24 y.o. female with oligomenorrhea

Endorama, 01/10/2012

Olesya Krivospitskaya, MD

History of past illness:

- 24 y.o. AA female who was seen by Ob&Gyn for irregular menses.
- She had menarche at the age of 11, never had regular menstrual cycles (2-3 cycles per year). At the age of 16 she was started on OCP to give her periods. With OCP had cycles every month. Discontinued OCP 1 year later (does not remember the reason).
- Menstrual cycles were again 2-3 cycles per year while off OCP. Cycles lasted 4-5 days on average.
- Has never been sexually active.
- No history of acne or hirsutism, no male pattern balding.
- Her Ob&Gyn did ovarian US, which showed very small follicles seen within both ovaries.

Past medical history:

- No significant past medical history.
- Medications: none.
- Family history: no fertility or menstrual problems in her mother, she does not have any siblings. No history of autoimmune problems, diabetes or thyroid problems.
- Social history: university student, does not smoke, drink or use any illegal drugs.

Review of systems:

- Constitutional: No fevers. No weight loss. No fatigue.
- HEENT: No vision changes. No hoarseness. Neck: No neck swelling or pain.
- Cardiovascular: No chest pain. No palpitations.
- Respiratory: No dyspnea. No orthopnea.
- Gastrointestinal: No diarrhea. No constipation.
- Musculoskeletal: No muscle pain. No LE edema.
- Genitourinary: **+Oligomenorrhea.**
- Skin: No rash. No skin changes. No hair loss.
- Neurologic: No tremor. No headache. No weakness.
- Psychiatric: No depression. No anxiety. Endo: No polyuria. No polydypsia.

Physical exam:

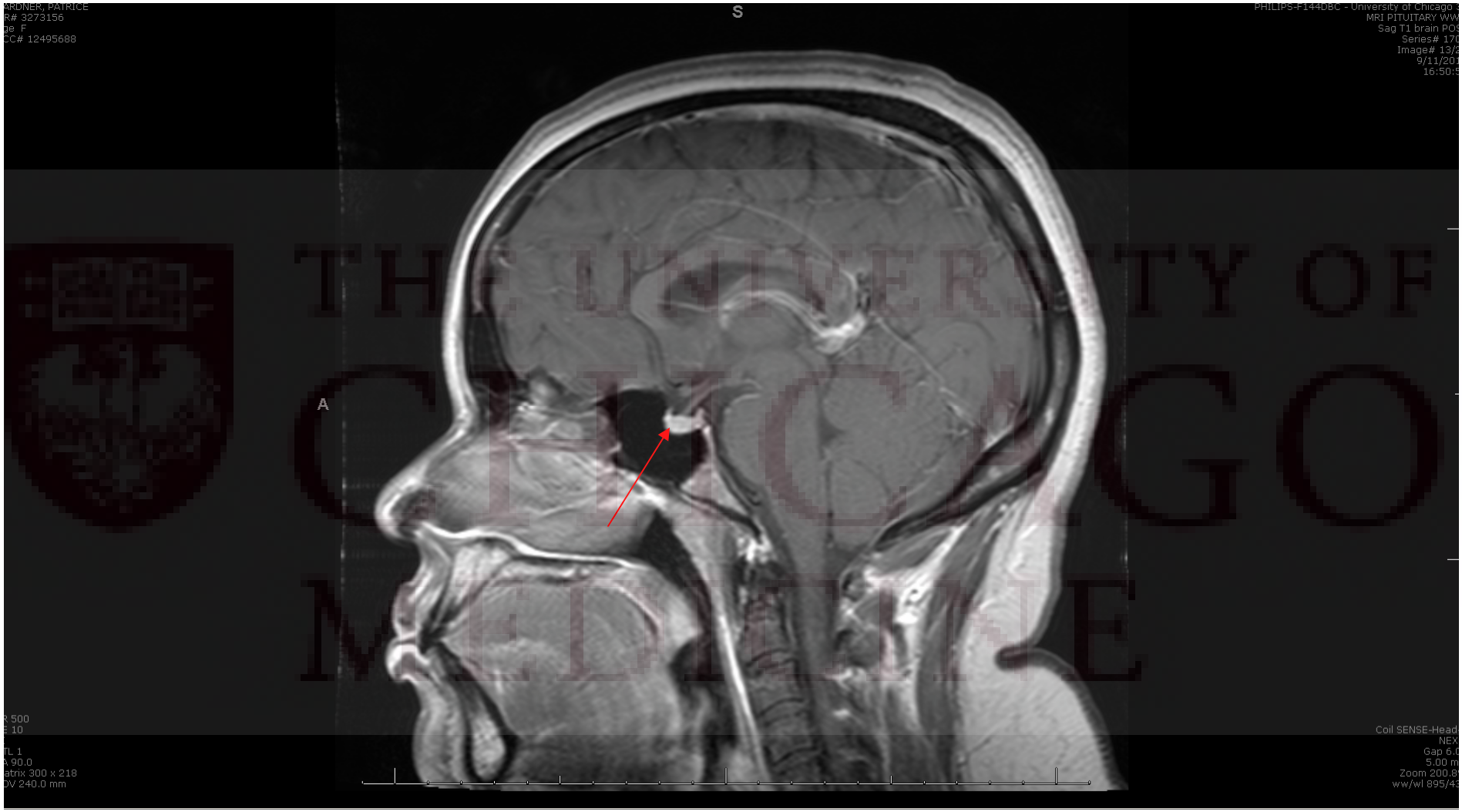
- Head: Normocephalic and atraumatic.
  Mouth/Throat: Oropharynx is clear and moist. No oropharyngeal exudate.
- Eyes: EOM are normal. Pupils are equal, round, and reactive to light. No scleral icterus.
- Neck: Normal range of motion. Neck supple. No JVD present**.** No tracheal deviation present. No thyromegaly present.
- Cardiovascular: Regularly heart rate and rhythm, normal heart sounds and intact distal pulses. No friction rub. No murmur heard.
- Pulmonary/Chest: Bilateral crackles. Moderate respiratory distress. No wheezes. No rales. No tenderness.
- Abdominal: Soft. Bowel sounds are normal. No distension and no mass. There is no tenderness. There is no rebound and no guarding. No stretch marks.
- Breast: Tanner 5.
- Musculoskeletal: Normal range of motion. No edema and no tenderness. No cervical adenopathy.
- Neurological: She is alert and oriented to person, place, and time. No cranial nerve deficit. Normal muscle tone. Coordination normal. Brisk reflexes in upper and lower extremities. No LE edema.
- Skin: Skin is warm. Not diaphoretic. No erythema. No pallor. Psychiatric: normal mood and affect, behavior is normal. Judgment and thought content normal.
- Vitals: BP 118/78, pulse 80, height 162.6 cm (5' 4"), weight 123.152 kg (271 lb 8 oz). BMI 46.6.

