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Original Study

# Hormonal Replacement Therapy in Surgically Induced Menopause: A Prospective Cross Section Study from a Tertiary Care Institution from A Sub-himalayan State

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**ABSTRACT**

**Background:** Early surgical menopause increases risk of cardiovascular disease, osteoporosis, fracture, cognitive impairment and sexual dysfunction than women with late menopause. Estrogen therapy (ET) remains the most effective therapy for vasomotor symptoms related to surgically induced menopause. **Meterials and Methods:** It was a prospective cross-section study. **Result:** Amongst 255 symptomatic women, 163 (63.92%) women had severe vasomotor symptoms and 54 (33.12% of 163 women) of them had very incapacitating symptoms with marked reduction in their quality of life. 59 (23.13%) women had moderate symptoms with mild disturbances in their sleep while 33 (12.94%) women had only mild symptoms. **Conclusion:** It is agreed that women who undergo bilateral oophorectomy before the onset of natural menopause should be considered for estrogen therapy for the management of vasomotor symptoms until the average age of natural menopause.

## INTRODUCTION

Menopause represents permanent cessation of menstrual periods. It can occur spontaneously (natural menopause) or can be induced surgically by hysterectomy with bilateral salpingo-oophorectomy. The ovarian function and menstrual activity decline gradually in a synchronized fashion over a period of 12 months or more in women who experience natural menopause; however women who underwent surgical menopause had abrupt cessation of both ovarian function and menstrual activity. Hot flashes are the hall mark symptom of menopause, occurs in up-to 70 to 80% of women [1,2,3] and only 25% seek medical advice.[4,5] Hot flashes persist for a median of 7.4 years, and under-diagnosis and under-treatment are common. The abrupt cessation of ovarian function in premenopausal women in surgically induced (bilateral oophorectomy) menopause is associated with more severe vasomotor symptoms (hot flashes and night sweats) and adversely affects the quality of life and relationship.

Early surgical menopause increases risk of cardiovascular disease, osteoporosis, fracture, cognitive impairment and sexual dysfunction than women with late menopause.[6] Estrogen therapy (ET) remains the most effective therapy for vasomotor symptoms related to surgically induced menopause, if not contraindicated. However, after the publication of initial results of Women's Health Initiative (WHI) in 2002; increased risk of cardiovascular disease, venous thromboembolism and invasive breast cancer, created a situation of uncertainty in the minds of treating clinicians, and discontinued the use of estrogen therapy.[7]

To the best of our knowledge no study on the use of estrogen therapy after surgically induced menopause is done in this part of the globe. Therefore, we conducted a prospective study, to know the pattern of use of hormonal replacement therapy (estrogen therapy) in women who underwent hysterectomy with bilateral oophorectomy in the out-door clinic of medicine department of Indira Gandhi Medical College, Shimla.

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## METHODOLOGY

It was a prospective cross-section study done in non-pregnant women patients presented to the out-patient medicine clinic of Indira Gandhi Medical College (IGMC) and hospital, Shimla from June 2014 through May 2017. Patients enrolled in the study were women (> 18 years) presented with history of hysterectomy with bilateral salpingo-oophorectomy with or without vasomotor symptoms (VMSs).

The vasomotor symptoms (hot flashes and night sweats) were graded according to the four point scale.[1]

: VMS not present.

Mild: VMSs doesn't interfere with usual activities.

Moderate: VMSs interfere with usual activities.

Severe: VMSs so bothersome that usual activity can't be performed.

Moreover, VMSs at night causing significant sleep disturbances and wakefulness during night were also noted.

All women underwent routine blood tests: complete haemogram, calcium, and phosphorous, albumin, liver and kidney functions, thyroid function tests, lipid profile, plasma glucose and serum 25-hydroxyvitamin D3 levels. Detailed history regarding smoking, alcohol intake, previous history of trivial fracture and steroid use were obtained and co-morbidity present were also noted. Duel-energy X-ray absorptiometry (DEXA scan) was done in women with five year post-hysterectomy. Indications for hysterectomy and name of hospital (Government run hospital or private hospital) were recorded. Detail of treatment given at the time of discharge from the hospital and awareness about the vasomotor symptoms, bone health and cardiovascular disease were noted.

