

Primary ovarian insufficiency: different approaches in three cases and a review of literature

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Summary

Primary ovarian insufficiency (POI) is the condition of intermittent or permanent gonadal insufficiency that occurs in women before the age of 40. We describe three cases of POI referred to the outpatient endocrinology clinic of a university hospital. The three patients met diagnostic criteria for POI and were managed by specific approaches tailored to individualized goals. In the first case, the main concern was fertility and the reproductive prognosis. The second patient was a carrier of a common genetic cause of POI: premutation of the *FMR1* gene. The third case was a patient diagnosed with a POI and established osteoporosis, a common complication of estrogen deprivation. This study reports the treatment and follow-up of these cases, with an emphasis on relevant aspects of individualized management, alongside a brief literature review.

Learning points:

- A diagnosis of POI should be considered in patients presenting with amenorrhea or irregular menses and high serum follicle-stimulating hormone (FSH) levels before age 40 years.
- Patients with POI without an established cause, especially in familial cases, should be tested for *FMR1* mutations.
- Estrogen/progestin replacement therapy is indicated since diagnosis until at least the estimated age of menopause, and is the cornerstone for maintaining the good health of breast and urogenital tract and for primary or secondary osteoporosis prevention in POI.
- Fertility should be managed through an individualized approach based on patient possibilities, such as egg or embryo donation and ovarian cryopreservation; pregnancy can occur spontaneously in a minority of cases.
- Women with POI should be carefully monitored for cardiovascular risk factors.

Background

Primary ovarian insufficiency (POI) is a rare condition, defined as the premature cessation of menstruation before 40 years of age. The incidence is approximately 1:1000 women before age 30, 1:250 at age 35, and 1:100 at age 40 (1). POI may result from depletion of ovarian follicles, accelerated follicular damage, or follicular dysfunction leading to estrogen deprivation. Most

women experience a 5-year delay in diagnosis since symptom onset (2).

The etiology of POI is diverse, although almost 65% of cases are considered idiopathic. Other causes include genetic diseases (Turner's syndrome, fragile X premutation, galactosemia, inhibin B mutations), enzyme defects (aromatase or 17,20-lyase deficiency), and autoimmunity



(lymphocytic oophoritis, polyglandular autoimmune syndrome, Addison's disease, Hashimoto's thyroiditis, or celiac disease); POI may also be iatrogenic, secondary to chemotherapy or radiotherapy exposure (3).

The clinical presentation generally involves menstrual irregularities (oligomenorrhea and amenorrhea). The absence of menarche in patients aged 15 years or older (primary amenorrhea) or an absence of menses for 3 months or more (secondary amenorrhea) should raise clinical suspicion of POI. These disturbances may recur intermittently for months or years until definitive amenorrhea occurs. Laboratory tests show increased follicle-stimulating hormone (FSH) levels and estradiol concentrations below the normal range for age (2, 3).

Early diagnosis of POI and a reasonable understanding of its management are essential to preserve quality of life, prevent osteoporosis, and optimize fertility prognosis in these patients. We describe three women with POI, who presented to an outpatient endocrinology clinic, highlighting the importance of individualized treatment and follow-up and discussing novel and relevant aspects

to the approach of POI, such as infertility, association with the fragile X premutation, and osteoporosis management.

Case presentation

Case 1

A 26-year-old woman presented with a 2-year history of amenorrhea and hot flushes. She had menarche at age 12, regular cycles over the next years, and started oral contraception at age 19. At the age of 24, she discontinued contraception because she was planning to get pregnant but her menstrual cycles did not recover. Her medical history was significant for hypothyroidism treated with levothyroxine. Physical examination showed no cardiovascular, respiratory, or abdominal abnormalities, blood pressure was 110/65 mmHg, and a BMI of 22.5 kg/m². Laboratory findings: FSH, 85 and 77 IU/mL; luteinizing hormone (LH), 37 IU/mL; estradiol, 16 pg/mL. The karyotype was 46,XX. Pelvic ultrasound revealed uterine volume 45 cm³, endometrial thickness 0.3 cm, right ovarian volume

Table 1 Investigation and evaluation of three cases of primary ovarian insufficiency.

