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The Invisible Epidemic: A Population-Based Cohort Study on the Rising Burden of Premature Ovarian Insufficiency in Pakistani Women and the Unmet Need for a Multidimensional Care Framework

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ABSTRACT

Premature Ovarian Insufficiency (POI) is a profound clinical syndrome with significant implications for fertility, metabolic, cardiovascular, and psychosocial health. While global data exists, population-specific epidemiology, etiological patterns, and comprehensive care models in low-resource, high-consanguinity settings like Pakistan remain critically underexplored. To determine the population-based prevalence, characterize the etiological and clinical profile, and evaluate the systemic gaps in the management of POI among women of reproductive age in Lahore, Pakistan. A prospective, cross-sectional cohort study was conducted from 1st January 2024 to 30th November 2025. Women aged 18-40 years presenting with ≥4 months of amenorrhea and two elevated serum Follicle-Stimulating Hormone (FSH) levels (>25 IU/L) measured ≥4 weeks apart were recruited from the outpatient clinics of Fatima Memorial Hospital and two affiliated community health centers. Participants underwent a standardized protocol including detailed history, physical examination, pelvic ultrasonography, karyotyping, FMRI premutation analysis, and screening for associated autoimmunity. Validated questionnaires (HADS, MENQOL) assessed psychological and quality-of-life impact. Among 15,342 screened women, 247 met the diagnostic criteria for POI, yielding a prevalence of 1.61% in our study population, significantly higher than the oft-cited global average of 1%. Consanguinity was reported in 38% of cases. A definitive etiological classification was possible in 52%: genetic causes (22%, predominantly FMRI premutation and Turner syndrome mosaicism), iatrogenic (18%, mainly post-oncological care), and autoimmune (12%). A striking 48% were classified as idiopathic. Over 85% of women presented with profound distress (HADS score ≥11) and significantly impaired quality of life. Less than 10% had previously been counseled on bone or cardiovascular health. This study reveals a potentially higher burden of POI in our population, with a substantial idiopathic fraction and a strong association with consanguinity, pointing to a likely polygenic and oligogenic inheritance pattern. The near-universal deficiency in holistic care underscores an urgent need for the development and implementation of a standardized, multidisciplinary national guideline for POI management in Pakistan, integrating reproductive health with long-term metabolic, skeletal, and psychological support.

INTRODUCTION

Premature Ovarian Insufficiency (POI), defined as the cessation of ovarian function before the age of 40 years, represents a complex endocrine disorder with consequences far beyond infertility (ESHRE Guideline, 2023). It is a diagnosis that carries a seismic psychosocial impact and predisposes women to a lifelong increased risk of osteoporosis, cardiovascular disease, neurocognitive decline, and all-cause mortality (Cartwright *et al.,* 2024). The global narrative on POI has largely been shaped by data from Western populations, citing a prevalence of approximately 1% (Webber *et al.,* 2023).

Pakistan, with its unique socio-cultural and genetic landscape—including a high prevalence of consanguineous marriages (over 60% in some communities)—presents a distinct epidemiological canvas (Shah & Yousafzai, 2024). Furthermore, healthcare priorities in low- and middle-income countries often sideline chronic, non-communicable gynecological endocrinopathies, leading to delayed diagnosis, fragmented care, and a paucity of region-specific data (Khan & Abbas, 2023). The idiopathic label, often a default in clinical practice, may cloak a multitude of yet-unidentified genetic and environmental factors prevalent in specific populations.

This study, therefore, was conceived to move beyond the clinic walls and establish the first population-anchored data on POI from Pakistan. We aimed not only to quantify its prevalence and etiological spectrum but also to audit the prevailing standards of care against international guidelines, thereby identifying critical gaps and laying the groundwork for a contextualized, multidimensional management framework.

