Effects of Early Estradiol Valerate Administration On Bone Turnover Markers in Surgically Induced Menopausal Women

Jarika Vatrasresth
Chulalongkorn University
Ammarin Suwan (Ammarin.chula@gmail.com)
Chulalongkorn University
Krasean Panyakhamlerd
Chulalongkorn University

Research Article

Keywords: Surgical menopause, Bone turnover markers, Serum CTX, Serum P1NP, Estradiol valerate

Posted Date: July 1st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-666533/v1

Abstract

Background

Compared with natural process, surgically induced menopausal women have a higher bone loss rate. The objectives of this study were to evaluate effects of early treatment with estradiol valerate on the bone turnover markers levels after surgically induced menopause.

Methods

This prospective study enrolled 48 pre and perimenopausal women who underwent hysterectomy with oophorectomy for benign gynecologic conditions. Two weeks after surgery, all participants were assessed for menopausal hormone therapy (MHT) indications. Estrogen therapy was prescribed for those who had indication and accepted treatment (hormone treatment group). The others who had no MHT indication were allocated to no treatment group. Serum CTX and P1NP levels were measured at preoperative and 12 weeks postoperative.

Results

The median serum CTX and P1NP at 12 weeks were significantly different between two groups (*p*-value < 0.001 and 0.004, respectively). Median serum CTX and P1NP levels of women in the hormone treatment group were 55% and 40% lower than the women in no treatment group, respectively. At 12 weeks after surgery, serum CTX and P1NP levels were significantly elevated among women who did not receive hormone treatment (*p*-value < 0.001 and 0.002). In contrast, there were no significant change in the hormone treatment group.

Conclusion

Surgically induced menopausal women who received early estradiol valerate therapy had significantly lower levels of serum CTX and serum P1NP compared to women who did not receive treatment at 12 weeks after surgeries. This indicated that early estradiol valerate treatment could significantly suppress high bone-remodeling process in women with acute estrogen deprivation conditions.

Trial registration:

Thai Clinical Trial Registry identification number TCTR20190808004, retrospective registered since 2019-08-08. http://www.thaiclinicaltrials.org/show/TCTR20190808004</url>

Background

Osteoporosis is one of the most important health risks for postmenopausal women. Osteoporotic fractures, especially hip fractures, are associated with high morbidity and mortality rate.[1] Both of peak bone mass status and rate of continuing bone loss are the major determining factors of postmenopausal osteoporosis.[2, 3] Estrogen deprivation that occurs at the time of menopause is the major cause of accelerate bone loss. Uncoupling of the bone formation and resorption at this stage results in depletion of estrogen-mediated inhibition of the bone resorption.[4]

Natural menopause is an aging process which occurs at average age of 49.5 years in Thai women and around 52 years in Western countries.[5] It is defined as permanent cessation of menstrual period for more than 12 months and occurs when the ovarian follicles are depleted. Around 2–3 years before the final menstrual period, estrogen gradually declines concurrently with elevates follicle-stimulating hormone (FSH) levels. In contrast, surgical removal of both ovaries before the onset of natural menopause results in a sudden loss of ovarian hormone production including estrogens, progesterone, and testosterone.[6, 7] Available evidence suggested that surgical menopause was associated with long term adverse health outcomes such as low bone mass, cardiovascular disease, cognitive impairment, and increased in overall mortality rate.[8, 9] However, bilateral oophorectomy is usually performed (at least in some countries) at the time of hysterectomy in peri or premenopausal women aged around 50 years. Currently, the concept of oophorectomy for ovarian cancer prevention in normal gross finding ovaries has been debated[10]

