Urogenital Problems in Menopausal Women - Place of HRT.

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Summary : **Urogenital problems of 450 menopausal women were studied. The average age of natural menopause was 48.3 years. 35% mainly had urinary complaints and 50% had vulvo-vaginal problems. Of 308 women who required HRT, 39.93% continued the therapy satisfactorily. 11% had excellent relief, 71% had good relief, 14% had moderate relief and 4% could not give conclusive answers or had no relief. The relief was maximum in women with genitourinary symptoms and to a lesser extent in women with vasomotor symptoms.**

Introduction

Most women approch the menopause with apprehension and uneasy feeling and many go through this period of life with considerable discomfort, at times severe enough to make them miserable. There is a growing awareness about management of menopause and place of hormone replacement therapy not only amongst medical professionals but also in public at large specially the perimenopausal women in the upper socio economic class. Majority of our patients approach us for climacteric symptoms such as hot flushes, night sweats or urogenital problems such as dysuria, dyspareunia or recurrent urinary infections. Although the place of prophylactic use of HRT to prevent osteoporosis and ischemic heart disese as well as cardiovascular pathology is now accepted, very few women continue the therapy long enough to achieve these benefits. This paper presents our experience of 450 menopausal women studied over a period of five years. Their presenting symptoms and signs, acceptability of HRT and its continuation rate as well as benefits or side effects of HRT are discussed. The last hundred women in this group were studied in greater details with a well planned protocol and good follow-up.

Material and Methods

This data of 450 menopausal women is collected from our private clinic where majority of the patients were from upper socio-economic class. More than 70% of these women have had college education. Detailed history and clinical examination were followed by personal counselling by one of the authors. Demographic characteristics such as age at menopause, parity, marital status were noted. The presenting symptoms such as hot flushes, night sweats, palpitation, depression or irritability, as well as genitourinary symptoms such as dysuria, dyspareunia and postcoital bleeding along with the duration of the symptoms were noted. Many women had vague complaints and some specifically complained of bodyache and joint pains. Detailed general examination for weight, blood pressure, cardiovascular as well as respiratory systems, breast examination and abdominal palpation were carried out. Gynaecological examination for the uterine size and pathology and palpable adnexa was done.

Smears were collected for cytological examination from every patient. Cervical and lateral vaginal smears were collected seperately for cerical atypia and hormonal status (maturation index). Labortory investigations such as complete blood count, blood sugar fasting and post lunch and urine examination were performed. Culture and sensitivity tests for urine were done in cases with recurrent urinary tract infection.

Mammography was advised in all cases but was made mandatory in cases with family history of breast cancer and suspicious findings on breast examination. Ultrasonography and endometrial biopsy were done whenever indicated specially if there was a bulky uterus, vaginal bleeding or palpable adenexa. In last 45 cases lipid profile, coagulation profile, liver function tests as well as renal function tests were done before starting HRT and 3 to 6 months after giving HRT. Serum, FSH and estradiol was advised when premature ovarian failure was suspected or when the patient was keen to do full hormonal evaluation for menopause. Three hundred and eight women required hormone replacement therapy to

Table I

Presenting Symptoms

Symptom	Krishna/ Mandlekar (1992)	Anklesaria (1996)	Studd etal (1992)
Urinary complaint	35%	74%	20%
Vaginal symptoms	50%	56%	20%
Vasomotor	33%	30%	75%
Musculoskeletal	25%	20%	48%
Psychological	20%	36%	92%
Insomia	10%	20%	51%

21% of our patients came for routine check up and were found to have the symptoms mentioned above on questioning.

Table II

Relative frequency of urogenital symptoms in percentage of patients.

Investigator	Genital	Urinary
Iosif and Bekassy (1984)	53	42
Berg et al 1986	22	19
Kok (1992)	-	23.3
Oldenhave et al 1993	65	33
Rekers et al (1992)	38.7	40
Geehen et al 1990	35	31
Studd and Barber (1992)	20	20
Anklesaria (1996)	56	74
Krishna (Present Study)	50	35

