Use of hormone therapy in patients with premature ovarian insufficiency in tertiary hospitals in Saudi Arabia

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Abstract

Objective: To examine diagnostic and treatment patterns of premature ovarian insufficiency (POI) in tertiary care settings in Saudi Arabia, with a focus on hormone therapy (HT) use.

Methods: A retrospective chart review was conducted at three hospitals from February 2002 to May 2024. POI was defined as follicle-stimulating hormone (FSH) > 25 IU/L. Patients aged 40 years or below, who underwent FSH testing on the basis of classic symptoms, were identified. Inclusion criteria were limited to women 40 years or below who had undergone FSH testing with a FSH concentration level of >25 IU/L; exclusion criteria included incomplete demographic or clinical data and duplicate test records. Among 255,204 eligible patients, 22,420 underwent FSH testing, of whom 1,132 met POI criteria. We performed a sample size calculation based on a pilot dataset (prevalence of HT use = 35.7%). Based on this, 205 notes were analyzed using descriptive statistics and comparative analysis.

Results: POI prevalence among tested women was 5.05% (95% CI: 4.77-5.34). Only 35.6% of women with POI received HT. Uptake was highest in genetically confirmed cases (62.1%) and lowest in cases with XY chromosomal abnormalities (8.3%) or iatrogenic causes (0%). Amenorrhea (42.4%) was the most common presenting symptom and significantly associated with HT use ($P = 0.001$). HT uptake remained low despite diagnoses of osteopenia (6.8%) and osteoporosis (4.9%).

Conclusions: HT is underutilized among women with POI in Saudi Arabia. Variability in prescription reflects systemic barriers, lack of national guidance, and insufficient physician training. Standardized protocols and structured follow-ups are urgently required to improve long-term health outcomes.

Key Words: Cancer, HT, Osteoporosis, Premature ovarian insufficiency.

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Premature ovarian insufficiency (POI) is a clinical condition characterized by the loss of ovarian function, causing irregular menstrual cycles, and confirmed biochemically in women aged below 40 years.[1] POI must be differentiated from menopause, as women with POI have distinctive needs and specific management options. These women are not only affected by symptoms associated with estrogen deficiency but also experience other issues that significantly impact their quality of life, such as fertility, bone health, cardiovascular health, sexual function, psychological health, and neurological function.[1] Thus, POI is a truly challenging condition for patients and health care professionals.

The European Society of Human Reproduction and Embryology guidelines provide clear diagnostic criteria for POI.[2] These include disordered menstrual cycles (defined as spontaneous amenorrhea or irregular menstruation) for a duration of at least 4 months and follicle-stimulating hormone (FSH) levels >25 IU/L. If the diagnosis is uncertain, FSH testing should be repeated after 4-6 weeks. However, FSH testing for POI does not need to be performed on a specific day of the menstrual cycle.

A systematic review and meta-analysis estimated the global prevalence of POI at 3.5%. The prevalence of POI varies across regions globally, as well as between developing and developed countries. Furthermore, POI prevalence has shown an increasing trend over the past 20 years.[3]

Genetic factors contribute significantly to the etiology of POI. Up to 15% of patients have a positive family history. POI is a multifactorial and clinically heterogeneous disorder, with most cases being idiopathic or spontaneous; however, genetic, autoimmune, and environmental factors also contribute to its etiology. Syndromic POI accounts for 10%-20% of cases,[4] with Turner syndrome in 4%-5% and Fragile X syndrome (FMR1 permutations) in 3%-15%.

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Hormone therapy (HT) is the cornerstone of treatment for women with POI and is recommended by international guidelines to manage symptoms and reduce long-term health risks.[1] Nevertheless, real-world studies indicate that HT remains underutilized, with variations in initiation, type, and duration of therapy.[5]

This study addressed the gaps in POI research by examining the diagnostic and treatment patterns of POI in a tertiary care setting in Saudi Arabia. The findings reflect patterns in a tertiary care referral population and may not be applicableto the general population.

