PREMATURE OVARIAN INSUFFICIENCY IN YOUNG WOMEN: A COMPREHENSIVE CASE SERIES HIGHLIGHTING DIVERSE ETIOLOGIES AND INTEGRATED DIAGNOSTIC APPROACHES

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Abstract. Background: *Premature Ovarian Insufficiency (POI) is a complex endocrinopathy characterized by loss of ovarian function before 40 years of age, manifesting as amenorrhea, elevated gonadotropins, hypoestrogenism, and infertility. Etiologies vary widely, including idiopathic, autoimmune, genetic, and iatrogenic causes. Early diagnosis and tailored management are critical to mitigating long-term sequelae.* ***Case series:*** *We present four cases of POI in women aged 29-35 years with varying etiologies: idiopathic, autoimmune thyroiditis-associated, chemotherapy-induced, and Fragile X premutation-related. Comprehensive hormone profiles consistently demonstrated elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH), suppressed estradiol, and reduced Anti-Müllerian Hormone (AMH) levels. Ancillary investigations – genetic testing, autoimmune markers, and pelvic ultrasonography – were instrumental in etiologic classification. Management included individualized hormone replacement therapy, autoimmune disease control, and genetic counseling alongside fertility preservation discussions.* ***Discussion and comparison:*** *Our cases align with recent literature highlighting a shifting etiological spectrum toward identifiable causes with improved diagnostics. Comparative analysis with major contemporary studies underscores consistent biochemical patterns and evolving diagnostic protocols. Despite advances, fertility outcomes remain suboptimal, reinforcing the need for multidisciplinary, patient-centric care.* ***Conclusions:*** *This case series underscores the heterogeneity and diagnostic challenges of POI while illustrating comprehensive multidisciplinary evaluation and personalized management strategies aimed at improving quality of life and reproductive outcomes in affected women.*

Key words: *premature ovarian insufficiency, POI, secondary amenorrhea, follicle-stimulating hormone, anti-müllerian hormone, autoimmune ovarian insufficiency, chemotherapy-induced ovarian failure, Fragile X syndrome, hormone replacement therapy, infertility*

Introduction

Premature Ovarian Insufficiency (POI) is a clinically significant reproductive endocrinopathy defined by the decline or failure of ovarian function before the age of 40, resulting in persistent menstrual irregularities (amenorrhea or oligomenorrhea), sustained elevations in gonadotropins – particularly follicle-stimulating hormone (FSH) – and hypoestrogenism. POI's global prevalence is estimated at 1-4%, with recent studies reporting rates as high as 3.7% worldwide, reflecting both increased recognition and delayed childbearing trends. The incidence in women younger than 30 is exceedingly rare (about 0.1%), but its impact on those affected is profound [1, 2]. The clinical spectrum of POI is highly heterogeneous, encompassing primary amenorrhea from ovarian dysgenesis to secondary amenorrhea due to acquired or congenital factors. Major clinical manifestations include abnormal or absent menstrual cycles, perimenopausal symptoms, such as hot flashes, night sweats, mood changes, insomnia, and genitourinary complaints (vaginal dryness, dyspareunia). POI's implications extend beyond reproductive health – affected women have increased risks of infertility, osteoporosis, cardiovascular disease, cognitive changes, and sexual dysfunction owing to the premature loss of oestradiol and other ovarian hormones [3, 4].

Diagnosis of POI is based on:

- Amenorrhea/oligomenorrhea lasting ≥ 4 months.
- Elevated FSH (> 25 U/L) on two separate occasions at least a month apart.
- Reduced oestradiol levels, alongside exclusion of secondary causes, such as pregnancy, thyroid dysfunction, or hyperprolactinemia.

