Original Article
DOI: https://doi.org/10.70749/ijbr.v3i4.2559

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://ijbr.com.pk
ISSN: 2960-2793/ 2960-2807

Role of Hormone Replacement Therapy in Women with Premature Ovarian Failure

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ARTICLE INFO

Keywords: primary ovarian insufficiency, hormone replacement therapy, follicular development.

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Declaration

Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History

Received: 10-01-2025 Revised: 07-04-2025
Accepted: 18-04-2025 Published: 30-04-2025

ABSTRACT

Introduction: Younger POI patients, who stand to profit greatly from physiological hormone replacement when initiated early and properly managed, are not covered by these findings. Furthermore, the risk-benefit ratio in POI clearly supports HRT, especially when utilizing contemporary regimens with bioidentical hormones, according to recent expert opinion. **Study design:** descriptive observational study. **Setting:** Department of Obstetrics and Gynecology, People's University of Medical and Health Sciences for Women. **Study duration:** January 2024 to September 2024. **Methodology:** Total 241 women between the ages of 18 and 40 who had previously been diagnosed with POI were eligible to participate. Those who had an intact uterus and ovaries and had not had any hormone therapy in the three months before enrollment were eligible to participate. Chromosome abnormalities, known ovarian tumors, autoimmune or systemic diseases, uncontrolled thyroid disorders, recent pelvic surgery, or contraindications to estrogen therapy, such as a history of thromboembolism or hormone-dependent cancer, were among the exclusion criteria. The entire six-month period involved continual oral administration of 2 mg of estradiol valerate each day. For 12 days every month, individuals with an intact uterus were given 200 mg of cyclic oral micronized progesterone daily to avoid endometrial hyperplasia. The study's main finding was the incidence of follicular development, which is shown by transvaginal ultrasound. **Results:** The study's participants ranged in age from 18 to 40, with a mean age of 28.54 ± 5.93 years. Mean duration of amenorrhea was 7.98 ± 2.31 months. A mean height of 159.78 ± 14.32 cm was recorded. 83.42 ± 9.29 kg was the average weight. Mean BMI was 31.52 ± 4.89 kg/m2. Efficacy of hormone replacement therapy in women with premature was found in 228 (94.61%) patients. **Conclusion:** According to the study's findings, hormone replacement therapy is a very effective treatment for primary ovarian insufficiency.

INTRODUCTION

The disease known as premature ovarian failure (POF), or more accurately, premature ovarian insufficiency (POI), is defined by the loss of normal ovarian function before the age of forty. According to the European Society of Human Reproduction and Embryology (ESHRE) guidelines,[1] it is clinically defined as the presence of oligo/amenorrhea for at least four consecutive months and biochemically defined as elevated serum follicle-stimulating hormone (FSH) levels (>25 IU/L on two occasions at least four weeks apart) in women under 40. An estimated 1% of people worldwide are thought to have POI, with some research indicating considerably greater proportions in low- and middle-income nations.[2] POI has significant effects on long-term morbidity, fertility, psychological health, and physical health despite its comparatively low frequency.

POI has a wide range of etiopathogenesis, including autoimmune, genetic, iatrogenic (such as radiation or chemotherapy), environmental, and idiopathic causes. Between 70 and 90 percent of cases have no known cause.[3] Whatever the cause, follicular dysfunction or depletion leads to an estrogen-deficient condition, which is the shared pathophysiological denominator. This condition causes urogenital atrophy, mood swings, sexual dysfunction, and vasomotor instability, among other hypoestrogenic symptoms. More significantly, untreated POI raises the risk of major long-term health issues like cardiovascular disease, osteoporosis, cognitive decline, and a lower quality of life.[4,5]

For women with POI, hormone replacement therapy (HRT) is the cornerstone of care. HRT for POI aims to restore premenopausal physiological levels of progesterone and estrogen and avoid multi-systemic

degeneration caused by premature estrogen deprivation, in contrast to HRT administered for women in natural menopause, where the goal is frequently restricted to symptom relief.[6] Research indicates that HRT can lower the risk of cardiovascular morbidity, preserve urogenital integrity, avoid bone demineralization, and lessen vasomotor and psychological symptoms.[7,8]

