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Original Article

Hormone Replacement Therapy Prescription After Premature Surgical Menopause

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Precis: In patients who undergo premature surgical menopause, more than half utilize hormone replacement therapy postoperatively.

Abstract

Study Objective: To assess hormone replacement therapy (HRT) prescription pattern in patients undergoing premature surgical menopause based on surgical indication.

Design: Retrospective cohort study

Setting: Academic tertiary care center

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

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

Measurements and Main Results: Sixty-three patients met inclusion criteria. Of those, 52% (n=33) were prescribed HRT in the 6-week postoperative period. Indications for surgical menopause included pelvic pain/endometriosis (31.7%), gynecological malignancy (20.6%), BRCA gene mutation (17.4%), breast cancer (9.5%), Lynch syndrome (4.8%), and other (15.8%). Eighty percent of pelvic pain patients, 25% of gynecological malignancy, 45% of BRCA patients, 33.3% of breast cancer patients, and 66.6% of Lynch syndrome patients used HRT postoperatively. In patients who utilized HRT postoperatively, 76% were offered preoperative HRT counseling. This is in contrast those who did not utilize HRT postoperatively, in which only 33% of patients were offered HRT counseling ($p<0.001$). Perioperative complications were not predictive of HRT use postoperatively. In patients who did not use HRT postoperatively 13.3% utilized alternative non-hormonal therapy.

Conclusions: In patients who underwent premature surgical menopause, 52% utilized HRT postoperatively. Patients with pelvic pain and Lynch syndrome were more likely to use HRT, whereas those with gynecologic or breast malignancy and BRCA gene mutations were less likely to use HRT. Preoperative HRT counseling is associated with postoperative HRT use.

Keywords: BRCA; endometriosis; estrogen replacement; pelvic pain; surgical menopause

Introduction

Most bilateral oophorectomies occur at time of hysterectomy and most hysterectomies occur between the ages of 35 and 45 years[1]. A consequence of this is surgically-induced premature menopause. This is associated with 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 study were published in 2002, more than 90% of women used estrogen therapy after bilateral salpingo-oophorectomy[1]. Currently that percentage has decreased to less than 10%[1]. This is largely influenced by the widespread fear of HRT based on the reports of the Women's Health Initiative, specifically the increase risk of breast cancer, heart disease, and stroke in postmenopausal women taking HRT. However, this study assessed predominantly older postmenopausal women[1,4].

Though data is limited, there is some thought that HRT after definitive surgery for endometriosis may stimulate growth of residual endometriosis implants, and the possibly stimulate malignant transformation, however there is no outcomes-based evidence to support this [5]. Another reason for withholding HRT is the theoretical increase in breast cancer risk in premenopausal women, especially in women with BRCA1 mutations[6]. However, several studies have shown no increase 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 is to assess HRT use in patients undergoing premature surgical menopause, and associate that with surgical indication for menopause.

Methods

A retrospective cohort study was completed after the Institutional Review Board (IRB) approved the study as exempt from review. Patients age 45 years and under who underwent 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 undergoing surgical menopause at this age or younger are deemed to be at highest risk of resulting health consequences[9,10]. Patients with history of prior surgical menopause were excluded. Patients with 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 pre-operative documentation. Surgical indications included pelvic pain/endometriosis, gynecologic malignancy, BRCA gene mutation, history of breast cancer, Lynch syndrome, and other. Presence or absence of counseling on HRT was determined by review of pre-operative and post-operative documentation within 6-weeks following surgery. Counseling points included discussing increased risk for coronary artery disease and bone loss, as well as cognitive and sexual dysfunction.

HRT was defined as systemic estrogen prescribed after surgical removal of the ovaries. Dose and route of HRT was determined by reviewing the prescriptions provided to the patient in the first 6-weeks after surgery. 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 post-operative period. A sample size of 60 patients provided a 95% confidence interval of +/- 12.5% for the estimate of HRT prescription. Secondary outcomes included peri-operative counseling and use of non-

hormonal treatments for menopausal symptoms. Differences in HRT use were examined by patient demographics, clinical characteristics (common medical co-morbidities that could potentially impact the decision to use HRT), and perioperative outcomes/complications. Continuous variables were analyzed with Krusak-Wallis rank sum test and categorical variables use the chi-square test for analysis. SAS version 9.4 (SAS Institute, Cary, NC) was used for analysis.

