PRIMARY OVARIAN INSUFFICIENCY
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AMENORRHEA
- No period by age 14 in absence of growth or secondary sexual characteristics
- No period by age 16 regardless of growth and secondary sexual characteristics
- Menstruating women: no period for 3 cycles or 6 months.

EVALUATION OF AMENORRHEA:
- Amenorrhea
  - TSH
  - Progesterin
  - FSH
  - Estradiol
  - (HCG)
EVALUATION

- **A- If high gonadotropins: FSH >20 and LH > 40** (after repeat measurements several months apart):
  - Primary ovarian insufficiency (POF premature ovarian failure)

- **B- Normal gonadotropins:** consistent with CNS/Hypothalamic etiology or Anovulation

- **C- low gonadotropins:**
  - Pituitary or CNS hypothalamic: Imaging
  - MRI better than CT

POF (OR POI)

- Premature ovarian failure (POF) or premature menopause generally is defined as the triad of
  - Amenorrhea
  - Hypergonadotropism
  - Hypoestrogenism

- Women under the age of 40 years

- At least 4 months of amenorrhea in association with menopausal level serum FSH concentrations on two occasions

POI

- The use of the term POF is inappropriate.
- In 5-10% of patients, spontaneous pregnancy has occurred many years after the initial diagnosis
- Hypergonadotropic amenorrhea
- Primary hypogonadism
- Hypergonadotropic hypogonadism
- **Primary ovarian insufficiency**
PATHOPHYSIOLOGY
- Premature loss of oocytes
  - Reduced germ cell endowment in utero
  - Accelerated atresia
  - Failure of all germ cells to migrate to the genital ridges in early development.
- There may be marked differences in oocyte endowment and rates of follicular atresia among women
- Genetic abnormalities are perhaps the most important cause of POI (10-15% are known)

GENETIC
- Gonadal dysgenesis:
  - 30-40% of primary amenorrhea
  - 50% 45 X: Turner
  - 25% mosaics
  - 25% 46XX
- Karyotype at any age < 40
- Remove the gonads of all patients with a Y chromosome (except AI)

TURNER SYNDROME
- 1 in 2500 to 1 in 3000 live-born girls
- Approximately half have monosomy X (45,X)
- 5 to 10 percent have a duplication (isochromosome) of the long arm of one X (46,X,i(Xq)).
- Most of the rest have mosaicism for 45,X, with one or more additional cell lineage
CLINICAL SIGNS

- Newborn girl with edema or hypoplastic left heart or coarctation of the aorta, puffy hands and feet. Short neck with a webbed appearance, a low hairline at the back of the neck, and low-set ears

- Teenage/ pubertal:
  - Short stature
  - Primary amenorrhea with delayed puberty

- Adult:
  - Secondary amenorrhea (mosaic Turner)

MANAGEMENT

- Karyotype (20 cells), if neg and high suspicion: 100 cells or skin biopsy of fibroblast karyotyping

- Growth: Comparisons of the final heights of girls treated with HGH with projected or predicted heights range from no gain to an increase of as much as 11.9 cm.

- Learning disabilities: 70%, nonverbal perceptual motor and visuospatial skill
MANAGEMENT

- Echocardiography (cardiac MRI): Coarctation of the aorta and bicuspid aortic valve
- Hearing test
- Renal ultrasonography
- TSH, Diabetes and Lipid screening

- HRT:
  - Low dose than increase
  - Start at age 14
  - Introduce progesterone after breast development

FAMILIAL MENTAL RETARDATION-1 (FMR1) GENE

- Normal individuals have 5-50 repeats of the cytosine-guanine-guanine (CGG) trinucleotide in the gene. (Located at Xq27)
- Expansion of this trinucleotide to greater than 200 repeats inactivates the gene and leads to the fragile X syndrome
- The presence of 50-200 is considered a premutation.