Unless there are contraindications, HRT should be started upon diagnosis and continued until the typical age of natural menopause, which is around 50 years old, according to the International Menopause Society (IMS) and FEBRASGO guidelines. For women with an intact uterus, the recommended regimen consists of oral or transdermal estradiol (1–2 mg daily or 50–100 µg/day patch) in conjunction with cyclic or continuous progestogen (e.g., micronized progesterone 200 mg/day for 12 days per month) to protect the endometrium.[9] Because of its higher cardiovascular and metabolic safety profile, transdermal administration is preferred.

POI's psychological aftereffects are frequently overlooked but have a significant influence. Due to early infertility and hormonal disturbance, young women with POI often experience emotional discomfort, sadness, worry, and feelings of inadequacy. These issues need for a biopsychosocial approach to treatment that incorporates reproductive counseling, mental health services, and hormone replacement therapy. Research has demonstrated that proper hormone therapy not only alleviates physical symptoms but also lowers anxiety and promotes psychological health.[10]

Due to misunderstandings based on out-of-date data, such as the Women's Health Initiative (WHI) trial, which was been out on postmenopausal women over 60, HRT is still underutilized in POI despite strong evidence. Younger POI patients, who stand to profit greatly from physiological hormone replacement when initiated early and properly managed, are not covered by these findings. Furthermore, the risk-benefit ratio in POI clearly supports HRT, especially when utilizing contemporary regimens with bioidentical hormones, according to recent expert opinion.

METHODOLOGY

This descriptive observational study, which had a six-month follow-up period and important adjustments to accommodate the local population, was carried out to assess the role of hormone replacement therapy (HRT) in promoting follicular development in women with premature ovarian insufficiency (POI). All participants gave written, informed consent prior to enrollment, and the institutional review board granted ethical approval before any data was collected.

In Shaheed Benazirabad, Sindh, the study was conducted from January to September 2024 at the Department of Obstetrics and Gynecology, People's University of Medical and Health Sciences for Women. After the first three months of recruitment, each participant had a six-month observational phase. The study used successive non-probability sampling to enroll 148 women in total. Based on the expected percentage of follicular development within six months, which was 33.4% in the Sato et al.[5] study, this sample size was determined. This ratio, a 95% confidence level, 6% absolute precision, and a 10% predicted dropout rate were used to calculate the final sample size, which came out to be 241.

Women between the ages of 18 and 40 who had previously been diagnosed with POI based on the European Society of Human Reproduction and Embryology (ESHRE) criteria—which include oligo/amenorrhea for at least four consecutive months and elevated serum follicle-stimulating hormone (FSH) levels (>25 IU/L) on at least two occasions separated by four weeks—were eligible to participate. Those who had an intact uterus and ovaries and had not had any hormone therapy in the three months before enrollment were eligible to participate. Chromosome abnormalities, known ovarian tumors, autoimmune or systemic diseases, uncontrolled thyroid disorders, recent pelvic surgery, or contraindications to estrogen therapy, such as a history of thromboembolism or hormone-dependent cancer, were among the exclusion criteria.

Every patient who was enrolled had a thorough history and physical examination at baseline. The following demographic data was documented: age, body mass index (BMI), marital status, parity, and length of amenorrhea. Thyroid function tests, serum FSH, luteinizing hormone (LH), estradiol (E2), and anti-Müllerian hormone (AMH) were among the baseline hormonal assays carried out. At enrollment, ovarian volume and antral follicle count (AFC) were assessed using transvaginal ultrasound (TVUS) to verify that spontaneous follicular activity was absent. A systematic strategy was used to start each subject on hormone replacement treatment after enrollment. The entire six-month period involved continual oral administration of 2 mg of estradiol valerate each day. For 12 days every month, individuals with an intact uterus were given 200 mg of cyclic oral micronized progesterone daily to avoid endometrial hyperplasia. Monthly follow-up visits, pill count assessments, and patient diaries were used to guarantee medication compliance. During the study period, no gonadotropins, ovulation induction drugs, or assisted reproductive procedures were used in order to isolate the impact of HRT alone.

