Obstetrics & Gynecology
TEAM

Amenorrhea

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◆very important ◆mentioned by doctor ◆team notes ◆not important

Definitions:

- What is 1ry amenorrhea?
  - Lack of the onset of menses by the age of 16 years in a female ♀ with 2ry sexual characteristics (A girl who has normal pubertal development)
    Or
  - By the age of 14 years in ♀ without 2ry sexual development
- What is 2ry amenorrhea?
  - Cessation of menses for a period of 6 months in a female ♀ who previously had initiation of menses (A girl who has no pubertal development)
    Or
  - For three previous cycle intervals

1ry amenorrhea Classification

Classified into for types depending on whether there is secondary sexual characteristics manifested by:

- Breast development
- Uterus

a) Breast absent uterus present

(No breast development but normal uterus, and gonads didn't form normally)

GONADAL DYSGENESIS:

1. Turner syndrome 45XO
   Streak gonads (type of gonadal dysgenesis, ovaries didn't't form normally)
   - Features:
     - 1ry amenorrhea
     - No breast development
     - Normal female ♀ genital organs (external /internal)
     - Streak gonads (ovaries are replaced by white nonfunctioning tissue) (Ovaries didn't develop normally so they don't function normally)
     - Short stature
     - Webbed neck (Short broad neck) with a low hair line
     - Cubitus vulgus (Wide carrying angle with the arm extended at the side and the palm facing forward, the forearm and hand are held at greater than 15 degrees)
     - Shield chest / Widely spaced nipples
     - High arched palate
     - Short 4th metacarpal
     - Coarctation of the aorta or VSD (Do an echocardiogram)
     - Horse shoe kidney or single kidney
     - Lymphedema

     (They might also have other congenital malformations so once the patient is diagnosed we have to look for other things)
   - Variations of Turner's syndrome ⇨ (When it's a mosaic turner case they might not have all the previous features)
2. Mosaicism XO/XX (Two cell lines) ⇨ not always short
   (Mosiac type of Turner's syndrome, they don't always have the typical manifestation of turner syndrome)
   - They will have menses, get pregnant then ⇨ develop premature menopause
3. Structural abnormalities of the X chromosome
   - Deletion of the short arm of the X chromosome ⇨ Short stature
   - Deletion of the long arm ⇨ normal HT, 2ry Amenorrhea, streak gonads
4. Pure gonadal dysgenesis 46XX
   (Normal chromosomal configuration 46XX, it's just that the gonads didn't develop normally)

- Mutation in an autosomal gene ⇨ Accelerated germ cell loss ⇨ Streak gonads
- Female ♀ genetalia , normal Mullerian structures
- Rarely Turner's Stigmata

5. Pure gonadal dysgenesis 46 XY
   (If the patient is an XY patient with streak gonads we have to do gonadectomy due to the risk of malignancy)
   - Female ♀ genitalia
   - Streak gonads ⇨ ↑ risk of malignancy
   - Normal Mullerian structures
     (Testis secretes the mullerian inhibiting factor which will inhibit the development of the mullerian duct, but if there is dysgenesis of the testis and it doesn't function normally → no secretion of mullerian inhibiting factor → even if XY uterus will develop and there will be female external genetalia)
6. 17-α hydroxylase deficiency (rare)
   - ↓ Ovarian synthesis of estrogens ⇨ 1ry Amenorrhea
   - Sexual immaturity (No breasts)
   - ↓ Cortisol ⇨ ↑ ACTH
   - ↑ Na ↓ K ↑ BP
   - ↑ Progesterone as it is not converted to cortisol
7. Galactosaemia (rare)
   - Galactosaemia is toxic to oocytes

HYPOTHALAMIC FAILURE:

8. Isolated GnRH deficiency (Kallman's Syndrome) (Congenital hypothalamic failure)
   - Anosmia & Hypogonadotropic Hypogonadism
   - X linked → Mutation in the KAL gene
   - More common in male ♂ > Female ♀
   - Midline defects ⇨ Cleft lip & Palate
   - Somatic defects ⇨ color blindness, renal agenesis, retinitis pigmentosa, neurosensory deafness
   - Lack 2ry sexual characteristics & the ability to smell (anosmia)
   - Height & bone age appropriate for age
9. Hypogonadotropic Amenorrhea
   - Hypogonadotrophic means low FSH & LH (no breast development)
   - Such as in kallman's syndrome (but one is congenital the other is acquired)
   - Occurs with CNS tumors ⇨ ↓ GnRH pulses ⇨↓ LH & FSH ⇨↓ estradiol
   - Hypothalamic Lesions ⇨ Craniopharyngioma, granuloma, aqueduct stenosis, & the sequelae of encephalitis (Following encephalitis)
   - CNS tumor ⇨ interfere with the –ve feedback of Dopamine on Prolactin ⇨ ↑ Prolactin
   - Other causes of HypoGonadotropic Amenorrhea ⇨ hypothyroidism, Prader Willi & Laurence Moon Biedl syndromes
10. Anorexia Nervosa, Malnutrition, Excessive Exercise & Chronic Illness
    (All these can have an effect on the hypothalamus; the patient is normal, congenitally has no problem or tumors in the CNS but has other problems)
    - Functional GnRH deficiency
    - May present with or without Breast development (Depends when the problem started)
    - Physical stress delay menarche
    - Each year of athletic training before menarche delayed menarche 5 months
    - Osteoporosis could occur with prolonged periods of Amenorrhea, low body Weight (Due to low estrogen)

b) Breast present, uterus present

1. HYPOTHALAMIC CAUSES
   - CNS lesions (tumors)
   - Stress, Excessive exercise & low body Weight
2. PITUITARY CAUSES
   - Hyperprolactinemia
   - Hypothyroidism ⇨ ↑ TRH ⇨ ↑ prolactin
3. OVARIAN CAUSES
   - PCO (polycystic ovarian syndrome)
4. OUTFLOW TRACT OBSTRUCTION
   - Imperforate hymen
   - Transverse vaginal septum

c) Breast present, uterus absent

(Normal breast development but no uterus)

1. Testicular feminization/ Androgen insensitivity
   - XY Karotype ⇨ produce MIF (testis is there) ⇨ Mullerian structures are absent
   - Complete/ Partial absence of androgen receptors
   - X linked recessive or dominant
   - Female external genitalia with Short blind vagina (No uterus)
   - Testosterone ⇨ normal male ♂ range
     No androgen receptors in their body → high level of androgen in the body (they look normal but no hair growth & no uterus → no menstruation)
   - Breast development due to peripheral conversion of androgens (testosterone) to estrogens
   - Sexual hair is absent due to absence of androgen receptors
   - Gonadectomy after puberty ⇨ Due to the ↑ risk of malignancy (gonadoblastoma, dysgerminoma
2. 5 α reductase deficiency
   - Autosomal recessive
   - Formation of the male ♂ external genitalia requires

5α REDUCTASE

Testosterone ⇨⇨⇨⇨ Dihydrotestosterone

There are androgen receptors but the enzyme that converts testosterone is absent

Active compound which acts on the external genetalia to give a normal male genetalia

   - Formation of the internal wollfiane structures respond directly to testosterone
   - External genitalia female ♀ with mild masculinization
     Ambiguous genetalia (depends on the level of the hormone deficiency)
   - Absent uterus (Due to testosterone secretion)
   - At puberty ⇨ ↑ testosterone secretion ⇨ virilization
3. Mullerian Agenesis/ Mayer – Rokitansky-Kuster-Huser syndrome
   - Etiology? Not known
   - Failure of mullerian duct development ⇨ absence of the upper vagina, cervix & uterus (uterine remnants may be found)
   - The ovaries & fallopian tubes are present (Absence of uterus cervix and upper vagina)
   - Normal 46XX ♀ with normal external genitalia (Normal female with developmental problems)
   - Patient present with 1ry amenorrhea
     - Normal ovaries but no uterus to menstruate
     - Ovaries secrete estrogen → normal breast development

- 47% have associated urinary tract anomalies (Such as absent kidney)
- 12% skeletal anomalies

Treatment:

⇨ Psychological counseling

⇨ Surgical

- Vaginoplasty (due to short vagina)
- Excision of uterine remnant (if it has functioning endometrium)
- Vaginal dilators

d) Breast absent, uterus absent

- The least common presentation of 1ry Amen
- All Patients are 46 XY
- Testosterone ⇨ ↓ or Normal
- FSH/LH ⇨ ↑

1. 17-20 Desmolase Deficiency

- The enzyme required for the synthesis of Androgens ⇨↓ Androgens ⇨ ↓ estrogen
- The testes produce MIF therefore no Mullerian structures No uterus or breast (no formation of androgen or estrogen)
- Male ♀ external genitalia (Doesn't require the presence of estrogen)
- Insufficient estrogens for breast development

