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Original Article

Hormone Replacement Therapy Prescription after Premature Surgical Menopause

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ABSTRACT **Study Objective:** To assess hormone replacement therapy (HRT) prescription pattern in patients undergoing premature surgical menopause on the basis of surgical indication.

Design: Retrospective cohort study.

Setting: Academic tertiary care center.

Patients: Surgically menopausal patients aged ≤45 years who underwent a minimally invasive hysterectomy with salpingo-oophorectomy.

Interventions: HRT prescription in the 6-week postoperative period.

Measurements and Main Results: A total of 63 patients met inclusion criteria. Of these, 52% (n = 33) were prescribed HRT in the 6-week postoperative period. Indications for surgical menopause included pelvic pain or endometriosis (31.7%), gynecologic malignancy (20.6%), *BRCA* gene mutation (17.4%), breast cancer (9.5%), Lynch syndrome (4.8%), and other (15.8%). In total, 80% of patients with pelvic pain, 25% with gynecologic malignancies, 45% with *BRCA* gene mutations, 33.3% with breast cancer, and 66.6% with Lynch syndrome used HRT postoperatively. In patients who used HRT postoperatively, 76% were offered preoperative HRT counseling. This is in contrast with those patients who did not use HRT postoperatively, of whom only 33% were offered HRT counseling (p <.001). Perioperative complications were not predictive of HRT use postoperatively. In patients who did not use HRT postoperatively, 13.3% used alternative nonhormonal therapy.

Conclusion: In patients who underwent premature surgical menopause, 52% used HRT postoperatively. Patients with pelvic pain and Lynch syndrome were more likely to use HRT, whereas those with gynecologic or breast malignancies and *BRCA* gene mutations were less likely to use HRT. Preoperative HRT counseling was associated with postoperative HRT use. Journal of Minimally Invasive Gynecology (2020) 00, 1−6. © 2020 Published by Elsevier Inc. on behalf of AAGL.

Keywords: *BRCA*; Endometriosis; Estrogen replacement; Pelvic pain

Most bilateral oophorectomies occur at the time of hysterectomy, and most hysterectomies occur between the ages of 35 and 45 years [1]. A consequence of bilateral oophorectomies in this age group is surgically induced premature menopause. Premature menopause is associated with an increased risk of cardiovascular complications, accelerated bone loss, cognitive impairment, sexual dysfunction, adverse emotional health outcomes, and bothersome menopausal symptoms [2]. Large prospective studies have demonstrated that the use of hormone replacement therapy (HRT) in premature surgical menopause improves many of these adverse health effects and reduces all-cause mortality [3].

Before the results of the Women's Health Initiative (WHI) study were published in 2002, more than 90% of women used estrogen therapy after bilateral salpingo-oophorectomy [1]. Currently, that percentage has decreased to <10% [1]. This is largely influenced by the widespread fear of HRT based on the reports of the WHI, specifically the increased risk of breast cancer, heart disease, and stroke in postmenopausal women taking HRT. However, this study assessed predominantly older postmenopausal women [1,4].

Although data are limited, there is some thought that HRT after definitive surgery for endometriosis may stimulate growth of residual endometriosis implants and possibly stimulate malignant transformation; however, there is no

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outcome-based evidence to support this [5]. Another reason for withholding HRT is the theoretic increase in breast cancer risk in premenopausal women, especially in women with *BRCA1* mutations [6]. However, several studies have shown no increased risk in breast cancer in this population when HRT is taken until the average age of menopause [7,8].

The current practice patterns for HRT use after surgical menopause in the United States are variable and unclear, and perioperative influences on these practice patterns such as surgical indication and preoperative counseling remain unknown. The objective of this study was to assess HRT use in patients undergoing premature surgical menopause and associate that use with surgical indication for menopause.

