بسم الله الرحمن الرحیم

Premature Ovarian Insufficiency

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در پایان این جلسه شما قادر خواهید بود:

- POI را تشخیص دهید،
- در زمان مناسب به متخصص زنان ارجاع دهید،
- دربارهٔ مدت درمان و داروهای مورد استفاده به بیمار مشاورهٔ لازم را ارائه کنید.

Management of primary ovarian insufficiency (premature ovarian failure)

Ovarian failure

- Ovarian failure occurs when few or no follicles remain that are capable of producing estradiol in response to pituitary gonadotropin stimulation.
- Follicular depletion may occur during embryonic life with no follicles remaining by infancy or early childhood, after puberty has begun but before menarche, or at some later time before menopause normally would be expected.
- Depending on when the available supply of ovarian follicles is functionally depleted, puberty may not occur, it may begin normally but stop before the first menses, or it may progress normally to and beyond menarche with the development of secondary amenorrhea at some later point in time.
- Regardless of age at onset, hypergonadotropic hypogonadism is the biochemical hallmark of ovarian failure.

Premature Ovarian Failure or Premature Ovarian Insufficiency

- POF is traditionally defined as hypergonadotropic hypogonadism and amenorrhea arising before the age of 40.
- This is a heterogeneous disorder that varies widely in cause and phenotype.
- Whereas the term POF is well-entrenched in the medical literature, an alternative term “premature ovarian insufficiency” or POI—has been proposed and increasingly adopted to more accurately reflect the continuum of decreased ovarian function observed in the affected women.
- while acknowledging that many may exhibit intermittent ovarian function and ovulation and that 5–10% may even conceive and achieve successful live birth.

Important known causes of POI

- numerical and structural chromosomal abnormalities
- fragile X (FMR1) premutations
- autoimmune disorders
- radiation therapy and chemotherapy

INTRODUCTION

- 46,XX primary ovarian insufficiency (POI) is defined as the development of primary hypogonadism before the age of 40 years in women who have a normal karyotype.

Incidence

- The age-specific incidence of spontaneous POI is approximately 1 in 250 by age 35 years and 1 in 100 by age 40 years.

Premature Ovarian Failure

- Many patients with spontaneous POI produce estrogen intermittently and ovulate, a few experience intermittent return of regular menses, and, in 5 to 10 percent of cases, women conceive and have a normal pregnancy.

Karyotype

- In all patients under age 30 with a diagnosis of POI, a karyotype should be obtained to exclude chromosomal translocations, deletions, and mosaicism that might offer an obvious explanation for premature failure of the ovaries.
- A karyotype will identify those missing an entire X chromosome in all (Turner syndrome) or some (Turner mosaic) of the tested cells. Chromosomal analysis will similarly identify those phenotypic phenotypic females having a Y chromosome in whom gonadectomy is indicated due to the significant risk for malignant transformation in occult testicular gonadal tissue elements (20–30%).
- Signs of virilization cannot reliably identify the subset of women at risk because many carrying a Y chromosome exhibit no signs of androgen excess.
- In women over age 30, ovarian failure reasonably can be regarded as premature menopause. Karyotype after age 30 generally is unnecessary because most tumors in patients with a Y chromosome arise before age 20 and virtually all before the age of 30.
- After age 30, women with short stature or a family history of early menopause still merit a karyotype to exclude X chromosome deletions and translocations that may affect other family members.
- Pelvic ultrasonography can exclude the rare tumor not recognized previously.

INFORMING THE PATIENT OF THE DIAGNOSIS

- The most important steps after making the diagnosis of spontaneous primary ovarian insufficiency (POI) are to inform the patient of the diagnosis in a sensitive and caring manner, provide accurate information, and offer referral to appropriate resources for emotional support.

- The most common words women use to describe their emotional state in the immediate hours after receiving the diagnosis are "devastated," "shocked," and "confused".

- Young women with POI are usually unprepared for the diagnosis, and the majority are unhappy with the manner in which they were informed.
- In one study of 100 women with POI, 71 percent were dissatisfied with how they were informed of their diagnosis.
- Specific areas of improvement suggested by women in the study included the need for clinicians to spend more time with the patient and provide more information about this condition.
- The diagnosis of POI brings with it the potential for development of related depression and anxiety disorders.

IMPORTANCE OF ESTROGEN THERAPY

- Unless there is an absolute contraindication to taking estrogen therapy, all women with primary ovarian insufficiency (POI) should receive estrogen therapy to reduce the risk of osteoporosis and cardiovascular disease.
- estrogen therapy is important to maintain sexual health and quality of life and to treat genitourinary syndrome of menopause.

Suggested estrogen regimens

- Estradiol (17-beta-estradiol; E2) and micronized progesterone are bioidentical hormones, eg, they have the same molecular structure as the estradiol and progesterone produced by the ovary.

- Medroxyprogestrone acetate.

