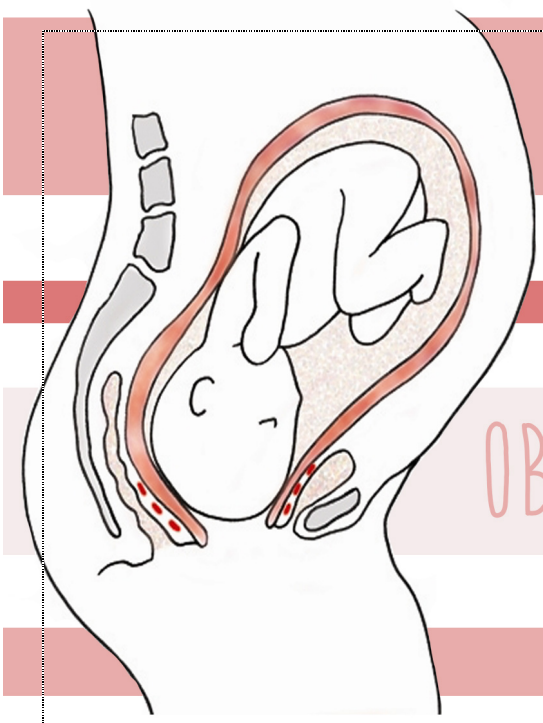

OBSTETRICS AND GYNECOLOGY

(17)Primary and Secondary Amenorrhea

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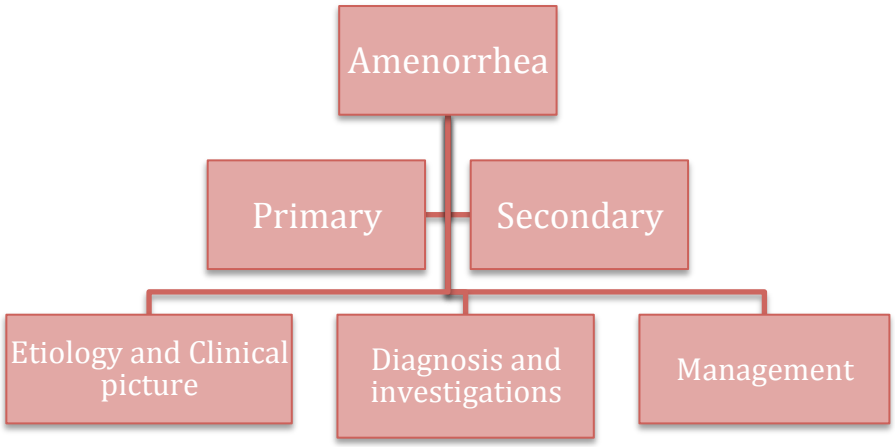
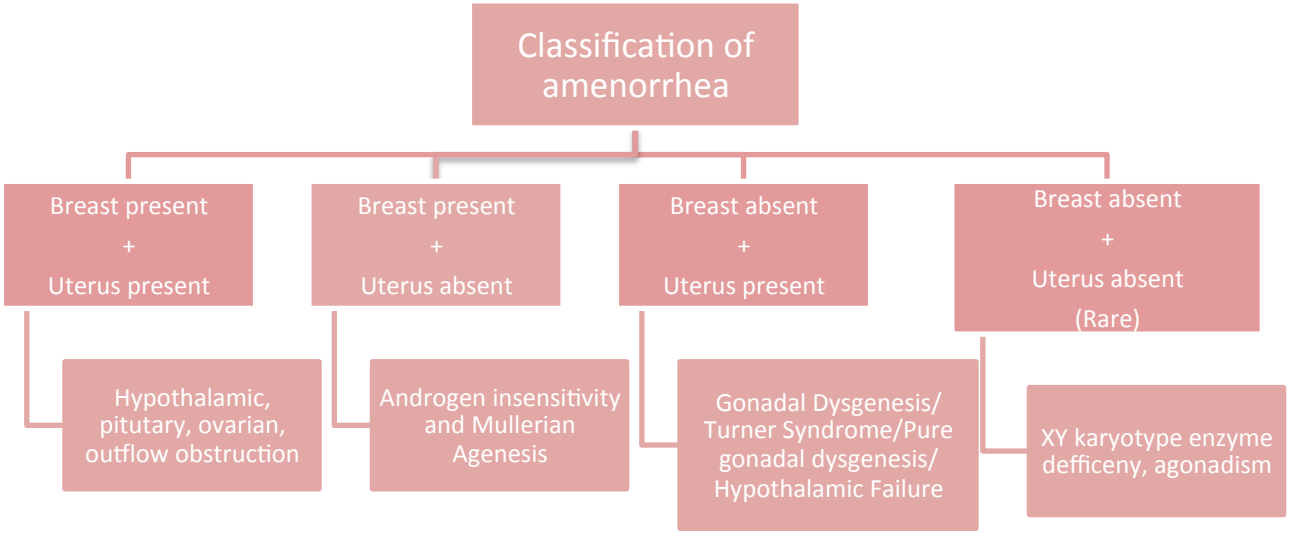
Doctor's note Team's note Not important Important 431 teamwork