LITERATURE REVIEW

Globally, Premature Ovarian Insufficiency (POI) is recognized as a significant endocrinopathy affecting approximately 1% of women under 40, with profound implications for reproductive, metabolic, and psychological health (Webber *et al.,* 2023). The etiological landscape is heterogeneous, encompassing genetic, autoimmune, iatrogenic, and environmental factors, yet a substantial proportion of cases remain idiopathic

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even in well-resourced settings with comprehensive diagnostic protocols (ESHRE Guideline Group on POI, 2023). Genetic causes, particularly FMRI premutations and chromosomal anomalies such as Turner syndrome, are well-documented, with their prevalence showing population-specific variability linked to founder effects and consanguinity patterns (Iqbal *et al.,* 2024).

In low- and middle-income countries (LMICs), the epidemiology of POI remains poorly characterized. Health systems in these regions often prioritize acute and infectious conditions, leaving chronic endocrine disorders like POI underdiagnosed and undertreated (Khan & Abbas, 2023). Studies from South Asia, though limited, suggest a potentially higher prevalence of POI and related ovarian dysfunction, possibly due to a combination of genetic susceptibility, environmental exposures, and high rates of consanguinity (Palli *et al.,* 2024). Consanguineous marriages, prevalent in Pakistan, are a known risk factor for autosomal recessive disorders and may contribute to a unique polygenic or oligogenic architecture of POI in this population (Rashid & Farooq, 2025; Palli & Kumar, 2023).

The management of POI extends far beyond fertility concerns, necessitating a lifelong, multidisciplinary approach to mitigate risks of osteoporosis, cardiovascular disease, and psychological morbidity (Nelson *et al.,* 2024; Cartwright *et al.,* 2024). However, in resource-constrained settings, holistic care frameworks are often absent. The focus remains predominantly on acute symptom relief, with significant gaps in long-term hormonal therapy, bone health monitoring, cardiovascular risk assessment, and psychosocial support (Palli *et al.,* 2024). This care chasm results in poorer health outcomes and diminished quality of life for affected women.

This review underscores the critical need for population-specific data to inform context-appropriate care models. The current study aims to address this gap by providing the first population-based epidemiological and clinical profile of POI in Pakistan, thereby laying the evidence base for a structured, multidimensional care framework tailored to local needs and constraints.

MATERIALS AND METHODS

Study Design & Setting

A hospital and community-based, prospective cross-sectional cohort study was conducted from 1st January 2024 to 30th November 2025. Ethical approval was obtained from the Institutional Review Board of Fatima Memorial Hospital (Approval Number: FMH-23/01/2023-IRB=1171; Date of Approval: September 3rd, 2024). Written informed consent was obtained from all participants.

Participants

Women aged 18-40 years, residing in Lahore for ≥5 years, who presented with at least 4 months of amenorrhea and had two serum FSH levels >25 IU/L, measured at least 4 weeks apart, were included. Exclusion criteria included pregnancy, history of bilateral oophorectomy, active chemotherapy, or known profound hypothyroidism/ prolactinemia not on treatment.

Study Protocol & Data Collection:

Phase 1 - Screening & Diagnosis: Eligible women were identified from gynecology, endocrinology, and medical outpatient departments.

Phase 2 - Etiological Workup: A standardized proforma captured socio-demographics, medical, surgical, and family history (with a three-generation pedigree). Consanguinity was specifically recorded. Investigations included:

Hormonal Assay

FSH, Luteinizing Hormone (LH), Estradiol (E2), Anti-Müllerian hPelvic Transvaginal Ultrasound: For antral follicle count (AFC) and ovarian volume.

Karyotyping (G-banding) on peripheral blood lymphocytes.

FMRI gene CGG repeat expansion analysis (PCR and Southern Blot).

Autoimmune Screen

Anti-adrenal antibodies, Anti-21-hydroxylase antibodies, Anti-thyroid peroxidase (TPO) antibodies.

Phase 3 - Impact Assessment: Participants completed the Hospital Anxiety and Depression Scale (HADS) and the Menopause-Specific Quality of Life (MENQOL) questionnaire, culturally validated in Urdu.

Statistical Analysis

Data were analyzed using SPSS v.28.0. Descriptive statistics were calculated. Chi-square and t-tests were used for comparisons. A p-value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Prevalence & Demographics

Out of 15,342 women screened, 247 were diagnosed with POI (prevalence: 1.61%; 95% CI: 1.41%-1.83%). The mean age at diagnosis was 32.4 ± 5.1 years, and the mean age at amenorrhea onset was 30.1 ± 5.8 years. A history of consanguineous marriage (first or second cousin) was present in 94 women (38.1%).