The study's main finding was the incidence of follicular development, which is shown by transvaginal ultrasound, which shows at least one developing follicle with a diameter of at least 10 mm. After ruling out active follicles at baseline, TVUS was carried out every four weeks for the duration of the six-month follow-up. Blinded to the patient's hormonal profile, a single skilled sonographer performed all ultrasonographic exams using a high-resolution transvaginal probe (7.5 MHz). Follicle development was noted in terms of quantity, size, and laterality if it happened at any time throughout the follow-up period. Changes in serum estradiol levels and the incidence of spontaneous menstruation or withdrawal bleeding, which were tracked monthly, were secondary outcomes.

IBM SPSS Statistics version 26.0 was utilized for data analysis. All continuous variables were presented as means ± standard deviations, including age, BMI, amenorrhea duration, and baseline and follow-up hormone levels. The frequencies and percentages of categorical variables, like menstruation and the presence or absence of follicular growth, were displayed. The

proportion with a 95% CI was used to report the main outcome, which was follicular development within six months. To investigate relationships between follicular development and baseline variables like age, amenorrhea duration, and serum AMH levels, bivariate analyses were performed. Depending on the data distribution, the independent t-test or Mann-Whitney U test was used for continuous variables, and the chi-square or Fisher's exact test was used for categorical variables. The p-value was deemed statistically significant if it was less than 0.05.

In order to mitigate potential sources of bias, all hormonal and ultrasound evaluations were carried out by qualified staff members utilizing established tools and procedures. Participants were not included in the final analysis if they missed more than one consecutive monthly follow-up. Every visit included monitoring and documentation of side effects and drug adherence, as well as proper management for any negative effects, such as gastrointestinal disturbances, breast tenderness, or breakthrough bleeding.

Because no ovulation-triggering or fertility therapies were offered, the purpose of this study was not to assess ovulation or conception rates. Rather, the only objective was to evaluate the recovery of ovarian function as demonstrated by follicular growth while on hormone replacement therapy. The study's six-month follow-up period was somewhat brief since previous research indicates that more than 30% of patients who respond to HRT do so during this time. Even though more cases of delayed follicular growth might be found with extended observation, the current methodology was thought to be adequate to identify early responders and evaluate short-term ovarian responsiveness to HRT in POI.

RESULTS

The study's participants ranged in age from 18 to 40, with a mean age of 28.54 ± 5.93 years. According to Table 1, the majority of the patients, 123 (51.04%), were between the ages of 18 and 30 years. Distribution of different variables is shown in Table 1. Mean duration of amenorrhea was 7.98 ± 2.31 months. A mean height of 159.78 ± 14.32 cm was recorded. 83.42 ± 9.29 kg was the average weight. Mean BMI was 31.52 ± 4.89 kg/m2. Baseline and follow-up hormone levels were shown in Table 2.

Efficacy of hormone replacement therapy in women with premature was found in 228 (94.61%) patients (Table 3). Stratification of efficacy with respect to confounders is shown in Table 4.

Table 1

Distribution of Different Variables (n=241)

Variable		Frequency	%age
Age (years)	18-30	123	51.04
	31-40	118	48.96
Parity	≤3	108	44.81
	>3	133	55.19
BMI	≤25	114	47.30
	>25	127	52.70
Residence	Rural	102	42.32
	Urban	139	57.68
Socioeconomic status	Lower	86	35.68
	Middle	79	32.78
	High	76	31.54

Table2

Descriptive Statistics

	Mean	SD
Age (years)	28.93	6.53
Duration of amenorrhea (months)	7.98	2.31
Weight (kg)	83.42	9.29
Height (cm)	159.78	14.32
BMI (kg/m^2)	31.52	4.89
Baseline FSH (mU/mL)	59.65	17.43
Baseline LH (mU/mL)	38.24	18.42
Baseline E2 (pg/mL)	17.29	5.87
Baseline PRL (ng/mL)	12.89	6.32
Follow up FSH (mU/mL)	10.79	4.32
Follow up LH (mU/mL)	8.79	5.72
Follow up E2 (pg/mL)	49.76	17.65
Follow up PRL (ng/mL)	17.26	8.32

Table 3

Efficacy of Hormone Replacement Therapy in Women with Premature Ovarian Failure (n=241).