Objectives:

1. *Definition of 1ry and 2ry amenorrhea*
2. *Classification of primary amenorrhea:*
3. *Evaluation and investigations*
4. *Management of primary amenorrhea*
5. *Secondary amenorrhea classification, evaluation, diagnosis and management*





Definition of Amenorrhea (primary and secondary):

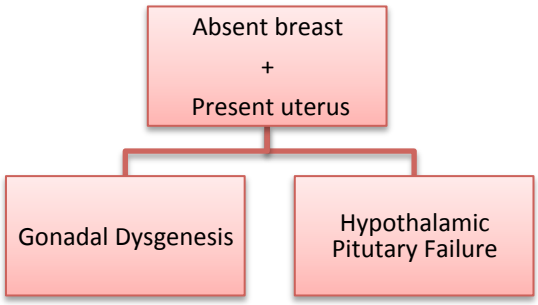
- Primary amenorrhea:

It is the lack of the onset of menses in a female at the age of 14 without secondary sexual characteristics (breast development) or at the age of 16 with secondary sexual characteristics.

- Secondary amenorrhea:

It is the cessation of menses for a period of 6 months in a female who previously had initiation of menses. (most common cause is pregnancy)

Breast absent + Uterus present (Gonadal Dysgenesis):



1. **Turner's Syndrome (45XO)**
   - Variations of Turner Syndrome including: These patients lack the typical features of Turner's syndrome
2. **Mosaicism XO/XX:** (not all the cell lines are the same, some are normal (XX) while others are (XO) abnormal.) → Not always short, they might be able to menstruate and get pregnant, however they will develop premature menopause.
3. **Structural abnormalities of the X chromosome:**
   - Deletion of the short arm of the X chromosome → these patients will have short stature.
   - Deletion of the long arm of the X chromosome → these patients will have normal height, secondary amenorrhea and streak gonads.

Features of Turner's syndrome:

- Primary amenorrhea
- No breast development
- Normal (external and internal) female genital organs (development of female external genitalia happens in the absence of androgen.
- Streak gonads (ovaries are replaced by white non-functioning tissue)
- Short stature
- Webbed neck
- Cubitus valgus/ wide carrying angle (is a deformity in which the forearm is angled away from the body to a greater degree than normal when fully extended)
- Shield chest/ Widely spaced nipples
- High arched palate
- Short 4th metacarpal
- Coarctation of the aorta or Ventricular Septal Defect (VSD)
- Horse shoe kidney or single kidney
- Lymphedema

4. **Pure gonadal dysgenesis (46XX):**
   Mutation in an autosomal gene→ accelerated germ loss→ streak gonads.
   These patients have normal female external genitalia, normal Mullerian structures (due to the lack of Mullerian inhibiting factor produced by the testes).
   Rarely have Turner's Stigmata (they don't have typical features of Turner's).
5. **Pure gonadal dysgenesis (46XY):**
   Female genitalia (testes didn't develop, no androgen), streak gonads→ increased chance of malignancy (in the abdomen) and these gonads should be removed. They might have normal, no or partial Mullerian structures (variable degrees).
6. **17-alpha hydroxylase deficiency (rare):**
   An enzyme deficiency which is involved in the synthesis of estrogen (low levels of estrogen)→ primary amenorrhea and sexual immaturity.
   Decreased cortisol→ increased ACTH (they have problems in the adrenals)
   High sodium low potassium→ High BP
   Increased progesterone as it is not converted to cortisol
7. **Galactosaemia (rare):**
   Galactosaemia is toxic to the oocytes→ no secretion of estrogen which results in primary amenorrhea
8. **Hypothalamic Failure:**
   - **Isolated GnRH deficiency (Kallman's Syndrome) :**
     - Anosmia (lack of the ability to smell) and hypogonadotropic hypogonadism (ovaries are normal)
     - X linked mutation in the KAL gene (more common in males than females)
     - Midline defects such as cleft palate and lip
     - Somatic defects → color blindness, renal agenesis, retinitis pigmentosa, neurosensory deafness.
     - They lack secondary sexual characteristics (no breasts)

- Height and bone are age appropriate (because the adrenals are functioning normally)