Results

In the time period of interest, 530 patients underwent minimally invasive hysterectomy with bilateral salpingo-oophorectomy, or unilateral salpingo-oophorectomy with a history of previous unilateral salpingo-oophorectomy. Sixty-three of these patients met inclusion criteria. Of those, 52.4% (n=33) were prescribed HRT in the 6-week postoperative period. Indications for surgical menopause included pelvic pain/endometriosis (31.7%), gynecological 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, VIN 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 majority white race (83.3% no HRT vs. 93.9% HRT, p= 0.622). Mean age (41 years no HRT vs. 40.7 years HRT, p= 0.724) and BMI (31 kg/m^2 no HRT vs. 27 kg/m^2 HRT, p=0.091) were similar for both groups (Table 1). With the exception of hypertension, the two groups were similar in regards to their medical comorbidities (hypothyroidism: 16.7% non-HRT vs. 18.2% HRT (p=0.874), diabetes: 13.3% non-HRT vs. 3.0% HRT (p=0.131), cardiac disease: 13.3% non-HRT vs. 6.2% HRT (p=0.389), obstructive sleep apnea: 6.7% non-HRT vs. 0% HRT (p=0.132)). Hypertension was more prevalent in those that did not use HRT (26.7%) compared to 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% of gynecological malignancy patients, 45% of BRCA patients, 50% of breast cancer patients, 67% of Lynch Syndrome patients, and 50% of other indications (Table 3). Within those with gynecological malignancy, 100% of cervical cancer patients, 22.2% of uterine cancer patients, and 0% of ovarian cancer patients used HRT (Table 3).

There was a positive association found between those who ultimately used HRT post-operatively and had received pre-operative counseling. In patients who utilized HRT postoperatively, 76% were offered preoperative HRT counseling. This is in contrast those who did not utilize HRT postoperatively, in which only 33% of patients were offered preoperative HRT counseling ($p<0.001$) (Table 4). Points covered in preoperative counseling are discussed in the methods section.

Median estimated blood loss (100mL non-HRT vs. 50mL for HRT, $p=0.269$) and uterine weight (136g non-HRT vs. 145g HRT, $p=0.888$) 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 significant differences noted between the two groups ($p=0.444$). There were also no cases of perioperative VTE noted in either group within in the first 6 weeks of surgery.

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

Discussion

In patients undergoing premature surgical menopause, 52% utilized HRT post-operatively. When assessed by surgical indication, the majority of those with pelvic pain/endometriosis used

HRT post-operatively, whereas patients with gynecologic malignancy, breast malignancy, or BRCA gene mutations were less likely to use HRT. Preoperative HRT counseling was associated with post-operative HRT use.

This study shows higher rates of postoperative HRT use compared to other similar studies in women with surgical menopause, which range from 12-40%[11–13]. Since the publication of the Women's Health Initiative in 2002, there has been a significant decline in the use of HRT overall, with an estimated 27-46% decrease in prescription rates[14–16]. Data on HRT usage patterns in the United States after surgical menopause is 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 utilization may also be related to differences in study design, where some studies included patients up to the age of 50[12,13].

This study shows 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. In fact, HRT is recommended in young patients in which 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 appear 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 length of follow-up and 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 post-operatively. Current evidence suggests that HRT use until the natural age of menopause does not diminish the protective effect of surgical menopause on breast cancer risk reduction[6,8,21,22]. The Women's Health Initiative showed a significant increase in the risk of breast cancer with combined

estrogen and progesterone therapy (conjugated equine estrogens and medroxyprogesterone acetate), but not with estrogen alone[23,24]. Though this data is in relation to post-menopausal 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 malignancy, 25% used HRT after surgical menopause. HRT use in the setting of a gynecologic malignancy is controversial[25]. There is limited data about HRT use after endometrial cancer treatment, but the few studies available show no difference in survival [25–27]. There is currently 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 & 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[25].