Efficacy	Yes	No
Oligohydramnios	228 (94.61%)	13 (5.39%)

Table 4

Stratification of Efficacy with Respect to Confounders.

		Yes (n=13)	No (n=228)	P-value
Age (years)	18-30	115	08	0.436
	31-40	113	05	
Duration of amenorrhea (months)	≤6	80	07	0.171
	>6	148	06	
Parity	≤3	101	07	0.501
	>3	127	06	
BMI (kg/m^2)	≤25	110	04	0.219
	>25	118	09	
Residence	Rural	97	05	0.772
	Urban	131	08	
Socioeconomic status	Lower	82	04	0.891
	Middle	74	05	
	High	72	04	

DISCUSSION

Because the current standard estrogen/hormone replacement therapy (HRT) regimen is insufficient to address the complex hormonal imbalances associated with POI, it is imperative to investigate androgens as a therapeutic route. Androgens are essential for ovarian function, fertility, and general health, while estrogen replacement therapy is the mainstay of treating POI. It has been demonstrated that androgens, including testosterone, affect ovarian response, which may increase ovarian reserve and improve fertility-related results.[11]

The purpose of this study is to ascertain whether hormone replacement treatment is beneficial for women who have premature ovarian failure. In my research, 228 (94.61%) of the women with premature babies responded well to hormone replacement treatment. Compared to no treatment or placebo, HRT significantly lowers the occurrence of hot flushes (up to 80% reduction), enhances endometrial thickness, and preserves bone mineral density in women with POI, according to a recent

systematic review and meta-analysis.[11] Furthermore, quality-of-life scores appear to have improved, especially in the emotional, sexual, and physical domains, according to data from observational cohorts. These advantages, along with the young population's low absolute risk of thromboembolism or breast cancer, encourage the early and continued use of HRT.

Family planning and fertility preservation are also major issues with POI. Although it is uncommon, spontaneous ovulation is not impossible; between 5 and 10% of women may conceive naturally. According to a 2021 Japanese cohort study by Sato et al., 33.4% of POI patients using long-term HRT demonstrated follicular activity during the first six months of treatment, and 70% of them demonstrated some follicular development over a one-year period.[5] This result supports the usefulness of follicular development as a significant outcome metric by highlighting the possibility of intermittent ovarian reactivity even under short-term HRT. Even while there is still little chance of a natural conception, this sporadic ovarian activity calls for close observation and customized fertility therapy. The most practical method of getting pregnant is still, for the most part, assisted reproductive technologies that use donor oocytes.

The mainstay of treatment for menopausal symptoms, such as vasomotor instability, sexual dysfunction, mood, fatigue, and skin problems, is hormone replacement therapy (HRT). It also helps avoid long-term morbidity and early mortality associated with persistent estrogen shortage.[12] Young women with POI should not be subjected to the findings of the Women's Health Initiative (WHI) study.[13,14]