Labs and imaging studies:

- Prolactin 28.93 (4.8-23.3 ng/mL)
- Total testosterone 19 (20-60 ng/dL)
- TSH 1.47 (0.30-4 mcU/mL)

Differential for elevated prolactin:

- **Physiologic causes: pregnancy, nipple stimulation, stress.**
- **Pathologic causes:**
  - **prolactinomas,**
  - **decreased dopaminergic inhibition of prolactin secretion** (tumors of the hypothalamus, both benign (eg, craniopharyngiomas) and malignant,
  - **infiltrative disease of hypothalamus** (eg, sarcoidosis),
  - **section of hypothalamic-pituitary stalk**,
  - **adenomas of pituitary other than lactotoph adenomas,**
  - **medications** (dopamine D2 receptor antagonists – risperidone, phenothiazines, haloperidol, and butyrophenones, and the gastric motility drugs metoclopramide and domperidone, antihypertensive drugs methyldopa and reserpine, verapamil).
- **Other causes: hypothyroidism, chest wall injury, chronic renal failure, idiopatic hyperprolactinemia, macroprolactinemia.**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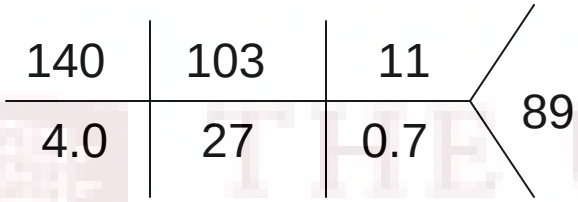
Pituitary MRI:

- MRI of pituitary: 1-2 mm hypoenhancing nodule within the midline, posterior, inferior aspect of the pituitary gland which may represent a microadenoma versus Rathke's cleft cyst based upon its location.

Labs:



Ca 9.2 (8.4 - 10.2 mg/dL)

HA1C 5.7

Estradiol 31 (30-400pg/dL)

LH 17.7
(Follicular: 2.0-6.2 mIU/mL, Mid-Cycle: up to 85 mIU/mL, Luteal: 1.0-11 mIU/mL, Postmenopausal: 13-44 mIU/mL)

FSH 20.5
(Follicular: 3.9-8.3 mIU/mL, Mid-Cycle: up to 19 mIU/mL Luteal: 1.7-7.7 mIU/mL, Postmenopausal: 20-135 mIU/mL)

Prolactin 7.04 (4.8 - 23.3 ng/mL)

Total testosterone 25 (20 - 60 ng/dL)

Free testosterone 8 (3 - 9 pg/mL)

TSH 1.92 (0.30-4 mcU/mL)

Free T4 1.31 (0.9 - 1.7 ng/dL)

1mg dexamethasone suppression test: 8 AM cortisol 1.6 (<5mcg/dL), dexamethasone 609 (180-550 ng/dL)

Karyotype: 46, XX.