Laboratory findings	Case 1	Case 2	Case 3	Reference ranges (follicular phase)
FSH, first measurement (IU/mL)	85	142	56	3.5–12.5
FSH, second measurement (IU/mL)	77	103	51	3.5–12.5
LH (IU/mL)	37	73	41	2.4–12.6
Estradiol (pg/mL)	16	33	4.1	12.5–166.0
Prolactin (ng/mL)			6.0	6.0–29.9
TSH (mIU/mL)	2.3		0.73	0.27–4.2
Anti-TPO (IU/mL)	150		NR	<35.0
β-HCG (mIU/mL)	Negative	Negative	Negative	<5.0 (not pregnant)
Lupus anticoagulant	Nonreagent	Nonreagent	Nonreagent	NR
Antibody antinuclear	Negative	Negative	Negative	NR
Factor LE cell	Nonreagent	Nonreagent	Nonreagent	NR
Pelvic US				
Uterine volume	45 cm ³	161 cm ³	24.8 cm ³	
Endometrial thickness	0.3 cm	0.5 cm	0.3 cm	
Right ovary volume	2.6 cm ³	2.17 cm ³	0.83 cm ³	
Left ovary volume	3.5 cm ³	1.28 cm ³	0.91 cm ³	
DXA	Z score –1.0 (lumbar spine and total femur)	Z score –2.2 (lumbar spine) and –1.8 (neck of femur)	T score –3.3 (0.779 g/cm ²) in lumbar spine; –2.28 (0.733 g/cm ²) in total femur; –2.5 (0.691 g/cm ²) in neck of femur	
Karyotype	46,XX	46,XX – positive for an expanded allele of <i>FMR1</i> for fragile X syndrome (premutation)	46,XX	

Anti-TPO, anti-thyroid peroxidase antibodies; DXA, dual-energy X-ray absorptiometry; FSH, follicle-stimulating hormone; HCG, human chorionic gonadotrophin; IU, international units; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; US, ultrasound.



2.6 cm³, and left ovarian volume 3.5 cm³. No follicles were visualized.

Case 2

A 38-year-old woman presented with intermittent irregular menses or amenorrhea since age 25, as well as hot flushes, dyspareunia, tachycardia, and emotional lability. Menarche had occurred at age 12, followed by regular menstrual cycles during the following years. She started oral contraception at age 24, after giving birth, but menstrual cycles did not return when she discontinued oral contraception. Physical examination was normal and there were no comorbidities. Laboratory findings: FSH, 142 and 103 IU/mL; LH, 53 and 92 IU/mL; estradiol, 33 pg/mL. Pelvic ultrasound revealed uterine volume 161 cm³; endometrial thickness 0.5 cm; right ovarian volume 2.17 cm³; and left ovarian volume 1.28 cm³. Dual-energy X-ray absorptiometry (DXA) showed a Z score of -2.2 in L1-L4 lumbar spine and -1.8 in the neck of femur. Regarding family history, the patient's mother had had her last menstrual period at age 36 and her child had received a diagnosis of fragile X syndrome at age 6 years. The patient had then undergone genetic evaluation, which was positive for an expanded allele (premutation) in the *FMR1* gene.

Case 3

A 56-year-old woman had been diagnosed with POI at age 37. At the time of diagnosis, she presented with a 1-year history of secondary amenorrhea and hot flushes. She had menarche at age 13 and regular cycles until age 35, with a pregnancy at age 20. Her medical history was remarkable for dyslipidemia and osteoporosis, treated with simvastatin and alendronate, respectively. She was an active smoker (20 cigarettes/day for 34 years) and had one sister with POI. She lived in Southern Brazil (city of Porto Alegre, latitude 30°). She also reported not eating dairy meals. Physical examination showed no cardiovascular, respiratory, or abdominal abnormalities, blood pressure

Table 2 Estrogen treatment for women with primary ovarian insufficiency.