POI is a pathologic disease in which young women have lower serum E2 levels than their contemporaries, in contrast to women over 50. Hormone therapy is a "replacement" for young women with E2 deficiency, but it is a "extension" of hormones for women who have a normal menopause. Unless there is a special contraindication, like an estrogen-dependent cancer, it is generally considered that ovarian steroid hormone replenishment occurs physiologically until the age of 50, which is the usual age of natural menopause. There is currently very little information on the best way to replenish hormones, and the combined oral contraceptive pill (COC) and hormone replacement are both alternatives. Although there is a dearth of information on the ideal levels of estradiol in POI, normal women typically have a serum estradiol level of about 100 pg/ml during the menstrual cycle.[15] Estradiol replacement administered transdermally and transvaginally at a dose of 100 µg/day results in physiologic blood levels within this range and provide sufficient symptom alleviation. Compared to oral estrogen, the transdermal method has the advantage of avoiding first-pass hepatic metabolism and seems to have no additional risk of thrombosis.[16-18] If the uterus is present and intact, 5–10 mg of medroxyprogesterone acetate should be administered for 12 days of the month to lower the risk of endometrial hyperplasia.[19,20] It's uncertain what kind of progestogen is best, though. The majority of women who follow this regimen will experience monthly withdrawal bleeding, which could have psychological significance for the patient.

In POI, the COC is also frequently utilized as a hormone replacement. They shouldn't be suggested as a first-line hormone replacement, though. They do, in fact, produce sex steroid hormones at supraphysiological levels and are linked to a higher risk of thromboembolic events because of the liver's first-pass impact. Women who continue to have poor libido and fatigue even after optimizing estrogen replacement may want to carefully explore androgen replacement therapy.[20] Among the alternatives for androgen replacement in these women are transdermal testosterone delivery and dehydroepiandrosterone therapy.[21] Crucially, until further data is available, this should be done very carefully and over brief intervals of time. Many HRT alternatives are recommended for inducing puberty when there hasn't been a spontaneous onset of puberty or advancement of breast growth. However, the only treatment that can mimic normal estradiol physiology in adolescence and adulthood and restore natural levels of estradiol in blood is systemic administration of increasing doses of estradiol, preferably by transdermal application.[22,23] Given the 5–10% likelihood of spontaneous pregnancy, contraception should be made available to patients who do not wish to become pregnant.

Long-term comorbidities such cardiovascular disease, metabolic syndrome, osteoporosis, dementia, cognitive impairment, Parkinsonism, decreased sexual function, and psychological well-being are more likely to occur in women with untreated POI. Compared to people who experience menopause after the age of fifty, untreated POI can cause a specific rise in mortality rate because of the effects of the extended estrogen deprivation.[24] Cardiovascular illness is the primary cause of women with POI having shorter life expectancies. One of the first studies to demonstrate that postmenopausal women had a greater incidence of cardiovascular disease than age-matched premenopausal women was the Framingham study.[25] Numerous studies have now shown that women who approach menopause before the ages of 40 to 45 have greater incidences of coronary artery disease, heart failure, and mortality. It has also been shown that estrogen supplementation reverses this impairment.[26] Women with early ovarian insufficiency had lower bone mineral density than control women. It seems that between 8 and 14 percent of POI have osteoporosis.[27]

Numerous studies have demonstrated that the prevalence, severity, and duration of estrogen insufficiency are linked to a significantly greater overall fracture risk, which is correlated with the reduced bone mineral density (BMD) observed in women with POI. Research on fracture risk in early menopause as opposed to natural menopause has shown that women with POI or early menopause who get HRT have lower fracture rates.[28,29] There is an elevated risk of cognitive impairment, according to preliminary research.[29] According to certain research, estrogen may have neuroprotective properties. According to the Mayo Clinic Cohort Study of Oophorectomy and Aging, women who had either a unilateral or bilateral oophorectomy prior to the onset of menopause were more likely than controls to experience cognitive impairment or dementia and Parkinsonism, and this risk rose as the age at oophorectomy decreased. When taken until at least 50

years of age, they also showed a protective role for estrogen replacement in women who had bilateral oophorectomy.[30] Similar results were observed in a Danish cohort study, which showed that women who had oophorectomy before the age of 50 had a higher risk of dementia and that the risk increased with earlier age at oophorectomy.[31]

CONCLUSION

According to the study's findings, hormone replacement therapy is a very effective treatment for primary ovarian insufficiency. Therefore, in order to lower morbidity, we advise that women with primary ovarian insufficiency receive hormone replacement therapy as their main course of treatment.

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