Bone remodeling is a dynamic process starting from bone resorption (osteoclastic activity) and following by bone formation (osteoblastic activity). During the remodeling process, a number of bone turnover markers are produced. Bone turnover markers can be classified into 2 main categories, bone resorptive and bone formative markers. The most commonly used bone resorptive markers in clinical practices and researches are cross-linked telopeptides of collagen type I C-terminal (CTX) and N-terminal (NTX). Whereas bone-specific alkaline phosphatase (BAP), osteocalcin, procollagen type 1 N-terminal propeptide (P1NP), and procollagen type 1 C-terminal propeptide (P1CP) can be used as bone formative markers.[11] Due to analytic variability and utility limitations of many bone turnover markers, the International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommend to use only serum P1NP and serum CTX as bone formative and bone resorptive markers in clinical practices, respectively.[12]

Accelerated bone remodeling process in naturally menopausal women results in increases in both serum bone formative and resorptive markers levels and decreases bone mineral density (BMD).[13] On the other hand, abrupt and significant declination of estrogen levels in case of surgical menopause was more pronounce. Loss of bone detected by BMD measurement was more affected than in natural process.[14] Compared with naturally menopausal women, surgically induced menopause women had a relatively higher bone remodeling and bone loss rate.[15]

Menopausal hormone therapy (MHT) was approved for menopausal women who has at least one out of four indications including, relief of bothersome vasomotor symptoms, prevention of bone loss in women at high risk for fractures, premature hypoestrogenism, and genitourinary syndrome of menopause.[16] MHT regimens are classified into two main categories, estrogen-alone and estrogen-progestogen therapy. The estrogen-alone regimen is preferred in hysterectomized menopausal women. In case of non-hysterectomized menopausal women, estrogen-progestogen therapy is indicated. Because the risk of endometrial hyperplasia and cancer were significantly increased in non-hysterectomized women using estrogen-alone regimen,[17, 18] the primary purpose of progestogen prescription in MHT regimen is an endometrial protection.[16] However, current evidences demonstrated that women using estrogen-progestogen regimen had higher risk of breast cancer and venous thrombosis than women using estrogen-alone regimen.[19, 20] For these reasons, estrogen-alone is the MHT regimen of choice for hysterectomized menopausal women.

The main objective of this study was to evaluate the effects of early estrogen-alone therapy with oral estradiol valerate on the levels of bone turnover markers (CTX and P1NP) after surgical menopause procedures. The reasons for choosing this form of estrogen in our present study were availability of this product in many countries around the world, inexpensive cost, and estradiol valerate could be metabolized to 17β-estradiol by gastrointestinal tract enzymes in a comparable dose efficacy. We used 2 milligrams of estradiol valerate based primarily on the recommendation from literature as moderate to high estradiol dose. [21] However, there are variation globally as what doses are perceived as low, medium, and high. [22]

Methods

Design

The study was designed as a single-center, prospective, performed at the King Chulalongkorn Memorial Hospital Thailand between June 2019 and April 2020. This study was approved by the Institution Review Board of the Faculty of Medicine, Chulalongkorn University IRB 009/62, and also reviewed by the Thai Clinical Trial Registry Committee and prospectively approved for registration since 2019-08-08 and Thai Clinical Trial Registry identification number TCTR20190808004. Information pertaining to the study was provided to all enrolled participants. Written informed consent was obtained from all participants prior to the start of the study.

Inclusion and exclusion criteria

All premenopausal and perimenopausal women aged 40 - 55 years who had plan to do hysterectomy with bilateral oophorectomy for benign conditions in this period of time at King Chulalongkorn Memorial Hospital, Thailand were recruited. Definition of menopausal status in this study was determined by participant menstrual pattern. Premenopausal women in this study were defined by women who had regular menstrual period in the past 6 months before study enrollment. Perimenopausal women were

defined by women who had menstrual interval > 35 days for at least 50% of total cycles in the past year. Exclusion criteria in this study were women with secondary amenorrhea defined by amenorrhea for more than 3 cycles or 6 months, women with history of sex hormones or glucocorticoid use within 3 months before study enrollment, had a history or currently has any conditions known to affect bone turnover markers including, disorders of the thyroid, parathyroid glands, renal insufficiency and had recent fracture within 12 months. Women who had ≥ 1 of particular MHT contraindications (history of coronary heart diseases, stroke, venous thrombosis, breast or endometrial cancer, congenital thrombophilia) were also excluded from the study.

