3) Primary Amenorrhea - Dr. Chro

Introduction

- Amenorrhea (absence of menses) can be a transient, intermittent, or permanent condition resulting from dysfunction of the hypothalamus, pituitary, ovaries, uterus, or vagina.
- It is often classified as either primary (absence of menarche by age 16) or secondary (absence of menses for more than three cycle intervals or six months in women who were previously menstruating).

Definition

- No periods experienced by the age of 16.
- Investigations of this condition may be divided according to whether secondary sexual characteristic are present or not.
- If absent, girls should be investigated at the age of 16.
- If present, investigation can wait until the age of 18.

Etiology

- Primary amenorrhea is usually the result of a genetic or anatomic abnormality. However, all causes of secondary amenorrhea can also present as primary amenorrhea.
- In a large case series of primary amenorrhea, the most common etiologies were Chromosomal abnormalities causing
- Gonadal dysgenesis (ovarian failure due to the premature depletion of all oocytes and follicles) 50 percent
- Hypothalamic hypogonadism including functional hypothalamic amenorrhea 20 percent
- Absence of the uterus, cervix and/or vagina, müllerian agenesis – 15 percent
- Transverse vaginal septum or imperforate hymen – 5 percent
- Pituitary disease – 5 percent

\[\text{Amenorrhea is a symptom not a disease. The final diagnosis should be pathological diagnosis.}\]

Classifications of Amenorrhea

- According to the cause
  - Physiological
  - Pathological
- According to the onset
  - Primary amenorrhea
  - Secondary amenorrhea
- According to Hidden or apparent
  - False amenorrhea (Crypto menorrhea)
  - True amenorrhea
- According to plan for workup
  - Physiological
  - Anatomical
  - Endocrinological
- (THESE CLASSIFICATIONS ARE COMPLEMENTARY TO EACH OTHER….)
Causes of primary amenorrhoea

- Hypothalamic (absence of gonadotrophic releasing hormone, GnRH) or hypogonadatrophic (no LH or follicle stimulating hormone, FSH).
- This may be:
  - Idiopathic
  - Following radiotherapy
  - Following surgery
  - Craniopharyngomas in childhood
  - Anorexia
  - Excessive exercise (ballet dancers)
  - Chromosomal
  - Congenital “anatomical”

Amenorrhea is only a manifestation of the problem.

Problem may be endocrinologic or embryologic:

+/- secondary sexual characteristic

+/- female internal genitalia

- The normal human has 46 chromosomes, 44 autosomes and two sex chromosomes. The number is halved in both gamete, when fertilization occurs the original number is restored in the resulting fertilized ovum.
- In the normal female the sex chromosomes are XX, in the normal male XY. All oocytes carry the X chromosome, while about half the spermatozoa carry X, the others Y. Thus, the resulting offspring are either XX (female) or XY (male).
- Sex chromosome abnormalities mainly arise from non-disjunction
- At the division of the primary oocyte while still sited in the ovary, the two chromosomes fail to separate so that a primary oocyte is produced which may have two X chromosomes or none; conversely, the first polar body will contain the converse—none or two. Fertilization by a spermatozoon which may carry X or Y can therefore result in abnormal patterns, XXX, XXY or XO. YO has not been described as this genetic combination is lethal.
- The description is a simplification as more complex anomalies may occur for example mosaics or individuals of mixed chromosomal patterns.

Endocrinological

Four Sub phenotypes (Breast & uterus)

1. Absent breast + presence of uterus
2. Presence breast + absence uterus
3. Absence breast + absence uterus
4. Presence breast + presence uterus

1. Absent breast + presence of uterus (Hypogonadism)

- FSH Serum level
- Low / normal → Hypogonadotropic hypogonadim (hypothalamic- pituitry)
- High → Hypergonadotropic Hypogonadism (gonadal dysgenesis)
A. Gonadal failure:

