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Relation between pelvic organ prolapse and menopausal hormone therapy: nationwide cohort study

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Objective
To analyze the relationship between pelvic organ prolapse (POP) and menopausal hormone therapy (MHT).

Methods
This retrospective cohort study used Korean National Health checkup and insurance data from 2002 to 2019. Women who used MHT for more than 6 months between 2002 and 2011 were included in the MHT group; postmenopausal women with no MHT use comprised the non-MHT group.

Results
In the non-MHT group, there were 1,001,350 women, while the MHT group had 353,206 women. Tibolone (adjusted hazard ratio [aHR], 0.87; 99% confidence interval [CI], 0.818-0.926) and combined estrogen plus progestin by the manufacturer (CEPM) (aHR, 0.821; 99% CI, 0.758-0.89) were associated with reduced POP risk. The other oral MHT groups and the transdermal estrogen group showed no significant difference in POP risk compared with the non-MHT group (other oral MHT: aHR, 1.045; 99% CI, 0.941-1.161) (transdermal estrogen: aHR, 1.252; 99% CI, 0.731-2.145). Lower body mass index (BMI) (<18.5) was associated with reduced POP risk (aHR, 0.822; 99% CI, 0.698-0.968), while a BMI between 23 and 29.9 was associated with increased risk (BMI 23-24.9: aHR, 1.143; 99% CI, 1.088-1.2) (BMI 25-29.9: aHR, 1.173; 99% CI, 1.12-1.228). All parities had a higher POP risk than parity 1 (parity 0 or no response: aHR, 1.785; 99% CI, 1.589-2.005; parity 2: aHR, 1.434; 99% CI, 1.292-1.592; parity ≥3: aHR, 1.916; 99% CI, 1.712-2.144).

Conclusion
Tibolone and CEPM use were associated with reduced POP risk in postmenopausal women. Other MHT types showed no significant association with POP.

Keywords: Estrogen; Hormone replacement therapy; Menopause; Pelvic organ prolapse; Tibolone

Introduction

Pelvic organ prolapse (POP) denotes a medical condition characterized by the protrusion of pelvic organs into the vaginal space [1]. According to the Korea National Health Insurance, the incidence rate of POP is 71 cases per 100,000 women of all ages and 180 cases per 100,000 women older than 50 years [2]. The risk factors for POP include vaginal delivery, old age, high body mass index (BMI), and a history of hysterectomy [1,3]. Menopausal hormone therapy (MHT) is used to relieve menopausal symptoms. MHT generally utilizes estrogen, estrogen with progestogen, or selective estrogen receptor modulators. However, estrogen is mainly used in MHT [4].

POP generally occurs after menopause, when MHT is administered [2,5-7]. Previous studies have revealed that estro-

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gen increases connective tissue synthesis in the pelvic floor, which may reduce the risk of POP [8-10]. However, a randomized trial of 124 menopausal women found that pelvic floor muscle (PFM) training increased PFM strength more in the non-MHT group than in the MHT group [11]. Additionally, a retrospective observational study conducted in Australia showed that MHT negatively affects pelvic organ support [12]. A Finnish study of 12,072 women who underwent vaginal hysterectomy also found that MHT may weaken the pelvic floor and cause uterine prolapse [13].

However, previous studies have included small research populations, have not sufficiently considered the risk factors for POP, and have rarely investigated the correlation between tibolone and POP. Therefore, in this study, we analyzed the relationship between POP and MHT, including tibolone, using extensive population data from the Korean National Health Insurance database.

Materials and Methods

1. Database

In South Korea, National Health Insurance is mandatory for most Koreans (about 51 million people) [14]. Thus, the National Health Insurance Service (NHIS) can provide medical information for most diseases (including the income decile, operation code, drugs prescribed, medical insurance type, diagnosis code, region, and hospital grades), with the exception of a few cases, such as cosmetic surgery [14]. Furthermore, the Health Insurance Corporation regularly conducts adult health checkups for public health management purposes. Therefore, data on BMI, parity, menarcheal age, menopausal age, drinking, smoking, and physical exercise for health checkup recipients are also available. This study utilized NHIS-provided national health checkup and health insurance data from 2002 to 2019.

2. Selection of individuals

The participants and outcomes of this study were selected using the International Classification of Diseases, 10th revision. We chose women aged over 40 years who reported menopause from 2002 to 2011. The MHT group consisted of women who were prescribed menopausal hormones for more than 6 months between 2002 and 2011. The onset date of MHT was defined as the first day of menopausal hormone prescription, and the last drug used for at least 6 months served as the reference when multiple hormones were used. To ensure a sufficient follow-up period for patients included in the final year (2011), we excluded patients from 2012 to 2019 from this study.

