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Archives of Obstetrics and Gynaecology Commentary

After Surgical Menopause, Should Menopausal Hormonal Therapy Started Only Before the Age of 45 Years?

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Abstract

The published study *Compliance and health consequences of menopausal hormonal therapy after surgical menopause: A retrospective study in Thailand* showed that menopausal hormonal therapy soon after bilateral oophorectomy before the age of natural menopause in Thailand possibly prevented subsequent osteopenia compared with menopausal hormonal therapy non-users, also without significant adverse breast outcomes comparing between hormonal therapy users and non-users. According to that study, additional data showed that the number of early hormonal users (initiated before age 45 years) who continued hormonal therapy until at least 50 years old (average natural menopausal age in Thailand) is less than that of late hormonal users (initiated at age ≥45 years). Therefore, hormonal replacement therapy after bilateral oophorectomy before the age of natural menopause, in the absence of contraindication, should be commenced soon at any age after surgery and maintained until at least the age of natural menopause to prevent possible long-term adverse health outcomes from early estrogen deprivation.

Keywords: Surgical menopause, Menopausal hormonal therapy, Health consequences

Natural menopause occurs at different ages in different countries ranging from as young as 46.9-47.8 years in the Middle-East region to 50.0-51.1 years in the European countries [1], and previously reported at the approximate age of 50 years in Thailand [2]. Natural menopausal age is reported to be influenced by both factors; host factors such as genetic factors, ethnicity, or body-mass index; and environmental factors such as smoking, parity, etc. Age at natural menopause was associated with subsequent risk of cardiovascular disease, low bone mass density, osteoporosis, and all-cause mortality [3]. However, surgical menopause from bilateral oophorectomy with or without hysterectomy before the age of natural menopause, which occurs at a much younger age than natural menopause, causes a more abrupt decline in ovarian hormones production especially estrogens. The majority of bilateral oophorectomy cases were reported at the ages between 35-45 years or younger [4,5]. In general, surgical menopause also results in subsequent adverse health consequences such as: sleep problems [6-8], genitourinary syndrome of menopause, metabolic diseases and cardiovascular events, dementia, osteoporosis, etc. [9-16]. On the contrary, surgical menopause for benign diseases with or without estrogen therapy was also reported to improve sexuality and psychological well-being as the results of reliefs from prior depression or sexual problems [17]. In recent years, surgical menopause has been globally an area of healthcare interest and much more studied and reviewed. A retrospective cohort study of 1,000 consecutive surgical menopause patients who underwent premenopausal surgery before age 50 years for benign indications from a tertiary-care hospital in Bangkok was performed, and the results were published in 2020 [18]. The results showed that 85.5% of the patients used menopausal hormonal therapy (MHT) after surgery. From that study, those with MHT initiated soon after surgery (87% initiated within the first postsurgical year, at the mean age of 42.6 ± 5.1 years, with a median follow-up time of 12.0 years) possibly prevented subsequent osteopenia compared with MHT non-users.

Many previous observational studies and randomized clinical trials showed that early menopause, especially bilateral oophorectomy before menopause, was associated with an increased risk of ischemic heart disease [19]. A prospective cohort study demonstrated that menopause

below both 40 and 45 years was associated with the same risk, especially more obvious among women after both early surgical and early natural menopause. However, MHT did not reduce this risk except for early surgical menopause (<40 years or 40-45 years) compared to MHT never-users [13]. A meta-analysis in 2006 [20] showed an increased pooled RR of cardiovascular diseases in surgically menopausal women [(age range <30 to 50 years) RR 2.62; 95%CI: 2.05, 3.35]. The Nurses' Health Study in 2009 [21] also showed an increased risk of coronary heart disease in women who underwent bilateral oophorectomy especially in women age <45 years, and also an increased risk of stroke in those who underwent surgery before 50 years without estrogen replacement. The data from the previously mentioned retrospective study [18] did not show these similar comparative results among different surgical menopause age groups.

Another report in 2008 from the Mayo Clinic Cohort Study of Oophorectomy and Aging showed an increased risk of cognitive impairment assessed by using a structured questionnaire, dementia, and Parkinsonism. And the risk increased for women of younger age at surgery compared with age matched referent women from the same population. These findings demonstrated a possible estrogen effect on neuroprotection [11]. The Religious Orders Study and Rush Memory and Aging Project reported in 2014 that earlier age at menopause including early surgical menopause was associated with a significantly faster decline in global cognition and Alzheimer pathology in women with a mean 18-year follow-up and after adjustment for age, education and smoking. In that study, MHT starting within a 5-year perimenopausal window in surgical menopause and when MHT was used ≥10 years was associated with a less decline in global cognition [22]. Interestingly, this association was not observed in naturally menopausal women without a clear explanation. One recent longitudinal population-based study showed that surgical menopause women who underwent surgery before age 46 years and without initial 18 chronic conditions at registration (mental health, cardiovascular or metabolic conditions, and other somatic conditions) were associated with significantly accumulated rate of those conditions when compared with the referent women born in the same year after a median of 14 years follow-up after adjustment for age, ethnicity, education, body mass index and smoking [23,24]. The findings implied that bilateral oophorectomy is the cause of multi-morbidity in later life and many conditions might benefit from early MHT.