Estrogen formulation	Dose (day)
Oral	
Conjugated equine estrogens	0.9–1.25 mg
Micronized estrogen	2–3 mg
Nonoral	
Transdermal estradiol (patch)	50–100 µg twice/week
Estradiol gel	1.5 mg/day

was 130/90 mmHg, and a BMI of 23.8 kg/m². Laboratory findings: FSH, 56 and 51 IU/mL; LH, 41 and 31 IU/mL; estradiol, 4.1 and 3.8 pg/mL; and vitamin D levels (20.5 ng/mL). Pelvic ultrasound revealed a uterine volume of 24.8 cm³, endometrial thickness 0.3 cm, right ovarian volume 0.83 cm³, and left ovarian volume 0.91 cm³, with no visible follicles. Her last DXA scan (performed 1 year earlier) showed T scores of -3.3 (0.779 g/cm²) in the lumbar spine (L1-L4), -2.28 (0.733 g/cm²) in the total femur, and -2.5 (0.691 g/cm²) in the neck of femur. The patient had received estrogen and progesterone replacement therapy until age 47. At that time, because all attempts to persuade the patient to quit smoking were unsuccessful and blood pressure levels were constantly slightly increased, indicating a risk for thromboembolic disease, hormone treatment was discontinued.

Investigation

Table 1 presents the results of the workup performed in each of the three cases.

Treatment

Case 1, infertility

Up to 5–10% of patients with POI may be fertile and achieve spontaneous pregnancy. For patients who remain infertile, available alternatives include egg donation, embryo donation, and ovarian cryopreservation (particularly useful before radiotherapy or chemotherapy). The patient described in case 1 was referred for *in vitro* fertilization (IVF) with egg donation.

Case 2, menopausal symptoms

POI is associated with menopausal symptoms in women at reproductive age and increased risk of cardiovascular

Table 3 Progesterone/progestin regimens used in women with primary ovarian insufficiency.

Progesterone/progestin formulation	Dose (day)
Micronized progesterone	10–12 day-cycle: 200 mg Continuous: 100 mg
Medroxyprogesterone acetate	10–12 day-cycle: 10 mg Continuous: 2.5 mg
Norethisterone	10–12 day-cycle: 0.7 mg Continuous: 0.35 mg
Dydrogesterone	10–12 day-cycle: 10 mg Continuous: 2.5 mg



disease and fractures, mainly due to estrogen deficiency. Therefore, estrogen replacement therapy is recommended once the diagnosis is confirmed. Estrogens can be administered via oral or nonoral routes (transdermal patch or gel). The oral route is most commonly prescribed, probably because of the low cost of oral formulations. Nonoral routes have the advantage of bypassing first-pass hepatic metabolism. The estrogen dose should be sufficient to achieve estradiol levels that are similar to those found in the follicular phase of age-matched healthy women, which corresponds to a higher dose than that used in symptomatic menopausal women (3, 4). Table 2 presents estradiol-equivalent doses for treatment of women with POI. Progesterone/progestins are added to estradiol treatment of POI patients who still have their uterus, to prevent endometrial hyperplasia and cancer. The progesterone dose depends on the route of administration and choice of hormonal regimen (cyclic or continuous) (3, 4). Table 3 presents progesterone/progestin prescription options.

The patient described in case 2, with amenorrhea, vasomotor symptoms, and genitourinary syndrome, had no contraindications for receiving oral hormone therapy and was treated with conjugated equine estrogens (0.9 mg/day) plus medroxyprogesterone acetate (10 mg/day in 12-day cycles), a treatment that is freely available through the Brazilian Unified Health Service. Although conjugated equine estrogens was acceptable to this specific patient, non-oral 17 β -estradiol should be the first-line choice for women with POI with metabolic comorbidities and/or at risk for cardiovascular and thromboembolic disease (3, 5).

Case 3, osteoporosis

Another major issue regarding management of women with POI is bone health. Estrogen deficiency leads to bone fragility and increases osteoporosis risk. The patient described in case 3 had osteoporosis and, in addition to estrogen/progestin treatment, was prescribed optimal doses of vitamin D (1000 IU/day) and a daily calcium intake of 1.2 g. After cessation of hormone therapy at age 47, she started alendronate treatment (70 mg/week).

Discussion

A diagnosis of POI has a strong impact on the physical and emotional health of affected women. Patients may develop depression, anxiety, and other disorders largely related to the uncertain reproductive prognosis. Therefore, suspected cases must be identified and management

should be individualized according to specific needs of each woman. In the present report, we described three cases of POI, each focusing on a different treatment approach.