➢ **Hypogonadotropic Amenorrhea: Acquired**

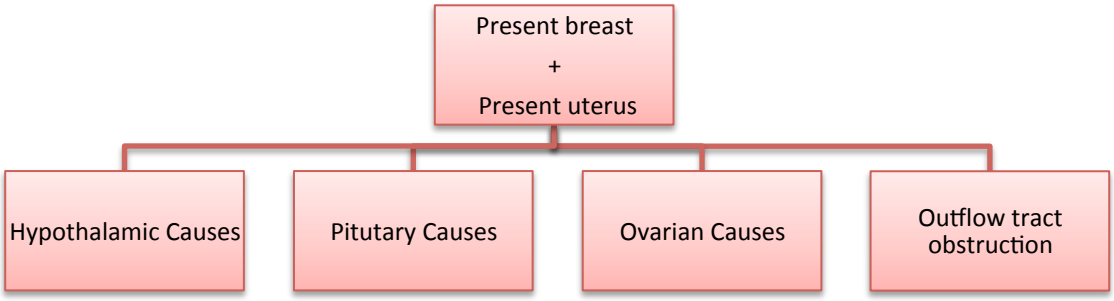
- CNS tumors→ decreased GnRH pulses → decreased LH and FSH→ decreased estradiol
- Hypothalamic Lesions→ Craniopharynioma granuloma, aqueduct stenosis, and the sequeale of encephalitis.
- CNS tr→ interfere with the –ve feedback of dopamine on prolactin→ increased prolactin
- Other causes of hypogonadotropic amenorrhea→ hypothyroidism, Prader Willi and Laurence Moon Biedl syndrome.

➢ **Anorexia Nervosa, Malnutrition, Excessive exercise and Chronic Illness**

- Functional GnRH deficiency
- May present with or without breast development
- Physical stress delays menarche.
- Each year of athletic training before menarche delays menarche by 5 months.
- Osteoporosis could occur with prolonged periods of amenorrhea, low body weight (If we have a patient with anorexia nervosa and she has prolonged amenorrhea you have to give her estrogen supplements to avoid osteoporosis)

Breast present + Uterus Present:

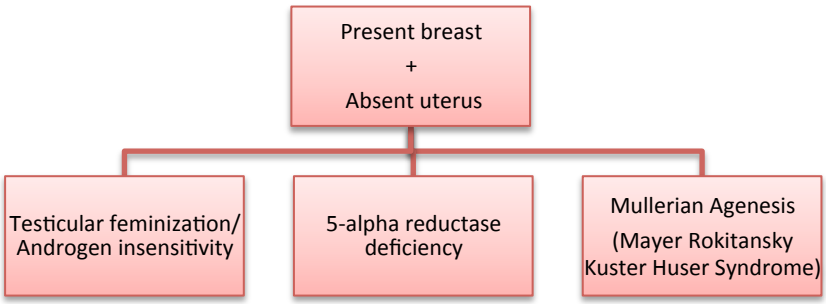
(Normal secondary characteristics but have primary amenorrhea)



1. **Hypothalamic causes:**
   - CNS lesions (tumors) stress, Excessive exercise and low body weight
2. **Pituitary causes:**
   - Hyperprolactinemia
   - Hypothyroidism→ High TRH → High prolactin
3. **Ovarian causes:**
   - Polycystic ovary syndrome
4. **Outflow tract obstruction:**
   - Imperforate hymen

- Transverse vaginal septum

Breast present + Uterus Absent:



1. ***Testicular feminization/ Androgen insensitivity***
   - XY Karotype → produce MIF→ Mullerian structures are absent
   - Complete/ Partial absence of androgen receptors
   - X linked recessive or dominant
   - Female external genitalia with Short blind vagina (no response to androgens due to lack of receptors)
   - Testosterone → normal male range
   - Breast development due to peripheral conversion of androgens to estrogens
   - Sexual hair is absent due to the absence of androgen receptors
   - Gonadectomy after puberty → due to ↑ risk of malignancy (gonadoblastoma, dysgerminoma)
2. ***5 α reductase deficiency***
   - Autosomal recessive
   - Formation of the male external genitalia requires

     5α REDUCTASE

     Testosterone →→→→ →→ dihydrotestosterone
   - Dihydrotestosterone is the hormone needed for the formation of male external genitalia)
   - Formation of the internal wolffian structures respond directly to testosterone
   - External female genitalia with mild masculinization
   - The degree of masculinization depends on the degree of enzyme deficiency (partial or complete)
   - Absent uterus
   - At puberty ⇨ ↑ testosterone secretion ⇨ virilization (slight enzymatic activity, with increased levels of testosterone)

3. ***Mullerian Agenesis/ Mayer –Rokitansky-Kuster-Huser syndrome***
   - Etiology is unknown
   - Failure of mullerian duct development → absence of the upper vagina (blind ending vagina), cx & uterus (uterine remnants may be found)
   - The ovaries & fallopian tubes are present