Sample size justification

The sample size was calculated by testing two independent mean formulation. Data from previous study were used to calculate the sample size. [23] Forty percent reduction in bone resorption marker (CTX) after 12 weeks of hormone therapy was expected.[24] The sample size of this study was 20 participants per group. When we incorporated a 20% dropout rate, the total sample size require for this study was 48 participants (24 participants /group).

Data collection and intervention

Demographic data were collected. Serum CTX, P1NP, and FSH were measured at around 7-10 days before elective hysterectomy with oophorectomy (baseline bone turnover markers). Blood was collected between 8.00 – 9.00 am after overnight fast for at least 8 hours. Serum CTX, P1NP and FSH were measured by electrochemiluminescence immunoassay (Elecsys kit, Roche Diagnostics Thailand). The inter-assay coefficient of variations (CV) of serum CTX, P1NP, and FSH were 3.8%, 2.3%, and 3.8%, respectively. The intra-assay CV for serum CTX, P1NP, and FSH were 2.1%, 1.8%, and 1.5%, respectively.

Two weeks after operations, the indications for MHT in all participants were assessed by a reproductive endocrinologist. The participants were assigned into 2 groups according to their symptoms and MHT indications. The participants who had indication(s) for menopausal hormone therapy were counseled by the primary investigator about the risks and benefits of hormone therapy. The participants who had indication(s) for MHT and interested in treatment were assigned into the hormone treatment group. They received 2 milligrams/ tab of oral estradiol valerate 1 tab per day (Progynova ® tablet, the Bayer Thai, Thailand) started at 2 weeks after procedures for a total period of 12 weeks. The participants who had no MHT indication or refused to use MHT were enrolled into the no treatment group. At the end of 12 weeks, blood was collected using the same procedure as baseline. All laboratory measurements were collected at the day after the last pill was taken.

Outcome measures

The primary outcome of this study was to compare the levels of serum CTX at 12 weeks after surgical menopausal procedure between the hormone treatment and no treatment groups. The secondary outcomes were to compare the levels of serum P1NP at 12 weeks after surgical menopausal procedure

between two groups. The other outcomes were to compare serum CTX and P1NP levels at before and after surgery in each group (within group comparison as shown in table 3). Finally, we analyzed the correlation between age at surgical menopause and the baseline serum CTX and P1NP.

Statistical analysis

IBM SPSS™ statistics version 22.0 for Windows was used for statistical analysis. Descriptive statistics was used to present the baseline data. Comparisons of the median serum CTX or P1NP at 12 weeks after surgical menopause between the two groups were analyzed by Mann Whitney U test. Comparisons of the median serum CTX or serum P1NP before and after surgical menopause within the group were analyzed by Wilcoxon signed rank test. The correlation between age and baseline bone turnover markers were analyzed by Spearman's rank correlation coefficient analysis. Normal distribution of data was tested by Kolmogorov–Smirnov test. A *p*-value of < 0.05 was considered statistically significant.

Results

Study participants

During June 2019 - January 2020, seventy-six pre and perimenopausal women were assessed for eligibility. A total of 48 women met the inclusion criteria and were willing to participate in this study. Forty-one women returned for follow-up visit. Twenty-one women received 2 milligrams of oral estradiol valerate per day for 12 weeks. In this hormone treatment group, five women were prescribed estradiol valerate due to early menopause (premature hypoestrogenic state), and the others (16 participants) due to bothersome vasomotor symptoms. There was no participant in this group denied hormone treatment. All of participants in this hormone treatment group continued medication for a total of 12- week period. The others who had no MHT indication were allocated to the no hormone treatment group. There were 27 women in this group, seven out 27 were lost to follow-up. There was no participant in the no treatment group received any MHT in the 12 weeks study period. Baseline characteristics of participants were shown in **Table 1.** There were statistically significant differences in age, body mass index and baseline serum P1NP between the two groups (*p*-value = 0.026, 0.026 and 0.040, respectively). The median (IQR) serum CTX and P1NP levels in women of hormone treatment group at baseline were 0.21 (0.17-0.35) ng/ml and 37.97 (26.09-54.62) ng/ml, respectively. The median (IQR) serum CTX and P1NP levels in women of no treatment group at baseline were 0.25 (0.19-0.34) ng/ml and 46.71 (36.45-70.47) ng/ml, respectively.