The primary objective was to determine the rate and patterns of HT use among women diagnosed with POI and to identify demographic and clinical factors associated with HT initiation.

The secondary objectives were as follows:

1. To estimate the percentage of women diagnosed with POI among those who underwent FSH testing
2. To determine the percentage of women aged below 40 years who underwent FSH testing at King Faisal Specialist Hospital and Research Centre (KFSH&RC) between February 2002 and May 2024.

By identifying POI prevalence and gaps in HT utilization and diagnostic testing, this study underscores the need for more consistent, evidence-based management strategies. Highlighting these deficiencies can help optimize early recognition, improve symptom control, and reduce long-term complications, such as osteoporosis, cardiovascular disease, and psychological distress. Furthermore, the findings may inform strategies for enhancing patient education, guiding physician decision-making, and ultimately improving the quality of life and health outcomes for women with POI.

METHODS

Participant identification and data abstraction

A retrospective chart review was conducted using the Integrated Clinical Information System database to identify female patients aged below 40 years who received care at KFSH&RC in Riyadh, Jeddah, or Madinah between February 2002 and May 2024. FSH testing was performed in this group based on physician suspicion of ovarian dysfunction, irregular menstrual cycles, amenorrhea, infertility evaluation, or other clinical concerns.

In total, 255,204 female patients aged below 40 years were identified. Inclusion criteria were limited to women 40 years or below who had undergone FSH testing with a FSH concentration level of >25 IU/L; exclusion criteria included incomplete demographic/clinical data and duplicate test records.

After applying the inclusion criteria and cleaning the data, the final analytical cohort consisted of 22,420 women. Among these, 1,132 were diagnosed with POI, defined as having an FSH concentration >25 IU/L. FSH levels were obtained from the electronic medical records. Among the patients included in the study, a vast majority had only a single measurement of FSH documented. Repeat tests were infrequent and not consistently available. For the few patients' records with multiple readings, we took their first elevated reading. Therefore, only one measurement was considered.

We had performed a sample size calculation based on a pilot dataset (prevalence of HT use = 35.7%), and on this basis, 205 women were selected to estimate the prevalence of HT use. This was ascertained through physician documentation and prescription records in the electronic medical system. The mode of HT delivery, which is either oral, transdermal, or vaginal, was inconsistently documented.

The study was approved by the KFSH&RC Research Ethics Committee (RAC# 2241141).

Sampling and sample size calculation

To determine the appropriate sample size for this retrospective cohort study, a pilot analysis was conducted using data from 14 women diagnosed with POI. Of these women, five had received HT, resulting in a preliminary prevalence rate of 35.7%.

Based on this estimate, a sample size of 205 women was calculated to estimate the percentage of HT use with a 95% CI and a margin of error of approximately $\pm 6.7\%$. The calculation was performed using Stata version 17 (College Station, TX). Out of 1,132 eligible women, a simple random sample of 205 women was drawn to estimate HT use.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics, underlying causes, presenting symptoms, and long-term complications among women diagnosed with POI. Continuous variables were reported as mean ± SD, while categorical variables were expressed as frequencies and percentages (n, %).

Comparisons between women who received HT and those who did not were conducted based on variable type. For HT uptake and patient characteristics, continuous variables—such as age at diagnosis, FSH level, and age at menarche—were analyzed using independent-samples *t* tests. Categorical variables—including nationality, marital status, smoking history, family history of POI, radiological procedures, autoimmune disorders, and diabetes—were compared using χ^2 tests. When expected cell counts were small, the Fisher exact test was applied.

To assess underlying causes of POI by HT status, the distribution of etiological categories (genetic, idiopathic, XY chromosome abnormalities, iatrogenic, post-chemotherapy/bone marrow transplantation, and others) was compared between HT and non-HT groups using χ^2 tests.