- Normal 46XX female with normal external genitalia
- Pt present with primary amenorrhea
- 47% have associated urinary tract anomalies
- 12% skeletal anomalies
- Rx → Psychological counseling
- Surgical → - Vaginoplasty
  - Excision of uterine remnant (functioning endometrium)
  - Vaginal dilators

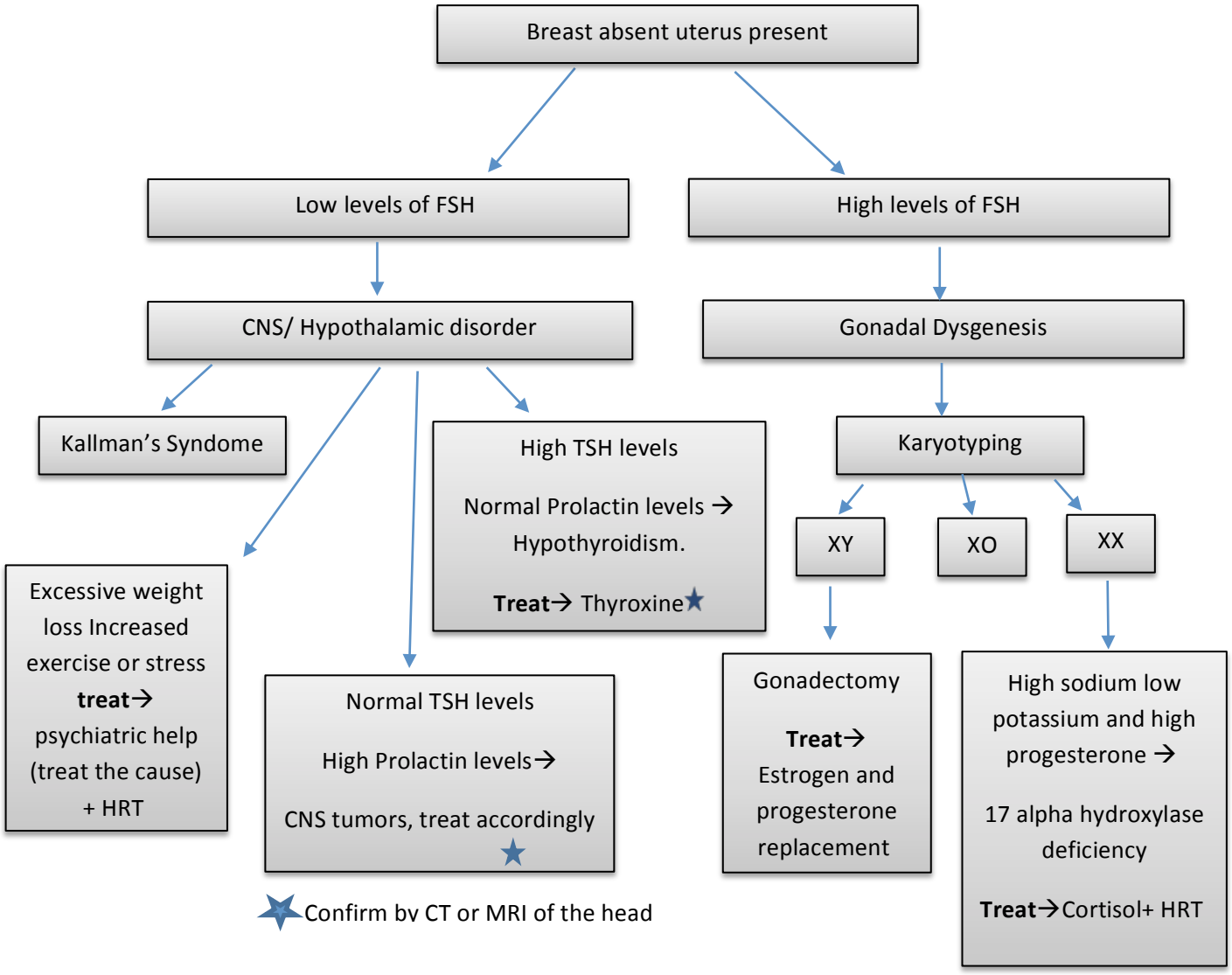
Breast Absent + Uterus Absent:

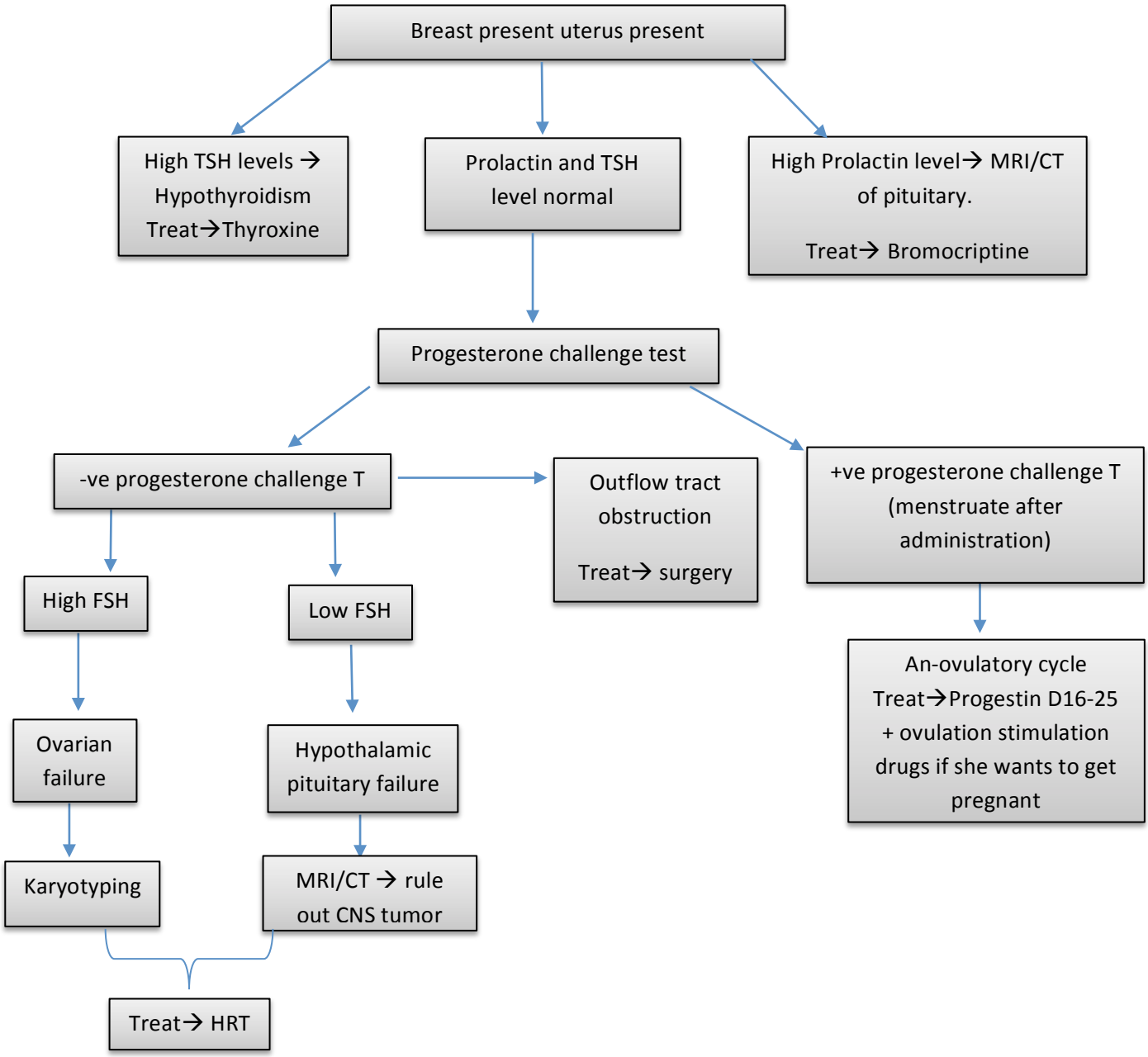
- The least common presentation of primary amenorrhea
- All Pt are 46 XY
- Testosterone → ↓ or N
- FSH/LH → ↑