*High FSH (hypergonadotropic)*

1. 45X (Turner’s Syndrome)
2. 46X; abnormal X (Deletion Disorders)
3. Mosaicism (X/XX, X/XX/XXX)
4. Pure XX (PGD, 46XX or Perrault syndrome)
5. 17 alpha-hydroxylase deficiency (46XX), CAH

B. CNS-hypothalamic pituitary disorders:

*Low FSH (hypogonadotropic)*

1. CNS lesions
2. Inadequate GnRH – Kallmann’s
3. Isolated gonadotrophin insufficiency

**Turner’s syndrome**

- Chromosome pattern XO.
- Incidence about three in 10 000 full-term births
- Present with primary amenorrhoea for there are either no ovaries or non-functioning streaks of tissue with no oogenesis.
- The vagina and uterus are present.
- Poor breast development.
- Little or no axillary and pubic hair.
- Short stature.
-Webbing of the neck.
- A wide carrying angle in the arms.
- Coarctation of the aorta.
- Congenital malformation of the kidneys may be found.

**Congenital adrenal hyperplasia (CAH)**

- Chromosomal pattern XX.
- Congenital adrenal hyperplasia is inherited as a Mendelian recessive.
- Female infants are born with ambiguous genitalia.
- Vagina and uterus are present.
- Ovaries are usually polycystic in appearance and anovulatory.
- Defective production of cortisol, most commonly due to 21-hydroxylase deficiency.
- Leads to overproduction of corticotrophic hormone and enlargement of the adrenal cortex.
- Increased adrenal androgen production.
- The clitoris is enlarged and the labia fused.
- Some of these babies are salt losers and become seriously ill in the first week of life.
- Teenagers often develop severe hirsutism and acne.
2. Presence breast + absence uterus

- Karyotype
- 46-XY → Androgen Insenitivity (TSF syndrome): Normal breasts & absent sexual hair
- 46-XX → Mullerian Agenesis (MRKH syndrome): Normal breasts & sexual hair

**Utero-vaginal Agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome)**

- 15% of primary amenorrhea
- Normal breasts and sexual hair development & normal looking external female genitalia
- Normal female range testosterone level
- Absent uterus and upper vagina & Normal ovaries
- Karyotype 46-XX
- 15-30% renal, skeletal and middle ear anomalies
- Treatment:
  - o STERILE? Vaginal creation Dilatation VS Vaginoplasty)

**Androgen insensitivity syndrome (AIS)**

- Chromosomal pattern XY.
- Due to lack of androgen receptors (deletion on X chromosome).
- Active breast development (hepatic oestrogens).
- Absent or scanty axillary and pubic hair.
- Usually absent uterus with a very short vagina.
- The gonads are testes or undifferentiated gonads and may be intra-abdominal or in the labia major.
- Male serum androgen levels.

3. Absence breast + absence uterus

- 17, 20 desmolase deficiency
- 17 a hydroxylase deficiency 46xy
- Agonadism
- Very rare

4. Presence   breast + presence uterus (Like secondary amenorrhea)

**Progesterone**

- Bleeding → Chronic anovulation e.g. PCOS
- No bleeding → Combined estrogen & progesterone → Bleeding → Ovarian failure (non dysgenetic) → serum FSH
  → No bleeding → Uterine Factor (Asherman syndrome)

**Anatomical causes**

- Menstruation not begun by the age of 17 must be distinguished from cryptomenorrhoea—hidden loss caused by obstruction to menstrual flow.
- This is most often caused by a septum across the vagina just above the hymen at the embryological junction of the Mullerian ducts and the urogenital sinus in the lower third of the vagina.
- It may be incomplete. A complete septum leads to cryptomenorrhoea (vagina filled with blood) and haematocolpos (uterus filled with blood).
- The lower part of the vagina may be a solid cord; haematocolpos and haematometra may form above this. On inspection of the vulva a bluish bulge is seen just inside the hymen. There may be cyclical attacks of abdominal pain and a mass may be palpable per abdomen, representing a large haematocolpos.
Treatment

- Under anaesthesia, incise the septum and express the haematocolpos by suprapubic pressure. If infection does not occur, subsequent menstruation and childbearing are normal.