For presenting symptoms by HT status, the presence or absence of symptoms—such as amenorrhea, oligomenorrhea, hot flashes, infertility, bone pain, and genitourinary manifestations—was compared between the two groups using χ^2 tests. The Fisher exact test was used when expected frequencies were fewer than 5.

No regression modeling or interaction testing was performed in this study, as the primary aim was descriptive.

Finally, long-term complications by HT status—including cardiovascular disease, osteoporosis, osteopenia, genitourinary complications, dementia, and malignancy—were compared between groups. Due to the sparse data distribution in several categories, Fisher exact test was applied.

All statistical tests were two-tailed, and a *P*-value of < 0.05 was considered statistically significant. Analyses were performed using Stata 18 (StataCorp, 2023).

RESULTS

Among the 22,420 women who underwent FSH testing, 1,132 met the diagnostic criteria for POI, corresponding to a prevalence of 5.05% (95% CI: 4.77-5.34) among tested women. The overall FSH testing rate among women aged below 40 years treated at KFSH&RC during the study period was 8.79% (22,420/255,204; 95% CI: 8.68-8.89).

Out of a subset of 205 women diagnosed with POI, 73 (35.6%) received HT, whereas 132 (64.4%) did not. The mean age at diagnosis and baseline FSH levels did not vary significantly between the HT and non-HT groups (Table 1).

HT use was higher among married women (41.9%) than in single women (32.6%), although the difference was not significant ($P = 0.445$). Notably, no non-Saudi patients received HT. Women with a documented family history of POI were more likely to receive HT (62.5%) than those without such a history (24.5%), with a borderline significant association ($P = 0.050$). No significant differences in HT use were observed based on smoking status, presence of autoimmune diseases, diabetes, or previous radiological evaluation.

The distribution of POI etiologies varied considerably in relation to HT use. (Table 2) Among women with genetically confirmed POI, 62.1% received HT. HT uptake was lowest among women with XY chromosomal abnormalities (8.3%) and those with iatrogenic or other unspecified causes (0%). Among patients with a history of chemotherapy or bone marrow transplantation (BMT), HT use was observed in 35.1% of those treated for malignancy and 34.0% for nonmalignant conditions. Approximately one-third of patients with idiopathic POI (33.3%) and those with undocumented etiologies (30.8%) received HT.

Amenorrhea was the most frequently reported presenting symptom and was significantly associated with HT use ($P = 0.001$) (Table 3). Furthermore, 50.6% of women presenting with amenorrhea received HT, compared with 24.6% among those who did not. Other symptoms, such as oligomenorrhea, hot flashes, infertility, bone pain, and genitourinary complaints, were not significantly associated with HT use.

Long-term complications were infrequently documented across the cohort and were often missing from records (33%-45% missing per variable) (Table 4). Osteopenia was the most commonly reported complication (6.8%), with 50.0% of affected patients receiving HT. Osteoporosis was reported in 4.9% of the cohort, only 20.0% of whom received HT. A single cardiovascular event occurred in a patient who had received HT. One patient had a genitourinary complication and one patient had a malignancy, and neither recived HT. No cases of dementia were recorded. None of the observed differences in complication rates between the HT and non-HT groups were statistically significant.