Bilateral oophorectomy before age 45 years was also shown to be a risk factor for osteoporosis [25]. An observational study reported in 2012 that early menopausal women with 39-year follow-up were at increased risk for osteoporosis and fracture, and the result from that study showed that oophorectomy before age 45 was also shown to be a risk factor for osteoporosis [26]. On the contrary, a systematic review and meta-analysis of one study in 2017 [27] did not show premenopausal surgical menopause effect on bone mineral density or prevalence of fracture when compared with natural menopause. That study mentioned about a possible bias of the extracted available studies.

Before 2002, more than 90% of women who underwent bilateral oophorectomy used MHT soon after surgery [28,29]. The percentages declined after the Women's Health Initiative study adverse results published. Since then, the role of MHT in menopause management has to be weighed between risks and benefits. Later, the Revised Global Consensus Statement on menopausal hormone therapy in 2016 [30] suggested MHT in iatrogenic menopause before the age of 45 years, and especially before age 40 years, since these women are at a higher risk of cardiovascular disease, osteoporosis, and dementia in later life. MHT in observational studies helped reduce those risks. Later, the North American Menopause Society (NAMS) recommendations in 2017 [31] published the FDA-approved indications of MHT with health benefits if without contraindications for women with premature surgical menopause. However, the NAMS recommendations did not specify the age of MHT initiation after surgical menopause. There have been very limited data on women initiating MHT after age 45 years in the surgically menopausal women.

Among all 1,000 patients included in the previously mentioned study [18], the patients were divided into the early surgical menopause subgroup (age at surgery <45 years, 557 cases) and the late one (age at surgery ≥45 years, 443 cases), and compared. When comparing the early subgroup with the late one, 90.5% (503 cases) of the early subgroup used MHT, while 79.3% (352 cases) of the late one used MHT. The median follow-up time from surgery of both subgroups were 12.0 years and 11.0 years, respectively. Therefore, 49.1% of MHT user continued MHT until age ≥50 years. The overall median age of stopping MHT was 47.0 years which was before the natural menopausal age for Thai women.

For 855 MHT users, 435 women used MHT until age <50 years and 420 women used until age ≥50 years. Of these two subgroups, the late one significantly used MHT less than the early one [P<0.001, OR2.48; 95% CI:1.72, 3.57 (small to medium effect)]. The results from the study (previously unpublished data, Table 1) also showed that the number of women with later age at surgical menopause (≥45 years, 352 cases) significantly used MHT less than earlier age [<45 years, 503 cases: OR 2.48 (small to medium effect)]. On the contrary, the later age at surgical menopause is a predictive factor for longer term use of MHT until age ≥50 years [P<0.001, OR 4.69; 95% CI:3.49-6.31 (medium effect)], with the comparable follow-up duration.

Table 1. Comparison of ages at starting MHT and percentages of cases stopping MHT [855 MHT users: 503 early users (starting age <45 years) vs. 352 late users (starting age ≥45 years)].

Patient group (cases)	Age stop MHT			Duration F/U from surgery-yr median (IQR)	Duration F/U from registration-yr median (IQR)
	≤45 yr case (%)	45.1-45.9 yr case (%)	≥50 yr case (%)		
Early MHT users <45yr (503)	198 (39.4)	134 (28.6)	171 (34.0) *P<0.001	11.0 (5.5-18.0) #P=0.958	8.0 (3.0-14.0) #P=0.338
Late MHT users ≥45yr (352)	5 (1.4)	98 (27.8)	249 (70.7)	12.0 (6.0-17.0)	9.0 (4.0-13.0)

IQR=Interquartile range; *=Chi-square test; #=Mann-Whitney test

In this study, the median years for MHT use and the median years of follow-up time since surgery of the early subgroup and the late one was not significantly different. Prevalence of breast cancer was also lowest in the MHT user until <50 years compared with the other two groups. This also supported the European Menopause and Andropause Society position statement in 2015 that MHT in women under 50 years does not increase risk of breast cancer compared with menstruating women [32]. Also, after age-adjustment at the follow up time of all the three groups from our study (MHT non-users, MHT-users until age < 50 years with the mean age at MHT starting of ~40.3 years, and MHT-users until age ≥50 years with the mean age at MHT starting of ~44.4 years, the only significantly adverse health consequence for MHT non-users was osteopenia (P<0.001).

Conclusion

The additional data presented in this article raised awareness for initiating MHT also in women at the age ≥45 years at the time of surgical menopause. Among MHT users in one published study from Thailand [18], 49.1% used until age ≥50 years which these patients complied to the international recommendation for MHT use for surgical menopause women. Surgically menopausal women whose age at starting MHT ≥45 years significantly used MHT for a longer period, until at least or beyond the natural age of menopause (50 years) in Thailand. Older at surgery (≥45 years vs. <45 years) significantly predicted MHT use until age ≥50 years with a bone density benefit. As MHT is clearly indicated after surgical menopause, however, MHT should not be started only before the age of 45 years. But should be started at any age after premenopausal oophorectomy and be maintained MHT until at least the natural menopausal age if there is no contraindication. Thus, the controversial age at which MHT should be initiated after bilateral oophorectomy before the age of natural menopause is of concern for possible long-term health benefits and should be further studied.

Strengths and Limitations

These were described in the previous publication [18].

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Conflict of Interests

The author declared no conflict of interest in this work.

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