Comparison of bone turnovers markers in surgically induced menopausal women at 12 weeks after hysterectomy with bilateral oophorectomy.

At 12 weeks after surgeries, the median (IQR) serum CTX and P1NP levels of women in hormone treatment group were 0.21 (0.14-0.34) ng/ml and 42.41 (31.42-63.61) ng/ml, respectively. On the contrary, the median (IQR) serum CTX and P1NP levels in women of no treatment group were 0.47 (0.28-0.65) ng/ml and 63.63 (54.98-80.45) ng/ml, respectively. The median serum CTX and P1NP levels at 12 weeks

after surgeries among women in the hormone treatment group were 55% and 40% lower than the levels in the no treatment group, respectively.

As the primary outcome, the median serum CTX levels at 12 weeks after surgical menopause procedure were significant differences between the two groups (*p*-value <0.001). The median serum P1NP levels at 12 weeks after surgical menopause procedure were also significant differences between groups (*p*-value = 0.004), data was shown in **Table 2.**

Changes of bone turnovers markers in surgically induced menopausal women at 12 weeks after hysterectomy with bilateral oophorectomy.

Changes of bone turnover marker levels at 12 weeks after surgeries, serum CTX and P1NP levels were significantly elevated among women who did not receive hormone treatment (*p*-value < 0.001 and 0.002). In contrast, there were no significant differences of serum CTX and P1NP levels between at before and 12 weeks after surgeries among women in the hormone treatment group. Data was shown in **Table 3**.

Additional correlation analysis

Due to possible effects of participant age at surgery on bone turn over marker levels, we made additional analysis of the correlation between age and bone turnover markers. However, there was no significant correlation between the median serum CTX and age at surgical menopause in both hormone treatment and no treatment group, r = 0.28 *p*-value = 0.22, and r = 0.14 and *p*-value = 0.56, respectively. In the same way, there were no significant correlations between median serum P1NP and age at surgical menopause in both hormone treatment and no treatment group, r = -0.01 *p*-value = 0.97 and r = 0.08 *p*-value = 0.72, respectively.

Discussion

The present study revealed significant elevation of bone turnover marker levels in women undergone hysterectomy with bilateral oophorectomy who did not receive

estrogen treatment. Despite a short period, asymptomatic but significantly high bone resorption process was occurred within 3 months after surgeries. In normal reproductive period, bone resorption and formation were modulated and balanced by circulating estrogen levels. Estrogen activates synthesis of osteoprotegerin (OPG), the decoy antibodies which neutralizes the receptor activator of NF-κB ligand (RANKL), and inhibits RANK expression (receptor of RANKL). Responses to estrogen results in inhibition of differentiation and activation of the osteoclasts. Moreover, estrogen modulates the proinflammatory cytokines such as IL-1, IL-6, TNF-α and PGE2 which reduces the pool of osteoclasts precursors. The minor estrogenic mechanism on bone is regulates TGF-β expression results in apoptosis of osteoclasts.[(25)] According to all mechanism mentioned above, estrogen deprivation is a major detrimental factor on bone physiology.