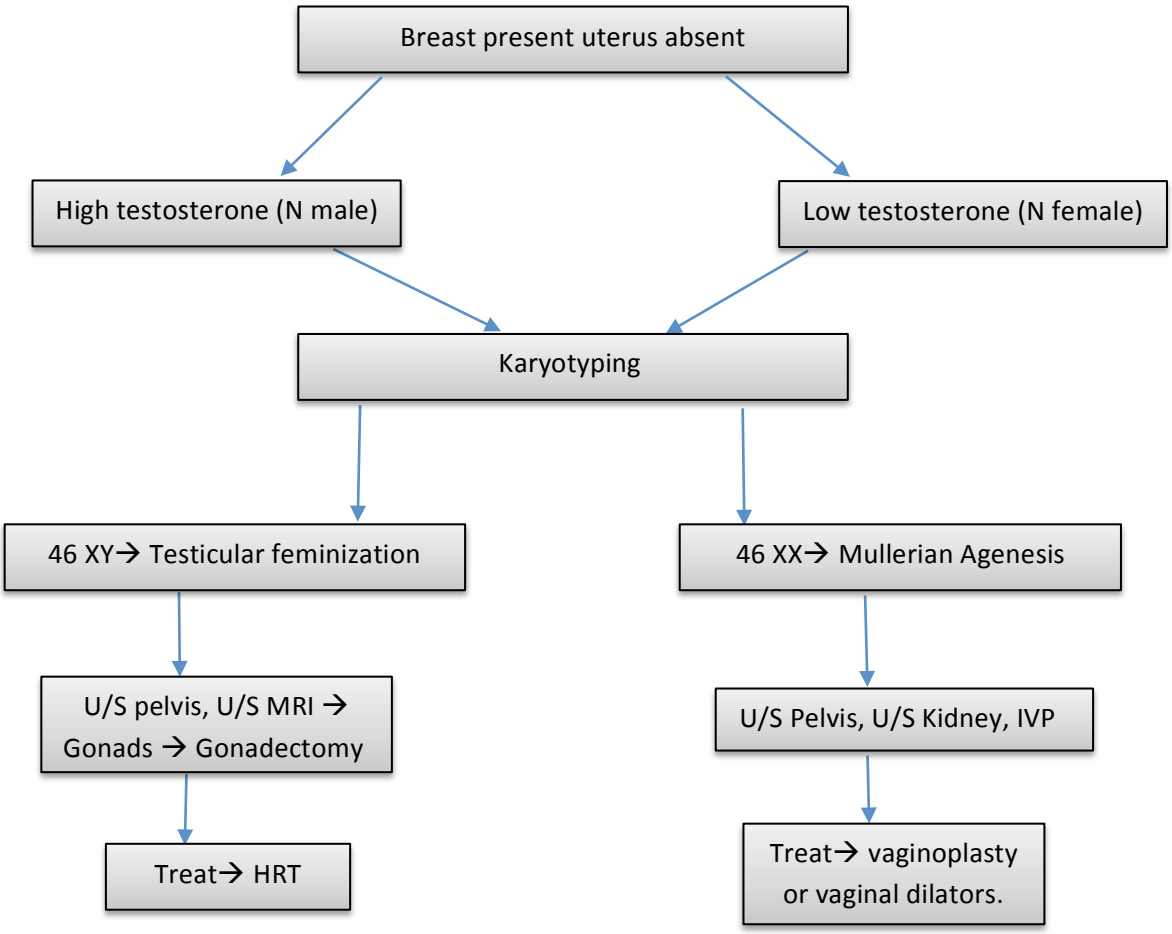
1. ***17-20 DESMOLASE DEFICIENCY***
   - The enzyme required for the synthesis of Androgens →↓ Androgens and↓estrogen
   - The testes produces MIF therefore no Mullerian structures
   - Female external genitalia
   - Insufficient estrogens for breast development
2. ***B- 17 α HYDROXYLASE DEFICIENCY***
   - 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
   - Female external genitalia

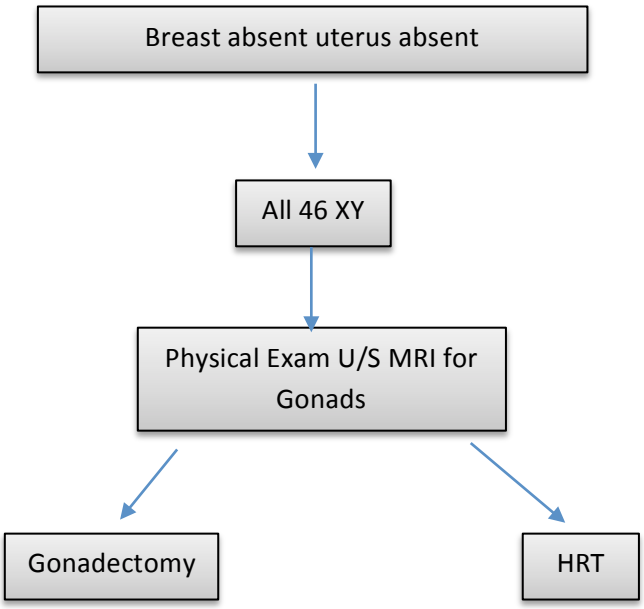
Investigations and Treatment:

- **History and physical examination to place the patient in one of the four categories.**




Breast present uterus present
High TSH levels → Hypothyroidism Treat→Thyroxine
Prolactin and TSH level normal
High Prolactin level→ MRI/CT of pituitary.
Treat→ Bromocriptine
Progesterone challenge test
-ve progesterone challenge T
Outflow tract obstruction
Treat→ surgery
+ve progesterone challenge T (menstruate after administration)
High FSH
Low FSH
An-ovulatory cycle
Treat→Progestin D16-25 + ovulation stimulation drugs if she wants to get pregnant
Ovarian failure
Hypothalamic pituitary failure
Karyotyping
MRI/CT → rule out CNS tumor
Treat→ HRT


Breast present uterus absent
High testosterone (N male)
Low testosterone (N female)
Karyotyping
46 XY→ Testicular feminization
46 XX→ Mullerian Agenesis
U/S pelvis, U/S MRI → Gonads → Gonadectomy
U/S Pelvis, U/S Kidney, IVP
Treat→ HRT
Treat→ vaginoplasty or vaginal dilators.