- What could be the cause of premature ovarian failure?
- What is the diagnosis of premature ovarian failure?
- What are the predictors of spontaneous ovarian function?
- Are there any fertility options?

- Premature ovarian insufficiency is defined as ovarian failure before age 40 years (which is two standard deviations below the age of normal menopause).

- The age specific incidence of spontaneous primary ovarian insufficiency is approximately 1 in 250 by age 35 and 1 in 100 by age 40.

Etiologies of primary ovarian failure

Accelerated follicular atresia:

1) **Genetic defects**

- Turner's syndrome
- Fragile X premutations
- X chromosome del and translocations
- Galactosemia

2) Ovarian toxins

- Chemotherapeutic drugs (especially alkylating agents)
- Radiation
- Mumps or cytomegalovirus infection

3) Autoimmune injury

- Isolated or part of polyglandular autoimmune syndromes

Abnormal follicular stimulation:

1) Intraovarian modulators

- BMP15, polymorphisms of inhibin alpha subunit

2) Steroidogenic enzyme defects

- CYP17 deficiency, StAR mutation

3) Aromatase gene mutations

- Gonadotropin receptor function
- FSH receptor mutations
- Gs alpha subunit gene mutations

Diagnosis:

- History or radiation exposure or chemotherapy
- History of viral infections
- Karyotype
- steroidogenic cell autoantibodies (antiovarian antibodies)
- Other autoimmune endocrinopathies

Types of endocrine and nonendocrine autoimmune syndromes associated with adrenal insufficiency

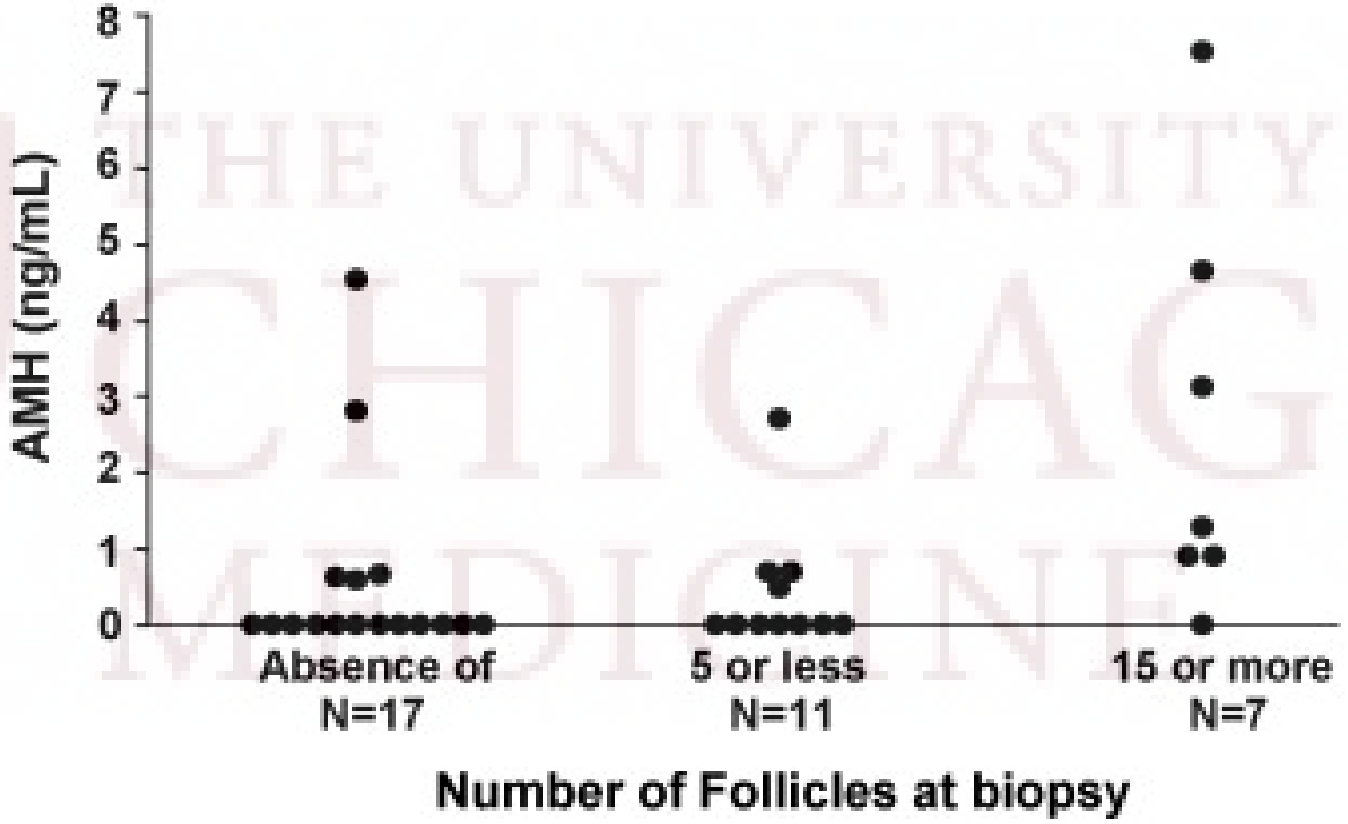
Disorder	Prevalence, percent
Polyglandular autoimmune syndrome type I	
Endocrine	
Hypoparathyroidism	89
Chronic mucocutaneous candidiasis	75
Adrenal insufficiency	60
Primary hypogonadism	45
Hypothyroidism	12
Type 1 diabetes mellitus	1
Hypopituitarism	<1
Diabetes insipidus	<1
Nonendocrine	
Malabsorption syndromes	25
Alopecia totalis or areata	20
Pernicious anemia	16
Chronic active hepatitis	9
Vitiligo	4
Polyglandular autoimmune syndrome type II	
Endocrine	
Adrenal insufficiency	100
Autoimmune thyroid disease	70
Type 1 diabetes mellitus	50
Primary hypogonadism	5-50
Diabetes insipidus	<1
Nonendocrine	
Vitiligo	4
Alopecia, pernicious anemia, myasthenia gravis, immune thrombocytopenia purpura, Sjogren's syndrome, rheumatoid arthritis	≤1