Etiological Distribution (n=247)

Genetic (n=55, 22.3%): FMRI premutation (55-200 CGG repeats) was the most common identifiable cause (n=28, 11.3%). Turner syndrome mosaicism (45,X/46,XX) was found in 15 (6.1%) women. Other chromosomal abnormalities included a balanced translocation in 2 women.

Iatrogenic (n=45, 18.2%): All were related to chemotherapy/radiotherapy for hematological or breast malignancies.

Autoimmune (n=29, 11.7%): Isolated ovarian autoimmunity (positive anti-ovarian antibodies with

normal adrenal screen) was found in 18, while 11 had evidence of associated autoimmunity (Addison's or Hashimoto's thyroiditis).

Idiopathic (n=118, 47.8%): No identifiable cause despite comprehensive workup.

Clinical & Psychometric Profile

Vasomotor symptoms were reported by 92% of participants. Pelvic ultrasound revealed a mean AFC of 1.2 ± 1.1 and a mean AMH level of 0.15 ± 0.08 ng/mL. Based on HADS, 87% (n=215) scored in the borderline or clinical range for anxiety/depression. MENQOL scores indicated severe impairment in the psychosocial and physical domains.

Care Gap Analysis

Only 23 women (9.3%) were on any form of Hormone Therapy (HT) at presentation. A prior Dual-energy X-ray Absorptiometry (DEXA) scan had been performed for only 8 (3.2%). Formal counseling regarding cardiovascular risk or fertility preservation options (where applicable) had been provided to less than 5%.

Discussion

Our finding of a 1.61% prevalence of POI suggests that the condition may be more common in our population than the global average. This elevated prevalence, coupled with the high rate of consanguinity (38.1% vs. a national average estimate of ~60% in marriages), provides compelling, novel evidence for a significant genetic component in the Pakistani population, likely involving recessive or oligogenic variants yet to be discovered (Rashid & Farooq, 2025). The high idiopathic fraction (47.8%) is a clarion call for advanced genomic research, including whole-exome sequencing, in this cohort.

The predominance of FMRI premutation as the leading identifiable genetic cause aligns with global trends but underscores the critical need for universal pre-diagnostic genetic counseling and testing, not only for the patient but for her male relatives at risk of Fragile X-associated Tremor/Ataxia Syndrome (FXTAS) and future generations (Iqbal *et al.,* 2024).

The most alarming finding is the near-total absence of comprehensive management. The low rates of HT use contradict the robust international evidence supporting its benefits for symptom control, bone density preservation, and likely cardiovascular protection until the average age of natural menopause (Nelson *et al.,* 2024). This "therapeutic inertia" stems from a lack of physician education, cultural misconceptions about hormones, and a fragmented healthcare system where long-term follow-up is not prioritized.

Proposed Multidimensional Care Framework for Pakistan:

We propose the "PAK-POI" model:

P: Protocolized Diagnosis & Etiological Workup (Mandatory FSH, AMH, Ultrasound, Karyotype, FMRI).

A: Active Counseling & Shared Decision-Making (Fertility options [donor oocyte, adoption], psychological first aid, genetic counseling).

K: Keystone Hormone Therapy (Standardized HT regimens with clear benefits/risks communication, aiming for physiological hormone levels).

POI: Preventive, Ongoing, Integrated Care (Annual DEXA, cardiovascular risk profiling [lipid, BP, glucose], mental health support groups, specialist transition at age 50).

CONCLUSION

This study establishes, for the first time, a potentially higher population-based burden of POI in Pakistani women, heavily influenced by genetic factors linked to consanguinity. It moves the discourse from a purely reproductive issue to a multisystem chronic health condition. The profound gaps in holistic care documented here represent a significant public health oversight. There is an urgent, non-negotiable need to develop, disseminate, and implement national evidence-based guidelines for POI. Empowering physicians with knowledge and providing structured, compassionate, and continuous care can transform the lives of these women, mitigating long-term health risks and restoring a sense of agency over their health.

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