ป่วยและความต้องการมีบุตร การติดตามผู้ป่วยเป็นระยะเวลานานจนเข้าสู่วัยหมดระดู เป็นสิ่งจำเป็นในการป้องกันการเสียเลือดจากโพรงมดลูกและการเปลี่ยนแปลงของเยื่อบุโพรงมดลูกไปเป็นมะเร็ง

คำสำคัญ : ภาวะเยื่อบุโพรงมดลูกหนา – การรักษา – การวิเคราะห์ย้อนหลัง

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