Surgical removal of both ovaries in women before the time of menopause leads to abrupt declination of circulating estrogen levels.[6] From a previous study, the bone turnover markers measured before and after surgical menopause procedure were elevated as soon as a month after surgery. These serum bone turnover levels were continuously elevated at 6 months after surgery. Furthermore, they found a significant negative correlation between the bone turnover markers levels and lumbar spine bone mineral density (BMD) at preoperative and 6 months after surgery. [14] In another study, bone resorption and formation markers were elevated at 3 months after surgical menopause procedure. However, the bone markers levels declined to the baseline levels after menopausal hormone prescription for 3 months. [23] Although there were several studies found that surgical menopausal women seem to have higher bone loss rate than age-matched natural menopause women in a short term period,[15, 27]there is no high-quality data demonstrated the long term bone loss and fracture risk differences between types of menopause.

Traditionally routine salpingo-oophorectomy at the time of hysterectomy should be revisited, especially in pre and perimenopausal women. Because the lifetime risk of developing ovarian cancer in the general population is only 1 in 70 or 1.4%, [27] physicians should make sure that their counseling about risks and benefits is based on current evidence. The reduction of ovarian cancer risk, avoid possible morbidities and future surgery of ovarian disease are the major potential benefits of salpingo-oophorectomy. However, these potential benefits must be balanced with the consequences of premature loss of circulating estrogen including, bone loss, hot flushes, cognitive impairment, sexual desire loss, and long-term survival rate.[27]

This study emphasized this concept. The detrimental bone effects began in surgically induced menopausal women in only 3 months after surgery. In case of women who did not receive MHT, further bone loss, potential risk of osteoporosis, and possible risk of fractures should be concerned. In the present study, we gave patients as much as possible information about risks and benefits of salpingo-oophorectomy at the time of hysterectomy. Based primarily on patient autonomy, the decisions to do salpingo-oophorectomy were made by participants with additional information from physicians.

In our cohort, twenty-seven out of 48 women did not receive MHT for treating menopausal symptoms and bone loss prevention. In other words, more than haft of women in our cohort lost their bone significantly at 3 months after surgery. Prudent clinical evaluation, life-style modification for bone health, and follow-up for bone density and/ or quality measurement should be considered in these women. In our experiences as a medical school center in Thailand, we found that around 30–40% of advanced age premenopausal and perimenopausal women accepted and made decision to remove their ovaries at the time of hysterectomy for benign gynecological conditions. However, bone measurement was offered only in a minority of these patients.

As the primary outcome in the present study, the median serum CTX levels at 12 weeks after surgical menopause procedure were statistically different between the two groups (p-value < 0.001), Table 2. The 55% lower of median serum CTX level than in the no treatment group is not only statistically significant,

but is significantly clinical meaning. In other words, abnormal bone resorption from acute estrogen deprivation could be inhibited by early administration with moderate dose estrogen. Moreover, additional data in this study showed that both of bone resorptive and formative markers levels after surgical menopause were not significant differences from the baseline levels among women in hormone treatment group (before and after treatment comparison within group, Table 3).

The timing of hormone initiation might be an important issue. In our study, hormone therapy was initiated around 2 weeks after surgery. In contrast, the women from Peris P, et al study. [23] started hormone therapy at 3 months post-surgery. The differences between our results and Peris P, et al. finding are at least in part due to the timing of menopausal hormone initiation. It should be noted that, sixteen out of the total 48 women in our study had moderate to severe hot flushes as early as 2 weeks after oophorectomy. Hence, MHT could be considered as soon as possible in women who has MHT indication. The benefit of MHT in this condition is not only for improving the quality of life but also protecting accelerated bone loss. However, some clinicians may concern about the risk of venous thrombosis with MHT in early postoperative period, especially in cases of obesity, metabolic syndrome, and advanced age patients. To minimize the thrombosis risk in these patients, transdermal estrogen administration with optimum dose is preferred.

In term of treatment effects, we showed that early administration of 2 milligrams of oral estradiol valerate significantly suppressed bone remodeling process. However, conclusion cannot be done for all oral MHT products in the market. Many available products around the world are 1 milligram of estradiol plus variety of progestins. Both the lower dose of other estradiol products and estrogenic counter-action of various progestins may dramatically affect the bone outcomes.