Breast absent uterus absent
All 46 XY
Physical Exam U/S MRI for Gonads
Gonadectomy
HRT

Secondary Amenorrhea:

- **WHAT IS 2RY AMENORRHEA?**
  Cessation of menses for a period of 6 months or 3 consecutive menstrual cycles in a female who previously had initiation of menses
- **WHAT IS THE PREVELANCE OF AMENORRHEA?**
  1.8-3%
- **WHAT IS THE CLASSIFICATON OF 2RY AMENORRHEA?**
  Classified according to the gonadotropin level or the anatomical level

• Hypergonadotropic	CNS/Hypothalamic
• Hypogonadotrpic	Pituitary
• Euogonadotrpic	Ovarian
• Hperprolactinemia	Outflow→ Uterine, Cervical, Vaginal
• Anatomic defects	

HYPOGONADOTROPIC AMENORRHEA "CNS / HYPOTHALAMIC "

- Stress ⇨ ↑ β-endorphins ⇨↓ GnRH ⇨
  ↓ FSH ↓ LH ⇨ ↓ Estrogens
- Exercise ⇨ Excessive strenuous exercise ⇨ Runners & Ballet dancers
  Mechanism ⇨ Similar to stress
- Weight loss "Anorexia nervosa" ⇨ More frequent in adolescent & young adults
  ⇨ 0.5-1% of women aged 15 –30 years
  ⇨ 15% < Ideal body weight
- Functional "None of the above causes" ⇨ No LH pulses or persistent pulse frequency of "luteal phase "
  2ry to neurotransmitter abnormality of the CNS (? ↑ Opioid activity)

- ***IS IT OF ANY CONCERN IF THESE YOUNG WOMEN BECOME AMENORRHEIC?***
  HYPOESTROGENISM is the main concern→ can lead to osteoporosis.
- ***WHY IS IT MORE WORRYING THAN THE MENOPAUSAL WOMEN?***
  During adolescence estrogen plays a critical role in determining PEAK BONE DENSITY which reached in the 2nd decade of life
- ***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 Pt ⇨↓ BMD (0.64) < Normal controls (0.72)
- Anorexia nervosa Pt may have osteoporotic fractures

SHEHAN'S SYNDROME

- Pituitary failure ⇨ following sever post partum hemorrhage
- Deficiency of all pituitary hormones
- ↓FSH & LH ⇨ Failure of ovarian follicular development
  ⇨↓ Estrogen ⇨ Amenorrhea
- Rx ⇨ HRT
  ⇨ hMG for ovulation induction

Treatment of Hypogonadotropic secondary amenorrhea:

- ↓ In training intensity to a level where regular menses resume
- HRT ⇨ Cyclic estrogen / progesterone
  Premarin 1.25 mg continuously
  Medroxyprogesterone acetate 5 mg /D for 12 D each cycle
  OCP ⇨ better compliance
- Anorexia nervosa ⇨ Psychiatric Rx
  Meanwhile ⇨ HRT
  Long term follow up ⇨ Frequent relapses after attaining ideal body weight
- Functional Hypogonadotropic Amenorrhea ⇨ HRT / ovulation induction

EUOGONADOTROPIC AMENORRHEA

➢ ***PCO***

- *Amenorrhea / anovulatory cycles*
- *Enlarged polycystic ovaries*
- *Infertility*
- *Hyperinsulinemia / Obesity*
- *Hyperandrogenism / hirsutism*
- *↑ LH*
- *Acyclic estrogen production / unopposed by progesrtrone ⇨ ↑ risk of endometrial hyperplasia/Ca*
- *Inheritable disorder with a complex inheritance pattern*

➢ **Treatment: all depends on the symptoms and what is bothering the patient the most.**

- **Amenorrhea and Irregular cycles →** Cyclic progesterone or OCP (both will protect endometrium, regulate the cycle and decrease menorrhagia)
- **Hirsutism→** OCP→ decrease ovarian androgen and increase SHBG + antiandrogens→ spironolactone, Cyproterone acetate, Flutamide → all will bind with androgen receptors, decrease the androgens and 5 alpha reductase activity.
- **Hyperinsulinism/Obesity →** Glucophage / weight reduction
- **Infertility→** Clomid (Ovulation 70% and pregnancy 40%), hMG, Ovarian drilling (Ovulation 92% and pregnancy 70%)