- strogen treatment in women with POI can take several forms.
- An increasing number of estrogen formulations are available for oral, transdermal (patch, gel, spray), and vaginal (creams, pessaries, tablets, rings) use.
- Physiologic levels of estrogen and symptom relief can be achieved in the majority using oral (e.g., micronized estradiol 1– 2 mg daily or conjugated equine estrogens 0.625–1.25 mg daily) or transdermal estrogen regimens (0.1 mg/24 hours).

- Attention to concepts of hormonal formulation, dose, and route and hormonal regimen merits attention given that estrogen requirements to achieve symptom benefit in young women with POI may be higher when compared to older menopausal women.

- Because most women with POF have an intact uterus, cyclic or continuous treatment with a progestogen is essential to prevent endometrial hyperplasia and neoplasia that can result from treatment with estrogen alone.

- Cyclic treatment with a progestogen (e.g., micronized progesterone 200 mg daily or MPA 10 mg daily for 12–14 days each month) is preferable for those still hoping to conceive.

Primary amenorrhea

- Girls or young women with primary amenorrhea in whom secondary sex characteristics have not developed should initially be given very low doses of estradiol (at first without a progestin) in an attempt to mimic gradual pubertal maturation.

Secondary amenorrhea

- We initiate full replacement doses of estrogen with oral estradiol (2 mg/day) or transdermal estradiol (100 mcg patch).
- An estradiol vaginal ring (100 mcg daily) is another option.
- This dose is higher than what is used for postmenopausal females and is based upon the average daily production of estradiol by the premenopausal ovary.

- Transdermal or vaginal delivery of estradiol have advantages over oral estradiol, including lower risks of venous thromboembolism and gallbladder disease.

- However, the advantages related to vascular safety are more important in older, postmenopausal females. Therefore, for those with POI who do not like or do not tolerate transdermal or vaginal estradiol, oral estradiol is perfectly acceptable.

monitoring of serum estradiol levels

- Starting with suggested dosing and titrating doses to alleviate symptoms or using a lower dose that is adequate to preserve bone density in patients who experience side effects.

Choice of progestin

- Most women with POI will have an intact uterus and require a progestin to prevent estrogen-induced endometrial hyperplasia and carcinoma.
- First-line progestin is micronized progesterone (MP) 200 mg per day for the first 12 days of the month.

Duration of therapy

- ACOG recommends systemic hormone therapy until age 50 to 51 years to all women with POI (without contraindications) to manage estrogen deficiency symptoms, prevent long-term health.
- Risks associated with POI reduction (osteoporosis, coronary heart disease, stroke), improve quality of life, and maintain sexual function (some women may need vaginal estrogen in addition to systemic estrogen).

COC as alternative option

- A combined estrogen-progestin oral contraceptive pill (COC) containing ethinyl estradiol and a progestin is an alternative option, which has the added advantage of providing contraception.

Options for pregnancy

- In vitro fertilization (IVF) with oocyte donation, embryo donation.
- Adoption.

FERTILITY

- Approximately 75 percent of women with 46,XX spontaneous primary ovarian insufficiency (POI) have potentially functional follicles remaining in the ovary.
- Inappropriate follicle luteinization is the most common pathophysiologic mechanism that prevents ovulation and pregnancy.

oocyte cryopreservation

- Women with known genetic risk for POI before ovarian function declines (fragile X messenger ribonucleoprotein 1 [FMR1] premutations, Turner mosaic, known autoimmune polyglandular syndrome type 2).
- It is less likely to be useful at the time of the POI diagnosis based on the paucity of oocytes left in the ovary.

medical therapies

- Clomiphene citrate and letrozole – An anti-estrogenic agent such as clomiphene citrate and the aromatase inhibitor letrozole are unlikely to be effective in women who are hypoestrogenic.
- Gonadotropin therapy – Exogenous gonadotropin therapy is ineffective
- Glucocorticoid therapy for treatment of suspected autoimmune ovarian failure, carries the risk of iatrogenic Cushing's syndrome and osteonecrosis of the hip requiring joint replacement.

Emotional health

- The diagnosis of primary ovarian insufficiency (POI) is emotionally traumatic for most women because it disrupts their life plans, hopes, and dreams with regard to future pregnancies.
- Women with POI may develop related depression and anxiety disorders.

Role of androgen replacement

- We suggest against the routine use of androgen therapy in women with POI.
- Although women with POI may have some degree of androgen deficiency when compared with young women without ovarian insufficiency, testosterone therapy has not been shown to be beneficial, and it is associated with important side effects.

- In several studies of women with POI, serum ovarian androgen concentrations (androstenedione and/or testosterone) were lower than age-matched women without ovarian insufficiency, but similar to those seen in older postmenopausal women .
- In contrast, levels of dehydroepiandrosterone sulfate (DHEAS), an adrenal androgen, were normal (although they would be expected to be low in women with coexisting primary adrenal insufficiency.
- Potential side effects of androgen replacement include hirsutism and acne and, with oral preparations (eg, dehydroepiandrosterone [DHEA]), dyslipidemia.
- In women with autoimmune ovarian failure and coexisting adrenal insufficiency, adrenal androgen therapy with DHEA may be beneficial.