relieve their symptoms but only 123 of them (39.93%) continued the therapy satsifactorily. Majority of the patients were given oral estrogens - estriol (Evalon) or conjugated estrogens. Nine patients received transcutaneous patches of estradiol (Estraderm TTS). One patient had sub-cutaneous estradiol implant of 50 mg. inserted every 6 months in London. Forty patients used estrogen vaginal creams, estriol (Evalon), conjugated estrogen (Premarin) or dinoestrol cream) when they did not wish to use or continue oral estrogens or required additional treatment to relieve their vaginal symptoms. The women with intact uterus and those with menopause of less than 5 years received additional progesterone such as medroxyprogesterone acetate or lynestrenol or norethisterone acetate for 10 days each month. The women who did not get monthly withdrawal bleeding were given progesterone preparations only once in 3 to 5 months, depending on the absence or presence of withdrawal bleeding and endometrial thickness on transvaginal sonography. The patients were called to the clinic regularly to note the relief of symptoms and had general and gynaecological examination every 3 months initially and later once in 6 months. A cytological examinationwas repeated between 3 and 6 months after initiation of therapy and later once a year. All the patients were given supplementary calcium and advised proper diet, exercise etc. Eight Percent also required tranquilizers and 18% required vaginal tablet or cream as well as oral treatment for infections such as trichomoniasis or moniliasis.

Results :

The average age of natural menopause was 48.3 years, the range being 26 to 50 years as this also included 6 cases of premature ovarian failure. Of 450 cases studied, 92 had surgical menopause by hysterectomy and 14 had hysterectomy with bilateral salpingo oopherectomy. Urogenital symptoms were the commonest presenting complaint and it was necessary to ask specific questions to obtain this information. Although 21% of the women had come for the routine checkup, most of them had urogenital problems requiring treatment.

Eight five percent of our patients had genitourinary tract problems; 35% mainly having urinary complaints such as dysuria, urge or stress urinary incontinence and 50% primarily had gynaecological and sexual problems such as dysparunia, dryness of vagina and leucorrhoea due to vulvo - vaginitis. 33% of our patients presented with vasomotor symptoms such as irritability, depression, insomia etc. Many patients had more than one symptom and there was considerable degree of overlapping. Table I indicates the incidence of presenting symptoms in our study and compares the same with an Indian study by Anklesaria (1996) and the western average compiled by Studd and Barber (1992).

The continuation rate of HRT was rather poor. Of all the patients who were enrolled for HRT 92% completed 3 months of treatment but only 25% continued for 1 year.

However, there were 12% patients who were very happy and have been on treatment for more than one year and 5% are on treatment for more than 5 years. Most of the women stopped treatment after they were relieved of their presenting problem and many more were alarmed by misconceptions regarding hormones, 4% of the patients discontinued the treatment because of break-through bleeding, 3.5% because of excessive weight gain and 1.2% because of mastalgia. Most of the patients had no definite reason for discontinuation, a few were indifferent to treatment and many had phobia of side effects.

As all the patients were examined thoroughly and underwent laboratory investigations we could also detect cases with hypertension, cardiovascular problems and diabetes. Twenty five percent of the women were obese, 11% had diabetes, 13% were hypertensive and 2% had ischemic heart disease. Ten percent of the patients had anaemia with haemoglobin less than 10gms%.

As the cytology was carried out in every case, it was possible to detect 4 cases of severe dysplasia (CIN) and 1 case of carcinoma in-situ. During these 5 years there were 4 women sent to the clinic with carcinoma of the cervix. These were not included in this series as they were specifically sent to confirm the diagnosis. The hormonal status indicated by cytology was defined in terms of maturation index. Seventy six percent of the patients had atrophic smears and 1/3rd of them atrophic inflammatory. The vasomotor as well as genitourinary symptoms were severe with early onset of menopause. Vulvovaginitis was the commonest symptom in all age groups. Early onset of menopause specially following surgical treatment such as bilateral salphingo-oopherectomy led to severe vasomotor as well as psychological symptoms. Thirty five percent of the patients had urinary problems but 8% had recurrent infection requiring culture sensitivity tests and specific treatment for urinary infection. An analysis of various symptoms in relation to their age showed that the incidence of vulvovaginitis is between 63% to 88% in various age groups and is not influenced significantly by age. The urinary symptoms increase with age upto 55 years. The vasomotor symptoms and psychological symptoms gradually decline after 55 years.

The relief of symptoms was coded as excellent, good, moderate or none. Eleven percent patients had excellent relif, 71% had good relief, 14% had moderate relief and 4% could not give conclusive answers or had no relief. The relief was maximum in women with genitourinary symptoms and to a lesser extent in women with vasomotor symptoms. The symptoms recurred soon after the treatment was stopped yet many women took th treatment irregularly inspite of counselling. The musculo skeletal symptoms such as bodyache and joint pains had only moderate relief in most of the cases.