Materials and Methods

A retrospective cohort study was completed after the institutional review board approved the study as exempt from review. Patients aged ≤45 years who underwent a minimally invasive hysterectomy with bilateral salpingo-oophorectomy at a single academic institution over a 6-year period (September 2012−June 2018) were included. All surgeries were performed by gynecologic surgery subspecialists, including minimally invasive gynecologic surgeons, female pelvic medicine and reconstructive surgeons, and gynecologic oncologists. An upper age limit of 45 years was chosen because those women undergoing surgical menopause at this age or younger are deemed to be at the highest risk of resulting health consequences [9,10]. Patients with a history of previous surgical menopause were excluded. Patients with a history of unilateral salpingo-oophorectomy were included if the remaining ovary was removed at the time of hysterectomy resulting in surgical menopause.

The indication for surgery was noted from preoperative documentation. Surgical indications included pelvic pain or endometriosis, gynecologic malignancy, *BRCA* gene mutation, history of breast cancer, Lynch syndrome, and other. The presence or absence of counseling on HRT was determined by a review of preoperative and postoperative documentation within 6 weeks after surgery. Counseling points included discussing increased risk for coronary artery disease and bone loss and cognitive and sexual dysfunction.

HRT was defined as systemic estrogen prescribed after surgical removal of the ovaries. The dose and the route of HRT were determined by reviewing the prescriptions provided to the patient in the first 6 weeks after surgery. The possible routes of HRT administration included oral estrogen, vaginal estrogen ring, transdermal estrogen patch, or transdermal estrogen cream.

The primary outcome was HRT prescription during the 6-week postoperative period. A sample size of 60 patients provided a 95% confidence interval of ± 12.5% for the estimate of HRT prescription. Secondary outcomes included perioperative counseling and the use of nonhormonal treatments for menopausal symptoms. Differences in HRT use were examined by patient demographics, clinical characteristics (common medical comorbidities that could potentially affect the decision to use HRT), and perioperative outcomes and complications. Continuous variables were analyzed with Kruskal-Wallis rank sum test, and categoric variables used the χ^2 test for analysis. SAS version 9.4 (SAS Institute, Cary, NC) was used for analysis.

Results

In the period of interest, 530 patients underwent minimally invasive hysterectomies with bilateral salpingo-oophorectomy or unilateral salpingo-oophorectomy with a history of previous unilateral salpingo-oophorectomy. A total of 63 patients met the inclusion criteria. Of these, 52.4% (n = 33) were prescribed HRT in the 6-week postoperative period. Indications for surgical menopause included pelvic pain or endometriosis (31.7%); gynecologic malignancy (20.6%), which included cervical cancer (1.6%), uterine cancer (14.2%), and ovarian cancer (4.8%); *BRCA* carrier (17.4%); breast cancer (9.5%); Lynch syndrome (4.8%); and other (abnormal uterine bleeding, pelvic mass, pelvic organ prolapse, vulvar intraepithelial neoplasia grade 3) (15.8%).

There were no statistically significant demographic differences between patients who used HRT and those who did not (Table 1). Both groups were mostly white (83.3% no HRT vs 93.9% HRT, p =.622). Mean age (41 years no HRT vs 40.7 years HRT, p =.724) and body mass index (31 kg/m^2 no HRT vs 27 kg/m^2 HRT, p =.091) were similar for both groups (Table 1). With the exception of hypertension, the 2 groups were similar in their medical comorbidities (hypothyroidism: 16.7% non-HRT vs 18.2% HRT, p =.874; diabetes: 13.3% non-HRT vs 3.0% HRT, p =.131; cardiac disease: 13.3% non-HRT vs 6.2% HRT, p =.389; obstructive sleep apnea: 6.7% non-HRT vs 0% HRT, p =.132). Hypertension was more prevalent in HRT nonusers (26.7%) than in HRT users (3.1%, p =.009) (Table 2). No patients in either group had a history of venous thromboembolism (VTE).

HRT was used postoperatively in 80% of patients with pelvic pain, 25% with gynecologic malignancies, 45% with *BRCA* mutations, 50% with breast cancer, 67% with Lynch syndrome, and 50% with other indications (Table 3). Of those with gynecologic malignancies, 100% of patients with cervical cancer, 22.2% with uterine cancer, and 0% with ovarian cancer used HRT (Table 3).