Fertility is a point of controversy in POI management, and additional evidence is required to support recommendations. Patients with POI can achieve spontaneous pregnancy in 5–10% of cases (6). Although menstrual cycles cease in these patients, some have ovaries containing residual small follicles. In a French cohort published in 2011 (6), 358 POI patients were followed from 1997 to 2010, and 4.4% had spontaneous pregnancies. Predictive factors for resumption of ovarian function in this cohort were family history of POI, secondary amenorrhea, visible follicles on ultrasound, and inhibin B and estradiol levels. Ovulation induction with clomiphene or gonadotropins is not effective in patients with POI. Women to whom fertility is a priority should be counseled to seek assisted conception through IVF with egg or embryo donors. An observational study showed a cumulative delivery rate of 86.1% after four cycles of oocyte donation in women with ovarian failure due to POI, oophorectomy, menopause, or chemotherapy (7). However, concerns exist regarding ethical and legal issues according to different countries that may limit the practicality of this procedure. In most of occidental countries, only anonymous egg donation is permitted. Another alternative currently at the research stage involves cryopreservation techniques for ovarian tissue in women at risk of POI (e.g. girls who need to undergo cancer chemotherapy). A group from Japan studied the efficacy of ovarian tissue cryopreservation followed by *in vitro* activation of dormant follicles and ovarian autotransplantation for infertility treatment in patients with POI. Of the 37 patients with POI included in the study, 20 had residual follicles, 9 were able to grow follicles, and 3 had successful pregnancies after cryopreservation and IVF. A shorter time elapsed from POI diagnosis to treatment and increased anti-Müllerian hormone levels were predictive of fertility success (8).

Etiologic diagnosis of POI remains challenging; almost 65% of cases are deemed idiopathic (3) and there is an association with autoimmune diseases (3, 4). Thyroid autoimmunity is the most prevalent, as shown in case 1. In a recent review (9), *FMR1* premutation was one of the commonest genetic causes related to POI. This premutation is believed to be present in approximately 11% of familial POI cases and 3% of sporadic cases (10). In light of this evidence, it is recommended that women with POI of unknown etiology, and particularly those



with a family history of POI, should undergo screening for *FMRI* premutations. The patient in case 2 had a child with fragile X syndrome and a mother who had also developed POI. Genetic evaluation confirmed that she was a carrier of the *FMRI* premutation, which is important information for familial planning and genetic advice.

Another concern highlighted in this review is bone health. The patient described in case 3 had osteoporosis, which is a common finding in estrogen deficiency, as her diagnosis of POI. Young women with POI frequently exhibit low bone mineral density (11). The literature also discusses whether testosterone deprivation in POI is associated with impaired bone mass. A clinical trial assessed the effect of testosterone treatment (150 µg/day via transdermal patch) in addition to estrogen (100 µg/day) and progestin therapy (medroxyprogesterone 10 mg/day for 12 days per month) on bone density in patients with POI (12). The trial showed a benefit of estrogen and progestin replacement in improving bone mass, but no significant effect of add-on testosterone. Regarding vitamin D and calcium supplementation, no specific recommendation indicates such treatment in this group of patients, and management of POI should include the usual recommendations for menopausal women: intake of 1200 mg of elemental calcium per day and maintenance of adequate vitamin D status (serum 25-hydroxyvitamin D level \geq 30 ng/mL). Adults with inadequate sun exposure may take 800–1000 IU of vitamin D3 per day.

In conclusion, diagnosis and management of POI still pose a challenge in clinical practice. Some mechanisms of this disease remain unexplained, and it is underdiagnosed in the majority of cases. During investigation, karyotype analysis with tests for *FMRI* premutation can be useful to elucidate the etiology and is important for genetic counseling. Evaluation of fertility prognosis and of bone mineral density, which are generally impaired by estrogen deficiency, is essential aspects of management.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent has been obtained from patients for publication of data while preserving their identity.

Author contribution statement

A M Moreira and P M Spritzer managed all three patients and drafted and edited the manuscript.

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