All women presented to us were treated with 1000 mg of elemental calcium and vitamin D3 60,000 IU/weekly for 8 weeks followed by 60,000 IU monthly. After discussion, women with mild VSM symptoms were treated with paroxitine in addition if they agreed. Women with moderate to severe vasomotor symptoms who agreed and didn't had contraindications (H/O Ca breast, coronary artery disease, stroke, deep vein thrombosis and active liver disease) for hormone replacement therapy were treated with conjugated estrogen (premarin) 0.625 mg daily for three to six month. Women who returned with marked reduction or with complete resolution of vasomotor symptoms, estrogen therapies were discontinued and were switched over to paroxitine. However, in women with persistent of symptoms, estrogen therapy (0.375mg) was extended over to next three to six months. Estrogen therapy was not given beyond one year.

## RESULTS

A total of 303 women were enrolled in the study, of which 48(15.84%) women were asymptomatic and 255 (84.15%) women were symptomatic. Amongst 255 symptomatic women, 163 (63.92%) women had severe vasomotor symptoms (hot flashes and night sweats) associated with marked disturbances in their sleep with frequent night wakefulness and 54 (33.12% of 163 women) of these women had very incapacitating symptoms with marked reduction in their quality of life. Further, 59 (23.13%) women had moderate symptoms with mild disturbances in their sleep, while 33 (12.94%) women had only mild symptoms.

The mean age of presentation was 50.63 years (range 30- 73 years) and mean age of hysterectomy with bilateral salpingo-oophorectomy was 43.44 years (range 22-59 years). Two hundred thirty three (76.89%) women were from rural areas. Two hundred and thirty nine (78.55%) women underwent hysterectomy in tertiary care teaching hospital, 27 (8.9%) women in Government district hospitals and 37 (12.21%) in private hospitals. The indications for hysterectomy in the present study were: Dysfunctional uterine bleeding because of fibroid in 279 (92.07%) women, rolapsed uterus in 9 (2.97%), Adenomyosis in 3 (0.99%) women, ovarian cyst in 3 (0.99%) women, carcinoma cervix and uterus in 2 (0.66%) women each and postpartum haemorrhage in 2 (0.66%) women and in 3 (0.99%%) women the records were not available. At discharge, all women were treated with calcium, multivitamins and vitamin D and were advised to take plenty of milk as a calcium supplement to prevent bone loss. All except 9% of women were off their calcium and vitamin D supplements at 3 to 6 months after discharge from the hospital. Women were not counselled about vasomotor symptoms and genitourinary syndrome after bilateral oophorectomy at the time of discharge and neither were they educated about increased risk for coronary artery disease, osteoporosis and cognitive decline. Sixty two (27.93%) women reported that they went back to their operating gynaecologist for discomfort they had because of hot flashes and excessive sweating. They were told by their operating surgeons that occurrence of such symptoms are common after bilateral oophorectomy and will disappear with time. However, for persistent unbearable discomfort, women with moderate to severe vasomotor symptoms had approximately 5-7 visits to different primary care providers before they visited this institution. They were treated with non-steroidal anti-inflammatory drugs, multivitamins and antidepressant in different combinations; however without any relief.

At first contact to the treating clinician in our outdoor clinic, 69 (31.08% of 222) moderately severe symptomatic women presented with the history of fever for variable period of time. On questioning they typically described that fever begins with hot sensation (hot flashes; which they sense as fever) followed after sometime by cold sensation. However; fever was never documented on measurement. For this feverish feeling they had several visits to their primary care doctors (both government and private) in past two to three years. Twenty nine (46.77% of 62) of these women were diagnosed with typhoid fever (based on rapid card test and history of fever) and were treated with anti-typhoid antibiotic, however; without any relief. Thirteen of these 29 women further revealed that for this feverish feeling, they were being treated repeatedly for typhoid fever (at least once in a year) over last three to four year.

Dual- energy X-ray absorptiometry (DEXA scan) of lumbar spine and neck femur was done in 121 women. Osteoporosis (T score > -2.5) was diagnosed in 74 (61.15%

of 121) women; while 31 (38.85% of 121) women were found to either osteopenia (T score between -1 to – 2.5) or normal bone mineral density. The mean age of osteoporotic women was 57.67 (47-72) years and mean age of surgically induced menopause (bilateral oophorectomy) was 44.03 (33-57) years. The difference in years from the time of bilateral oophorectomy to the diagnosis of osteoporosis in this study is 13.64 years. The mean age of women with either osteopenia or normal bone mineral density was 46.71 (30-65) years and mean age of surgically induced menopause was 37.53 (22-54) years. The bone mineral density is maintained until 9.18 years after surgically induced menopause (bilateral oophorectomy) and suggests that osteoporosis develops approximately after a decade (mean13 years) in women who undergo premenopausal (before age 50 years) bilateral oophorectomy.