TABLE 1. HT uptake and patient characteristics

Characteristic	Total (N = 205)	HT (n = 73)	No HT (n = 132)	% HT	*P*
Age at diagnosis (mean ± SD)	28.15 ± 8.45	28.36 ± 7.71	28.03 ± 8.86	—	0.792
FSH reading (mean ± SD)	83.18 ± 42.26	86.70 ± 45.11	81.23 ± 40.64	—	0.376
Age at menarche (mean ± SD)	14.28 ± 1.90	14.25 ± 1.60	14.30 ± 2.21	—	0.941
Nationality	—	—	—	—	0.299
Saudi	201	73	128	36.3	—
Non-Saudi	4	0	4	0.0	—
Marital status					0.445
Single	138	45	93	32.6	—
Married	62	26	36	41.9	—
Divorced	4	2	2	50.0	—
Widowed	1	0	1	0.0	—
Smoking history					0.723
Yes	3	1	2	33.3	—
No	96	31	65	32.3	—
Not documented	106	41	65	38.7	—
Family history of POI	—	—	—	—	0.050
Yes	8	5	3	62.5	—
No	53	13	40	24.5	—
Not documented	144	55	89	38.2	—
Radiological procedure	—	—	—	—	0.811
Ultrasound	65	25	40	38.5	—
MRI	19	8	11	42.1	—
Both	16	5	11	31.3	—
None	105	35	70	33.3	—
Autoimmune disorders	—	—	—	—	0.571
Yes	32	14	18	43.8	—
No	118	41	77	34.7	—
Not documented	55	18	37	32.7	—
Diabetes	—	—	—		0.361
Yes	11	2	9	18.2	—
No	135	47	88	34.8	—
Not documented	59	24	35	40.7	—

HT, hormone therapy; FSH, follicle-stimulating hormone; POI, premature ovarian insufficiency; MRI, magnetic resonance imaging.

DISCUSSION

This retrospective study is among the first large-scale evaluations of POI in a Saudi tertiary care setting. Our decision of using a single FSH value > 25 IU/L to define POI was pragmatic, given the retrospective design, inconsistent follow-up, and missing repeat testing. All the tests were sent to the same institutional laboratory, ensuring consistency.

Restricting testing to women 40 years or below with strong clinical suspicion increased diagnostic specificity. Thus, a single elevated FSH was a practical and standardized marker to identify likely POI cases in this cohort.

TABLE 2. Distribution of underlying causes of premature ovarian insufficiency by HT status

Underlying cause	Total (N = 205)	HT (n = 73)	No HT (n = 132)	% HT
Genetic	29	18	11	62.1
Idiopathic	9	3	6	33.3
XY chromosome abnormalities	12	1	11	8.3
Iatrogenic	2	0	2	0.0
Post chemo/BMT (malignancy)	77	27	50	35.1
Post chemo/BMT (nonmalignancy)	47	16	31	34.0
Other	3	0	3	0.0
Not documented	26	8	18	30.8

HT, hormone therapy; BMT, bone marrow transplantation.

Prevalence and presenting symptoms

We found a POI prevalence of 5.05% among women tested, greater than global estimates.[3]

This most likely reflects referral bias in a tertiary center. Amenorrhea was the most common presenting complaint (42.4%), consistent with previous reports.[6] Infertility was documented in 11.7%, which reflects the single most alarming feature in our cohort population.[7] We have seen in this study that vasomotor symptoms were less frequently reported (5.3%) than in other populations,[7] which most likely reflects cultural differences in symptom perception, younger patient age, or under documentation. These findings highlight the need for systematic symptom assessment and documentation in suspected POI.

Etiology: cancer and Hematopoietic Stem Cell Transplantation (HSCT) -related Premature Ovarian Insufficiency (POI)

The increasing effectiveness and widespread use of modern chemotherapy and hematopoietic stem cell transplantation (HSCT) have led to a corresponding rise in the incidence of iatrogenic POI among young patients, particularly cancer survivors. A systematic review of 36 studies conducted between 1990 and 2017, with sample sizes ranging from 15 to 3,749 participants, reported the prevalence of POI at 2.1%-82.2% among female survivors of childhood and adolescent cancers (aged 0-24 years) globally.[8,9]

In our study, 37.6% of women diagnosed with POI had previously undergone chemotherapy for malignancy, with 22.9% developing POI following chemotherapy or BMT for nonmalignant conditions. These findings align with previous evidence that cytotoxic regimens used in the treatment of malignant and serious nonmalignant diseases, such as cyclophosphamide for systemic lupus erythematosus or mitoxantrone for multiple sclerosis, can significantly increase the risk of POI.[10–12]

This also confirms that alkylating agents and myeloablative regimens cause irreversible ovarian damage, as seen in studies across the globe.[8–13] The growing survival of cancer patients has expanded this at-risk population.