Pathophysiologically, POI may arise from diminished numbers of primordial follicles, accelerated follicular atresia, arrested follicle maturation, or follicular dysfunction. While established causes include genetic syndromes (notably X chromosome abnormalities, such as Turner syndrome and FMR1 premutations), autoimmune disorders (e.g., thyroiditis), iatrogenic damage (chemotherapy, radiation, surgery), infections, and environmental exposures, most cases (estimated 39-90%) remain idiopathic. Advancing genetic and molecular research has clarified some mechanisms – for example, the Fragile X premutation confers a > 20% risk of POI, and familial clustering underscores the heritable nature of menopausal age. Chromosomal and genetic assessments are first-line tests in suspected cases, aimed at identifying syndromic or inherited forms [5, 6].

Environmental and lifestyle factors – smoking, chemical exposures, stress, and certain personality traits – have also been implicated, although the strength of these associations remains under examination [7].

Management focuses on hormone replacement therapy (HRT) to restore estrogenic effects, reduce osteoporosis and cardiovascular risks, and address psychological and sexual health concerns. Fertility preservation – including oocyte cryopreservation, oocyte donation, and emerging cellular therapies – should be considered and discussed early in the

process [8]. POI represents a diagnostic and therapeutic challenge requiring multidisciplinary care and individualized management strategies. Early recognition and comprehensive evaluation are crucial to improve not only reproductive outcomes, but also long-term health and quality of life for women affected by this lifelong condition.

Case presentations and investigations

This series includes four women aged 29 to 35, presenting with secondary amenorrhea and hypoestrogenic symptoms suggestive of premature ovarian insufficiency, with divergent etiologies confirmed through comprehensive diagnostic evaluation (Table 1).

Case 1: Idiopathic POI (Mrs. R, 35 years old)

Mrs. R presented with 6 months of secondary amenorrhea, preceded by one year of irregular cycles. She experienced vasomotor symptoms, including hot flashes and night sweats, along with vaginal dryness. There was no history of pelvic surgery, chemotherapy, or radiation. Family history revealed a maternal aunt with early menopause. Examination showed pallor and atrophic genital mucosa. Hormonal testing demonstrated elevated FSH (55 mIU/mL) and LH (38 mIU/mL), with low oestradiol (15 pg/mL) and markedly reduced AMH (0.1 ng/mL). Genetic and autoimmune tests were negative. Ultrasound revealed a small uterus and streak-like ovaries with diminished antral follicles. Diagnosis of idiopathic POI was made. Hormone replacement therapy (HRT) and fertility counseling were initiated.

Case 2: Autoimmune POI with thyroiditis (Mrs. A, 29 years old)

Mrs. A reported 8 months of amenorrhea and severe menopausal symptoms. Her medical history was notable for autoimmune hypothyroidism. Clinical examination revealed dry skin and vaginal dryness. Laboratory analysis confirmed elevated FSH (60 mIU/mL), LH (36 mIU/mL), low oestradiol (18 pg/mL), and very low AMH (0.05 ng/mL). Thyroid studies showed elevated TSH (8.0 µIU/mL) and positive anti-thyroid peroxidase antibodies. Pelvic ultrasound demonstrated small ovaries with diminished follicular activity. Diagnosis of autoimmune POI was made. She was managed with optimized thyroid replacement, HRT, and surveillance for other autoimmune conditions.

Case 3: Chemotherapy-induced POI (Mrs. S, 33 years old)

Mrs. S, a survivor of Hodgkin lymphoma treated with chemotherapy 2 years earlier, presented with 5 months of amenorrhea and infertility. Physical findings included features consistent with estrogen deficiency. Laboratory workup disclosed markedly elevated FSH (72 mIU/mL), LH (40 mIU/mL), suppressed oestradiol (12 pg/mL), and nearly undetectable AMH (< 0.01 ng/mL). Imaging confirmed loss of follicular activity with atrophic ovaries. This case was identified as iatrogenic POI secondary to gonadotoxic chemotherapy. She commenced HRT with osteoporosis monitoring and received fertility counseling reflecting her limited reproductive potential.

Case 4: Fragile X-associated POI (Mrs. K, 30 years old)

Mrs. K, with a family history of Fragile X syndrome, exhibited secondary amenorrhea of 4 months with menopausal symptoms. Her hormonal profile revealed elevated FSH (45 mIU/mL), LH (30 mIU/mL), low oestradiol (25 pg/mL), and reduced AMH (0.2 ng/mL). Genetic testing confirmed the FMR1 premutation (100 CGG repeats). Pelvic imaging showed small ovaries and thin endometrium consistent with hypoestrogenism. She was managed with HRT, genetic counseling, and reproductive planning support.

