Minor Side Effects of Hormonal Replacement Therapy in Menopausal Thai Women

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Abstract :

Objective : To evaluate type and incidence of minor side effects of hormonal replacement therapy (HRT).

Design : Cross-sectional, descriptive study.

Patients : 114 women, who were follow up at Menopause Clinic in July 2001.

Method : All women were interviewed about their experience in various symptoms possibly related to HRT side effects. The symptoms before and during HRT were recorded. The symptoms that were present only during HRT but not before HRT were considered as side effects.

Results : The study showed that breast pain was the most common side effect of both cyclic HRT (40%) and continuous HRT (38.1%) groups; whereas the complaint of weight gain was more pronounced in the estrogen only (30.77%).

Conclusion : Although minor side effects of HRT are not life threatening, they may have influence on the compliance of HRT. The incidence of minor side effects of HRT is varied depending on the HRT regimens. However, the symptoms similar to the HRT side effects are already present prior to HRT in a certain number of patients.

เรื่องย่อ : ผลข้างเคียงของฮอร์โมนเสริมทดแทนในสตรีไทยวัยหมดระดู

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สารศิริราช 2545; 54: 271-278.

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วัตถุประสงค์ เพื่อศึกษาอุบัติการณ์ผลข้างเคียงของการใช้ฮอร์โมนเสริมทดแทน
รูปแบบการศึกษา การศึกษาแบบตัดขวางเชิงพรรณา
ประชากรที่ศึกษา ผู้ป่วยจำนวน 114 คน ที่มารับบริการที่คลินิกวัยทอง ในเดือนกรกฎาคม พ.ศ. 2544
ผลการศึกษา อาการปวดเต้านมเป็นผลข้างเคียงที่พบได้มากที่สุดในผู้ที่ใช้ฮอร์โมนเสริมทดแทนชนิดเป็นรอบและชนิดต่อเนื่อง (ร้อยละ 40 และ 38.1 ตามลำดับ) ส่วนอาการน้ำหนักเพิ่มมากขึ้นพบได้มากที่สุดในผู้ที่ใช้ฮอร์โมนเสริมทดแทนชนิดที่มีฮอร์โมนเอสโตรเจนอย่างเดียว (ร้อยละ 30.77)
สรุป ผลข้างเคียงของฮอร์โมนเสริมทดแทนมีผลต่ออัตราการคงใช้ยาของผู้ป่วย อุบัติการณ์ผลข้างเคียงขึ้นอยู่กับชนิดของฮอร์โมนเสริมทดแทน อย่างไรก็ตามอาการของผลข้างเคียงอาจมีลักษณะคล้ายกับอาการผิดปกติที่พบได้ในผู้ป่วยวัยหมดระดู

INTRODUCTION

Menopause is the period of life after complete cessation of ovarian function. During this period, many physiologic changes occur as a result of the aging process but some are consequences of declining ovarian function. Therefore, menopausal women may encounter not only general health problems related to aging, but also particular problems of the menopause, e.g. menopausal symptoms and osteoporosis.

Nowadays, men and women are living longer. For women, the extra years occur in the post-menopausal period. In the year 2,005-2,010, the life expectancy of Thai women is estimated to be 73 years[1] but the age at menopause is stable at 48 ± 2 years old[2]. This means that Thai women have to spend approximately 30 years of their life in the post-menopausal period. The ultimate goal of taking care the post-menopausal women is for them to have a "good quality of life". The goal can be achieved using the principle of preventive medicine including health promotion, prevention of common health problems, treatment of diseases, and rehabilitation. Although the majority of the women can have a good quality of life by means of health promotion and prevention of common health problems, some may need medical treatment.

Hormonal replacement therapy (HRT) is the standard treatment of severe menopausal problems. Menopausal symptoms are the most common presenting symptoms that bring patients to see physicians[2,3]. These symptoms can be grouped into vasomotor and psychological symptoms. The former includes hot flushes, excessive perspiration and palpitation. The latter includes anxiety, depression, dizziness, headache, insomnia etc. HRT can improve the quality of life in menopausal women suffering from these symptoms[3].

Although the beneficial effects of HRT are well documented, the majority of menopausal women do not take HRT[3]. The major hindrance is the fear of side effects[3,4,5]. The serious side effects of HRT include venous thromboembolism (VTE) and breast cancer. In the first year of treatment, HRT doubles the risk of VTE[4]. After 5 years, the risk of breast cancer increases from background risk. The incremental risk of breast cancer after taking HRT is time-dependent, varying from 0.2 to 1.2% after 5 to 15 years of therapy[5]. Although the actual risk of these serious side effects is small, the perception of risk is far greater.