The non-MHT group included women who did not use menopausal hormones from 2002 to 2019. Their non-MHT status began on the date of their first health checkup, where they reported having menopause.

Excluded cases included: 1) women reporting menopause in 2002 for washout. 2) Hysterectomy before the 180th days after participation. And 3) women with POP (N81) or any cancer before the 180th days after participation.

3. Outcome

POP was defined as three or more visits to a medical institution with a POP diagnosis code (N81) for the first or second diagnosis. We tracked these results through December 31, 2019.

4. Variables

Menopausal hormones were classified into the following groups: tibolone; combined estrogen plus progestin by the manufacturer (CEPM; estradiol valerate [EV]/medroxyprogesterone acetate [MPA], estradiol hemihydrate [EH]/1 mg norethisterone acetate [NA], EH/drospirenone, EH/dydrogesterone, EV/cyproterone acetate, EH/NA, EV/NA); other oral MHT (estrogen [conjugated estrogen, EV, EH] plus progestogen [micronized progesterone, MPA, dydrogesterone]); and transdermal estrogen (except vaginal estrogen). Based on the inclusion date, the independent variables included age, Charlson comorbidity index (CCI), socioeconomic status (SES), BMI, region, parity, menarcheal age, menopausal age, physical exercise, alcohol consumption, smoking, and the period from menopause to inclusion. The CCI was computed using the diagnosis code obtained from medical institution visits 1 year prior to the start of the study. When medical aid health insurance was utilized, the SES was considered low. Age was stratified into 10-year intervals, and BMI categorization adhered to the standards outlined by the Asia-Pacific perspective [15]. If the medical institution was not located in a metropolitan area, the region was considered rural. Parity incorporated non-responses by combining them into the "0 or no response" category, along with "1", "2", and "over 3" levels. Smoking history was defined as "never", "past",

or "current" while alcohol consumption was quantified by the weekly number of drinks. Physical exercise was considered for sessions lasting at least 30 minutes per week, categorized by their frequency.

5. Statistics

SAS Enterprise Guide 6.1 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Statistical significance was achieved when the *P*-value was less than 0.01. All statistical analyses were performed using two-sided tests. Continuous variables are expressed as median values (interquartile range) and categorical variables are defined as numbers (percentages). The study's start date was defined as the date of the first MHT prescription or national health checkup, and follow-up was determined as the earliest of death, December 31, 2019, or the date of the last health insurance data record. The Cox proportional hazards model was used to adjust for confounding factors. For the sensitivity test to confirm the robustness of this study, women who received a prescription from a gynecologist were compared with the non-MHT group. Additionally, the pairwise deletion method was used to treat missing values in this study.

Results

We recruited 2,506,271 women with menopausal records from health examinations conducted between 2002 and 2011. Among them, 1,001,350 were in the non-MHT group, and 353,206 were in the MHT group (Fig. 1). The median age was 53 (51-57) years in the non-MHT and MHT groups, 52 (50-56) years in the tibolone group, 52 (50-56) years in the CEPM group, 54 (50-59) years in the other oral MHT group, and 54 (51-59) years in the transdermal estrogen group. The median BMI in each group was 24 (22.1-26.1) in the non-MHT group, 23.4 (21.8-25.3) in the tibolone group, 23.1 (21.5-25.0) in the CEPM group, 23.7 (21.9-25.7) in the other oral MHT group, and 23.6 (21.8-25.5) in the transdermal estrogen group (Table 1). The median follow-up period was 11.5 (9.5-13.5) years for the non-MHT group and 12.9 (10.7-15.0) years for the MHT group. Table 1 shows the detailed characteristics of the participants, and the features of each MHT