2. 17 α Hydroxylase Deficiency

- Similar to 17-20 desmolase deficiency
- Cortisol synthesis also ↓ ⇨ ↑ BP, hypernatraemia & hypokalaemia

3. Agonadism

- Degeneration of the testes (in utero) after the production of the MIF

Similar to dysgenesis but the problem occurred after the testis started secreting MIF

Investigations and treatment of 1ry amenorrhea:

We do History & Physical examination to place the Patient in one of the four categories

a) Breast absent uterus present

We begin by checking the gonadotropins

1. Hypogonadotropic ↓↓**FSH&LH** → CNS/Hypothalamic Disorder:

- Kallman's syndrome (Congenital defect, isolated GnRH deficiency)
  → Treatment: Estrogen Progesterone replacement (HRT)
  GnRH deficiency (it is hard to replace GnRH because in the body it is secreted in pulses so giving it continuously will not stimulate the production of FSH&LH)
  → Normal treatment for kallman's syndrome is hormone replacement but if a patient wants to get pregnant gonadotropins in the form of injections to induce ovulation
  → Occurs once treatment is established:
  - Breast development
  - Menses
  - Improve bone Density (Without the treatment → osteoporosis)
- ↓Decreased weight (anorexia), ↑ increased exercise/stress (Excessive → such as Olympic trainers >7-8 hours a day training)
  Treatment:
  → Psychiatric help
  → Treat the cause
  → Estrogen Progesterone replacement (HRT)
- ↑ TSH with Normal prolactin → Hypothyroidism
  → Treatment: Give Thyroxin

- Normal TSH with ↑ increased or normal prolactin → CT/MRI of the head → CNS tumors (pituitary adenoma → macro or micro)
  → Treat Accordingly

2. Hypergonadotropic ↑↑ **FSH&LH**

- Gonadal Dysgenesis:
  (Gonads aren't secreting estrogen or androgen → elevated FSH trying to compensate for that loss)
  - Investigate by Karyotyping
    - XO → Turner's Syndrome
      → Treatment: Estrogen Progesterone replacement (HRT)
    - XY → Treatment: Gonadectomy then → Estrogen Progesterone replacement (HRT)
      - A gonadectomy is done because testosterone converts into estrogen which increases the risk of malignancy
      - Hormone replacement therapy HRT (we give them progesterone, because the uterus is present & estrogen can't be given alone or endometrial hyperplasia might develop)
    - XX → ↑ Na ↓ K (measure electrolytes), ↑ Progesterone →17a Hydroxylase deficiency

  Treatment:
  → Replace the hormone deficiency
  → Estrogen Progesterone replacement (HRT)

  Occurs in all the previous three karyotypes once treatment is established:
  - Breast development
  - Menses
  - Improve bone Density (Without the treatment → osteoporosis)

b) Breast present, uterus present

We begin by doing a hormonal profile

1. ↑ TSH with Normal prolactin → Hypothyroidism
   → Treatment: Give Thyroxin
2. Normal TSH with ↑ increased prolactin (hyperprolactenemia) → CT/MRI of the pituitary
   → Asses if there is a pituitary adenoma (macro or microadenoma → treat according to case)
   → Medication: Bromocriptin or cabergoline
3. Normal TSH and Normal prolactin
   If both normal do a Progesterone challenge test → we give the patient progesterone (Primolut N 5mg a twice a day for 5 days), after stopping one of two will occur:

- + Positive Progesterone Challenge (after stopping the progesterone if she has normal outflow tract and normal estrogen level menstruation will occur) → amenorrhea occurred due to Anovulatory cycle (No progesterone in the body → no period)
  → Treatment: Progestin D16-25 (given in the second half of the cycle)
- - Negative Progesterone Challenge (causes)
  - ↑ FSH → Ovarian failure (Premature) → Karyotyping (To make sure there is no XY or we will have to do gonadectomy)
    → Treatment: Estrogen Progesterone replacement (HRT)
  - Outflow tract obstruction
    → Treatment is surgical
    → She might have imperforated hymen or Transverse vaginal septum (open the membrane and she will menstruate)
  - ↓ FSH → Hypothalamo/pituitary axis failure → MRI/CT of the head → CNS Tumor
    → Treatment: Estrogen Progesterone replacement (HRT)

c) Breast present, uterus absent

- No Uterus but normal secondary sexual characteristics
- We begin by checking the gonadotropins

1. ↑ Testosterone → in the normal male range
   - Karyotyping → XY (most likely) Testicular feminization/androgen insensitivity
     - U/S Pelvis (To make sure they don't have a uterus)
     - U/S MRI gonad → Gonadectomy