Discussion

Premature Ovarian Insufficiency (POI) is now widely recognized as a multifactorial disorder with profound implications for reproductive and general health. It is defined by amenorrhea or oligomenorrhea, elevated FSH (> 25 IU/L) on two occasions, low oestradiol, and onset before the age of 40. In this case series, we examined four contemporary cases representing idiopathic, autoimmune, chemotherapy-induced, and Fragile X-associated POI, systematically comparing their features to recent major studies for the last decade [9].

Etiologic landscape: changing trends

Contemporary evidence shows idiopathic POI remains the largest group, accounting for approximately 36-39% of new cases, but its frequency is declining as new diagnostic biomarkers, genetic testing, and improved follow-up reveal more autoimmune and iatrogenic (especially chemotherapy/radiation) cases. A major tertiary center study (2025) of 111 POI women found etiological frequencies of genetic (9.9%), autoimmune (18.9%), iatrogenic (34.2%), and idiopathic (36.9%) POI, with statistically significant decrease in idiopathic cases and a corresponding increase in iatrogenic and autoimmune forms over time. Our study reflects this spectrum with one idiopathic, one autoimmune (Hashimoto's thyroiditis), one iatrogenic (ABVD chemotherapy for Hodgkin lymphoma), and one genetic (FMR1 premutation) case [10, 11].

Table 1. Comprehensive comparative investigations in four cases of premature ovarian insufficiency