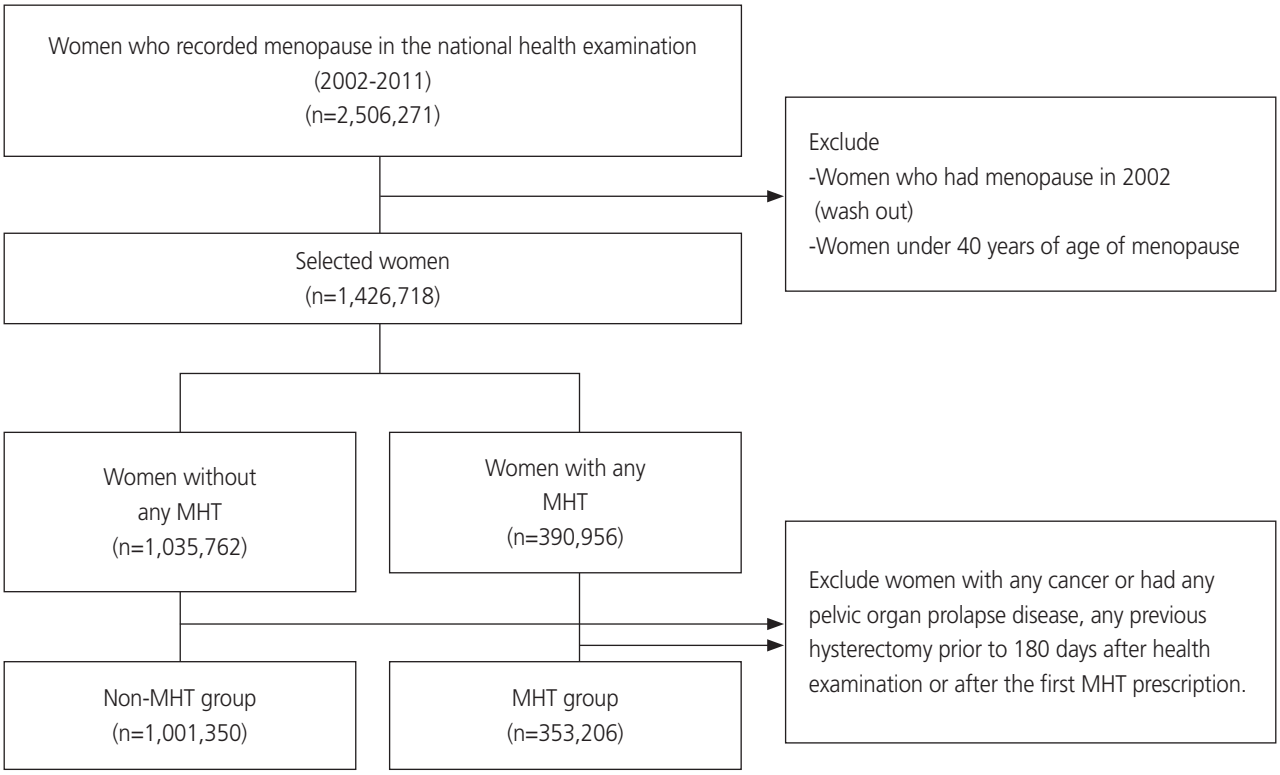


Fig. 1. Flowchart outlining the selection of participants based on menopausal hormone therapy in the Korea National Health Insurance Data, spanning 2002 to 2019. MHT, menopausal hormone therapy.

Table 1. Characteristics of women according to menopausal hormone exposure status at recruitment, Korea National Health Insurance Data, 2002-2019