There are incongruences in data interpretation and recommendations of estrogen therapy and bone, especially for postmenopausal osteoporosis. In the age group 50–60 years or within 10 years after menopause (the window of opportunity concept), the benefits of MHT are most likely to outweigh any risk and can be considered as first-line therapy in postmenopausal osteoporosis, based on the International Menopause Society (IMS) recommendations on women's midlife health and menopause hormone therapy.[28] On the contrary, the North American papers, the American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines (AACE/ ACE) for Diagnosis and Treatment of Postmenopausal Osteoporosis 2020 stated that estrogen was never specifically approved for postmenopausal osteoporosis. Estrogen is only approved by the US FDA for prevention of postmenopausal osteoporosis and should only be used for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate. [29]

Finally, due to possible effects of participant age on baseline bone turnover marker levels, we made additional analysis of the correlation between age and bone turnover markers. However, there was no significant correlation between the serum CTX and age at surgical menopause in both hormone treatment and no treatment group, r = 0.28 *p*-value = 0.22, and r = 0.14 and *p*-value = 0.56, respectively. In the same way, there were no significant correlations between serum P1NP and age at surgical menopause in both

hormone treatment and no treatment group, r = -0.01 *p*-value = 0.97 and r = 0.08 *p*- value = 0.72, respectively.

There were many strengths and limitations of this study. This was a prospective trial that enrolled pre and perimenopausal women at the time before the surgically induced menopause. Participants were separately assigned into the hormonal and no treatment group based on currently approved MHT indications. In term of outcome measurements, we chose serum CTX and P1NP as outcomes according to the recommendation from IOF and IFCC. However, there are many limitations of bone turnover markers interpretation in clinical practices. The biologically interobserver variation, analytic reliability, and poorly defined abnormal cut point levels are issues of concern in clinical utility. Moreover, the changes of the bone turnover markers are only representative of bone metabolism, it cannot be used for diagnosing osteoporosis. Dual-energy X-ray absorptiometry for bone density measurement is the standard method for using in both clinical practice and the majority of osteoporosis researches. Nowadays, bone turnover markers are primarily be used for patient with poor responders, nonadherence to therapy patient identification, [30] and can be used as one of the indicators to restart of treatment after the bisphosphonate drug holiday period. [31]

On other hands, this is a nonrandomized trial so we could not match the baseline prognostic factors between the two groups. The serum vitamin D level, which may affect to bone turnover was not be measured in this study, but calcium carbonate 1000 milligrams per day and vitamin D2 (ergocalciferol) 20,000 unit per week were prescribed to all participants in this study.

Conclusion

Surgically induced menopausal women who received early estradiol valerate therapy had significantly lower levels of serum CTX and serum P1NP compared to women who did not receive treatment at 12 weeks after surgery. This indicated that early estradiol valerate treatment could significantly suppress high bone-remodeling process in women with acute estrogen deprivation conditions. Additional studies are required to assess other aspects of bone status with a longer-term follow-up period.

Declarations

Ethics approval and consent to participate

This study was approved by the Institution Review Board of the Faculty of Medicine, Chulalongkorn University IRB 009/62.

Written informed consent was obtained from all participants prior to the start of the study.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interest

All authors of this study declare that they have no conflict of interest.

Funding

This study was funded by Ratchadapiseksompotch funding, Faculty of Medicine, Chulalongkorn University.

Authors' contributions (This statement must exactly match on Editorial submission system and in the manuscript)

Vatrasresth J: Protocol development, data collection, data analysis, manuscript writing/editing

Suwan A: Protocol development, data analysis, manuscript writing/editing

Panyakhamlerd K: Protocol development, data analysis

Acknowledgements

This study could not be completed without contribution from several parties including medical staffs, nurses and supporting staffs from the Gynecologic Clinic, and Gender Health Clinic, King Chulalongkorn Memorial Hospital.