The fear of these side effects does not only preclude menopausal women from taking HRT but it also has negative impact on compliance with HRT. Minor side effects such as breast pain, vaginal bleeding, nausea vomiting, etc. intensify this problem. Many studies have reported that they decrease compliance with HRT[6,7].

Although minor side effects of HRT are not life threatening, this negative effect on the compliance prevents menopausal women from receiving the beneficial effect of long-term HRT. Moreover, some of these minor side effects are similar to psychosomatic symptoms that may normally occur in the peri/postmenopausal period. The actual type and incidence of minor side effects of HRT may be

affected by these symptoms. The primary objective of the present study is to evaluate the actual type and incidence of minor side effects of HRT.

MATERIALS AND METHODS

The study population comprised 114 women aged 33-65 years who were followed up at the Menopause Clinic, Division of Gynecologic Endocrinology, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, in July 2001. Clinically the patients may be perimenopausal, or have experienced natural or surgical menopause. Perimenopausal patients were those who had menopausal symptoms but were still menstruating within 1 year of starting HRT. Natural menopause patient were those who had not menstruated for at least 1 year before starting HRT. Surgical menopause patients were those who had a hysterectomy with oophorectomy. All the patients had been using HRT for some time before the interview.

All women were interviewed about their experience of various symptoms, which were similar to HRT related side effects. Symptoms occurring in patients before starting HRT were recorded as present or absent. Symptoms experience while taking HRT were recorded as present, absent, improved or worse. Side effects were defined as symptoms that were absent before HRT and present only during HRT, or symptoms that were present before HRT started and became worse during HRT.

All women were divided into three groups according to HRT-regimens, i.e. estrogen only group (Es), continuous combined estrogen-progestogen (Cc) or cyclic estrogen-progestogen group (Cy). Each group was divided into two subgroups, one was the group that had symptoms before HRT and the other did not.

Demographic data including age at menopause (age), age at starting HRT (sHRT), duration of HRT (yHRT) and current HRT regimens were extracted from the medical records.

The data were analysed using a computerized program (SPSS 10.0) and presented as mean ± SD or percentage. The student t-test was used to compare the means between the 2 groups. ANOVA was used to compare means among the 3 groups.

RESULTS

The patient demograhpic data is shown in Table 1. All of the patients in the Es group (52 cases) had had a surgical menopause, while 50% (10 in 20 cases) of the patients in the Cy group were perimenopausal and the majority (22 in 42 cases) in the Cc group had had natural menopause. Patients in the Es group were younger than those in the Cy and the Cc groups. All the surgical menopause patient in the Cy group (2 cases) and Cc group (8 cases) had undergone radical surgery (total hysterectomy and salpingo-oophorectomy) for endometriosis. The age at surgery of the surgical menopause patients (42.52 ± 5.00 yr) was significantly less than the age at menopause of the natural menopause patients (47.83 ± 6.56) ($P = 0.002$, Student t-test). The duration of HRT (yHRT) in the perimenopausal group (3.93 ± 2.15 yr) was significant longer than the other 2 groups (1.93 ± 2.24 and 2.44 ± 2.14) ($P = 0.002$, ANOVA).

Table 2 shows the incidence of symptoms similar to the side effects of HRT in all women before and during HRT. The incidence of various symptoms before HRT ranged from 2.63% to 35.96% and the 3 most common symptoms were bloating (35.96%), weakness (35.05%) and headache (34.21%).

Table 3 and 4 demonstrated the incidence of minor side effects of HRT. In Table 3 the incidence of side effect was derived from number of the patients with the certain symptom present only during HRT but absent before HRT. According to this definition, the most common side effect in the Es group was weight gain (30.77%), and in the Cy and the Cc groups was breast pain (40% and 38.10%, respectively). In Table 4 when the side effect was defined as a symptom that was present only during HRT and a symptom that got worse during HRT, the most common side effect in the Es group was weight gain (34.62%), in the Cy was weight gain and breast pain (40%), and in the Cc groups was breast pain (40.48%).

Table 1. Demographic data of the 114 patients studied.