	Non-MHT	Tibolone	Combined estrogen plus progestin by the manufacturer	Other oral MHT	Transdermal estrogen	Total
Number of women	1,001,350	184,879	126,118	40,941	1,268	1,354,556
Median age (yr)	58 (53-65)	53 (51-57)	52 (50-56)	54 (50-59)	54 (51-59)	56 (52-63)
Age at inclusion (yr)						
40-49	79,428 (7.9)	31,223 (16.9)	28,444 (22.6)	8,459 (20.7)	195 (15.4)	147,749 (10.9)
50-59	481,379 (48.1)	121,235 (65.6)	84,102 (66.7)	22,476 (54.9)	792 (62.5)	709,984 (52.4)
60-69	304,151 (30.4)	28,625 (15.5)	12,502 (9.0)	8,161 (19.9)	252 (19.9)	353,691 (26.1)
70~	136,392 (13.6)	3,796 (2.1)	1,070 (0.8)	1,845 (4.5)	29 (2.3)	143,132 (10.6)
Median BMI (kg/m^2)	24 (22.1-26.1)	23.4 (21.8-25.3)	23.1 (21.5-25.0)	23.7 (21.9-25.7)	23.6 (21.8-25.5)	23.8 (21.9-25.9)
BMI (kg/m^2)						
<18.5	18,988 (1.9)	3,220 (1.8)	2,549 (2.0)	666 (1.6)	32 (2.6)	25,455 (1.9)
18.5-22.9	336,111 (34.3)	74,688 (40.8)	56,987 (45.5)	15,051 (37.2)	490 (39.1)	483,327 (36.3)
23.0-24.9	259,254 (26.4)	50,778 (27.7)	33,690 (26.9)	11,310 (27.9)	332 (26.5)	355,364 (26.7)
25.0-29.9	323,966 (33.0)	49,797 (27.2)	29,556 (23.6)	12,183 (30.1)	367 (29.3)	415,869 (31.2)
≥30	42,490 (4.3)	4,540 (2.5)	2,437 (1.9)	1,292 (3.2)	31 (2.5)	50,790 (3.8)
SES						
Mid-high SES	957,777 (95.6)	178,158 (96.4)	122,920 (97.5)	39,645 (96.8)	1,224 (96.5)	1,299,724 (96.0)
Low SES	43,573 (4.4)	6,721 (3.6)	3,198 (2.5)	1,296 (3.2)	44 (3.5)	54,832 (4.0)
Region						
Urban area	294,206 (29.4)	58,075 (31.4)	42,875 (34.0)	13,666 (33.4)	567 (44.7)	409,389 (30.2)
Rural area	707,144 (70.6)	126,804 (68.6)	83,243 (66.0)	27,275 (66.6)	701 (55.3)	945,167 (69.8)
CCI						
0	651,064 (65.0)	124,959 (67.6)	88,863 (70.5)	27,888 (68.1)	791 (62.4)	893,565 (66.0)
1	199,282 (19.9)	36,354 (19.7)	23,030 (18.3)	7,802 (19.1)	252 (19.9)	266,720 (19.7)
≥2	151,004 (15.1)	23,566 (12.7)	14,225 (11.3)	5,251 (12.8)	225 (17.7)	194,271 (14.3)
Parity						
0 or not respond	160,637 (16.0)	28,108 (15.2)	15,486 (12.3)	8,536 (20.8)	270 (21.3)	213,037 (15.7)
1	58,738 (5.9)	16,022 (8.7)	13,113 (10.4)	2,789 (6.8)	107 (8.4)	90,769 (6.7)
2	662,404 (66.2)	124,226 (67.2)	88,342 (70.0)	25,315 (61.8)	773 (61.0)	901,060 (66.5)
≥3	119,571 (11.9)	16,523 (8.9)	9,177 (7.3)	4,301 (10.5)	118 (9.3)	149,690 (11.1)
Age at menarche (yr)						
<13	153,130 (15.4)	26,296 (14.3)	17,775 (14.2)	7,037 (17.4)	225 (17.9)	204,463 (15.2)
≥13	843,498 (84.6)	157,176 (85.7)	107,638 (85.8)	33,353 (82.6)	1,029 (82.1)	1,142,694 (84.8)
Age at menopause (yr)						
40-44	115,398 (11.5)	20,658 (11.2)	13,516 (10.7)	7,857 (19.2)	237 (18.7)	157,666 (11.6)
45-49	286,130 (28.6)	59,326 (32.1)	42,036 (33.3)	13,615 (33.3)	446 (35.2)	401,553 (29.6)
50-54	510,255 (51.0)	90,367 (48.9)	62,012 (49.2)	16,910 (41.3)	496 (39.1)	680,040 (50.2)
55~	89,567 (8.9)	14,528 (7.9)	8,554 (6.8)	2,559 (6.3)	89 (7.0)	115,297 (8.5)

Table 1. Characteristics of women according to menopausal hormone exposure status at recruitment, Korea National Health Insurance Data, 2002-2019 (Continued)

	Non-MHT	Tibolone	Combined estrogen plus progestin by the manufacturer	Other oral MHT	Transdermal estrogen	Total
Smoking						
Never	912,041 (96.4)	166,599 (93.7)	114,121 (93.5)	37,258 (95.2)	1,153 (96.4)	1,231,172 (95.7)
Past	9,720 (1.0)	3,064 (1.7)	2,248 (1.8)	530 (1.4)	21 (1.8)	15,583 (1.2)
Current	24,678 (2.6)	8,136 (4.6)	5,723 (4.7)	1,354 (3.5)	22 (1.8)	39,913 (3.1)
Alcohol (times/week)						
None	812,658 (85.5)	138,908 (77.6)	93,200 (75.9)	32,286 (81.8)	1,013 (83.6)	1,078,065 (83.4)
~2	117,392 (12.4)	33,993 (19.0)	25,282 (20.6)	6,262 (15.9)	174 (14.4)	183,103 (14.2)
3-6	14,636 (1.5)	4,698 (2.6)	3,454 (2.8)	654 (1.7)	18 (1.5)	23,460 (1.8)
Daily	5,279 (0.6)	1,422 (0.8)	889 (0.7)	265 (0.7)	7 (0.6)	7,862 (0.6)
Physical exercise (times/week)						
None	626,538 (65.8)	106,649 (59.6)	73,562 (59.9)	23,684 (60.1)	641 (53.2)	831,074 (64.2)
1-2	155,077 (16.3)	34,070 (19.0)	23,992 (19.5)	7,349 (18.6)	259 (21.5)	220,747 (17.1)
3-4	85,646 (9.0)	20,499 (11.5)	14,331 (11.7)	4,331 (11.0)	177 (14.7)	124,984 (9.7)
5-6	28,759 (3.0)	6,695 (3.7)	4,706 (3.8)	1,343 (3.4)	51 (4.2)	41,554 (3.2)
Daily	55,547 (5.8)	11,014 (6.2)	6,260 (5.1)	2,730 (6.9)	78 (6.5)	75,629 (5.8)
The period from menopause to inclusion (yr)						
<5	383,985 (38.3)	107,708 (58.3)	86,202 (68.4)	18,816 (46.0)	568 (44.8)	597,279 (44.1)
5-9	207,588 (20.7)	41,909 (22.7)	24,681 (19.6)	10,404 (25.4)	345 (27.2)	284,927 (21.0)
10~	409,777 (40.9)	35,262 (19.1)	15,235 (12.1)	11,721 (28.6)	355 (28.0)	472,350 (34.9)