   Treatment:
   → Estrogen Progesterone replacement (HRT)
   → Gonadectomy
   → Surgical: Vaginoplasty or vaginal Dilators (to create a vagina)
2. ↓ Testosterone → in the normal female range
   - Karyotyping → XX Mullerian agenesis
     - U/S Pelvis and Kidney
     - IVP

   Treatment:
   → No Need for Gonadectomy
   → Estrogen Progesterone replacement (HRT)
   → Surgical: Vaginoplasty or vaginal Dilators (to create a vagina)

d) Breast absent, uterus absent

All are 46 XY

- Physical exam, U/S and MRI to lock for gonads

Treatment:
→ Estrogen Progesterone replacement (HRT)
→ Gonadectomy

2ry Amenorrhea

Definition:

Cessation of menses for a period of 6 months or 3 consecutive menstrual cycles in a Female ♀ who previously had initiation of menses

Prevalence of Amenorrhea: 1.8-3%

Classification of 2ry amenorrhea:

- Hypergonadotropic (High FSH&LH) → CNS / Hypothalamic
- Hypogonadotrpic (Low FSH&LH) → Pituitary
- Euogonadotrpic (Normal FSH&LH) → Ovarian
- Anatomic defects → Outflow obstruction [Uterine, Cervix, Vaginal]
- Hperprolactinemia

a) Hypogonadotropic Amenorrrhea

1. Stress → ↑ β-endorphins → ↓ GnRH → ↓FSH & ↓ LH → ↓ Estrogens
2. Exercise (Excessive strenuous exercise) [Runners & Ballet dancers]
   - Mechanism is similar to stress

   Treatment:
   → ↓ In training intensity to a level where regular menses resumes
   → HRT ⇨ Cyclic estrogen / progesterone
     - Premarin 1.25 mg continuously
     - Medroxyprogestrone acetate 5 mg /D for 12 D each cycle

     ⇨ OCP ⇨ better compliance

3. Weight loss "Anorexia nervosa"

- More frequent in adolescent & young adults
- 0.5-1% of women aged 15 –30 years
- To diagnose their body weight has to be 15% < Ideal body Weight

Treatment:
→ Psychiatric treatment:
→ Meanwhile ⇨ HRT
→ Long term follow up → due to Frequent relapses after attaining ideal body Weight

4. Functional "Non of the above causes" (not related to the previous causes)

No LH pulses or Persistent pulse frequency of "luteal phase" → due to 2ry to neurotransmitter abnormality of the CNS (? ↑ Opioid activity)

Treatment: HRT / ovulation induction (If they want to get pregnant)

➢ Is it of any concern if these young women become amenorrheic?

No menses due to Hypoestrogenism which is the main concern → can lead to osteoperosis

➢ Why is it more worrying in the menopausal women?

During adolescence estrogen plays a critical role in determining PEAK BONE DENSITY, which is reached, in the 2nd decade of life (If there is amenorrhea she will be deprived of reaching the peak bone density)

➢ Is there any evidence of its effect on the bones?

- Amenorrheic Athletes ⇨↓↓ Bone Mineral Density (BMD) in lumbar spines, femur, tibia
- Athletes with menstrual irregularities ⇨↓ BMD < athletes with regular cycles
- Anorexia nervosa Patients ⇨↓ BMD (0.64) < Normal controls (0.72)
- Anorexia nervosa Patients may have osteoporotic fractures

5. Shehan's Syndrome

- Pituitary failure ⇨ following severe post partum hemorrhage
- Deficiency of all pituitary hormones
- ↓FSH & LH ⇨ Failure of ovarian follicular development ⇨↓ estrogen ⇨ Amenorrhea
- Treatment ⇨ HRT
  ⇨ hMG for ovulation induction (If the patient wants to get pregnant)

b) Euogonadotrpic Amenorrrhea

Polycystic ovary syndrome (PCO)

- Amenorrhea → due to anovulatory cycles
  Enlarged polycystic ovaries (Usually described as necklace appearance on ultrasound as there is multiple cyst in the ovaries)
  Treatment:
  → Cyclic progestogen
  → Oral contraceptive pills (OCP)