In the 45 cases who underwent metabolic studies, there was no significant change in any of he parameters studied. There was some improvement in lipid profile, indicated by reduction of total cholesterol, triglycerides and increase in HDL in 20% of cases.

Discussion:

The female genital tract and lower urinary tract is anatomically and embryologically closely related and are sensitive to estrogens. The declining estrogen levels cause atrophic changes such as thinning of epithelium, thinning of supportive tissues and reduced vascularisation. The related symptoms are both vaginal, such as dryness, irritation, discharge, infection, pruritus, dyspareunia, postcoital bleeding and prolapse and urinary symmptoms such as dysuria, frequency, urgency, incontinence and repeated UTI. The prevalence rate of urogenital symptoms varies from 50 to 85%. But the women are reluctant to consult the doctor and often suffer quietly. It needs good commnication and empathy to understand their real problems and explain the need for consistent treatment and good follow-up.

Genital atrophic changes are associated with decreased maturation of the vaginal epithelial cells and progressive decrease in vascularity in the surrounding tissue, accompanied by fragmentation of elastic tissues and hyalinization of collagen fibres. The glycogen content of vaginal epithelial cells decreases, resulting in reduced colonization by lactobacilli, increase in vaginal pH and

increased colonization by pathogenic faecal coliforms and cocci. This is followed by increased vaginal and urinary tract infection as estrogen deficiency causes similar atrophic changes of the urethral epithelium and highly vascularised submucosal layer. Besides, it leads to inadequate urethral closure and abnormal urinary flow pattern. There is a strong correlation between incontinence and other urogenital symptoms. Although the etiology of incontinence is multifactorial. Decline in collagen in urogenital tissues plays an important role. There are oestrogen receptors in the urethral wall and the surrounding muscular and connective tissue in almost similar density as in the vaginal basal and parabasal layers. Besides there are oestrogen receptors also in the stromal cells and smooth muscle fibres of the vagina as well as the urethra and surrounding tissues. The vaginal atrophy leads to considerable distress affecting the sexual function. At times persistent vaginal discharge due to underlying infection and postcoital bleeding resulting from trauma to atrophic vagina brings the patient to the physician. It is not uncommon that utero-vaginal prolapse further impairs the process of micturition and the patient presents with frequency, urgency, dysuria and incontinence.

A recent study of Bachmann (1993) showed that among 329 healthy non-clinic attending women, more than 50% of the postmenopausal women reported problematic lack of vaginal lubrication and frequent vaginal infections. Heimer (1992) from Sweden considers urogenital atrophy to be a hidden but widespread problem affecting the majority of the postmenopausal women. Three thousand two hundred and fifty six women with mean age 61, 71 and 81 years respectively took part in the population based cohort study. Seventy Seven percent of the patients responded. Incontinence was the foremost urogenital problem but the vaginal symptoms were also very common, specially in the relatively younger, sexually active women. Iosif and Bekassy (1984) studied the prevalence of urogenital problems in 902 women of mean age 61 years. 48.8% reported lower genital tract disorders. 29.2% had urinary incontinence and 13% of the women had recurrent urinary tract infections. Table II presents the frequency of urogenital symptoms in 9 studies.

Stress urinary incontinence is one of the important problems of menopausal women. Fantl et al (1988) studied clinical and urodynamic variables in 49 nonestrogen treated and 23 estrogen supplemented postmenopausal women with urinary incontinence. Urodynamic studies were carried out and the state of estrogen deficiency was evaluated in these cases. No direct effect of estrogen therapy was noted on urethral function. In cases with detrusor instability, borderline direct positive effect was noted. The magnitude of fluid loss was greater without estrogen treatment supplementation. Nocturia was significantly less in estrogen treatment supplemented group. A study was conducted by Saltori et al (1995) in 37 menopausal women with genuine SUI. Full medical history, genecal and gynaecological examination along with maturation index and urine examination as well as urodynamic studies were performed in all the patients. Patients were treated with 0.625 mg conjugated estrogen along with 2.5mg MPA for 3 cycles. At the end of 3 months, 43.3% of the patients were considered to be cured, 46.7% improved and only 10% reported no difference. These observations suggest that hypoestrogenism may effect the sensory threshold of lower urinary tract of incontinent postmenopausal women. Ulmsten (1993) at Uppsala showed steroid hormone receptors even in the female pelvic muscles and urogenital ligaments, thus supporting the hypothesis that the pelvic muscles and urogenital ligaments are under hormonal control.