Investigation Parameter	Case 1: Idiopathic POI (Mrs. R, 35F)	Case 2: Autoimmune POI (Mrs. A, 29F)	Case 3: Chemotherapy-induced POI (Mrs. S, 33F)	Case 4: Fragile X-associated POI (Mrs. K, 30F)	Reference range	Clinical significance	Normal/ Abnormal
DEMOGRAPHIC AND CLINICAL HISTORY							
Age (years)	35	29	33	30	< 40 years for POI	Defines premature onset in all cases	Abnormal
Duration of amenorrhea	6 months (after 1 year irregular cycles)	8 months	5 months	4 months	≥ 4 months diagnostic	All meet POI diagnostic criteria	Abnormal
Menarche age	13 years	12 years	14 years	13 years	10-15 years	Normal pubertal development	Normal
Parity/pregnancy history	No pregnancies	No pregnancies	No pregnancies	No pregnancies	Variable	Primary infertility present	Abnormal
Vasomotor symptoms	Hot flashes, night sweats	Severe hot flashes	Mild hot flashes	Moderate hot flashes	Absent in normal women	Hypoestrogenic symptoms	Abnormal
Vaginal dryness	Present	Present	Mild	Mild	Absent in normal women	Vaginal atrophy from low estrogen	Abnormal
Mood changes	Mild anxiety	Depression	Mild mood changes	Significant mood swings	Absent	Menopausal symptoms	Abnormal
FAMILY HISTORY							
Family history of early menopause	Maternal aunt, menopause age 38	Negative	Negative	Negative	Negative or late menopause	Genetic predisposition in Case 1	Abnormal (Case 1)
Family history of autoimmune disease	Negative	Positive (mother with thyroiditis)	Negative	Negative	Negative	Autoimmune predisposition	Abnormal (Case 2)
Family history of cancer	Negative	Negative	Negative	Negative	Negative	-	Normal
Family history of Fragile X syndrome	Negative	Negative	Negative	Positive (maternal uncle affected)	Negative	Genetic screening indication	Abnormal (Case 4)
PAST MEDICAL HISTORY AND EXPOSURES							
Prior chemotherapy	Negative	Negative	Hodgkin lymphoma treated 2 years prior (ABVD regimen)	Negative	No chemotherapy	Gonadotoxic exposure	Abnormal (Case 3)
Prior pelvic radiation	Negative	Negative	Negative	Negative	No radiation	Ovarian damage risk	Normal
Prior ovarian surgery	Negative	Negative	Negative	Negative	No surgery	Mechanical ovarian loss	Normal
Medications (at presentation)	Multivitamins	Levothyroxine 75 mcg daily	Multivitamins	Multivitamins	Variable	Levothyroxine relevant in Case 2	Case 2 on therapy
HORMONAL INVESTIGATIONS							
Follicle stimulating hormone (FSH)	55 mIU/mL	60 mIU/mL	72 mIU/mL	45 mIU/mL	3-10 mIU/mL (follicular phase)	Diagnostic for ovarian insufficiency (> 25-40)	Abnormal (all cases)
FSH interpretation	Elevated, confirms POI	Elevated, confirms POI	Very elevated, severe ovarian failure	Elevated, confirms POI	≥ 25 mIU/mL diagnostic	All cases meet FSH criterion	Diagnostic
FSH trend	Consistent elevation	Consistent elevation	Consistent elevation on repeat testing	Consistent elevation	Should be consistently elevated	Confirms diagnosis	Abnormal
Luteinizing hormone (LH)	38 mIU/mL	36 mIU/mL	40 mIU/mL	30 mIU/mL	2-12 mIU/mL	Elevated in ovarian insufficiency	Abnormal (all cases)
LH/FSH ratio	0.69	0.60	0.56	0.67	0.3-3.0 (variable)	Inverted ratio in POI	Abnormal pattern
Oestradiol (E2) – early morning fasting	15 pg/mL	18 pg/mL	12 pg/mL	25 pg/mL	30-400 pg/mL (follicular phase)	Hypoestrogenism present in all cases	Abnormal (all cases)
Oestradiol interpretation	Low, consistent with ovarian failure	Low, with autoimmunity	Very low, severe gonadotoxic damage	Low, Fragile X-associated	< 50 pg/mL in POI	All cases significantly suppressed	Diagnostic
Anti-Müllerian hormone (AMH) – baseline	0.1 ng/mL	0.05 ng/mL	< 0.01 ng/mL	0.2 ng/mL	1.5-4.0 ng/mL	Reflects ovarian follicle pool	Abnormal (all cases)
AMH interpretation	Very low, depleted reserve	Severely depleted reserve	Undetectable, near-complete reserve loss	Low-normal for POI, modest reserve	< 0.5 ng/mL indicates POI	Most reliable marker of ovarian reserve	Diagnostic
Prolactin (PRL)	12 ng/mL	15 ng/mL	10 ng/mL	9 ng/mL	5-20 ng/mL	Normal in all cases	Normal
Prolactin significance	Rules out prolactinoma	Rules out hyperprolactinemia	Excludes alternative diagnosis	Normal lactotroph function	Elevated if > 20 ng/mL	Differential diagnosis excluded	Normal
THYROID FUNCTION TESTS							
Thyroid-stimulating hormone (TSH)	2.5 µIU/mL	8.0 µIU/mL	3.0 µIU/mL	2.0 µIU/mL	0.4-4.0 µIU/mL	TSH elevated only in Case 2	Case 2 Abnormal

Table 1. Comprehensive comparative investigations in four cases of premature ovarian insufficiency. Continuation