Cryptomenorrhea “in summary”

- Intermittent abdominal pain
- Possible difficulty with micturition
- Possible lower abdominal swelling
- Bulging bluish membrane at the introitus or absent vagina (only dimple)

Diagnosis "primary amenorrhea”

1. History
2. Exam
3. Investigation
4. Workup

History in primary amenorrhea

- Developmental milestones (age of growth spurt, age of thelarche, adrenarche)
- Chronic illness (CRI, TB, Bl disease)
- Cyclic symptoms of menstruation
- Weight changes.
- Excessive exercise
- History of anosmia
- A history is taken including a family history as AIS may affect other females in the family.

Physical examination

The general examination

- Should begin by recording the girl’s height—if by 16 she is less than 147 cm there is a possibility of ovarian agenesis (Turner’s syndrome) or (pan)hypopituitarism. If there is a decrease in body weight, calculate Body Mass Index (wt(kg)/ht(m2)). A general examination checks the development of secondary sexual characteristics, hair patterns and density.

A pelvic examination

- Should be performed if the examiner really thinks a positive finding will be there. For most young women with primary amenorrhoea it will not be useful particularly at first consultation. The vulva is inspected to see that the introitus is patent; there may be cryptomenorrhoea, congenital absence of the vagina or a blind vagina as in AIS.

Investigations—a buccal smear and an examination of the polymorphonuclear leucocytes to determine if chromatin positive (probably XX) or chromatin negative (probably XO or XY); in other cases a full chromosome analysis may be needed to exclude mosaicism and AIS.

- Hormonal investigations should include LH, FSH, oestradiol and testosterone levels.
- Ultrasound will help determine the presence, state and size of the ovaries and any follicular activity.
- Uterine size can also be seen. It is rarely necessary to perform a laparoscopy to assess the pelvic organs.
Workup for Diagnosis

- Exclude physiologic (pregnancy)
- Exclude anatomical:
  - Crypto menorrhea
  - Ambiguous genitalia
- Endocrinological:
  - Four sub-phenotypes

Treatment

- If the girl is normally developed, with normal breast development, the uterus and vagina are normal and she is chromatin positive, the most likely diagnosis is delayed menarche. It is reasonable to await events; menstruation is not established in some individuals before 18 years.
- For those with a diagnosable pathological cause, the aim must be to restore normal function as far as possible and, although fertility may not be possible, enable the individual to lead as normal a sexual life as possible.
- Cases of Turner’s syndrome should receive long term treatment with cyclical hormones, oestrogen and progestogen (hormone replacement therapy). There is a small risk of uterine carcinoma.
- In AIS, the gonads are testes that are often found inside the abdomen or inguinal canal. Since these testes have a 25% risk of becoming malignant (teratoma or dysgerminoma) they should be removed soon after puberty and an artificial vagina may be constructed or dilators used to permit sexual intercourse. Treatment with oestrogen should also be given to augment breast development and prevent osteoporosis.
- In cases of congenital absence of the vagina and uterus the ovaries are usually normal. An artificial vagina may be constructed to permit sexual intercourse.
- Abnormalities of pituitary secretion should be treated with oestrogen or progesterone until fertility is desired.

### Evaluation of Primary Amenorrhea

- History and physical examination completed for a patient with primary amenorrhea
  - Secondary sexual characteristics present
    - Yes
      - Perform ultrasonography of uterus
    - No
      - Measure FSH and LH levels
        - FSH and LH < 5 IU/L
          - Hypogonadotropic hypogonadism
          - CNS; HP Disorder
        - FSH > 20 IU/L and LH > 40 IU/L
          - Hypergonadotropic hypogonadism
          - Karyotype analysis
            - 46, XY
              - Androgen Sensitivity Syndrome
            - 46, XX
              - Mullerian Agenesis
              - Imperforate hymen or transverse vaginal septum
          - Karyotype analysis
            - Outflow obstruction
              - Yes
              - Evaluate for secondary amenorrhea
            - No