HRT Regimens	Total		Perimenopause			Natural menopause				Surgical menopause			
			Age (yr)	sHRT (yr)	yHRT (yr)		Age (yr)	sHRT (yr)	yHRT (yr)		Age[b] (yr)	sHRT (yr)	yHRT (yr)
	n	n	X±SD	X±SD	X±SD	n	X±SD	X±SD	X±SD	n	X±SD	X±SD	X±SD
Estrogen only	52	NA	NA	NA	NA	NA	NA		NA	52	43.00 ± 5.17	48.65 ± 5.96	2.56 ± 2.20
Cyclic	20	10	NA	51.00 ± 5.52	3.70 ± 2.36	8	45.63 ± 10.97	54.38 ± 7.84	3.25 ± 2.29	2	39.00 ± 8.49	40.00 ± 7.07	0.50 ± 0.71
Continuous combined	42	12	NA	55.08 ± 3.85	4.17 ± 2.04	22	48.67 ± 3.93	55.50 ± 5.24	1.45 ± 1.79	8	41.00 ± 2.83	44.75 ± 2.49	2.13 ± 1.81
Total	114	22	NA	53.23 ± 5.01	3.95 ± 2.15	30	47.83 ± 6.56	55.20 ± 5.29	1.93 ± 2.24	62	42.52 ± 5.00	47.87 ± 5.92	2.44 ± 2.14

Note Age = age at menopause; sHRT = age at start HRT; yHRT = duration of hormonal replacement therapy at the time of interview; NA = not applicable; (a) = Current HRT regimen; (b) = Age at surgery

Table 2. The incidence before HRT of symptoms similar to HRT side effects.

Symptoms	Incidence (%)
Breast tenderness	14.0
Feeling of weight gain	17.5
Leg cramp	32.5
Dizziness	7.9
Hair loss	31.6
Spotting	4.4
Constipation	33.3
Acne, oily skin	18.4
Dry vagina	33.3
Dyspepsia	36.0
Vaginal discharge	14.9
Sexual problem	24.6
Skin pigmentation	28.1
Headache, migrane	34.2
Itching	13.2
Depression	26.3
Puffiness	2.6
Weakness	35.1

Note Es = Estrogen only; Cy = cyclic estrogen-progestogen; Cc = continous combined estrogen-progestogen; NA = not applicable

Table 3. The incidence of minor side effects of HRT including only cases without symptoms before HRT.

Symptoms	Incidence (%)		
	Es	Cy	Cc
Acne, oily skin	15.38	15.00	14.29
Breast tenderness	28.85	40.00	38.10
Constipation	3.85	5.00	9.52
Depression	9.62	10.00	7.14
Dizziness	3.85	5.00	23.81
Dryness of vagina	17.31	5.00	9.52
Dyspepsia	7.69	5.00	9.52
Feeling of weight gain	30.77	30.00	33.33
Hair loss	13.46	0.00	16.67
Headache, migrane	15.38	15.00	9.52
Itching	7.69	20.00	7.14
Leg cramp	25.00	10.00	21.43
Puffiness	3.85	0.00	9.52
Sexual dysfunction	13.46	10.00	11.90
Skin pigmentation	23.08	15.00	9.52
Vaginal bleeding or spotting	3.85	15.00	21.43
Vaginal discharge	7.69	15.00	11.90
Weakness	15.38	10.00	2.38

Note Es = Estrogen only; Cy = cyclic estrogen-progestogen; Cc = continous combined estrogen-progestogen

Table 4. The incidence of minor side effects of HRT including cases without symptoms before HRT and cases with symptom deterioration during HRT.

Symptoms	Incidence (%)		
	Es	Cy	Cc
Acne, oily skin	17.31	15.00	14.29
Breast tenderness	28.85	40.00	40.48
Constipation	5.77	5.00	21.43
Depression	11.54	15.00	9.52
Dizziness	7.69	5.00	28.57
Dryness of vagina	19.23	5.00	14.29
Dyspepsia	11.54	5.00	14.29
Feeling of weight gain	34.62	40.00	38.10
Hair loss	21.15	0.00	23.81
Headache, migrane	23.08	20.00	9.52
Itching	7.69	20.00	9.52
Leg cramp	28.85	20.00	28.57
Puffiness	3.85	0.00	9.52
Sexual dysfunction	15.38	15.00	11.90
Skin pigmentation	30.62	20.00	9.52
Vaginal bleeding or spotting	3.85	15.00	21.43
Vaginal discharge	9.62	20.00	11.90
Weakness	19.23	10.00	4.76

Note Es = Estrogen only; Cy = cyclic estrogen-progestogen; Cc = continous combined estrogen-progestogen

DISCUSSION

Minor side effect of HRT can be caused by estrogen (nausea, headache, migraine, etc.), progestogen (fatigue, negative mood, etc.) or both (breast tenderness, bloating, leg cramps, etc). Some of these symptoms can't be distinguished from menopausal symptoms. The others are similar to premenstrual symptoms. The effect of progesterone metabolites on central nervous system is believed to cause these symptoms[8], thus the premenstrual like symptoms related to HRT are believed to be side effects related to progestogen.