Free T4 (FT4)	1.1 ng/dL	0.7 ng/dL	1.0 ng/dL	1.0 ng/dL	0.8-1.8 ng/dL	Low normal in Case 2 (on levothyroxine)	Case 2 Low-normal
Anti-thyroid peroxidase antibodies (TPO-Ab)	Negative (< 35 IU/mL)	Positive (320 IU/mL)	Negative (< 35 IU/mL)	Negative (< 35 IU/mL)	< 35 IU/mL (negative)	Autoimmune thyroiditis only in Case 2	Case 2 Abnormal
Anti-thyroglobulin antibodies (Anti-Tg)	Negative (< 40 IU/mL)	Positive (125 IU/mL)	Negative (< 40 IU/mL)	Negative (< 40 IU/mL)	< 40 IU/mL (negative)	Supports autoimmune etiology in Case 2	Case 2 Abnormal
AUTOIMMUNE AND METABOLIC MARKERS							
Anti-21-hydroxylase antibodies (21OH-Ab)	Negative (< 1.0 U/mL)	Negative (< 1.0 U/mL)	Negative (< 1.0 U/mL)	Negative (< 1.0 U/mL)	< 1.0 U/mL (negative)	Screens for adrenal autoimmunity	Normal (all cases)
Anti-adrenal cortex antibodies (ACA)	Negative	Negative	Negative	Negative	Negative	Screens for Addison's disease	Normal (all cases)
Tissue transglutaminase IgA (tTG-IgA)	Negative (< 2 U/mL)	Negative (< 2 U/mL)	Negative (< 2 U/mL)	Negative (< 2 U/mL)	< 2 U/mL (negative)	Screens for celiac disease	Normal (all cases)
Total IgA	180 mg/dL	200 mg/dL	175 mg/dL	185 mg/dL	70-400 mg/dL	Normal in all. Confirms valid celiac screening	Normal
Antinuclear antibody (ANA)	Negative	Negative	Negative	Negative	Negative/homogeneous	Screens for systemic autoimmunity	Normal (all cases)
METABOLIC AND BONE MARKERS							
25-Hydroxyvitamin D	22 ng/mL	18 ng/mL	15 ng/mL	24 ng/mL	30-100 ng/mL	Vitamin D deficiency in all. Osteoporosis risk	Abnormal (all cases)
Calcium (Total)	8.2 mg/dL	8.0 mg/dL	7.9 mg/dL	8.3 mg/dL	8.5-10.2 mg/dL	Low-normal calcium, supplement needed	Low-normal
Phosphorus	3.5 mg/dL	3.2 mg/dL	3.4 mg/dL	3.6 mg/dL	2.5-4.5 mg/dL	Normal phosphate metabolism	Normal
Alkaline phosphatase (ALP)	65 U/L	70 U/L	75 U/L	62 U/L	30-120 U/L	Normal bone turnover	Normal
Magnesium	2.0 mg/dL	1.9 mg/dL	1.8 mg/dL	2.1 mg/dL	1.7-2.2 mg/dL	Normal/low-normal magnesium	Normal/Low
Bone-specific alkaline phosphatase (BSAP)	18 µg/L	22 µg/L	25 µg/L	16 µg/L	11.0-29.0 µg/L	Normal bone formation markers	Normal
Bone turnover marker (C-Telopeptide/CTX)	0.65 ng/mL	0.78 ng/mL	0.82 ng/mL	0.58 ng/mL	0.16-0.97 ng/mL	Elevated bone resorption risk	High-normal/ Abnormal
GENETIC TESTING							
Karyotype analysis	46,XX	46,XX	46,XX	46,XX	46,XX (normal female)	Normal chromosomes in all cases	Normal (all cases)
Fragile X (FMR1) premutation testing	Negative (normal CGG repeats < 55)	Negative	Negative	Positive (100 CGG repeats, premutation range)	< 55 CGG repeats (normal)	Diagnostic for Fragile X-associated POI (Case 4)	Abnormal (Case 4)
FMR1 gene interpretation	No premutation or full mutation	No FMR1 abnormality	No FMR1 abnormality	Confirmed premutation carrier (60-200 repeats)	Normal < 55 repeats	FMR1 premutation is associated with increased POI risk (FXPOI)	Diagnostic for Case 4
X-chromosome inactivation pattern	Random (normal)	Random (normal)	Random (normal)	Random (60:40)	Random 50:50 typical	Skewed pattern may contribute to FMR1 disease expression	Potentially relevant (Case 4)
Whole exome sequencing	Not performed (idiopathic case)	Not performed	Not performed	Not performed	Case-dependent	Potentially useful in refractory cases	Not performed
IMAGING FINDINGS							
Pelvic ultrasound – uterine size	Small uterus (4.2 cm length)	Normal uterus (6.5 cm length)	Normal uterus (6.8 cm length)	Small uterus (5.0 cm length)	6-10 cm length (normal)	Atrophic uterus in hypoestrogenism	Abnormal (Cases 1, 4)
Pelvic ultrasound – endometrial thickness	3 mm (thin)	4 mm	4 mm	3 mm (thin)	8-14 mm (proliferative phase normal)	Thin endometrium from low estrogen	Abnormal (all cases)
Pelvic ultrasound – ovarian size (right)	1.8 cm × 1.0 cm	2.2 cm × 1.5 cm	1.5 cm × 0.9 cm	2.0 cm × 1.2 cm	3.5-5.0 cm × 2.5-3.0 cm	Small ovaries in all cases	Abnormal (all cases)
Pelvic ultrasound – ovarian size (left)	1.7 cm × 1.0 cm	2.1 cm × 1.5 cm	1.4 cm × 0.8 cm	1.9 cm × 1.1 cm	3.5-5.0 cm × 2.5-3.0 cm	Bilateral reduction in ovarian volume	Abnormal (all cases)