HYPERGONADOTROPIC AMENORRHEA

- ***WHAT IS PREMATURE OVARIAN FAILURE (POF)?***
  - 2ry Amenorrhea
  - ↑ FSH & LH
  - ↓ estrogen
  - Before the age of 40 Y
- ***WHAT IS THE INCIDENCE OF POF?***
  - 1%
- ***WHAT IS THE CAUSE?***
  - Unknown / autoimmune / genetic factors
  - Associated autoimmune disease 39%
- ***WHAT ARE THE PATHOLOGICAL CHARACTERISTICS OF POF?***
  TWO TYPES
  - Ovarian sclerosis & lack of follicles
  - Resistant ovary syndrome
- ***HOW TO MANAGE POF?***
  - R/O other autoimmune diseases ⇨ RH factor ANA, Antithyroid Antibodies Antichromosomal Antibodies, glucose, cortisol, Ca , Ph, TSH
  - HRT ⇨ to prevent osteoprosis
  - Spontaneous pregnancy can occur in women with POF on HRT 8%
  - hMG/HCG glucocorticoids have been claimed to give better pregnancy rates

HYPERPROLACTINEMIA

- The most common pituitary cause of 2ry Amenorrhea
- Causes
  -Pituitary adenoma
  -Idiopathic
  -Loss of inhibition by dopamine ⇨ Hypothalamic or pituitary stalk lesions
  -Hypothyroidism
  -PCOS
  -Medications ⇨ (especially antipsychotic meds) phenothiazines , haloperidol monoamineoxidase inhibitors, TCA, H2 receptors blockers
- Galactorrhea ⇨ 1/3 of Pt
- Amenorrhea/ Hyperprolactinemia Pt ⇨ at risk of osteoporosis due to ↓ estrogen
- ***TREATMENT***
  - Hypothyroidism ⇨ L-Thyroxin ⇨ If still amenorrheic after RX ⇨ Parlodel + Thuroxin
  -If no substitute for the medications that cause hyperprolactinemia ⇨ HRT
  -Hypothalamic or pituitary stalk lesions ⇨Surgical excision

TREATMENT OF HYPERPROLACTINEMIA

- ***PITUITARY ADENOMA (PROLACTINOMA)***

- Macroadenoma ⇨ > 10 mm ⇨ Respond to medical Rx ⇨ Dopamine agonist (bromocriptine) ⇨ ↓ size of the tumor & ↓ prolactin level
  ⇨ Pt not responding to medical Rx or not tolerating it ⇨ Surgery/Irradiation
- Microadenoma ⇨< 10mm ⇨ remain stable in size Rx ⇨ Bromocriptine ⇨ ↓ prolactin level
  Normalize the menstrual cycle

- ***IDIOPATHIC HYPERPROLACTINEMIA***
  Rx ⇨ Dopamine agonist ⇨ Bromocriptine or Pergolide
- ***Side effects of dopamine agonists***
  -Postural hypotension
  -Nausea
  -Headache
  -Nasal stuffiness

  Start with a low dose & gradually ↑ in order to reduce the side effects experienced.

ANATOMICAL CAUSES

- *Uncommon cause of 2ry Amenorrhea*
- *Asherman's Syndrome ⇨ Hx of D/C for RPOC after abortion / puerperium or previous uterine infection (this patient will have a negative progesterone challenge test)*
- *Intrauterine Adhesions*
- *Normal hormones*
- *-ve progesterone challenge test*
- *Dx ⇨ HSG / HYSTROSCOPY*
- *Rx ⇨ Hysteroscopic resection of the adhesions (insert intrauterine device to prevent further adhesions) followed by estrogen therapy*

Summary:

1- Primary amenorrhea is diagnosed with absence of menses at age of 14 **without** secondary sexual development or age 16 with secondary sexual development.
2- Breast are endogenous assay of estrogen ==> presence of breast indicate adequate estrogen production and absence of breast indicate inadequate estrogen exposure.
3- **Kallman Syndrome**: primary amenorrhea + breast absent and uterus present + Anosmia.
4- **Pregnancy** is the most common cause of 2^{ry} amenorrhea.

MCQ's:

1- The first evidence of pubertal development in the female is usually:

a. Onset of menarche
b. Appearance of breast buds
c. Appearance of axillary and pubic hair
d. Onset of growth spurt

2- Which of the following is consistent with a diagnosis of delayed puberty?

a. Breast budding in a 10-year-old girl
b. Menarche delayed beyond 16 years of age
c. Menarche 1 year after breast budding
d. FSH values less than 20 mIU/mL

3- Delayed puberty and sexual infantilism associated with hypergonadotropic hypogonadism can be seen in patients with which of the following?

a. Adrenogenital syndrome (testicular feminization)
b. McCune-Albright syndrome
c. Kallman syndrome
d. Gonadal dysgenesis
e. Mullerian agenesis

Answers:

1- B
2- B
3- D

For mistakes or feedback

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