There was a positive association found between those who used HRT postoperatively and those who had received preoperative counseling. In patients who used HRT postoperatively, 76% were offered preoperative HRT counseling. This is in contrast to those who did not use HRT

Table 1

Patient demographics by HRT use

Demographic	No HRTn = 30	HRTn = 33	Totaln = 63	p-value
Race, n (%)	—	—	—	.622*
American Indian	1 (3.3)	0 (0.0)	1 (1.6)	—
Asian	1 (3.3)	1 (3.0)	2 (3.2)	—
Black	1 (3.3)	0 (0.0)	1 (1.6)	—
Hispanic	1 (3.3)	1 (3.0)	2 (3.2)	—
Unknown	1 (3.3)	0 (0.0)	1 (1.6)	—
White	25 (83.3)	31 (93.9)	56 (88.9)	—
BMI, kg/m^2	—	—	—	.091†
Mean (CI)	31.0 (27.9−34.0)	27.0 (24.3−29.7)	29.0	—
Age, yrs	—	—	—	.724†
Mean (CI)	41.0 (40.0−42.0)	40.7 (39.6−41.8)	40.85	—

BMI = body mass index; CI, confidence interval; HRT = hormone replacement therapy.
* Pearson χ^2 test.
† Kruskal-Wallis rank sum test.

Table 2

Medical comorbidities by HRT use

Comorbidity	No HRTn = 30	HRTn = 33	Totaln =63	p-value
Hypertension	8 (26.7)	1 (3.1)	9 (14.5)	.009*
Hypothyroidism	5 (16.7)	6 (18.2)	11 (17.5)	.874*
Diabetes	4 (13.3)	1 (3.0)	5 (7.9)	.131*
Cardiac disease	4 (13.3)	2 (6.2)	6 (9.5)	.389*
Obstructive sleep apnea	2 (6.7)	0 (0.0)	2 (3.2)	.132*
History of VTE	0 (0)	0 (0)	0 (0)	1.000*

HRT = hormone replacement therapy; VTE = venous thromboembolism.
Values are given in numbers (%).
* Pearson χ^2 test.

Table 3

Surgical indications and HRT use

Surgery indication*	No HRTn = 30	HRTn = 33	Totaln = 63
BRCA1/2	6 (20.0)	5 (15.1)	11 (17.4)
Lynch syndrome	1 (3.3)	2 (6.1)	3 (4.8)
History of breast cancer	4 (13.3)	2 (6.1)	6 (9.5)
Pelvic pain	4 (13.3)	16 (48.5)	20 (31.7)
Gynecologic malignancy			
Cervical cancer	0 (0.0)	1 (3.0)	1 (1.6)
Uterine cancer	7 (23.3)	2 (6.1)	9 (14.2)
Ovarian cancer	3 (10)	0 (0.0)	3 (4.8)
Other			
Abnormal uterine bleeding	2 (6.7)	3 (9.1)	5 (7.9)
Pelvic mass	2 (6.7)	1 (3.0)	3 (4.8)
Pelvic organ prolapse	0 (0.0)	1 (3.0)	1 (1.6)
VIN3	1 (3.3)	0 (0.0)	1 (1.6)

HRT = hormone replacement therapy; VIN3 = vulvar intraepithelial neoplasia grade 3.
Values are given in number (%).
* p =.082 by Pearson χ^2 test.

Table 4

Preoperative counseling and HRT use

Preoperative counseling	No HRTn = 30	HRTn = 33	Totaln = 63	p-value
No	20 (66.7)	8 (24.2)	28 (44.4)	<.001*
Yes	10 (33.3)	25 (75.8)	35 (55.6)	

HRT = hormone replacement therapy.
Values are given in number (%).
* Pearson χ^2 test.

postoperatively, of whom only 33% were offered preoperative HRT counseling (p <.001) (Table 4). Points covered in preoperative counseling are discussed in the Materials and Methods section.