Menopausal symptoms are the most common presenting symptoms. The incidence of menopausal symptoms varies according to the methods used and population studied. Asian women seem to have fewer and less severe symptoms than Caucasian[9]. Jarueyporn et al[10] reported a symptom incidence of 25-80 % and the most common symptom was moodiness (77.4%). Jong-Ling Fuh et al[11] reported a symptom incidence of 8.2-52.3 % and the most common symptom was headache (35.9%). In our study, symptoms that were present before HRT was started were considered to be menopausal symptoms. The incidence of symptoms ranged from 2.63% to 35.96% and the most common symptom was bloating (35.96%). The incidence is less than in others studies. A possible explanation is that the symptoms prior to HRT were recalled retrospectively after a long period of taking HRT.

HRT is an effective therapy for menopausal symptoms. These symptoms are dramatically reduced with in the first few months of HRT[12]. The symptoms that persist during HRT might not be related to the menopause. Adverse symptoms that are present only during HRT or those getting worse during HRT might be side effects of HRT.

The incidence and type of HRT side effects in our study varied between HRT regimens. Moreover, the side effects may be dependant on other factors such as dose, route, drug interaction and individual response. In our study the complaint of

weight gain, breast pain, vaginal bleeding, and headache were the most common side effects.

The complaint of weight gain was the most common in the Es group. This complaint may not be related to HRT since there was a good evidence that HRT does not produce weight gain[13], Weight gain may be a physiologic change, which is more marked in the perimenopausal years[14]. Since the patients in Es group all had a surgically induced menopause and were mostly in the perimenopausal period at the time of surgery, HRT was strongly indicated and usually provided to the patients soon after surgery, in the perimenopausal years when there is a trend for weight gain. Interestingly, the patient in the perimenopausal group did not complain much about weight gain. In this study although they were perimenopausal by definition, they had already passed the perimenopausal yçars (usually in the 40s). In fact, they were the patients who had entered menopause later than average.

Breast pain was common in patients who received Cc or Cy. Most of the patients had had natural menopause who had consulted a doctor some time after the menopause. These patients would have some degree of atrophy in estrogen-dependent organs such as the breast and the vagina. During HRT, the stimulatory effect of estrogen reversed the atrophic changes. Moreover, the progestogen would augment such as effect in breast tissue, consequently causing breast pain. The longer the duration of menopause, the more pronounced the breast pain experienced with HRT[15]. This could explain why the incidence of breast pain was high in the Cc and Cy groups. The patients in these groups would have had longer menopause before they started used HRT than those in the Es group. However, we could not confirm this assumption because the actual duration of menopause before HRT in the surgical menopause patients was indeterminable, as some patients did not have bilateral oophorectomy at the time of surgery. Therefore, the YSM in those patient with surgical menopause shown in Table 1 was probably longer than the actual duration of menopause because the retained ovaries could produce hormone for some time before cessation of function.

Vaginal bleeding is a major complaint and significant problem affecting compliance with HRT[6,7]. The incidence in our study is similar to other reports. Actually this problem depends on the duration and type of HRT. Menopausal women with an intact uterus need progestogen supplemented HRT in order to protect the endometrium[16]. There are 2 types of progestogen supplemented HRT, i.e. cyclic estrogen-progestogen (Cy) and continuous combined estrogen-progestogen (Cc) regimens. Both regimens are effective in endometrial protection. Cc is more effective than Cy in endometrial protection but causes a higher incidence of vaginal bleeding; the incidence of which varies from 0 to 93% in the first 6 months of HRT. Fortunately, more than 75% of the patients were amenorrhoeic in the second 6 months of treatment[17].

Use of data from this study to advice patients may contribute to improving the quality of health care in menopausal women.

CONCLUSION

Although minor side effects of HRT are not life threatening, they may have an influence on compliance with HRT. The incidence of the various side effects of HRT varies depends on the HRT regimens used. Various combinations of such symptoms are actually present prior to HRT, implying that they are not true side effects in a certain number of patients. Evidence from other studies has shown that common side effects such as breast pain and vaginal bleeding usually disappear within a few months of starting HRT. Helping the patients to understand this fact would increase their compliance and would consequently be beneficial to their health.

ACKNOWLEDGEMENT

The authors would like to thank the Head of the Department of Obstetrics and Gynecology for the permission to report this data. Special thanks to the staff members of the Division of Gynecologic Endocrinology, especially Ms. Somchit Koanantakul and the Nurses of the Gynecologic Outpatient Department for their contribution in taking care of the patients in the Menopause Clinic.

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