### Treatment and Follow-up

Amongst 222 moderate to severe symptomatic women, 10 women refused for hormonal replacement therapy (estrogen therapy) and 3 women have contraindication for the use of estrogen therapy. Off 209 symptomatic women who agreed for hormonal replacement therapy, were treated with conjugate oestrogen 0.625 mg once a day. Off 209 women on hormonal replacement therapy; 168 (80.38%) women came for subsequent follow-up at 3 and 6 month. One hundred and six (63.09% of 168) women have either marked reduction and or complete resolution in their vasomotor symptoms and were changed over to either to paroxitine. Forty nine (29.16% of 168) women have partial response to hormonal replacement therapy at six month and conjugate oestrogen was continued for next 6 month. At 12 month, 41 women came for follow-up with complete resolution of their symptoms and 8 women didn't return. At 15 month; 142 women treated with ET for variable period ranging from 6 to 12 month came for follow up. Off these 142 women, 108 (76.05% of 142) women have complete resolution of their vasomotor symptoms and were treated with calcium and vitamin D3. Thirty four (23.94% of 142) women were mildly symptomatic and were continued on paroxitine and calcium and vitamin D3. At 24 month, 121 women came for follow-up; all except 21 women were asymptomatic and they were continued on calcium and vitamin D3. Twenty one symptomatic women have relapse of their vasomotor symptoms and were treated with three month short course of conjugate oestrogen with complete resolution of symptoms and were subsequently treated with calcium and vitamin D3. Women diagnosed osteoporosis on DEXA scan (T score > -2.5) were either treated with Alendronate (150 mg/monthly) or with injection Zolendronic (5mg yearly) as per their preference.

Thirty nine gynaecologists (consultant and resident) opinion regarding the use of hormonal replacement therapy for the relief of hot flashes in premenopausal women undergoing bilateral salpingo-oophorectomy were taken. They were not in favour of use of hormonal replacement therapy for the relief of vasomotor symptoms for the simple reason of fear of development of adverse side effects most notably carcinoma breast and for which they quote the results of women health initiative (WHI) study.

## DISCUSSION

The results of our study showed that hormonal replacement therapy was generally not prescribed in women who had surgically induced menopause before the age of 50 years, even after they had marked depletion in quality of life and sexual dysfunction.

Hot flashes and night sweats, the cardinal symptoms of menopause were seen in more than 80% of women in this study and were consistent with various previous studies.[1,2,3] Estrogen therapy (ET) is the most effective and gold standard for the relief of vasomotor symptoms after surgically induced menopause in young women as treatment with estrogen therapy cut down the number of hot flashes by 75% and severity by 87% with improved quality of life.[4] However, the use of hormonal replacement therapy (estrogen) decreased by approximately 80% since the publication of Women's Health Initiative (WHI) clinical trials[7]; showing detrimental effects of estrogen on the heart, breast, brain and other organs or tissues.[8] This created a situation of uncertainty in the mind of practicing clinicians and they stop estrogen therapy or avoided starting estrogen therapy at all and Food and Drug Administration (FDA) issued a warning about the risks of cardiovascular and breast cancers and stated that hormonal replacement therapy to be used at the lowest effective doses and for the shortest possible duration. A study from the Mayo Clinic revealed that only 60% of the women were prescribed estrogen therapy after bilateral salpingo-oophorectomy and only 20% were treated with ET through age 50 years.[9] However, the current scientific evidence suggests that the beneficial or detrimental effects of estrogen treatment vary across women by age at the time of treatment, type of menopause (natural versus surgically induced) and stage of menopause.[10-14] Early uses of estrogen therapy immediately after bilateral oophorectomy at younger age at least up to the age of natural menopause (age of 51 years) probably have best benefit: risk ratio compared to use of estrogen therapy in the late menopausal stage (ages 65-79 years) where the risk outweigh the benefit.[8] The results from WHI clinical trials have been inappropriately extrapolated from women late post menopausal stage (ages 65-79 years) to young women in early post-menopausal stage (ages 50-60 years) and even further to women underwent surgical menopause before the onset of natural menopause (age <50 years). Meta-analysis by Salpeter et al in 2009 showed 25% reduced mortality in young women given oestrogen immediately after surgically induced menopause compared to no-treatment and a sub-analysis from the WHI in women treated with estrogen alone immediately after the onset of menopause had shown reduced risk of invasive breast cancer, reduced coronary calcified-plague burden and 25% reduced mortality compared to no hormonal treatment.[15,16] After the widespread controversy and discontent following the publication of initial WHI clinical results; Manson et al and Rossouv et al re-examined the WHI data and suggested that estrogen therapy in young women immediately after menopause is safe, effective and