FAMILIAL MENTAL RETARDATION-1 (FMR1) GENE

- Mutation: > 200 repeats
  - Male: severe mental retardation, long narrow faces, increased head circumference, dysmorphic ears, prominent jaws and foreheads, and large testes
  - Female: not affected usually

- Premutation: 50-200
  - Female: further expansion and transmit the full syndrome to their offspring; can be transmitted for several generations before expansion occurs
  - Male: never have further expansion in germ cells but can transmit the premutation to their female offspring
**FMR 1 GENE**
- POI develops in about 20% of female premutation carriers
- 2% of women with sporadic POI and 14% of women with familial POI have this unstable mutation
- Screening for mutations in FMR1

**OTHER GENETIC MUTATIONS**
- Blepharophimosis-ptosis-epicanthus inversus (BPES) type I syndrome
- Inhibin alpha gene (INHA)
- Bone morphogenetic factor 15 (BMP15)
- Galactosemia
- 17α-hydroxylase deficiency
- Aromatase deficiency
- FSH receptor (FSHR)
- The "resistant ovary" syndrome: Savage syndrome

**AUTOIMMUNE LYMPHOCYTIC OOPHORITIS**
- Women with steroidogenic cell autoimmunity have lymphocytic oophoritis resulting POI
- POI + adrenal insufficiency, the ovarian failure presents first about 90% of the time
- 21-hydroxylase enzyme: occult adrenal insufficiency, should be followed, subsequent development of adrenal insufficiency
POI: AUTOIMMUNE
- Inconsistent result with ovarian antibodies
- Risk of hypothyroidism 10%, diabetes 3% and adrenal insufficiency 3%
- Labs every few years
  - Ca, Ph
  - Glucose
  - Adrenal antibodies to 21 hydroxylase; if positive do ACTH stimulation test
  - Free T4, TSH, if abn thyroid antibodies

POI
- Chemo/radiation:
  - Depend on age and dose
  - Function can resume after many years of amenorrhea
  - Dose 250-500 rads: 60% sterile age 15-40
  - Dose 800 rads or more: 100% sterilized
  - Alkylating agents very toxic
  - Prevention
    - Possible use of GnRH agonist before treatment
    - Harvesting and cryopreservation of eggs
    - Laparoscopy and transposition of ovaries from the pelvis before radiation
    - Surprising recovery after many years

MANAGEMENT
- Estrogen replacement to prevent the accelerated bone loss
- Either in the form of combined oral contraceptives, or sequential therapy with exogenous estrogen and progestin (more physiologic)
- 100 mg of estradiol per day by a skin patch, combined with 5-10 mg of medroxyprogesterone acetate for 12 calendar days each month
PREGNANCY RISK: 5-10%
- May conceive while on estrogen therapy: a pregnancy test if withdrawal bleeding does not occur or if signs and symptoms suggestive of pregnancy develop.
- Need for contraception?
- More pregnancies in patient who have LH higher than FSH or High estradiol

FERTILITY
- Ovulation induction likely to be ineffective
  - Some pregnancies can occur
- IVF with donor oocyte
- Risk of aortic dissection in patient with Turner: cesarean if aortic root is enlarged.

CASE STUDY 1
- A 30-year-old woman presents with a history of no menses since she stopped taking oral contraceptives 6 months ago in order to conceive.
- She had undergone puberty that was normal in both timing and development, with menarche at 12 years of age.
- At 18 years of age, she started taking oral contraceptives for irregular menses. She reports stress at work.
- Her weight is 59 kg, and her height 1.66 m; her body-mass index (the weight in kilograms divided by the square of the height in meters) is 21.3.
- There is no galactorrhea, hirsutism, or acne. The pelvic examination is normal, a pregnancy test is negative.
WORK UP
- FSH is elevated at 107
- E2 < 20 pg/ml
- Karyotype is normal
- FMR 1 gene: no premutation or mutation

WORK UP
- TSH: 10
  - 21 hydroxylase antibodies: elevated

MANAGEMENT
- Symptoms
- Fertility
- Follow up
CASE STUDY 2
- 18 years old present to your office with primary amenorrhea
- She is healthy otherwise
- Height is 4 ft 9 in, Weight is 110 lb
- Having some difficulty in some college classes

WORK UP
- FSH : 96
- E2 : < 20
- Karyotype : 45X

WORK UP
- Normal TSH
- Normal Audiometry
- Normal dxa scan
- Normal echocardiogram
- Normal Glucose challenge test
MANAGEMENT

- Hormones:

- Fertility:

- Follow up: