



# Italian Journal of Gynæcology & Obstetrics

December 2024 - Vol. 36 - N. 4 - Quarterly - ISSN 2385 – 0868

## Menopause and HRT (use and concerns) among Jordanian women: a cross-sectional study

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### ARTICLE INFO

#### History

Received: 01 March 2024

Received in revised form: 18 April 2024

Accepted: 03 May 2024

Available online: 17 December 2024

DOI: 10.36129/jog.2024.168

#### Key words

Menopause; symptoms; hormone replacement therapy.

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### ABSTRACT

**Objective.** Menopause is the permanent end of menstruation where a woman suffers from variable symptoms. Hot flushes are the most prevalent, and hormone replacement therapy is frequently prescribed for relieving menopausal symptoms, specifically hot flushes. In this study, we aimed to study menopause in the Jordanian population in regard to average age, most common symptoms, awareness, and attitude toward using hormone replacement therapy (HRT) as an available treatment option.

**Materials and Methods.** A self-reported questionnaire was distributed online and the answers of 566 menopausal women between the ages of 45-65 were analysed in the study.

**Results.** The average age of menopause was 48.2. Fatigue and muscle pain were the most reported symptoms of the 260 women who sought a doctor for their symptoms, and 81 of them were prescribed HRT for symptom relief. The majority of them reported improvements in symptoms like hot flushes by 40.7% and 3.5% reported improvements in night sweats. Women were evaluated for the most common side effects of HRT, and breast cancer was identified as the most common side effect among both HRT and non-HRT users, with a P-value < 0.001. Interestingly, both groups showed high intentions for not using HRT in the future, with 59.4% all menopausal women users and 62.7% of non-HRT users citing concerns over side effects.

**Conclusions.** This highlights the need to raise awareness about HRT perhaps through brochures, campaigns, and direct advice from primary health care doctors.

### INTRODUCTION

Menopause is the permanent end of menstruation and the non-reproductive stage of a woman's life that occurs 12 months after the absent of the menstrual cycle [1]. It most commonly affects women between the ages of 45 and 55, with the average age being 51 [2]. Women may suffer a variety of

physical, endocrine, and psychological changes as they approach menopause, which are influenced by ethnic, psychological, and social factors [3]. Reduction in the sex steroid hormones of oestrogen and progesterone is a prominent development of natural ageing and gonadal function loss, and it may have an influence on hormone-responsive tissues such as bone, the cardiovascular system, and

the brain[4]. The most common postmenopausal symptoms are hot flashes, nocturnal sweats, vaginal dryness, mood swings, and sleep disturbances [5]. A woman's symptoms of menopause can be managed with a range of treatments, including hormone replacement therapy (HRT), non-hormonal medicines, and lifestyle modifications [6]. Even though HRT is the most effective treatment for menopausal symptoms, certain women may prefer non-hormonal approaches or it may not be appropriate for them [7]. Oestrogen therapy can be administered systemically via an oral or transdermal route or locally via vaginal creams or suppositories. Systemic treatment is used for vasomotor symptoms while local treatment is used for local symptoms of atrophic vaginitis. Despite the advantages of oestrogen treatment, there are several side effects that appear depending on the route of administration. Breast discomfort, bloating, nausea, headaches, and leg cramps are the most frequent adverse effects that occur when treatment is used alone [8]. Moreover, abnormal uterine bleeding is common in perimenopausal and postmenopausal women, with a range of differential diagnoses [9] such as uterine fibroids, pelvic masses [10], or even endometrial cancer in postmenopausal women which is less likely for whom using HRT [11]. Despite that, excess oestrogen increases endometrial and breast cancer risk, with a relative risk of 1.7 (95%CI 1.1-2.7) for those taking oestrogen for over nine years and 1.8 (95% CI 0.7-4.6) for oestradiol for over six years. Furthermore, oestrogen medication has been linked to an increased risk of developing venous and pulmonary thromboembolism [12]. The risk for venous thromboembolism (VTE) has been strongly linked with the oral route of oestrogens in comparison to the transdermal route, despite having shared benefits in terms of enhancement of the metabolic profile (*e.g.*, glucose metabolism, and lipid levels). Moreover, there was no significant difference between the two routes in terms of risk for endometrial disease, breast cancer, and cardiovascular issues [13]. Progestin is added to HRT to protect against the risk of endometrial hyperplasia and adenocarcinoma [14].

HRT usage rate varies between communities. It has been used by 2.5% and 18% of peri-menopausal women in Japan and Spain respectively, but by 55% in France [15, 16].

Furthermore, the level of awareness about HRT differs among communities and periods of time. For example, HRT usage increased significantly in

the UK between 1981 and 1990 [17]. The rise of using HRT in the UK continued all through the time period 2010 up to 2021 [18].

Several factors have been discovered to be associated with the level of awareness about HRT. Better socioeconomic class, better education, nulliparity, and smoking were associated with more frequent HRT usage [19]. It has been advised that educational programs are necessary to raise awareness. To ascertain the parameters influencing HRT usage, a population-based study of Swedish women was conducted to determine the factors that contribute to the acceptance and continuation of HRT among women born between December 2, 1935 and December 1, 1945. The study concluded that education, working conditions, lifestyle, interest in prevention, and severity of climacteric symptoms were determinants for both acceptance and compliance with HRT [20].

Therefore, in response to the shortage of statistics on the awareness of HRT as well as its usage, especially in the Arabian zone, our study aimed to explore the prevalence of HRT usage among menopausal women in Jordan in addition to their awareness and attitude toward HRT. According to our knowledge, this is the first study in the region addressing this topic.

## MATERIALS AND METHODS

### *Study design: cross sectional descriptive*

#### *Population*

The inclusion criteria were women in menopause who live in Jordan and have access to the internet and social media. The exclusion criterion was women in the reproductive age.

#### *Sample size*

There are no statistics available about the number of menopausal women in Jordan. Therefore, the age range was chosen to be 45-65 years old. At a margin of error of 5% and confidence interval of 95%, the calculated representative sample size was 384 from a population of 682,480 women in Jordan between 45-65 years old according to the Jordanian Department of Statistics [21, 22].

#### *Ethics*

The Institutional Review Board (IRB) approval was obtained from Yarmouk University (IRB No:

2023/21). This study has been performed in accordance with the Declaration of Helsinki.

### Measures

There was a face-to-face and self-reported questionnaire. Participants received a survey link via social media messaging and were asked to help to find more possible participants by including a connection to another woman who could respond to the questionnaire [23].

The questionnaire was composed of four sections. The first section was about the demographics, the second section about menopausal history, the third about menopausal symptoms (hot flashes, night sweats, vaginal dryness, low libido, difficulty sleeping, fatigue, weight gain, frequent urination, urinary incontinence, joint and muscle pain, forgetfulness, depression, and anger), and the fourth was about HRT usage (visiting doctor for symptoms, treatments prescribed, duration of use, reason for stopping treatment, and the effect of hormonal replacement on improving the menopausal symptoms) in addition to the awareness about the possible complications of HRT and the willingness to use HRT if prescribed.

Three experts in the field tested the validity of the questionnaire and their comments were taken into consideration. Then it was tested for reliability among 20 participants and changes were made as required. Each participant gave her agreement before beginning the questionnaire, and the study was conducted at her own initiative. The information provided by research participants was likewise kept anonymous.

The research was carried out between December 2022 and July 2023 created on Google Forms in the Arabic language, which is the official language of the Hashemite Kingdom of Jordan.

### Statistical analysis methods

Incomplete surveys were removed from the analysis after the completed questionnaires were checked for mistakes and missing variables.

Categorical variables were summarized with frequencies and percentages, and numerical variables were represented with means, standard deviation (SD), minimum (min), maximum (max), and median. Since two women had a body mass index (BMI) higher than 69, the BMI descriptive statistics were calculated based on 1% winsorized

data, which replaces the values larger than the 99<sup>th</sup> percentile with the 99<sup>th</sup> percentile value, and the values lower than the 1<sup>st</sup> percentile with the 1<sup>st</sup> percentile value. A chi square test, or alternatively, a Fisher's Exact Test for Count Data was used to test differences in the distributions of categorical variables. Spearman's rank correlation rho was used to describe the relationship between two numerical variables when one or both were not normally distributed. Kruskal-Wallis test was employed as an alternative to ANOVA in testing the differences in a numerical variable between more than two groups when the assumptions of ANOVA were not met. All analyses and graphs were produced in R [24] version 4.2.2.

## RESULTS

### Demographic characteristics of the sample of menopausal women

There were 566 women who completed the questionnaire and were included in the analysis. **Table 1** demonstrates the demographic characteristics of the sample included.

**Table 1.** Demographic characteristics of the sample of menopausal women ( $n = 566$ ).

Demographic	n = 566
Age (years)	
Mean (SD)	52.6 (5.42)
Median [Min, Max]	52.0 [38.0, 85.0]
1% winsorized BMI (kg/m <sup>2</sup> )	
Mean (SD)	30.0 (5.49)
Median [Min, Max]	29.4 [20.2, 47.5]
Missing	2 (0.4%)
Educational level	
Less than secondary	30 (5.3%)
Secondary	149 (26.3%)
College (University, Associate)	327 (57.8%)
Graduate (Master, Doctoral)	60 (10.6%)
Occupation	
Employed	180 (31.8%)
Housewife	286 (50.5%)
Retired	100 (17.7%)
Monthly income (JD)	
≤ 250	125 (22.1%)
251-500	245 (43.3%)
≥ 501	196 (34.6%)



Demographic	n = 566
<b>Residence</b>	
Ajloun	41 (7.2%)
Amman	217 (38.3%)
Aqaba	1 (0.2%)
Balqa	28 (4.9%)
Irbid	143 (25.3%)
Jerash	9 (1.6%)
Karak	20 (3.5%)
Ma'an	5 (0.9%)
Madaba	14 (2.5%)
Mafraq	14 (2.5%)
Tafila	1 (0.2%)
Zarqa	73 (12.9%)
<b>Smoking</b>	
Current smoker	91 (16.1%)
Never smoker	440 (77.7%)
Previous smoker	35 (6.2%)
<b>Exercise</b>	
No	244 (43.1%)
Yes	322 (56.9%)
<b>Marital status</b>	
Divorced	32 (5.7%)
Married	450 (79.5%)
Single	38 (6.7%)
Widow	46 (8.1%)
<b>Number of children</b>	
Mean (SD)	4.3 (2.35)
Median [Min, Max]	4.0 [0, 12.0]
Missing	42 (7.4%)
<b>Blood type</b>	
A-	20 (3.5%)
A+	202 (35.7%)
AB-	5 (0.9%)
AB+	57 (10.1%)
B-	10 (1.8%)
B+	69 (12.2%)
O-	14 (2.5%)
O+	161 (28.4%)
Do not know	28 (5.0%)

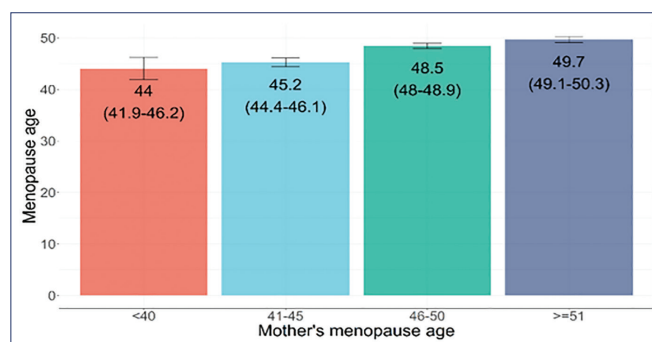
### Menstrual history

The mean age of menopause and mean age of menarche of the participants were 48.2 and 13.5 respectively which is clarified in **Table 2**. 23 (4.1%) women had premature ovarian insufficiency.

**Table 2.** Menstruation and menopausal history of the sample of menopausal women (n = 566).

Variable	n = 566
<b>Age at menarche (years)</b>	
Mean (SD)	13.5 (1.69)
Median [Min, Max]	14.0 [7.0-18.0]
Missing	1 (0.2%)
<b>Age at menopause</b>	
Mean (SD)	48.2 (4.52)
Median [Min, Max]	49.0 [29.0, 64.0]
<b>Years since last period</b>	
Mean (SD)	4.6 (4.90)
Median [Min, Max]	3.00 [1.00, 32.0]
<b>Mother age at menopause</b>	
≤ 40	33 (5.8%)
41-45	80 (14.1%)
46-50	210 (37.1%)
≥ 51	215 (38.0%)
Do not know	28 (4.9%)
<b>Cause of menopause</b>	
Natural	558 (98.6%)
Hysterectomy	0 (0%)
Oophorectomy	8 (1.4%)
Treatment	0 (0%)

There was no significant correlation between age of menarche and age of menopause (Spearman's rank correlation rho = 0.049, P-value = 0.248). On the other hand, there was a significant positive relationship between menopause age and mother's menopause age (Spearman's rank correlation rho = 0.405, P-value < 0.001, n = 538 excluding those who did not know their mother's menopause age). The mother's menopausal ages with the menopausal ages of the sample are shown in **Figure 1**.



**Figure 1.** Bar plot depicting the relationship between the subject's age at menopause and the mother's age at menopause. Mother's menopause age is a categorical variable and menopause age is a numerical variable (n = 538).

Moreover, there was no significant difference of the age of menopause between women of different blood groups (Kruskal-Wallis  $\chi^2 = 5.8358$ ,  $df = 7$ ,  $P$ -value = 0.559).

**Prevalence of menopausal symptoms**

“Joint and muscle pain” and “fatigue” were the most frequently experienced symptoms. On the other hand, urinary incontinence was the least frequently experienced symptom.

**Table 3** demonstrates the frequency of menopausal symptoms.

**History of seeking medical or natural treatments for menopausal symptoms**

The number of women who visited the doctor seeking advice, the treatment being prescribed, the duration of usage, and the reason for stopping the treatment are shown in **Table 4**.

**Effects of hormonal replacement therapy**

HRT treatment was most effective in the case of hot flashes and night sweats, with 40.7% and 3.5% respectively. **Table 5** clarifies the percentages of women whose menopausal symptoms improved by using HRT.

**Table 3.** Menopausal symptoms suffered by the women in the sample with their frequencies (n = 566).

Symptom	Having symptoms	Does not have the symptom
Hot flashes [N (%)]	474(83.7%)	92 (16.3%)
Night sweats [N (%)]	446 (78.8%)	120 (21.2%)
Vaginal dryness [N (%)]	447 (79%)	119 (21.0%)
Low libido [N (%)]	481 (85%)	85 (15.0%)
Difficulty sleeping [N (%)]	477(84.3%)	89 (15.7%)
Fatigue [N (%)]	538 (95%)	28 (4.9%)
Weight gain [N (%)]	493 (87.1%)	73 (12.9%)
Frequent urination [N (%)]	473 (83.6%)	93 (16.4%)
Urinary incontinence [N (%)]	389(68.7%)	177 (31.3%)
Joint and muscle pain [N (%)]	531 (93.8%)	35 (6.2%)
Forgetfulness [N (%)]	500 (88.4%)	66 (11.7%)
Depression [N (%)]	481 (85.0%)	85 (15.0%)
Anger [N (%)]	506 (89.4%)	60 (10.6%)

**Table 4.** History of seeking medical or natural treatment for menopausal symptoms (n = 566).

n = 566	
Visited doctor for symptoms	
Yes	260 (45.9%)
No	275 (48.6%)
No symptoms	31 (5.5%)
Treatment prescribed	
HRT	81 (14.3%)
Natural alternative treatments	43 (7.6%)
Other	46 (10.4%)
No prescription	77(13.6%)
Duration of treatment	
< 6 months	81 (14.3%)
6-12 months	21 (3.7%)
13-18 months	6 (1.1%)
19-24 months	5 (0.9%)
> 24 months	57 (10.1%)
No prescription	77 (13.6%)
No doctor's visit	275 (48.6%)
Reason for stopping treatment	
Symptom improvement	25 (4.4%)
Treatment side effects	10 (1.8%)
Fears associated with treatment	37 (6.5%)
Medication unavailability	2 (0.4%)
Stopped for other reasons	30 (5.3%)
Haven't stopped	67 (11.8%)
No prescription	77(13.6%)
No doctor's visit	275 (48.6%)

**Table 5.** Menopausal symptoms that improved after prescribed HRT use (n = 81).

Symptom	Improved (%) n = 81
Hot flashes	33 (40.7%)
Night sweats	29 (35.8%)
Vaginal dryness	13 (16.0%)
Low libido	8 (9.9%)
Difficulty sleeping	19 (23.5%)
Fatigue	15 (18.5%)
Weight gain	8 (9.9%)
Frequent urination	4 (4.9%)
Urinary incontinence	2 (2.5%)
Joint and muscle pain	10 (12.3%)
Forgetfulness	2 (2.5%)
Depression	8 (9.9%)
Anger	10 (12.3%)
No improvement	24 (29.6%)

**Table 6.** Differences in responses about possible side effects of HRT, the whole sample versus women prescribed HRT.

Side effect	Menopausal n = 566	Menopausal prescribed HRT n = 81	P-value
Breast cancer	65 (11.5%)	20 (24.7%)	< 0.001
Deep vein thrombosis	30 (5.3%)	7 (8.6%)	0.208
Uterine cancer	35 (6.2%)	10 (12.3%)	0.041
Stroke	15 (2.7%)	2 (2.5)	1.000
Ovarian cancer	28 (4.9%)	6 (7.4%)	0.420
Coronary heart disease	12 (2.1%)	5 (6.2%)	0.050
Gall bladder stones	6 (1.1%)	1 (1.2%)	1.000
I don't know	343 (60.6%)	49 (60.5%)	0.985
None	151 (26.7%)	13 (16.0%)	0.040

**Menopausal women's attitudes and awareness toward the use of HRT**

Women were asked what the side effects of HRT were. **Table 6** demonstrates their answers and the whole sample in comparison to the women who were prescribed HRT. Breast cancer was the most frequently perceived side effect of HRT.