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

This study highlights the impact of physician counseling, as our results showed a positive association between those who used HRT post-operatively and had received pre-operative counseling. Other studies on this topic also support this finding. In a Taiwanese study of surgically menopausal women, over 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 five-fold increase in HRT use in those who received physician counseling[28]. Effective counseling should include a

collaboration between physician and patient and allow for consideration of patient values as well as 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 conjugated equine estrogen (CEE) actually had a decreased risk of breast cancer compared to the general population[1,25]. 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 [25,29]. 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 [24]. In our study, of the four women taking oral estrogen, only one was prescribed CEE. Further studies are needed to measure the effect of these specific counseling points on HRT uptake.

Limitations of this study include inherent bias to a retrospective study design. Chart review is limited by the possibility of inaccurate or incomplete documentation of counseling, as well as possible HRT prescriptions provided by alternative providers that are therefore not in the electronic medical record. Additionally, this study used HRT prescription as a proxy for HRT utilization, which may overestimate the use of HRT. The study only included patients who underwent premature surgical menopause with minimally invasive hysterectomy, therefore patients who had only bilateral salpingo-oophorectomy without hysterectomy, or laparotomy were not included. In addition, only patients 45 years and younger were included to capture patients in most need for HRT. This may overestimate the use of postoperative HRT compared to other studies that use higher age limit. Also, this study reports HRT use in a single practice with a majority white patient population, and results may not be generalizable to all gynecologic practices. Finally, our study was not designed to capture specific discussions between patient and provider during HRT counseling, which could have provided further insight into understanding the use of HRT post-operatively. Due 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.

Strengths of this study include diverse pathologies in the patient population, with both benign and oncological surgical indications. This allows for better generalizability of results for a variety of surgical practices. Moreover, this study assesses 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 post-operatively. Results obtained from this study are reassuring, but future studies describing postoperative HRT use at a national level are encouraged.

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

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Table 1: Patient demographics by HRT use

	No HRT (n=30)	HRT (n=33)	Total (n=63)	p-value
Race (n, %)				0.622[1]
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)				0.091[2]
Mean	31.0	27.0	29.0	
CI	27.9 – 34.0	24.3 – 29.7		
Age (years)				0.724[2]
Mean	41.0	40.7	40.85	
CI	40.0 - 42.0	39.6 - 41.8		

[1]Pearson's Chi-squared test
[2]Kruskal-Wallis rank sum test

Table 2: Medical comorbidities by HRT use

	No HRT (n=30)	HRT (n=33)	Total (n=63)	p-value
Hypertension	8 (26.7%)	1 (3.1%)	9 (14.5%)	0.009[1]
Hypothyroidism	5 (16.7%)	6 (18.2%)	11 (17.5%)	0.874[1]
Diabetes	4 (13.3%)	1 (3.0%)	5 (7.9%)	0.131[1]
Cardiac disease	4 (13.3%)	2 (6.2%)	6 (9.5%)	0.389[1]
Obstructive sleep apnea	2 (6.7%)	0 (0.0%)	2 (3.2%)	0.132[1]
History of VTE	0 (0%)	0 (0%)	0 (0%)	1.000[1]

[1]Pearson's Chi-squared test

Table 3: Surgical indications and HRT Use

Surgery indication	No HRT (N=30)	HRT (N=33)	Total (N=63)	P = 0.082[1]
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%)	

[1]Pearson's Chi-squared test

Table 4: Preoperative counseling and HRT use

	No HRT (n=30)	HRT (n=33)	Total (n=63)	p-value
Pre-op counseling				< 0.001[1]
N	20 (66.7%)	8 (24.2%)	28 (44.4%)	
Y	10 (33.3%)	25 (75.8%)	35 55.6%)	

[1]Pearson's Chi-squared test

Table 5: Types of hormonal and non-hormonal therapies utilized in each group

HRT users	n=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	n=30
Paroxetine	2 (6.7%)
Gabapentin	1 (3.3%)
Venlafaxine	1 (3.3%)