**Amenorrhea**

* **Primary Amenorrhea** : (is defined either as )
  + absence of menses by age 14 years with no development of secondary sexual characteristics
  + OR as absence of menses by age 16 years with normal development of secondary sexual characteristics.
  + prevalence about 0.3%
* **Secondary amenorrhea :** 
  + No menses for 3 months 🡪 if previous menses were regular.
  + No menses for 6 months 🡪 if previous menses were irregular .
  + prevalence about 3%
* 10 - 20% of women complaining of infertility have amenorrhea .
* Up to 50% of competitive runners (training 80 miles per week) and up to 44% of ballet dancers have amenorrhea (strenuous exercise 🡪 stress related amenorrhea ) .
* **Oligomenorrhea** : (infrequent periods)
  + Interval of more than 35 days between periods .
  + From 5 weeks – 3 months 🡪 if previous menses were regular .
  + From 5 weeks – 6 months 🡪 if previous menses were irregular.
* **Events of Puberty :**
  + Thelarche (breast development) :
    - Requires estrogen
  + Pubarche/adrenarche (pubic and axillary hair development) :
    - Requires androgens
  + Menarche , Requires :
    - GnRH from the hypothalamus
    - FSH and LH from the anterior pituitary
    - Estrogen and progesterone from the ovaries
    - Normal outflow tract
* **Etiologies of Primary Amenorrhea :**
  + Secondary sexual characteristics present :
    1. Constitutional delay
    2. Genito-urinary malformation, e.g. imperforate hymen, transverse vaginal septum, absent vagina with or without a functioning uterus
    3. Androgen insensitivity
    4. Resistant ovary syndrome
    5. Pregnancy
  + Secondary sexual characteristics absent :
    1. Hypothalamic dysfunction, e.g. chronic illness, anorexia nervosa, weight loss, 'stress'
    2. Gonadotrophin deficiency, e.g. Kallman's syndrome
    3. Hypopituitarism
    4. Hyperprolactinemia
    5. Hypothyroidism
    6. Gonadal failure, e.g. ovarian dysgenesis/agenesis (turner syndrome) , premature ovarian failure
* **Ambiguous external genitalia :**
  + Congenital adrenal hyperplasia :
    - Deficiency in pathway of production of cortisone. Most common enzyme deficiency is “21-hydroxylaze enzyme”.
    - Fusion of labia majora and enlargement of clitoris .
  + Androgen-secreting tumor :
    - Sertoli-Leydig Cell Tumor (ovarian tumor that produces testosterone 🡪 clitoro-megaly and Ambiguous external genitalia)
    - 1/3 of cases may present with virilization. In other patients, oligomenorrhea followed by amenorrhea may occur. Progressive masculinization and hirsuitism may also occur .
    - Removal of the tumor results in a nomral menses in about 4 weeks .
  + 5-Alpha-reductase deficiency :
    - This enzyme is important for development of external genitalia .
    - 5-Alpha-reductase is responsible for reducing level of testosterone , so deficiency in this enzyme will increase testosterone level .
* **Gonadal dysgenesis :**
  + Classic turner’s syndrome (45XO) “most common”
  + Turner variants (45XO/46XX),(46X-abnormal X) 🡪 mosaic
  + Mixed gonadal dysgenesis (45XO/46XY) 🡪 swyer`s syndrome
  + Patient have uterus , cervix , tubes , but ovaries are streaks of connective tissue .
  + If the variant have Y chromosome (eg. 46XY) do gonadectomy because of high risk of malignancy (dysgerminoma ).
  + Turner's syndrome :
    - Is caused by either a complete absence or a partial abnormality of one of the two X chromosomes.
    - Features: short stature, web neck, lymphedema, shield chest with widely spaced nipples, short metacarpal bones and renal anomalies.
    - Wide carrying angle, coarctation of the aorta.
    - High FSH (because ovaries don’t produce estrogen 🡪menopause ) and LH levels.
    - Bilateral streaked gonads.
    - Karyotype : 80 % 🡪 45 X0 “these will never get pregnant” , 20% 🡪 mosaic forms (46XX/45X0) or (45X/46XY) “these might get pregnant”
    - Treatment: HRT (just to prevent osteoporosis and heart disease ) .
* **Uterovaginal agenesis :**
  + 15% of primary amenorrhea . Second most common cause of Primary amenorrhea.
  + Normal secondary development & external female genitalia , Normal breasts and Sexual Hair
  + Normal female range testosterone level
  + Absent uterus and upper vagina & normal ovaries and tubes .
  + Karyotype 46-XX (Mayer-Rokitansky-Kuster-Hauser syndrome)
  + 15-30% associated renal (pelvic kidney , double ureter), skeletal and middle ear anomalies
  + Treatment : Vaginal creation (Dilatation VS Vaginoplasty) 🡪 just for intercourse .
* **Androgen insensitivity syndrome :**
  + Normal breasts (normal range estrogen) but no or scanty sexual hair and Normal looking female external genitalia
  + Absent uterus (so no menses) and upper vagina
  + Karyotype 46, XY
  + Male range testosterone level
  + Treatment : gonadectomy after puberty + HRT
  + The testes present in the inguinal canal and liable to trauma, torsion and malignancy
  + The receptors in the external genitalia are not sensitive to testosterone and sometimes deficiency of 5-alpha reductase which converts T to T2
* **Imperforate hymen :**
  + Imperforate hymen represents the most common and most distal form of vaginal outflow obstruction.
  + Clinical presentations range from an incidental finding on physical examination of an asymptomatic patient to discovery on an evaluation for primary amenorrhea , abdominal distension or abdominal or back pain .
  + Normal secondary sexual characteristics , normal period (blood accumulates in vagina not uterus) but anatomical problem .
  + As the blood accumulates in vagina it will distend and cause pressure on urethra which leads to urine retention
  + The differential diagnosis of uterovaginal obstruction includes disorders of vaginal development, such as transverse vaginal septum or complete vaginal agenesis.
  + Could be complete imperforation or transverse vaginal septum with perforated hymen .
  + No need for karyotyping , US will show blood in vagina , and by inspection of external genitalia we will see bulging of the hymen (bluish discoloration )
  + Treatment : Incise the Hymen “cruciate incision“ remove the edges to prevent closure of hymen , drain the blood .
  + Needs IVP (Intravenous pyelogram) as there is up to 30% association with renal tract abnormalities. Also risk for endometriosis due to outflow obstruction and retrograde period .
  + After 1 year of treatment we should do laparoscope to exclude endometriosis .
* **Hypogonadotrophic Hypogonadism :**
  + Normal height
  + Normal external and internal genital organs (infantile size uterus)
  + No GnRH so 🡪 Low FSH and LH
  + 30-40% anosmia (kallmann’s syndrome also known as olfactory genital syndrome)
  + Treat with HRT, patient can get pregnant (GnRH pump which releases the hormone in pulsatile pattern , if not available do IVF)

* **Constitutional delay :**
  + There is no anatomical abnormality or endocrine investigations show normal results
  + It is caused by immature pulsatile release of gonadotrophin-releasing hormone; maturation eventually occurs spontaneously
  + delayed bone age ( X-ray Wrist joint)
  + Positive family history
  + Diagnosis by : exclusion , X-ray of wrist bone (patient age 14 while bone age 12 ) and +ve family hx .
  + No treatment needed , just wait .
* **Weight-related amenorrhoea** : (Anorexia Nervosa )
  + 1o or 2o Amenorrhea is often first sign
  + A body mass index (BMI) <17 kg/m²🡢 menstrual irregularity and amenorrhea
  + Hypothalamic suppression 🡪Low estradiol 🡪 risk of osteoporosis
  + Treatment : ↑ body wt. (Psychiatrist referral)
* **Etiology of secondary amenorrhea :**
  + No features of androgen excess present :
    - Physiologic, e.g. pregnancy, lactation, menopause
    - Iatrogenic, e.g. depot medroxyprogesterone acetate contraceptive injection (mostly injectable and implantable contraception), radiotherapy, chemotherapy
    - Systemic disease, e.g. chronic illness, hypo- or hyperthyroidism
    - Uterine causes, e.g. cervical stenosis (in case of complete closure which is very rare) , Asherman's syndrome (intra-uterine adhesions)
    - Ovarian causes, e.g. premature ovarian failure, resistant ovary syndrome
    - Hypothalamic causes, e.g. weight loss, exercise, psychological distress, chronic illness, idiopathic
    - Pituitary causes, e.g. hyperprolactinaemia, hypopituitarism, Sheehan's syndrome (pan-hypopituitarism)
  + Features of androgen excess present :
    - Polycystic ovary syndrome
    - Cushing's syndrome
    - Late-onset congenital adrenal hyperplasia
    - Adrenal or ovarian androgen-producing tumor
* Polycystic ovary syndrome and Hyperprolactinemia : (mentioned in details in previous lecture )
* **Asherman’s Syndrome :**
  + Secondary amenorrhoea (or oligomenorrhea or hypomenorrhea which is low blood amount) following destruction of the endometrium by vigorous curettage🡪 multiple intrauterine Synechiae show up on “Hysterography 🡪 filling defect , or hysterescopy”.