Women were asked if they would use HRT if it was prescribed, and 59.4% of all menopausal women and 62.7% of menopausal women not prescribed HRT would not accept using HRT (**Table 7**). The most frequent reason reported for refusal was HRT side effects.

**Table 7.** Attitudes of all menopausal women and menopausal women prescribed HRT toward the use of HRT to treat menopausal symptoms.

	Menopausal women n = 566	Menopausal women not prescribed HRT n = 485
Intent to use HRT		
No	336 (59.4%)	304 (62.7%)
Yes	229 (40.5%)	180 (37.1%)
Missing	1 (0.2%)	1 (0.2%)
Reason for refusing use		
Side effects	205 (36.2%)	179 (36.9%)
HRT causes breast cancer	39 (6.9%)	30 (6.2%)
Doctor advised against use	31 (5.5%)	28 (5.8%)
Family history of breast cancer	37 (6.5%)	32 (6.6%)
Previous case of breast cancer	4 (0.7%)	2 (0.4%)
Other	250 (44.2%)	214 (44.1%)

**DISCUSSION**

We found that the mean age of menopause in our sample was 48.2, which is different from other areas in the world. In India it was determined as 46.2 [25], while it is average in Europe to be 54 [26].

Several factors affect the age of menopause, such as age of menarche, marriage duration, parity, blood group types, smoking, environmental factors, mother's menopause age, and nutritional, social and lifestyle habits. Also, some medical and surgical conditions, level of education, and chronic infections such as HIV-related immunodeficiency and chronic hepatitis C virus (HCV) have been linked to their effect on menopausal age [25, 27-29]. Accordingly, the observed differences in the mean age of menopause among countries could be attributed to environmental factors and differences in lifestyles in addition to genetic effects.

We explored if there is any possible association between the age of menopause and the age of menarche, blood type, and mother's age of menopause. We found a significant positive relationship with mother's age of menopause. Our findings contradict the findings of Maninder Ahuja *et al.* [25] where they found a correlation between age of menopause and marital status, educational level, parity, and socioeconomic status. The strong boundaries between the mother's age of menopause and daughter's onset of menopause have been estimated emphasizing the hereditary role in the process [30, 31]. A population study including 336,788 women in Norway found a non-significant relationship between the age of menarche and age of menopause [32]. However, some studies still indicate the correlation between the onset of menarche and menopause in the woman [33]. As we indicated, there is no significant relationship between the ABO blood grouping and the onset of menopause. A systematic review and meta-analysis published in 2021 reflected no effect of the ABO blood group on the diminishing of the ovarian reserve [34].

We found that muscle pain and fatigue were the most prevalent menopausal symptoms among the participants. This is similar to the Singaporean women where the most prevalent reported symptoms reported were low backache with aching muscles and joints (51.4%) [35].

On the other hand, emotional problems (crying spells, depression, and irritability) and headaches were the most common symptoms among Indian

women (90.7% and 72.9%) respectively. Furthermore, it has been found that the most prevalent menopausal symptoms among Chinese women were insomnia, fatigue, and mood swings at 44.7%, 40.4%, and 37.2% respectively [36].

The prevalence of HRT use among participants was 14.3% while in Spain the prevalence of HRT use was 7.19% in 2001 and 0.21% in 2014 [37]. Moreover, in Korea in 2002, 7.8% of menopausal women used HRT, but this number decreased to 6.3% in 2013 [38]. In Japan in 1992 the prevalence of HRT use was 2.5% [15]. According to our finding, this prevalence is the highest in Jordan, but there are no recent data about HRT use neither in the nearby areas nor worldwide. This could be due to the increase in the awareness about the benefits of HRT in addition to possible discrepancies of frequency and severity of menopausal symptoms among different societies. Moreover, HRT use dropped after the announcement of the Women's Health Initiative (WHI) study results in 2002 [39].