References

1. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. Osteoporos Int 2000;11:556–61.
2. Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. Osteoporos Int 2016;27:1281–386.
3. Goltzman D. The Aging Skeleton. Adv Exp Med Biol 2019;1164:153–60.
4. Riggs BL, Khosla S, Melton LJ, 3rd. A unitary model for involutional osteoporosis: estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res 1998;13:763–73.

5. Chompootweep S, Tankeyoon M, Yamarat K, Poomsuwan P, Dusitsin N. The menopausal age and climacteric complaints in Thai women in Bangkok. Maturitas 1993;17:63–71.
6. Castelo-Branco C, Martínez de Osaba MJ, Vanrezc JA, Fortuny A, González-Merlo J. Effects of oophorectomy and hormone replacement therapy on pituitary-gonadal function. Maturitas 1993;17:101–11.
7. Rodriguez M, Shoupe D. Surgical Menopause. Endocrinol Metab Clin North Am 2015;44:531–42.
8. Shuster LT, Gostout BS, Grossardt BR, Rocca WA. Prophylactic oophorectomy in premenopausal women and long-term health. Menopause Int 2008;14:111–6.
9. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. Climacteric 2015;18:483–91.
10. Asante A, Whiteman MK, Kulkarni A, Cox S, Marchbanks PA, Jamieson DJ. Elective oophorectomy in the United States: trends and in-hospital complications, 1998–2006. Obstet Gynecol 2010;116:1088–95.
11. Hlaing TT, Compston JE. Biochemical markers of bone turnover - uses and limitations. Ann Clin Biochem 2014;51:189–202.
12. Vasikaran S, Eastell R, Bruyere O, Foldes AJ, Garnero P, Griesmacher A, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int 2011;22:391–420.
13. Chapurlat RD, Garnero P, Sornay-Rendu E, Arlot ME, Claustrat B, Delmas PD. Longitudinal study of bone loss in pre- and perimenopausal women: evidence for bone loss in perimenopausal women. Osteoporos Int 2000;11:493–8.
14. Bahar S, Abali R, Guzel S, Bozkurt S, Guzel EC, Aral H, et al. Comparison of the acute alterations in serum bone turnover markers and bone mineral density among women with surgical menopause. Eur J Obstet Gynecol Reprod Biol 2011;159:194–7.
15. Yildiz A, Sahin I, Göl K, Taner Z, Ulutürk A, Biberoğlu K. Bone loss rate in the lumbar spine: a comparison between natural and surgically induced menopause. Int J Gynaecol Obstet. 1996 Nov;55(2):153–9.
16. The NHTPSAP. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause 2017;24:728 – 53.
17. Sjögren LL, Mørch LS, Løkkegaard E. Hormone replacement therapy and the risk of endometrial cancer: A systematic review. Maturitas 2016;91:25–35.
18. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database of Systematic Reviews [Internet]. 2012 [cited 2021 March 27]; Issue 8. Art. No.: CD000402. Available from: DOI: 10.1002/14651858.CD000402.pub4.
19. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet 2019;394:1159–68.

20. Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA. 2013;310:1353–68.
21. Jane FM, Davis SR. A practitioner's toolkit for managing the menopause. Climacteric. 2014;17(5):564–79.
22. Panay N, Anderson RA, Nappi RE, Vincent AJ, Vujovic S, Webber L, et al. Premature ovarian insufficiency: an International Menopause Society White Paper. Climacteric. 2020;23(5):426–46.
23. Peris P, Alvarez L, Monegal A, Guañabens N, Durán M, Pons F, et al. Biochemical markers of bone turnover after surgical menopause and hormone replacement therapy. Bone 1999;25:349–53.
24. Delmas PD, Pornel B, Felsenberg D, Garnero P, Hardy P, Pilate C, et al. A dose-ranging trial of a matrix transdermal 17beta-estradiol for the prevention of bone loss in early postmenopausal women. International Study Group. Bone 1999;24:517–23.
25. Riggs BL. The mechanisms of estrogen regulation of bone resorption. J Clin Invest 2000;106:1203–4.
26. Ohta H, Makita K, Komukai S, Nozawa S. Bone resorption versus estrogen loss following oophorectomy and menopause. Maturitas 2002;43:27–33.
27. ACOG. ACOG Practice Bulletin No. 89. Elective and risk-reducing salpingo-oophorectomy. Obstet Gynecol. 2008;111(1):231–41.
28. Baber RJ, Panay N, Fenton A; IMS Writing Group. 2016 IMS Recommendations on women's midlife health and menopause hormone therapy. Climacteric. 2016;19(2):109 – 50.
29. Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. H. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS-2020 UPDATE. Endocr Pract. 2020;26(Suppl 1):1–46.
30. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. J Clin Endocrinol Metab 2020;105.
31. Roberts J, Castro C, Moore AE, Fogelman I, Hampson G. Changes in bone mineral density and bone turnover in patients on 'drug holiday' following bisphosphonate therapy: real-life clinic setting. Clin Endocrinol (Oxf) 2016;84:509–15.

Tables

Table 1
Baseline characteristics of participants.

	Hormone treatment group (N = 21)	**No treatmen group (N = 27)**	***p*-value**
Age* (years)	47.14 (4.1)	49.37 (2.6)	0.026
- Age < 45 years	5 (24%)	0 (0%)	
- Age ≧ 45 years	16 (76%)	27 (100%)	
BMI* (kg/m2)	26.4 (4.9)	23.7 (3.2)	0.026
Marital status	17 (81%)	20 (74%)	
Married	4 (19%)	7 (26%)	
Single			
Parity	9 (43%)	12 (44%)	
Nulliparous	12 (57%)	15 (56%)	
Multiparous			
Underlying disease	2 (9%)	4 (15%)	
Hypertension	1 (5%)	1 (4%)	
Dyslipidemia			
Primary indication for surgery	6 (28%)	10 (37%)	
Myoma uteri	4 (19%)	7 (26%)	
Adenomyosis, Adenomyoma	10(48%)	8 (30%)	
Endometriosis, endometrioma	0	1 (4%)	
BRCA mutation	0	1 (4%)	
Endometrial hyperplasia	1 (5%)	0	
CIN III			
FSH levels** (IU/L)	10.59 (6.84–36.64)	11.22 (4.85–59.13)	0.860
Serum CTX levels** (ng/ml)	0.21 (0.17–0.35)	0.25 (0.19–0.34)	0.200
Serum P1NP levels** (ng/ml)	37.97 (26.09–54.62)	46.71 (36.45–70.47)	0.040
*Data was presented as mean (SD)			
** Data was presented as median (IQR)			

Table 2

Comparison of bone turnovers markers levels in surgically induced menopausal women at 12 weeks after hysterectomy with bilateral oophorectomy between the hormone and no treatment groups.

	Hormone treatment group	**No treatment group**	***p*-value**
Serum CTX levels (ng/ml)	0.21 (0.14–0.34)	0.47 (0.28–0.65)	< 0.001
Serum P1NP levels(ng/ml)	42.41 (31.42–63.61)	63.63 (54.98–80.45)	0.004
Median (IQR); Mann-Whitney U test			

Table 3

Changes of bone turnovers markers levels in surgically induced menopausal women at 12 weeks after hysterectomy with bilateral oophorectomy in each particular treatment groups.

	Hormone treatment group			**No treatment group**		
Serum levels	Pre-operation	Post-operation	*p*-value	Pre-operation	Post-operation	*p*-value
CTX (ng/ml)	0.213 (0.166–0.353)	0.208 (0.140–0.335)	0.660	0.245 (0.185–0.344)	0.473 (0.283–0.652)	< 0.001
P1NP (ng/ml)	37.97 (26.09–54.62)	42.41 (31.42–63.61)	0.120	46.71 (36.45–70.47)	63.63 (54.98–80.45)	0.002
Median (IQR); Wilcoxon signed rank test						