Premature ovarian failure

Modern methods preserve and renew fertility

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Premature ovarian failure (POF) is a disorder affecting 1% of women and causing hypergonadotrophic hypogonadism. The diagnosis is based on finding amenorrhea before age 40, and elevated levels of follicle-stimulating hormone (FSH) in the menopausal range. Most cases are idiopathic.

Known causes include iatrogenic ones such as radio- or chemotherapy; genetic chromosomal aberrations, autoimmune ovarian damage; and environmental factors like viral infections and toxins. Ovarian biopsy has no role in making the diagnosis. Management essentially involves hormone replacement therapy (HRT), while the only proven infertility treatment is assisted conception with donated oocytes. Embryo, ovarian tissue and oocyte cryopreservation hold promise in cases where ovarian failure is foreseeable.

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Definition

- POF
  - amenorrhea; FSH > 40 IU/L, estrogen deficiency
  - women under 40 years old
  - not necessarily early menopause
  - 15% of POF patients – intermittent, unpredictable ovarian function

Etiology

Iatrogenic, e.g. cancer therapy

- chemotherapy, radiation; surgery

Spontaneous

- mostly idiopathic
- Genetic
  - 10% of cases
  - in familial POF, 14% have the FMR1 gene responsible for fragile X syndrome
  - Turner's syndrome — 45XO — most are affected
  - other — rare — FSH receptor mutation, GALT enzyme of galactosemia
- Autoimmune
  - 4% of cases with normal karyotype
  - autoimmune lymphocytic oophoritis — may precede adrenal insufficiency (Addison's disease)
  - in decreasing order — thyroid autoimmunity, parietal cell antibodies, insulin-dependent diabetes, myasthenia gravis, systemic lupus erythematosus
  - may exist at subclinical level only
  - pathogenic role of anti-ovarian antibodies is questionable
- Viral infections, toxins
  - anecdotally, mumps oophoritis

Counselling

- prognosis — ovulation more likely if high antral follicle count (AFC)
- baseline evaluation for depression, anxiety, coping skills
  - psychologic support necessary
  - support group, e.g. **http://pofsupport.org**

Workup

- at first visit — evaluate ≥ 3 consecutive menstrual irregularities
- symptoms and signs:
  - secondary amenorrhea
  - menopausal symptoms may present — e.g. hot flashes, sleep disturbance, vaginal dryness

Initial evaluation

- pregnancy test, serum prolactin, FSH, LH, estradiol (E_2), TSH
- elevated FSH — repeat FSH, E_2 to confirm hypergonadotrophic hypogonadism
- normal FSH, high E_2 — repeat both — FSH may be artificially suppressed by E_2
- progestin-withdrawal test – misleading, as 50% will respond due to intermittent ovarian function
- baseline ultrasound of pelvis
  - day 2-5 of cycle
  - AFC < 5
  - thin endometrium < 5 mm

Additional tests

- family history — POF, fragile X syndrome, unexplained mental retardation, dementia, a child with developmental delay, tremor/ataxia syndrome
- if positive — genetic counselling
- spontaneous POF — as 20% develop autoimmune hypothyroidism, TSH, free T_4, serum thyroid peroxidase autoantibodies
- indirect immunofluorescence for adrenal antibodies
- autoimmune lymphocytic oophoritis — risk of adrenal crisis — endocrinologist
- dry eye syndrome — 20% of patients — ophthalmologist

Fertility treatments

- 5–10% spontaneously conceive sometime after diagnosis
- pregnancy loss 20%, similar to normal
- outcome depends on age of onset
- gonadotropin therapy — no significant improvement
- primary amenorrhea — no ovulation detectable
- secondary amenorrhea
  - intermittent ovarian function
  - stop HRT for 3 months every year to see if regular menstruation continues; if yes, check FSH and E_2
  - ovulation-inducing treatment with corticosteroids — questionable
- autoimmune disease — control may induce ovarian function, e.g. thymectomy for myasthenia gravis
- IVF and embryo transfer using donor oocytes
  - high success rate
  - fertility treatment of choice

Management

- replace ovarian hormones with HRT — taper at age 50 to menopausal range
- consider all estrogen preparations, vaginal estrogen, testosterone supplements
- titrate dose to prevent symptoms
- oral contraceptives (OCP)
  - not recommended as HRT
  - if used for contraception, add barrier
- avoid bone loss — calcium 1,200-1,500 mg/d, exercise, daily multivitamin, smoking cessation, moderate alcohol

Preserving fertility

- important for all women and girls undergoing cytotoxic treatments
- GnRH analog co-treatment to inhibit pituitary-gonadal axis during cytotoxic chemotherapy
- freezing ovarian tissue for later use
  - also for mosaic Turner's syndrome, still have follicles in their ovaries
- cryopreserved ovarian tissue
  - autograft – live birth reported, but success rate low
  - in vitro oocyte maturation (IVM)
- oocyte vitrification
  - new hope
  - used for patient at higher risk of POF
  - 85%-90% oocyte survival rate
  - clinical pregnancy rate, 40% per cycle