Values are median (25 percentile-75 percentile) or presented as number (%).
MHT, menopausal hormone therapy; BMI, body mass index; SES, socioeconomic status; CCI, Charlson comorbidity index.

group are shown in Table 2.

The non-MHT group took 7 (2-15) years from menopause to inclusion in the study, and the incidence of POP was 1.7% (16,856). In the MHT groups, the period from menopause to inclusion and the POP incidence rates were 3 (1-8) years and 1.2% (2,233), respectively, in the tibolone group; 2 (0-6) years and 1% (1,251), respectively, in the CEPM group; 5.5 (1-10.5) years and 1.7% (693), respectively, in other oral MHT group; and 5.5 (1.5-10.5) years and 2.1% (26), respectively, in the transdermal estrogen group. The incidence rates per 100,000 person-years are detailed in Supplementary Table 1.

According to the multivariate Cox proportional analysis, tibolone and CEPM were associated with a reduced risk of POP (tibolone: hazard ratio [HR], 0.87; 99% confidence interval [CI], 0.818-0.926; CEPM: HR, 0.821; 99% CI, 0.758-0.89). The risk of POP was increased in the other oral MHT and transdermal estrogen groups; however, the differences were not statistically significant (other oral MHT: HR, 1.045; 99% CI, 0.941-1.161; transdermal estrogen: HR, 1.252; 99% CI, 0.731-2.145; Fig. 2, Table 3).

Table 3 shows the risk of POP with respect to age, BMI, CCI, SES, parity, menstrual age, menopausal age, alcohol consumption, physical exercise, smoking, and the period from menopause to inclusion. The risk of POP was reduced with a BMI <18.5 (HR, 0.822; 99% CI, 0.698-0.968) and increased with a BMI of 23-29.9 (BMI 23-24.9: HR, 1.143; 99% CI, 1.088-1.2; BMI 25-29.9: HR, 1.173; 99% CI, 1.12-1.228). The POP risk increased in all parities compared with that in parity 1 (parity 0 or no response: HR, 1.785; 99% CI,

Table 2. Characteristics of women with menopausal hormone, Korea National Health Insurance Data, 2002-2019

MHT characteristic	Tibolone	Combined estrogen plus progestin by the manufacturer	Other oral MHT	Transdermal estrogen	Total MHT
Median duration (months)	25 (11-58)	25 (11-58)	12 (8-28)	12 (8-22)	23 (10-55)
Duration (yr)					
<5	139,874 (75.7)	95,525 (75.7)	36,126 (88.2)	1,220 (96.2)	272,745 (77.2)
5-9.9	33,172 (17.9)	23,445 (18.6)	3,356 (8.2)	43 (3.4)	60,016 (17.0)
≥10	11,833 (6.4)	7,148 (5.7)	1,459 (3.6)	5 (0.4)	20,445 (5.8)
Duration of previous other MHT (yr)					
<5	179,945 (97.3)	124,177 (98.5)	39,385 (96.2)	1,248 (98.4)	344,755 (97.6)
5-9.9	4,393 (2.4)	1,765 (1.4)	1,221 (3.0)	19 (1.5)	7,398 (2.1)
≥10	541 (0.3)	176 (0.1)	335 (0.8)	1 (0.1)	1,053 (0.3)
Last dosage of Tibolone (per days)					
1.25 mg	1,756 (0.9)				
2.5 mg	182,931 (99.0)				
Over 5 mg	172 (0.1)				
Prescribed specialty					
Gynecology	63,129 (34.1)	58,104 (46.1)	17,447 (42.6)	367 (28.9)	139,047 (39.4)
Non-gynecology	121,750 (65.9)	68,014 (53.9)	23,494 (57.4)	901 (71.1)	214,159 (60.6)

Values are median (25 percentile-75 percentile) or presented as number (%).
MHT, menopausal hormone therapy.