Median estimated blood loss (100 mL non-HRT vs 50 mL for HRT, p =.269) and uterine weight (136 g non-HRT vs 145 g HRT, p =.888) were comparable between both groups. Reported perioperative complications included cystotomy (n = 1), enterotomy (n = 1), rectotomy (n = 1), inferior vena cava injury (n = 1), and ureteral injury (n = 2), with no statistically significant differences noted between the 2 groups (p =.444). There were also no cases of perioperative VTE noted in either group within the first 6 weeks of surgery.

Of those patients who did use HRT postoperatively, 12.1% used oral estrogen (75% used oral estradiol and 25% used oral conjugated equine estrogen [CEE]) and 87.9% used a transdermal patch. No patients used vaginal rings, bioidentical hormones, or transdermal creams (Table 5). In patients who did not use HRT postoperatively, 13.3% (n = 4) used alternative nonhormonal therapy (paroxetine n = 2, venlafaxine n = 1, or gabapentin n = 1) (Table 5).

Discussion

In patients undergoing premature surgical menopause, 52% used HRT postoperatively. When assessed by surgical indication, most of those with pelvic pain or endometriosis used HRT postoperatively, whereas patients with gynecologic malignancies, breast malignancies, or *BRCA* gene mutations were less likely to use HRT. Preoperative HRT counseling was associated with postoperative HRT use.

Table 5

Types of hormonal and nonhormonal therapies used in each group

Type of therapy	n (%)
HRT users	33
Oral estradiol	4 (12.1)
Estradiol patch	29 (87.9)
Vaginal estrogen ring	0 (0)
Bioidentical hormones	0 (0)
Transdermal estrogen cream	0 (0)
Non-HRT users	30
Paroxetine	2 (6.7)
Gabapentin	1 (3.3)
Venlafaxine	1 (3.3)

HRT = hormone replacement therapy.

This study shows higher rates of postoperative HRT use than those of other similar studies in women with surgical menopause, which range from 12% to 40% [11−13]. Since the publication of the WHI in 2002, there has been a significant decline in the use of HRT overall, with an estimated 27% to 46% decrease in prescription rates [14−16]. In the United States, data on HRT usage patterns after surgical menopause are limited. However in Canada, only 40% of women used HRT after surgical menopause before the age of 50, and studies in Italy and Taiwan also showed rates of 19% and 31%, respectively [11−13]. The difference in postoperative HRT use may also be related to differences in the study design, wherein some studies included patients up to the age of 50 [12,13].

This study showed that the largest cohort of patients using HRT after premature surgical menopause are those with pelvic pain and/or endometriosis. Based on the current body of literature, HRT is not contraindicated after bilateral salpingo-oophorectomy for endometriosis. HRT is recommended in young patients in whom the benefits of HRT outweigh the risks [5,17]. Endometriosis may recur in up to 15% of women whether or not they are treated with postoperative HRT, and recurrence risks seem to be higher (up to 43%) in those with deep infiltrating endometriosis [18,19]. The variation in reported recurrence rates is unclear but likely related to differences in the length of follow-up and the definition of recurrence. There also appears to be no evidence to support fewer recurrences of endometriosis if HRT is delayed after surgery [17,20].

In this study, 45% of *BRCA* mutation carriers started HRT postoperatively. Current evidence suggests that the use of HRT until the natural age of menopause does not diminish the protective effect of surgical menopause on breast cancer risk reduction [6−8,21]. The WHI showed a significant increase in the risk of breast cancer with combined estrogen and progesterone therapy (CEE and medroxyprogesterone acetate) but not with estrogen alone [22,23]. Although this data is in relation to postmenopausal women,

this information may be reassuring to *BRCA* mutation carriers who have had a concurrent hysterectomy with their prophylactic salpingo-oophorectomy and are considering HRT.