beneficial.[17,18] Recently, several studies have linked surgically induced menopause (bilateral oophorectomy) under 45-50 years of age to increased risk of death, 40% increased risk of coronary disease and increased risk of cognitive impairment without hormone replacement while a ET therapy eliminates the risk.[19-24] The "time hypothesis" of hormonal therapy suggests the lower absolute risk of adverse events among women less than 50 years of age, and should be considered for hormonal treatment until approximately age 51 years.[25,26] Consistent with the present study; Sherwin's and colleagues have shown organ protective and symptom relief effect of short duration of oestrogen therapy after surgically induced bilateral oophorectomy.[27] However; to reduce long- term health risks, hormonal replacement therapy is recommended until the expected age of natural menopause after surgically induced menopause.[28] Paroxetine mesylate is the only non hormonal therapy approved by FDA[29], for symptomatic women who have contraindications to hormone therapy or for whom the side effects are unacceptable or women who prefer to avoid hormonal therapy.

In accordance with the present study; bilateral salpingo-oophorectomy during hysterectomy is a common procedure in premenopausal women and is performed in two third of women before the age of 50 years and in approximately 90% of cases it is done for benign pathology.[30] Consistent with the present study; bilateral oophorectomy under 45 years of age is a strong risk factor for the osteoporosis and 20% of bone loss occurs in first 18 month and more than 75% bone is lost in first 20 years after menopause and is attributed to estrogen deficiency.[31-33]

A discordinance between the recent scientific evidence favouring the safety and effectiveness of hormonal replacement therapy in young premenopausal women after bilateral oophorectomy and non prescription of hormonal therapy by operating surgeons as observed in the present study is in agreement with the recent data suggesting that medical school graduates, as well as residents (obstetrics/gynaecology and medicine) receive very little or no training in the management of menopausal women.[34,35] and there is urgent need for better education of students, residents and junior faculty in menopausal medicine.

## CONCLUSION

The early use of estrogen therapy immediately after surgically induced menopause at younger age for short term use probably results into the best benefit: risk ratio at least in alleviating the troublesome hot flashes and night sweats. In agreement with the 2010 guidelines of the European Menopause and Andropause (EMAS), it is agreed that women who undergo bilateral oophorectomy before the onset of natural menopause should be considered for ET for the management of vasomotor symptoms until the average age of natural menopause[18,19] and results from WHI trial should not applied to them.

## KEY MESSAGE

Bilateral salpingo-oophorectomy during hysterectomy for benign pathology is a common procedure in premenopausal women and women who undergo this procedure feel inadequately informed about the occurrence of troublesome vasomotor symptoms, cardiovascular disease prevention and bone loss prevention; and cognitive impairment and sexual dysfunction. Gynaecologic surgeons should play the most influential role in educating women undergoing bilateral oophorectomy.

Early use of ET immediately after surgically induced menopause at younger age for short duration is not only effective for alleviating hot flashes and night seats but also safe and helps in improving the quality of life and relationship. The operating gynaecologic surgeons; with the availability of best medical evidence should make it routine practice to prescribe ET in young premenopausal women in the absence of contraindications; who undergo bilateral oophorectomy for shortest possible time only for alleviating trouble vasomotor symptoms; not for the prevention of cardiovascular disease and bone loss.

There is gap between the available scientific evidence and in the prescription of estrogen therapy by clinicians (obstetrics/genecology and medicine) after bilateral oophorectomy in young premenopausal women. There is need for the better education of students, residents and junior faculty in menopausal women.

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### Ethical Issues

Informed consent taken from all the participants.

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