  + Can get pregnant but rare , and high risk of miscarriage .
  + MANAGEMENT: Under G.A. 🡪breakdown Adhesions through hysteroscope🡪insert an IUCD to prevent reformation 🡪hormone therapy (Estrogen to promote growth of uterus + P)
* **Premature ovarian failure :**
  + Menopause/ovarian failure occurring before the age of 40 years is considered premature
  + Auto-immune disease is the most common cause; auto-antibodies to ovarian cells, gonadotrophin receptors, and oocytes have been reported in 80% of cases
  + Before puberty or in adolescents, ovarian failure is usually due to a chromosomal abnormality, e.g. Turner mosaic, or previous radiotherapy, or chemotherapy
* **Autoimmune related dysfunction :**
  + The most common association is with thyroid disease, but the parathyroids and adrenals can also be affected
  + Several studies have shown laboratory evidence of immune problems in about 15-40% of women with premature ovarian failure
  + In general, ovarian biopsy is not indicated in patients with premature ovarian failure since no clinically useful information will be obtained
* **Weight-related amenorrhoea :**
  + A regular menstrual cycle is unlikely to occur if the body mass index (BMI) is less than 19 (normal range 20-25)
  + Weight loss may be due to illness, exercise, or eating disorders, among which anorexia nervosa lies at the extreme end of the spectrum
* **Progestogen-associated amenorrhea :**
  + Depot medroxyprogesterone acetate inhibits the secretion of gonadotrophins and thus suppresses ovulation
  + After 1 year of use, 80% of women have amenorrhoea or very scanty, infrequent vaginal bleeding
  + There is partial estrogen deficiency in women who use depot medroxyprogesterone acetate
  + The progestogen-only pill leads to reversible long-term amenorrhoea in a minority of women, due to complete suppression of ovulation
  + The levonorgestrel-releasing intra-uterine device MIRENA commonly results in amenorrhoea after a few months. This is thought to be mainly a local effect, but suppression of ovulation can occur in some women (in some cycles)
* **Assessment of secondary amenorrhea :**
  + History :
    1. A good history can reveal the etiologic diagnosis in up to 85% of cases of amenorrhea
    2. symptoms of pregnancy
    3. Associated symptoms, e.g. galactorrhoea, hirsutism, hot flushes, dry vagina, symptoms of thyroid disease
    4. Recent change in body weight
    5. Recent emotional upsets
    6. Previous menstrual and obstetric history
    7. Previous surgery, e.g. endometrial curettage, oophorectomy
    8. Previous abdominal, pelvic, or cranial radiotherapy
    9. Family history, e.g. of early menopause
    10. Drug history, e.g. progestogens, combined oral contraceptive, chemotherapy
  + Examination :
    1. Height and weight: calculate body mass index if appropriate.
    2. Signs of excess androgens, e.g. hirsutism, acne
    3. Signs of virilization, e.g. deep voice, clitoromegaly in addition to hirsutism, and acne
    4. Signs of thyroid disease
    5. Acanthosis nigricans: this hyperpigmented thickening of the skin folds of the axilla and neck is a sign of profound insulin resistance. It is associated with polycystic ovary syndrome (PCOS) and obesity.
    6. Breast examination for galactorrhoea
    7. Pelvic examination
* **Complications and prognosis :**
  + Osteoporosis: women with amenorrhoea associated with estrogen deficiency are at significant risk of developing osteoporosis. This increased risk persists even if normal menses are resumed. Estrogen deficiency is of particular concern in younger women as a desirable peak bone mass may not be attained
  + Cardiovascular disease
  + Young women with amenorrhoea associated with estrogen deficiency may be at increased risk of cardiovascular disease
  + Women with polycystic ovary syndrome have an increased risk of developing cardiovascular disease, hypertension, and type 2 diabetes .
  + Endometrial hyperplasia: women with amenorrhoea but no associated oestrogen deficiency are at increased risk of endometrial hyperplasia and endometrial carcinoma
  + Infertility: women with amenorrhoea generally do not ovulate
  + Psychological distress: amenorrhea often causes considerable anxiety, many women have concerns about loss of fertility, loss of femininity, or worry about an unwanted pregnancy. The diagnosis of Turner's syndrome, testicular feminization, or developmental anomaly can be traumatic for both girls and their parents
* **Treatment :** 
  + According to the cause

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Check pictures in the slide