Data from: Leshin M, Am J Med Sci 1985; 290:77, and Neufeld M, Maclaren NK, Blizzard RM, Medicine 1981; 60:355.

Potential predictors of a spontaneous ovarian function

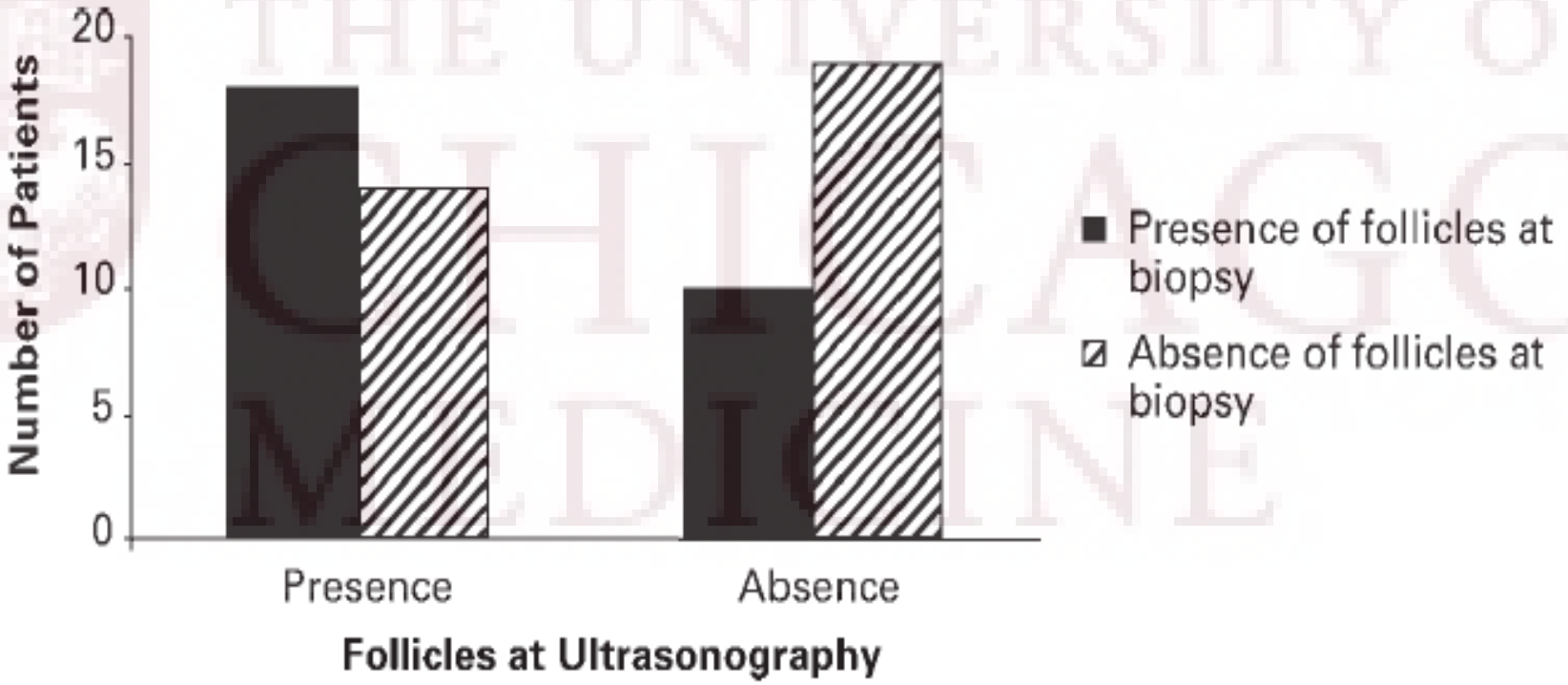
- Poor predictors: primary amenorrhea, long duration of amenorrhea
- anti-Mu¨llerian hormone (AMH) levels have a positive correlation with antral follicle count (AFC) on ultrasound an association between number of follicular structures (on biopsy)
- Weak predictors: causes of premature ovarian failure, levels of FSH, ultrasound
- 5-10% chances to conceive spontaneously