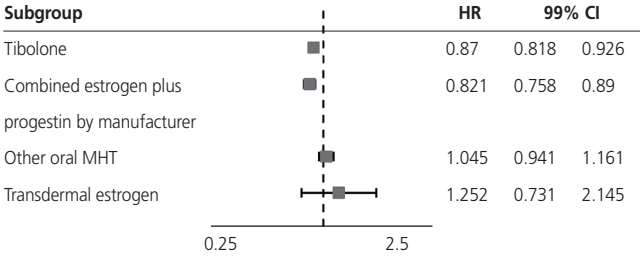


Fig. 2. Comparative assessment of hazard ratios for pelvic organ prolapse associated with various MHT drugs: findings from the Korea National Health Insurance Data, 2002-2019. HR, hazard ratio; CI, confidence interval; MHT, menopausal hormone therapy.

1.589-2.005; parity 2: HR, 1.434; 99% CI, 1.292-1.592; parity ≥3: HR, 1.916; 99% CI, 1.712-2.144). All smoking groups, including past and current smokers, showed a reduced POP risk (past: HR, 0.846; 99% CI, 0.688-1.04; current: HR, 0.815; 99% CI, 0.713-0.932). Alcohol consumption less than six times weekly reduced the POP risk (~2 times/weeks: HR, 0.779; 99% CI, 0.731-0.831; 3-6 times/weeks: HR, 0.648; 99% CI, 0.532-0.79). One to six instances of weekly physical exercise reduced the POP risk (1-2 instances: HR, 0.909; 99% CI, 0.862-0.959; 3-4 instances: HR, 0.894; 99% CI, 0.835-0.957; 5-6 instances: HR, 0.91; 99% CI, 0.813-1.019). The tibolone and CEPM groups showed similar results in the sensitivity tests.

The risk of POP in MHT by age is detailed in Supplementary Table 2. In a sensitivity test that analyzed only gynecologists' prescriptions, demonstrating the robustness of our study, tibolone and CEPM were associated with lower POP, consistent with the main results, while other oral MHT and transdermal estrogen showed no association with POP (tibolone: HR, 0.804; 99% CI, 0.723-0.894; CEPM: HR, 0.792; 99% CI, 0.703-0.893; other oral MHT: HR, 0.931; 99% CI, 0.785-1.105; transdermal estrogen: HR, 0.395; 99% CI, 0.064-2.443).

Discussion

This study showed that tibolone and CEPM were associated with a lower risk of POP, but other hormones did not affect the risk of POP. The effect of the MHT on POP risk remains

Table 3. Hazard ratios for risk of POP according to significant variables, Korea National Health Insurance Data, 2002-2019

Variable	Model 1[a]		Model 2[b]	
	HR (99% CI)[a]	*P*-value	HR (99% CI)[a]	*P*-value
MHT				
Tibolone	0.847 (0.797-0.9)	<0.001	0.87 (0.818-0.926)	<0.001
Combined estrogen plus progestin by the manufacturer	0.795 (0.736-0.859)	<0.001	0.821 (0.758-0.89)	<0.001
Other oral MHT	1.062 (0.959-1.176)	0.13	1.045 (0.941-1.161)	0.28
Transdermal estrogen	1.326 (0.799-2.2)	0.15	1.252 (0.731-2.145)	0.281
Age at inclusion (yr)				
40-49	1		1	
50-59	1.812 (1.656-1.983)	<0.001	1.51 (1.371-1.663)	<0.001
60-69	3.351 (3.055-3.675)	<0.001	2.093 (1.852-2.366)	<0.001
70~	3.38 (3.054-3.74)	<0.001	2.018 (1.761-2.313)	<0.001
BMI (kg/m^2)				
<18.5	0.824 (0.698-0.968)	0.002	0.822 (0.698-0.968)	0.002
18.5-22.9	1		1	
23-24.9	1.141 (1.088-1.196)	<0.001	1.143 (1.088-1.2)	<0.001
25-29.9	1.177 (1.125-1.232)	<0.001	1.173 (1.12-1.228)	<0.001
≥30	1.007 (0.912-1.111)	0.86	0.997 (0.901-1.103)	0.949
SES				
Mid-high SES			1	
Low SES	0.959 (0.853-1.078)	0.356	0.954 (0.845-1.077)	0.317
Region				
Urban area			1	
Rural area	0.974 (0.936-1.014)	0.089	0.958 (0.919-0.998)	0.006
CCI				
0	1		1	
1	1.014 (0.968-1.062)	0.437	1.012 (0.966-1.06)	0.511
≥2	0.964 (0.914-1.017)	0.074	0.959 (0.908-1.013)	0.051
Parity				
0 or no response	1.854 (1.656-2.075)	<0.001	1.785 (1.589-2.005)	<0.001
1	1		1	
2	1.464 (1.323-1.62)	<0.001	1.434 (1.292-1.592)	<0.001
≥3	1.942 (1.741-2.166)	<0.001	1.916 (1.712-2.144)	<0.001
Age at menarche (yr)				
<13			1	
≥13	0.961 (0.894-1.011)	0.095	1.05 (0.985-1.119)	0.049
Age at menopause (yr)				
40-44	1		1	
45-49	1.06 (0.991-1.134)	0.026	1.154 (1.074-1.24)	<0.001
50-54	1.072 (1.003-1.145)	0.008	1.26 (1.169-1.358)	<0.001
55~	1.144 (1.05-1.246)	<0.001	1.461 (1.321-1.616)	<0.001
Smoking				
Never			1	
Past			0.846 (0.688-1.04)	0.038
Current			0.815 (0.713-0.932)	<0.001

Table 3. Hazard ratios for risk of POP according to significant variables, Korea National Health Insurance Data, 2002-2019 (Continued)

Variable	Model 1[a]		Model 2[b]	
	HR (99% CI)[a]	*P*-value	HR (99% CI)[a]	*P*-value
Alcohol (times/week)				
None			1	
~2			0.779 (0.731-0.831)	<0.001
3-6			0.648 (0.532-0.79)	<0.001
Daily			0.853 (0.654-1.112)	0.122
Physical exercise (times/week)				
None			1	
1-2			0.909 (0.862-0.959)	<0.001
3-4			0.894 (0.835-0.957)	<0.001
5-6			0.91 (0.813-1.019)	0.03
Daily			1.023 (0.952-1.099)	0.41
The period from menopause to inclusion (yr)				
<5			1	
5-9			1.307 (1.232-1.387)	<0.001
10~			1.511 (1.396-1.636)	<0.001

POP, pelvic organ prolapse; HR, hazard ratio; CI, confidence interval; MHT, menopausal hormone therapy; BMI, body mass index; SES, socioeconomic status; CCI, Charlson comorbidity index.
[a]HRs were adjusted for age group, BMI, SES, region, CCI, parity, age at menarche, and age at menopause.
[b]HRs were adjusted for age group, BMI, SES, region, CCI, parity, age at menarche, age at menopause, smoking, alcohol, physical exercise, and period from menopause to inclusion.

controversial. Anatomical factors influencing the risk of POP include weakening of the pelvic connective tissue. Because estradiol receptors are present in the female reproductive tract, estrogen affects the synthesis of connective tissue in the pelvis [9,10]. Estrogen inhibits matrix metalloproteinase synthesis and activity, reduces collagen degeneration, and increases pelvic floor connective tissue maintenance. Therefore, estrogen can be used to prevent POP [9,10]. However, several studies have argued that increased pelvic floor elasticity, resulting from increased collagen levels due to estrogen, may increase the risk of POP [12]. In a randomized controlled trial involving 88 women, increased pelvic floor muscle strength was observed in the non-MHT group [11].

POP and MHT have been investigated in several studies. In a study conducted in Finland, the risk of uterine prolapse was higher for combined MHT (estradiol and progestin) [13]. In an Australian study, hiatal distensibility and rectal ampulla descent increased in the MHT group, resulting in a higher POP risk. However, this finding was not clinically significant [12]. These results differ from those of the present study, which showed a reduced POP risk in the CEPM group and insignificant results for other forms of oral MHT. The Finnish study did not consider variables that may influence POP risk, such as BMI, SES, region, CCI, parity, menarche, menopause, smoking, and alcohol consumption. The analysis did not adjust for established POP risk factors, including parity and BMI, potentially impacting the observed results. The Australian study did not classify MHT; we classified MHT into CEPM, tibolone, and other MHT hormones and studied each hormone. Furthermore, the number of participants in the Australian study was 725, which is relatively small compared with the number included in this study (1,354,556) [12]. Finally, the classification of MHT and the study size may have affected the study results.

1. Tibolone

Unlike other hormones, tibolone contains synthetic steroids with an androgenic reaction, which may have a different mechanism from that of CEPM [5]. Androgen receptor expression levels were fourfold higher in POP women than in non-POP women [16]. However, it is not yet known whether the androgenic effects of tibolone affect POP. Only one Finnish study investigated whether tibolone influences the occurrence of POP. That study showed that tibolone reduced

the POP risk, similar to the present study's findings [13]. However, while the Finnish study included only 155 women in the tibolone group, the number of women in the present study was much higher at 184,878. The reduced incidence of POP in the CEPM and tibolone groups may be related to the effects of estrogen and progesterone. Further research is required to determine the androgenic effects of tibolone on POP.

2. Transdermal estrogen

In this study, transdermal estrogen levels were not associated with POP risk. These findings align with those of a previous Austrian study of 103 women, which found no beneficial effect of transdermal estrogen therapy on POP symptoms [17]. However, there have been no large-scale studies on the effects of transdermal estrogen on pelvic floor diseases. Although vaginal transdermal estrogen is not used to relieve vasomotor symptoms, it is frequently used to reduce complications associated with pelvic organ prolapse (e.g., vaginal discharge and vaginal erosion caused by pessaries), and further research in this area is needed [18].

3. BMI

The significant risk factors for POP include parity, vaginal delivery, old age, and high BMI [19,20]. This study showed a high POP occurrence in all women over 50 years of age. Those with a BMI <18.5 had a lower risk of POP, and those with a BMI of 23-29.9 had a higher risk. However, the risk was not significant for those with a BMI >30. This result is consistent with those of previous studies [20-23]. However, the present study showed different results from those of previous studies, in which a parity of 0 did not increase POP risk. The present study also showed a higher POP risk in the parity 0 or no-response group [20,24,25]. This result may be due to the combination of no response and a parity of 0.

4. Other risk factors

Furthermore, in rural areas, individuals who were current smokers, consumed alcohol one-six times weekly, and engaged in physical exercise one-four times a week had a lower risk of POP. No significant associations were observed between daily alcohol intake or physical activity level and risk of POP in this analysis. Previous studies have suggested a reduced occurrence of POP with PFM training, which may partially explain the lower risk of POP associated with exercise, but the exact causal relationship requires further research on the type of exercise [11,26-29]. However, the relationship between POP risk, smoking, and drinking remains unclear, as previous studies have shown inconsistent results [19,30,31]. Additionally, the exact mechanisms through which female sex hormones and MHT impact POP are not well understood. Further research is needed to explore these relationships and determine optimal MHT regimens.

5. Strengths and limitations

This study had several strengths. The study was a large-scale population study with approximately 800,000 participants, which is comparable to previous observational studies conducted in Asia. The MHT group was subdivided into different subgroups, allowing for a detailed analysis of the correlation between MHT and POP. Factors influencing POP occurrence were considered, including age, BMI, CCI, SES, parity, menarcheal age, menopausal age, time from menopause to inclusion, alcohol consumption, smoking, and physical exercise. The age range was also controlled to reduce the effect of age, a significant risk factor for POP. Furthermore, the study included multiple types of CEMP drugs. However, this study had some limitations. First, it was not possible to determine the most effective drug for preventing POP owing to unknown usage details in the CEPM group. Further research is needed in this area for clinical practice. Second, the inclusion of only women diagnosed with POP in medical institutions by diagnosis codes for prolapse without pelvic examination or questionnaire may have missed women who had symptoms but did not seek medical attention or did not mention prolapse, and the study did not consider the tendency to visit medical institutions. However, the study included many women diagnosed with POP (21,059). Third, the variables in this study were identified based on the study's start date. For example, BMI was only measured at the start of the study. Therefore, even if there was a significant change in BMI after the start of the study, it could not be reflected in the outcome. This study has a limitation in that it cannot correct changes over time.

In conclusion, MHT using tibolone and CEPM were associated with a reduced risk of POP compared to non-MHT treatment after menopause. Other types of oral MHT and transdermal estrogen levels were not associated with the risk of POP.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Study approved by Sanggye Paik Hospital IRB (approval no. SGPAIK-2020-08-002). National Health Insurance Service removed identification variables before data provision. Individuals unidentifiable and inclusion uncompromised.

Patient consent

Per to the Bioethics and Safety Act of South Korea, obtaining informed consent from patients was unnecessary.

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