Despite this, HT uptake in oncology-related POI was low (35%), markedly less than reported elsewhere.[14] Barriers likely include limited survivorship pathways, insufficient integration of reproductive endocrinology into oncology, and unaddressed safety concerns due to a lack of updated evidence. We know that current evidence supports HT in POI post-HSCT for symptom control and bone preservation without increasing recurrence risk.[15,16]

TABLE 3. Presenting symptoms of women with premature ovarian insufficiency by HT status

Symptom	Total (N = 205)	HT (n = 73)	No HT (n = 132)	% HT	*P*
Amenorrhea	—	—	—	—	0.001
Yes	87	44	43	50.6	—
No	118	29	89	24.6	—
Oligomenorrhea	—	—	—	—	1.000
Yes	7	2	5	28.6	—
No	198	71	127	35.9	—
Hot flashes	—	—	—	—	1.000
Yes	11	4	7	36.4	—
No	194	69	125	35.6	—
Infertility	—	—	—	—	0.510
Yes	24	10	14	41.7	—
No	181	63	118	34.8	—
Bone pain	—	—	—	—	0.100
Yes	10	1	9	10.0	—
No	195	72	123	36.9	—
Genitourinary	—	—	—	—	0.126
Yes	2	2	0	100.0	—
No	203	71	132	35.0	—

HT, hormone therapy.

TABLE 4. Long-term complications among women with premature ovarian insufficiency by HT status

Complication	Total (N = 205)	HT (n = 73)	No HT (n = 132)	% HT	Fisher exact test *P*-value
Cardiovascular					
Yes	1	1	0	100.0	0.326
No	131	42	89	32.1	—
Missing	73	30	43	41.1	—
Osteoporosis					
Yes	10	2	8	20.0	0.302
No	74	31	43	41.9	—
Missing	121	40	81	33.1	—
Osteopenia					
Yes	14	7	7	50.0	0.373
No	58	21	37	36.2	—
Missing	133	45	88	33.8	—
Genitourinary					
Yes	1	0	1	0.0	1
No	61	14	47	23.0	—
Missing	143	59	84	41.3	—
Dementia					
Yes	0	0	0	0	1
No	52	13	39	25.0	—
Missing	153	60	93	39.2	—
Malignancy					
Yes	1	0	1	0.0	1
No	162	54	108	33.3	—
Missing	42	19	23	45.2	—

HT, hormone therapy.

We believe that all tertiary care hospitals will benefit from multidisciplinary survivorship programs incorporating reproductive health counseling.[17,18]

HT use and sociodemographic factors

Only 35.6% of women with POI received HT. Uptake was higher in married women (41.9%) and those with a family history of POI (62.5%), though differences were not always statistically significant. Non-Saudi patients did not receive HT, which was most likely due to the fact that many of the non-Saudi patients are not eligible for treatment in these government tertiary hospitals.

We also note the etiology-specific variations, where HT was most frequent in genetic POI (62.1%) and lowest in XY chromosomal abnormalities and iatrogenic causes. These inconsistencies reflect both patient factors and clinician perception of risk influence prescribing practices.

Long-term health risks and HT knowledge gaps

POI increases the risks of cardiovascular disease and osteoporosis.[19–25] The protective effects of estrogen are well established, yet two thirds of women in our cohort were not offered HT. Osteopenia was documented in 6.8% and osteoporosis in 4.9% of cases, though incomplete documentation likely underestimates prevalence.

The clinical consequences include increased incidence of osteoporosis and fragility fractures,[25] sarcopenia (loss of skeletal muscle mass and function),[26] and osteosarcopenia (sarcopenia associated with bone loss),[26] all of which lead to weakness, balance issues, falls, and ultimately, fractures.