Table 1. Comprehensive comparative investigations in four cases of premature ovarian insufficiency. Continuation

Pelvic ultrasound – follicle count (AFC)	2 follicles (< 3 mm)	1 follicle (< 3 mm)	0 follicles	3 follicles (< 3 mm)	10-20 follicles	Low antral follicle count in all	Abnormal (all cases)
Pelvic ultrasound – ovarian vascularity	Reduced blood flow on Doppler	Reduced blood flow	Minimal/absent blood flow	Reduced blood flow	Normal ovarian stromal vascularity	Decreased ovarian perfusion	Abnormal (all cases)
Pelvic ultrasound – ovarian appearance	Bilateral streak-like ovaries	Small, multiple small cysts	Atrophic, fibrotic appearance	Small, scattered small cysts	Normal ovoid shape with follicles	Reflects follicular depletion	Abnormal (all cases)
CLINICAL ASSESSMENT AND DIAGNOSIS							
Number of diagnostic criteria met	3/3 (amenorrhea, elevated FSH twice, low E2)	3/3	3/3	3/3	≥ 2 of 3 criteria required	All cases meet full POI diagnosis	Diagnostic
FSH testing timing	Two measurements 1 month apart: 52, 55 mIU/mL	Two measurements: 58, 60 mIU/mL	Two measurements: 70, 72 mIU/mL	Two measurements: 43, 45 mIU/mL	≥ 2 measurements 1 + month apart	All confirmed with serial FSH	Diagnostic
Probable etiology	Idiopathic POI (no identifiable cause)	Autoimmune POI (positive TPO)	Iatrogenic POI (chemotherapy-related)	Genetic POI (FMR1 premutation)	Variable depending on investigations	Diverse etiologies represented	Classification
Age of POI onset (approximate)	Age 34-35	Age 28-29	Age 32-33 (2 years post-chemo)	Age 29-30	< 40 years	All premature	Diagnostic
ASSOCIATED COMPLICATIONS AND RISK							
Bone mineral density (T-score)	-2.2 (osteoporosis)	-2.0 (osteoporosis)	-2.5 (severe osteoporosis)	-1.8 (osteopenia)	> -1.0 (normal)	Significant fracture risk, especially Case 3	Abnormal (all cases)
Fracture risk assessment 10-year (FRAX)	High risk	High risk	Very high risk	Moderate-high risk	Low risk < 10%	Increased fracture probability	Elevated (all cases)
Cardiovascular risk (Framingham score)	Elevated (due to hypoestrogenism)	Elevated	Elevated	Elevated	< 10% normal risk	Long-term CV risk from estrogen deficiency	Abnormal (all cases)
Psychological symptoms	Mild anxiety, coping well	Depression, anxiety, requiring counseling	Mood lability, post-cancer stress	Significant anxiety, mood swings	Absent	Menopausal and adjustment issues	Abnormal (all cases)
Sexual function	Mild dyspareunia from vaginal atrophy	Significant dyspareunia, reduced libido	Mild dyspareunia	Moderate dyspareunia	Normal	Low estrogen-related dysfunction	Abnormal (all cases)
Infertility status	Primary infertility, wanting children	Primary infertility, desiring pregnancy	Primary infertility, accepting of limited fertility	Primary infertility with fertility wishes	Fertility variable based on ovarian reserve	All have reduced fertility potential	Abnormal (all cases)
MANAGEMENT INITIATED							
Hormone replacement therapy (HRT) regimen	Estradiol 2 mg daily + MPA 5 mg for 12 days/month	Estradiol 1.5 mg daily + micronized progesterone 100 mg for 12 days/month	Estradiol patch 0.1 mg twice weekly + norethindrone 0.5 mg daily	Estradiol 1.5 mg daily + MPA 5 mg for 12 days/month	Individualized based on symptoms	HRT essential for symptom and bone health	Standard care
Calcium supplementation	Calcium citrate 1,000 mg daily	Calcium carbonate 1,200 mg daily	Calcium carbonate 1,500 mg daily	Calcium citrate 1,000 mg daily	1,000-1,200 mg daily (RDA)	Prevents osteoporotic progression	Therapeutic
Vitamin D supplementation	Cholecalciferol 2,000 IU daily	Cholecalciferol 2000 IU daily	Cholecalciferol 4,000 IU daily	Cholecalciferol 2,000 IU daily	1,000-2,000 IU daily (RDA)	Corrects deficiency, bone protection	Therapeutic
Bisphosphonate therapy	Not initiated (consider if T-score < -2.5)	Not initiated (consider if worsens)	Initiated: Alendronate 70 mg weekly	Not initiated (monitor)	Indicated if T-score ≤ -2.5	Case 3 severe osteoporosis indication	Case 3 therapeutic
Lifestyle modifications	Regular weight-bearing exercise, dietary counseling	Regular aerobic and strength training	Gentle exercise, post-cancer rehabilitation	Yoga, regular walking	Universal recommendation	All cases counseled	Preventive
Psychological support	Optional counseling offered	Active counseling, antidepressant considered	Counseling + cancer survivorship support	Counseling offered, considering anti-anxiety	Recommended as needed	Mental health is important	As needed
Fertility counseling	Discussed ART (IVF) options, egg donor referral	Discussed fertility preservation options retroactively	Limited fertility options discussed; adoption counseled	Discussed IVF with donor eggs; genetic counseling	Individualized counseling essential	Referral to reproductive endocrinology	Standard care
Follow-up plan	3-month hormone titration, 12-month bone density recheck	3-month endocrine assessment, monitor autoimmune markers	3-month oncology follow-up, 6-month bone density	3-month genetic counseling follow-up, 12-month imaging	Regular monitoring essential	Multidisciplinary follow-up	Ongoing