Contraception

- Women with POI should be informed that estradiol/progesterone replacement therapy regimens do not provide effective contraception.
- since spontaneous ovarian activity may resume, contraception is required for those who are not pursuing pregnancy .
- Women who are concerned about the possibility of spontaneous ovulation and pregnancy can choose hormonal contraception or a barrier method of contraception.

- ACOG suggests combined oral estrogen-progestin contraceptives.

- Other contraceptive options include lower, noncontraceptive doses of estradiol (to treat estrogen deficiency symptoms and provide protection against future disease) combined with a levonorgestrel intrauterine contraceptive device (IUD) or oral norethindrone 0.35 mg/day (a contraceptive dose of progestin).

- Women with POF should be screened for antiadrenal antibodies (most easily demonstrated against the 21-hydroxylase enzyme, CYP21) and for antithyroid antibodies (antithyroid peroxidase and antithyroglobulin antibodies) to help quantify their lifetime risk for respective end-organ damage.

- The presence of antiadrenal antibodies strongly implies autoimmune oophoritis as the cause of POI and identifies women who should be carefully evaluated and should undergo periodic surveillance for early detection of adrenal insufficiency.

- The presence of thyroid autoantibodies does not prove autoimmune ovarian failure but identifies women at risk for developing autoimmune thyroid disorders, and these women should similarly undergo periodic surveillance for early detection of thyroid dysfunction.

Autoimmune endocrinopathies

- Young women with POI are at increased risk for developing other autoimmune endocrinopathies including autoimmune adrenal insufficiency, a potentially fatal disorder .

- If proper screening with adrenal autoantibodies is performed, approximately 3 percent of women with spontaneous POI will be found to have asymptomatic autoimmune adrenal insufficiency.

Women with positive adrenal autoantibodies

- Even if their adrenal function is found to be normal at initial evaluation, women with positive adrenal antibodies should be followed annually by an annual 8 AM serum cortisol test.
- If <15 mcg/l a corticotropin(ACTH) stimulation test is necessary.

Women with negative adrenal autoantibodies

- If adrenal autoantibodies are not present in a woman with POI, a reasonable strategy is to test baseline adrenal function at the time of diagnosis, and if normal, repeat the test only if clinical symptoms develop that suggest adrenal insufficiency (ie, increased skin pigmentation, excessive fatigue, orthostatic hypotension, etc)

Autoimmune hypothyroidism

- Young women with spontaneous POI are at increased risk for developing autoimmune hypothyroidism and should therefore have a yearly serum thyroidstimulating hormone (TSH) measurement.

WOMEN WITH AUTOIMMUNE POI

- The management of women with autoimmune primary ovarian insufficiency (POI) is the same as for anyone with POI.
- Management focuses on:
- Consequences of estrogen deficiency (vasomotor symptoms, vaginal atrophy, osteoporosis, and a possible increased risk of coronary heart disease and stroke if not treated with estrogen)
- Emotional health/psychosocial support
- Contraception and fertility, which is dramatically reduced
- Evaluation for other autoimmune disorders

Radiation Therapy

- The adverse effects of radiation on the ovary depend on the age of the patient, the dose of radiation, and the radiation field.
- In young women, radiation therapy may result only in transient amenorrhea that ends after a period of 6–18 months, probably reflecting the interval required to reestablish the mechanisms that govern the initiation of follicular growth and the size of their follicular reserve.
- However, some will suffer immediate and irreversible ovarian failure, and even those who recover may later exhibit early ovarian aging and an early menopause.
- The ovaries of older women are more sensitive to the effects of radiation. Whereas doses greater than 6 Gy (gray units, 1 Gy = 100 rad) almost uniformly cause ovarian failure in women over age 40, younger women have achieved successful pregnancies after having received far higher doses.

Chemotherapy

- Most chemotherapeutic drugs target actively dividing cells and therefore might not be expected to have significant adverse effects on oocytes; nonetheless, many do.
- In fact, the fixed supply of oocytes is extremely sensitive to cytotoxic drugs. Chemotherapy causes depletion of the primordial follicular pool in a drug- and dose-dependent manner and is a relatively common cause of POI.
- The ovarian toxicity of common chemotherapeutic agents varies significantly. Alkylating agents such as cyclophosphamide, which alters base pairs and causes DNA cross-links and breaks, can affect both resting and dividing cells.
- The risk for ovarian failure after chemotherapy increases with the age of the patient.

Cancer survivors

- Women with POI due to cytotoxic drugs or radiation therapy are often candidates for estradiol therapy.
- The decision to treat with estradiol depends upon the type of cancer.
- As an example, systemic (but not low-dose) vaginal estrogen is contraindicated in women with breast cancer); conversely, estrogen is prescribed for women with Hodgkin lymphoma and ovarian insufficiency to preserve bone health and prevent cardiovascular disease.
- Like women with other causes of POI, the current approach is to continue estradiol until approximately age 50 years, the average age at natural menopause.

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