It is of concern that only half the women with osteopenia and 20% with osteoporosis received HT, despite FDA approval for prevention and treatment in POI.[27] These findings highlight missed opportunities for long-term risk reduction in these women.

Barriers in the Saudi context

Low use of HT in POI reflects barriers at various levels. A recent national survey found that over half of Saudi physicians cite challenges in prescribing HT, including patient reluctance, difficulty in communicating benefits and risks, and limited availability of products.[28] In tertiary care, initiation of HT was often inconsistent, and continuity depended on primary care, where provider confidence and training are limited. We highlight that the absence of national guidelines for POI further contributes to variability and underuse of HT. Persistent apprehension rooted in the 2002 Women's Health Initiative trial also appears to influence practice despite its inapplicability to young women with POI.[29] Updated propagation of evidence-based guidelines is needed to support clinician confidence and patient access.

Clinical and public health implications

Our results demonstrate that POI is definitely prevalent in tertiary care populations, with a substantial burden arising from cancer and Hematopoietic Stem Cell Transplantation (HSCT) treatments. We highlight that the low rates of HT use represent a missed opportunity to lessen the known long-term cardiovascular and skeletal risks of early estrogen deficiency. These findings have particular relevance not only in Saudi Arabia but in all tertiary care hospitals across the world. The excellence in these tertiary care oncology centers leads to the rising prevalence of cancer survivorship. The lack of standardized POI care pathways leads to the burden of long-term poor health outcomes. Thus, we highlight the critical need for national strategies and for integrating reproductive endocrinology into oncology survivorship programs. This can only be achieved through cultivating a culture of specific hormone health physician training and developing local guidelines that reflect current best evidence.

Strengths of the study

This is the first study, to the best of our knowledge, conducted in the Middle East and North Africa region to examine diagnostic and treatment patterns of POI in a tertiary care setting. We established the rate and patterns of HT use among women diagnosed with POI and determined the number of patients initiated on HT in line with international guidelines. This study highlights critical gaps in POI management, underscoring the urgent need for standardized, guidelines-based care to mitigate long-term risks and improve the quality of life for affected women.

Limitations of the study

This study's retrospective design and reliance on a single FSH measurement limit diagnostic precision. Missing follow-up data and incomplete documentation of complications likely underestimate the burden of POI-related morbidity. Findings reflect a tertiary referral population and may not be generalizable to the wider Saudi community.

The use of HT was ascertained through physician documentation and prescription records in the electronic medical system. The mode of HT delivery, whether it is oral, transdermal or vaginal, was inconsistently documented in the notes. We know that this is an important aspect as the mode of delivery can have implications on the effects and complications of HT.

We report that long-term complications, such as osteopenia and osteoporosis, were underdocumented and undertreated in this study. Important non-reproductive symptoms, such as cognitive impairment, sexual dysfunction, and mood disturbances, were not recorded in the vast majority of patients. Patients with iatrogenic POI were particularly not followed up or referred for HT.

CONCLUSIONS

This study provides valuable insights into real-world diagnostic patterns, etiologies, and treatment gaps in POI patients. The findings of this study emphasize the requirement for necessary training in POI management and greater adherence to international guidelines among health care professionals managing patients with confirmed POI. Current guidelines clearly recommend HT until the average age of natural

menopause for the primary prevention of morbidity and mortality, irrespective of symptom presence.

As an evidence-based intervention, HT mitigates estrogen deficiency–related complications, including cognitive decline, dementia risk, neurodegenerative changes, adverse cardiovascular outcomes, and skeletal deterioration. Given the increased risks of cardiovascular disease and osteoporosis in this population, structured follow-up through to the average age of menopause is essential to ensure optimal long-term health outcomes.

Unfortunately, application of the Women's Health Initiative conclusions to the POI population has left many affected young women without optimal management, representing a form of collateral harm from the trial's legacy. Consequently, women with POI are likely to discontinue HT even if they had initially been prescribed to receive it, due to the misinformation stemming from the results of WHI study.

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