Clinical and investigative features

All cases presented with several months of amenorrhea, vasomotor symptoms, and hypoestrogenic manifestations. Each had consistently elevated FSH, low oestradiol, and severely reduced AMH. Imaging confirmed small/streak ovaries and thin endometrium. Associated conditions mirrored recent cohort findings: Hashimoto's thyroiditis in autoimmune POI, chemotherapy/radiation exposure in rising-oncological iatrogenic POI, and FMR1 premutation in genetic POI. Our study adds granular hormonal and ultrasonographic data that aligns closely with findings from large cohort analyses and recent guideline papers, reinforcing the utility of combined clinical imaging and molecular assessment in real-world practice [12, 13].

Long-term sequelae and management

Recent evidence draws attention to the multi-systemic risks: osteoporosis, fracture, cardiovascular disease, cognitive effects, and psychological impact [14, 15]. All our cases showed osteopenia/osteoporosis based on bone densitometry, requiring HRT and bone-specific therapies, consistent with recommendations from ASRM and ESHRE guidelines. Only modest improvements in reproductive outcomes have been recorded in recent cohorts (2025 study: 10 pregnancies and 7 live births among 111 patients), mirroring the reproductive impairment seen in our series. Fertility preservation and ART are recommended, though success rates remain low for women diagnosed at advanced follicular depletion [2, 3, 5].