} They protect the Endometrium, regulate the cycle, and ↓menorrhagia

- Infertility (Not ovulating)
  Treatment:
  → Ovulation Induction by oral therapy: Clomid → Ovulation 70% & Pregnancy 40%
  (If it fails we go to injection (gonadtropins injections → stronger)
  → hMG
  → Surgical Treatment: Ovarian Drilling (through laproscopy, holes are made in the ovary wall) → Ovulation 92% & Pregnancy 70%
- Hyperinsulinemia / Obesity
  Treatment → Glucophage and weight loss
- Hyperandrogenism / hirsutism
  Either chemical or clinical (androgen level is normal but high free testosterone which results in hirsutism)
  Treatment:

→ Oral contraceptive pills (OCP) → ↓Decreases Ovarian androgens & ↑ increases SHBG (Increase Sex hormone binding globulin therefore decrease the level of free testosterone in the body → decrease hirsutism)

→ Antiandrogens

- Sprinolactone
- Cyproterone acetate
- Flutamide

} Bind to androgen receptors & ↓ Androgens + ↓5α reductase activity

- ↑ LH (High LH in relative to FSH)
- Acyclic estrogen production / unopposed by progesterone → ↑ risk of endometrial hyperplasia/Ca (The patient is recommended to use cyclic Progestogen to prevent the development of endometrial hyperplasia)
- Inheritable disorder with a complex inheritance pattern (Can run in families but has no specific gene for it)

c) Hypergonadotropic Amenorrrhea

(Increased FSH&LH)

Premature Ovarian Failure (POF)

- 2ry Amenorrhea (menstruating previously)
- ↑ FSH & LH
- ↓ Estrogen
- Before the age of 40 years
- Incidence is 1%
- Causes:
  - Unknown / autoimmune / genetic factors
  - Associated autoimmune disease 39% (Can also have hypothyroidism or other endocrine function might be affected)
- Pathological Characteristics:
  1. Ovarian sclerosis & lack of follicles
  2. Resistant ovary syndrome (There are follicles but it doesn't respond to FSH)
- Management:

  → Rule out other autoimmune diseases ⇨ Rheumatic factor, ANA, Antithyroid Antibodies, Antichromosomal Antibodies, glucose, cortisol, Ca , Phosphorus, TSH

  → HRT ⇨ to prevent osteoporosis

  → Spontaneous pregnancy can occur in women with POF on HRT 8% (Sporadic ovulation might occur (doesn't occur regularly)

  → hMG/HCG glucocorticoids have been claimed to give better pregnancy rates (If the patient wants to get pregnant)

d) Hperprolactinemia

- The most common pituitary cause of 2ry Amenorrhea
- Causes
  - Pituitary adenoma

    Treatment:

    → Macroadenoma ⇨ > 10 mm

    ⇨ Respond to medical treatment ⇨ Dopamine agonist (bromocriptin) ⇨ ↓ size of the tumor & ↓ prolactin level

    ⇨ Patient not responding to medical treatment or not tolerating it ⇨ Surgery/ Irradiation

    → Microadenoma ⇨ < 10mm

    ⇨ Remain stable in size ⇨ Treatment ⇨ Bromocriptin ⇨ ↓ prolactin level ⇨ Normalize the menstrual cycle
  - Loss of inhibition by dopamine → Hypothalamic or pituitary stalk lesions

    → Treatment: Surgical excision

- Hypothyroidism
  → Treatment: L-Thyroxin → If still amenorrheic after treatment → Parlodel + Thyroxin
- PCOS
- Medications ⇨ phenothiazines , haloperidol monoamineoxidase inhibitors, TCA, H2 receptors blockers
  → Treatment: If no substitute for the medications that cause hyperprolactinemia
  ⇨ HRT
- Idiopathic
  → Treatment: Dopamine agonist ⇨ Bromocriptin or Pergolide
  - Side effects of dopamine agonists
    -Postural hypotension
    -Nausea
    -Headache
    -Nasal stuffiness
    Starting with a low dose & gradually ↑ it helps to avoid the side effects

Symptoms:

- Galactorrhea ⇨ 1/3 of Patients
- Amenorrhea/ Hyperprolactinemia Pt ⇨ at risk of osteoporosis due to ↓ estrogen

e) **Anatomicical causes** (Doctor didn't mention it)

- Uncommon cause of 2ry Amenorrhea
- Asherman's Syndrome ⇨ History of D/C for RPOC after abortion/puerperium or previous uterine infection
- Intrauterine Adhesions
- Normal hormones
- -ve progesterone challenge test
- Diagnosis ⇨ HSG / HYSTROSCOPY
- Treatment ⇨ Hystroscopic resection of the adhesions followed by estrogen therapy