Just less than half (45.9%) of the participants sought medical advice due to menopausal symptoms. This is less than the percentage reported in the United States (US) 60% [40]. This difference could be explained by two reasons. First, the number in the US included menopausal and perimenopausal women while all our participants were just in menopause. Furthermore, the lack of medical insurance in Jordan could prevent suffering women from seeking medical advice.

A small percentage (7.6%) of the Jordanian women used natural alternative treatments. The most commonly self-prescribed treatments and herbs included marjoram used by 63 women (11.1%), sage by 41 women (7.2%), and anise by 45 women (8%). Phytoestrogens have been used for treating vasomotor symptoms. However, the efficacy depends on the daily dose and the type used. For example, lignans and coumestans, ginseng, and matcha have been used with different levels of evidence ranging from B to C [41]. Anise has been found to reduce the severity and frequency of hot flashes compared to a placebo group. This is a good option if we take in consideration the potential toxicity that may happen ranging from nausea and vomiting to allergic reactions [42]. The mechanism of action for herbs like sage, fenugreek, black cumin, fennel, and licorice among others on menopause symptoms have been illustrated [43]. Some herbs do not have enough data against being used including fenugreek, hops, valerian, and soybean

in the context of relieving menopausal symptoms [44]. The amount of herb extracts used along with the proper mixture of herbs plays a significant role in bettering menopausal symptoms [45].

We found that HRT treatment was the most effective in relieving hot flashes and night sweats (40.7% and 35.8% respectively). Other studies that support that finding indicate that vasomotor symptoms were best treated effectively with HRT [46, 47].

A randomized control study among 2,763 women which was published in 2002 evaluated the effect of HRT and side effects on menopausal women. It showed that after 1 year of therapy, women who were prescribed HRT were less likely to report hot flashes, vaginal dryness, and trouble sleeping, but they were more likely to report vaginal discharge, genital irritation, and pelvic cramps compared to women assigned a placebo. After 4 years of treatment, women who were assigned HRT were more likely to report nausea or vomiting and headaches. There was no difference between the treatment group and placebo group in the proportion of sleep disturbances and weight gain [48].

We asked the participants about the possible side effects of HRT. Breast cancer was the most frequently perceived side effect of HRT (24.7%) among menopausal women prescribed HRT. No previous studies that assessed the awareness about the HRT side effects were found to compare our results with. Furthermore, participants who refused using HRT were asked about the reason behind that. The most frequent cause for refusal of HRT use was side effects. This is similar to what has been found among Korean postmenopausal women [49].

Promising novel techniques like ovarian tissue cryopreservation (OTC) is under study to be used in postmenopausal women and show optimistic results with almost very few side effects compared to HRT [50], but its clinical validity still needs to be proven [51].

As the severity of menopausal women varies and the quality of life in some can be affected extensively in terms of work and activity, especially for the vasomotor symptoms as example, the subsequent rising awareness about the availability of highly effective medication that can improve menopausal symptoms will aid in enhancing the quality of life of menopausal women. The study highlights the gap in HRT awareness and concerns and its availability for treating menopausal symptoms in Jordan, reflecting the urgent need to raise awareness about HRT as precious therapy.

### Study strengths

Our study is characterized as being the first to address this topic in the region. Furthermore, a large sample size strengthens the results.

### Study limitations

Depending on self-reported questionnaires may result in discrepancy in the responses of different questions. The longitudinal follow up for women prescribed HRT to track the improvement of symptoms and the compliance along with complications that might result was limited to obtain following the questionnaire-based study design.

## CONCLUSIONS

Less than 50% of menopausal women suffering from menopausal symptoms sought medical advice, and this reflects either a reduced level of awareness about HRT or misconceptions. Therefore, awareness about the benefits, safety, and possible complications of HRT should be raised. Health awareness campaigns, brochures, and family doctors and gynaecologists play a major role in increasing awareness about HRT usage.

## COMPLIANCE WITH ETHICAL STANDARDS

### Authors' contribution

S.A., R.A.B.: Conceptualization. R.A.B.: Methodology. S.A., R.A.B., R.A.Z., G.W.: Writing – original draft. R.A.B., R.A.Z., G.W.: Investigation. S.A.: Writing – reviewing & editing.

### Funding

None.

### Study registration

N/A.

### Disclosure of interests

The authors declare that they have no conflict of interests.

### Ethical approval

The Institutional Review Board (IRB) approval was obtained from Yarmouk University (IRB No: 2023/21). This study has been performed in accordance with the Declaration of Helsinki.

### Informed consent

Obtained. The questionnaire was started by a question: agree or disagree to participate.

### Data sharing

Data are available under reasonable request to the corresponding author.

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