In patients with gynecologic malignancies, 25% used HRT after surgical menopause. HRT use in the setting of a gynecologic malignancy is controversial [24]. There are limited data about HRT use after endometrial cancer treatment, but the few available studies have shown no difference in survival [24−26]. Currently, there are insufficient data to adequately counsel patients regarding the risk of ovarian or endometrial cancer recurrence with postoperative HRT use. Clinical stage, anticipated survival, and severity of symptoms likely affect the clinician's decision to prescribe HRT. The American College of Obstetricians and Gynecologists encourages clinicians and patients to jointly consider the risks and benefits of HRT in this setting. Most other gynecologic cancers are not hormone-dependent. Thus, previous cervical, vulvar, or vaginal cancer should not be a contraindication against HRT [24].

The rate of perioperative complications in this study was 9.5%. This relatively high complication rate can be explained by the complexity of cases that were referred to this group of surgeons. Because most of these patients have advanced pathology, this rate of perioperative complications is likely appropriate.

This study highlights the impact of physician counseling because our results showed a positive association between those who used HRT postoperatively and had received preoperative counseling. Other studies on this topic also support this finding. In a Taiwanese study of surgically menopausal women, more than half of the women who did not use HRT claimed that they would have used it if their doctors had explained how the benefits outweigh the risks [13]. Another study in Turkey examined postmenopausal women and showed a 5-fold increase in HRT use in those who received physician counseling [27]. Effective counseling should include a collaboration between the physician and the patient and allow for consideration of patient values and evidence-based practice.

When providing counseling, care should be taken to properly interpret the existing evidence and convey this unbiased information to patients. Looking at the WHI study, women in the estrogen-only arm taking CEE had a decreased risk of breast cancer compared with the general population [1,24]. Nonetheless, because of the link made between HRT and breast cancer, the rates of HRT prescription use dropped dramatically after the release of the WHI [24,28]. Furthermore, many providers are likely to prescribe different formulations of HRT (lower dose, transdermal, etc.) than the one studied in the WHI to help mitigate the increased risk of VTE and stroke, now known to be associated with CEE [23]. In our study, of the 4 women taking oral estrogen, only 1 was prescribed CEE. Further studies are needed to measure the effect of these specific counseling points on HRT uptake.

Limitations of this study included the inherent bias to a retrospective study design. Chart review is limited by the possibility of inaccurate or incomplete documentation of counseling and possible HRT prescriptions provided by alternative providers that are therefore not in the electronic medical record. In addition, this study used HRT prescription as a proxy for HRT use, which may have overestimated the use of HRT. The study only included patients who underwent premature surgical menopause with minimally invasive hysterectomy; therefore, patients who had only a bilateral salpingo-oophorectomy without hysterectomy or a laparotomy were not included. In addition, only patients aged ≤45 years were included to capture patients who need HRT the most. This may have overestimated the use of postoperative HRT compared with other studies that used a higher age limit. In addition, this study reported HRT use in a single practice with mostly a white patient population, and results may not be generalizable to all gynecologic practices. Finally, our study was not designed to capture specific discussions between the patient and the provider during HRT counseling, which could have provided further insight into understanding the use of HRT postoperatively. Owing to the lack of available data, results obtained from this study will add to the existing literature describing the use of postoperative HRT in surgically menopausal patients.

The strengths of this study included diverse pathologies in the patient population, with both benign and oncologic surgical indications. This allows for better generalizability of results for a variety of surgical practices. Moreover, this study assessed a poorly reported topic with great clinical significance and is the first study to examine the relationship between surgical indication for premature surgical menopause with the use of HRT postoperatively. Results obtained from this study are reassuring, but future studies describing postoperative HRT use at a national level are encouraged.

In conclusion, HRT use postoperatively in prematurely surgically menopausal patients varies significantly by surgical indication, and preoperative counseling is positively associated with HRT use postoperatively. Providers are encouraged to appropriately counsel patients who are at risk preoperatively, and future studies to evaluate preoperative counseling methods and discussion points are necessary to further improve appropriate HRT use.

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