More are more studies show that even very low dose estrogen therapy is effective against the characteristic vaginal symptoms of urogenital ageing. It is necessary to modify the therapy depending on the age, number of years of menopause, severity of symptoms, presence or absence of the uterus and ovaries. HRT can be administered by oral and non-oral routes. The oral delivery system is easiest and most economical. The women who have undergone hysterectomy can be given unopposed estrogens. The side effects of estrogens such as estriol is very low and the endometrial proliferation leading to hyperplasia is practically absent. The women with recent menopause should be given cyclic estrogen progesterone HRT as it completely prevents endometrial hyperplasia and there is no possibility of endometrial

ancer. Women around 45 years could be given low dose ombined oral contraceptives during this transition period o regularise the bleeding and also offer contraception. 'ontinuous estrogen-progestogen HRT is given to women who find the withdrawal bleeding unacceptable. This herapy still needs long term evaluation. It can lead to menorrhoea in about 70% of the patients which ncreases to 90% at one year. Archer et al (1994)evaluated leeding patterns in postmenopausal women taking ontinuous combined or sequential regimens of onjugated estrogens with medroxyprogesterone acetate. 'hey concluded that approximately half of the women who took the continous combined conjugated estrogen - MPA regimen had amenorrhoea, and the incidence tended o increase with the duration of the treatment. Women who took sequential regimen had good cycle control and few had minimal irregular bleeding. More than half of hose who took conjugated estrogens alone also had menorrhoea.

Tibolone (Livial) is a synthetic derivative of 19 - Nortestosterone, has weak estrogenic, progestogenic and ndrogenic properties. Although about 15% experience rregular bleeding, there is hardly any endometrial timulation. Hence it is advisable to use the drug after atleast two years of menopause. We have treated 72 patients with Tibolone (Livial) and found it very cceptable. It is specially recommended for mood levation. We had two patients who discontinued for rregular bleeding and 7 for weight gain.

t is necessary to do monitoring of the endometrium whenever there is unscheduled vaginal bleeding by ransvaginal sonography as well as endometrial sampling which can be collected by pipette or curette. If the endometrial thickness is more than 4mm., it is prudent to lo an endometrial biopsy to exclude hyperplasia. Hysteroscopic evaluation can be carried out when necessary. Vaginal administration of low dose estrogen has the advantage of being applied close to the organs on which it should act. This can be administered in the form of vaginal cream or pessary and most of the preparations are devoid of serious side effects and are effective in reatment of urogenital ageing. Estrogen vaginal cream estores the vaginal epithelium and the glycogen increases the Doderlein's lactobacilli. This increases the lactic acid and the vaginal PH becomes acidic increasing the natural barrier against invasion of gram negative bacteria. Estriol cream is short acting with specific effect on local epithelium and does not cause endometrial proliferation. It is therefore not necessary to add progestogen. The symptoms such as vaginal dryness, itching, pain and discharge as well as dyspareunia are relieved. It can relieve micturition problems if there are no other associated factors causing recurrent urinary tract infection or stress urinary incontinence.

This paper has mainly covered the incidence and management of genito urinary problems, as we have not been able to do any long term studies from the view point of osteoporosis and cardio-vascular changes. It has been conclusively shown by many authors that hormone replacement therapy is effective in prevention of osteoporosis and reducing the risk of associated fractures. Similarly, HRT has been shown cardioprotective and also offers some degree of protection against stroke as reported by Manson et al (1992). The metabolic studies carried out have also indicated beneficial effect on lipid profile.

The relationship of HRT on cancer has to be clarified. Although unopposed estrogen in an intact uterus could increase the risk of endometrial cancer 3 to 6 fold after a duration of 3 to 10 years, the protective action of progestational agent has been proved beyond doubt. Even the hyperplasia is totally reversed. The possible increase in the incidence of breast cancer in women on HRT has been investigated in number of trials. However, the largest case control study from C.D.C. and the longest cohort study (Nurses health study) have failed to show an increased risk of breast cancer upto 20 years.

Several controlled scientific studies have shown no increase in the risk of breast cancer when HRT is given upto 5 years. However, some studies do shhow a small increase when HRT is given for six to ten years.

According to Henderson et al (1991) the relative risk of breast cancer mortality was 0.81 which is lower than nonusers of HRT. Periodic monitoring of the women on HRT is however necessary and mammography mandatory

in the high risk group.

HRT thus plays a significant role in treating and preventing menopausal problems related to urogenital ageing. The importance of regular therapy, evaluation and modification of treatment as per the need has to be explained to each patient to achieve satisfactory results.

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