Comparative analysis with recent studies (Table 2)

Below is a comparative table summarizing our series against major case series and cohort studies from 2015-2025.

Key points of comparative analysis

- The etiological distribution of POI is shifting: idiopathic forms decrease as diagnosis of autoimmune and iatrogenic forms improves.
- Consistent laboratory findings (high FSH, low oestradiol, low AMH) remain universal; ultrasonography confirms ovarian depletion.
- Genetic screening (FMR1/Turner) and autoimmune workup (Hashimoto/Addison's/SLE markers) are increasingly recommended per guidelines.
- Reproductive outcomes and quality of life remain challenging, with only incremental improvements despite advances in ART and HRT strategies.
- Multidisciplinary management – endocrinology, reproductive medicine, psychology, and oncology – is vital for optimizing care.

Conclusion

Our contemporary POI case series aligns with and reinforces trends observed in major studies across the last decade: a slow but real diagnostic shift from idiopathic to autoimmune and iatrogenic causes, advances in genetic and molecular testing, and persistent systemic challenges in symptom control, fertility, and long-term health outcomes. Universal adoption of comprehensive, guideline-driven, and multidisciplinary care is critical to improving both reproductive and general health for women diagnosed with POI.

Table 2

Feature	Present case series (2025, n = 4)	Large contemporary cohort (2025) (n = 111) [2]	Genetic mutational landscape study (2023) (n = 245) [3]	ESHRE/ASRM guidelines and reviews (2024) [5]	Notable findings from previous studies (2015-2025)
Age (years)	29-35	27.8 ± 5.7	15-39	< 40	Patients are consistently young women The mean age is early 30s across studies.
Sample size (n)	4	111	245	NA	Cases range from small series to large cohorts.
Idiopathic etiology (%)	25%	36.9%	31.1%	40-72%	Idiopathic remains the most common, but is declining with better diagnostics.
Autoimmune etiology (%)	25%	18.9%	13.2%	4-30%	Autoimmune cases are increasing. Thyroiditis is a frequent comorbidity.
Iatrogenic etiology (%)	25%	34.2%	20.6%	7.6-34%	Iatrogenic cases are rising due to improved cancer survivorship.
Genetic (e.g., Fragile X) (%)	25%	9.9%	9.3%	6-11%	Remains stable. Genetic screening is increasingly recommended.
Mean FSH (mIU/mL)	58	56.3 ± 19.2	> 40	> 25	Elevated FSH universal. Strict cutoff varies (25-40 IU).
Mean estradiol (pg/mL)	17.5	18.1 ± 7.8	< 30	< 50	Low oestradiol is common to all cases. Clinical hypoestrogenism hallmark.
Mean AMH (ng/mL)	0.087	0.09 ± 0.08	< 0.5	< 0.5	Severely reduced ovarian reserve measured by AMH consistently.
Bone mineral density (T-score)	-2.1	-2.3 ± 0.5	-2.2	< -1.0	Early onset osteopenia/osteoporosis is prevalent.
Pregnancy rate (%)	0	~ 6.3%	4-14%	4-12%	Fertility outcomes remain poor despite advances in ART.
Psychological morbidity	Present (anxiety, mood swings)	High	Underreported	High	Psychological distress is well-documented.
Hormone replacement therapy (HRT)	Prescribed for all	Majority	Majority	Recommended	Standard of care to mitigate hypoestrogenic sequelae.
Genetic testing routine	Done in 1 case (Fragile X)	Increasing frequency	Comprehensive in research	Recommended universally	Genetic testing is increasingly integrated.
Autoimmune testing	Positive in 1 case (thyroid)	Frequently performed	Limited	Recommended for suspected cases	Autoimmune screening growing.
Longitudinal trends	Cross-sectional	Compared contemporary to historic cohort	Genetic mutation spectrum profile	Professional guideline evolution	Shift from idiopathic to identifiable etiologies with better diagnostics.
Limitations	Small sample, single center	Single center retrospective	Genetic finding focus	Expert consensus	Need for larger multi-center longitudinal studies.

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