anti-Mu¨llerian hormone levels and number or follicles on biopsy



Massin N, Méduri G, Bachelot A, Misrahi M, Kuttenn F, Touraine P. Evaluation of different markers of the ovarian reserve in patients presenting with premature ovarian failure. Mol Cell Endocrinol. 2008 Jan 30;282(1-2):95-100.

Ultrasound for prediction of ovulation



Massin N, Gougeon A, Meduri G, et al. Significance of ovarian histology in the management of patients presenting a premature ovarian failure. Hum Reprod 2004; 19:2555–2560

Fertility treatments:

- Estogens: based on the assumption that estrogen replacement therapy would enhance resumption of ovulation and thereby the chance of pregnancy.
- Estrogens followed hMG/recombinant FSH stimulation
- Estrogens followed hMG/recombinant FSH stimulation with concomitant estrogen use
- GNRH-a-induced gonadotropin suppression followed by hMG or recombinant FSH stimulation
- GNRH-a-induced gonadotropin supression alone
- Corticosteroids + GNRH-a-induced gonadotropin suppression followed by concomitant hMG or recombinant FSH stimulation

Outcome	*Group 1: GnRHa + Gn + dexamethasone (n = 29)*	*Group 2: GnRHa + Gn + placebo (n = 29)*
Serum FSH (IU/ml) (after down-regulation)	14.1 ± 4.1	16.1 ± 3.2
Ovulation (*n*)	6 (20.7%)[1]	3 (10.3%)[1]
Serum oestradiol (pg/ml)	190.0 ± 30.4	183.1 ± 40.3
Serum progesterone (ng/ml)	6.3 ± 1.2	5.4 ± 2.3
Endometrial thickness (mm)	5.3 ± 1.2	4.8 ± 3.1
Pregnancy (*n*)	2	0

Values are mean ± SD, unless otherwise stated.

[1,2] $P = 0.02$; Gn = gonadotrophin therapy; GnRHa = gonadotrophin-releasing hormone agonist.

Badawy A, Goda H, Ragab A. Induction of ovulation in idiopathic premature ovarian failure: a randomized double-blind trial. Reprod Biomed Online. 2007 Aug;15(2):215-9

Estrogen replacement:

- Girls or young women with primary amenorrhea in whom secondary sex characteristics have failed to develop should initially be given very low doses of estrogen (at first without a progestin) in an attempt to mimic gradual pubertal maturation.
- women who have an intact uterus, an effective progestin regimen to fully reduce the risk of endometrial hyperplasia and carcinoma is recommended
- Duration: until age 50, the average age at natural menopause.
- Benefits: prevents bone loss, improves symptoms of estrogen deficiency, including vasomotor flushes, vaginal dryness, night sweats, fatigue, and mood changes.

Take home points:

- Premature ovarian failure is a relatively common condition: incidence is 1 in 250 by age 35 and 1 in 100 by age 40.
- No effective fertility treatment exist at this point, however spontaneous pregnancies still happen.
- Estrogen replacement and osteoporosis screening at the time of diagnosis are important.

References:

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