**Primary Amenorrhoea: Dr Ban Hadi**

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* **Primary amenorrhoea:**

 Described as the absence of menstruation by 16 years of age irrespective of the presence or absence of secondary sexual characteristics (the girl has never menstruated before)

***Aetiology***: is classified according to the presence or absence of secondary sexual characteristics:

**A. Secondary sexual characteristics normal:**

Imperforated hymen-

Transverse vaginal septum-

Absent vagina and functioning or non functioning uterus-

Absent uterus **(Rokitansky syndrome)** -

XY female – Androgen insensitivity-

Resistant ovary syndrome-

-Constitutional delay

**B. Secondary sexual characteristics absent:**

*1.* ***Normal stature****:*

**Hypogonadotrophic hypogonadism**

 -Congenital ( Isolated gonadotrophin-relesasing hormone deficiency,

 Olfactogenital syndrome )

 -Acquired (Weight loss/anorexia, excessive exercise, hyperprolactinaemia)

**Hypergonadotrophic hypogonadism**

 Gonadal agenesis (formation failure) and dysgenesis (abnormal formation), turner mosaic, ovarian failure and galactosaemia

 *2.****Short stature:***

**Hypogonadotrophic hypogonadism**

 -Congenital ( Hydrocephalus )

 -Acquired ( Trauma, empty sella syndrome or cong. absence of pituitary, tumours )

**Hypergonadotrophic hypogonadism**

 - Turner's syndrome and other X deletions or mosaic

* **C. Heterosexual development:**
* Congenital adrenal hyperplasia-
* -Androgen-secreting tumour
* 5α Reductase deficiency-
* -Partial androgen receptor deficiency
* True hermaphrodite-

**Management: (diagnosis and treatment of primary amenorrhea)**

***A. Diagnosis:***

**History:**

**-** cyclical abdominal pain and sometimes urinary retention suggestive of outflow obstruction

- features of virilization such as hirsutism

- medical diseases such as cushing syndrome

- sexual history

- drug history, previous radiotherapy and chemotherapy

- weight changes, visual field defects

- family history of the same problem in the family

**Examination:**

*General*: height, weight, secondary sexual characteristics(breast development, pubarche and adrenarche), features of endocrine diseases, stigmata of chromosomal abnormalities such as turner's syndrome (webbing of the neck), galactorrhea, visual field exam.

*Abdominal examination for* masses

*Perineal inspection*: inspect the vulva for any abnormality such as tense bulging bluish membrane (imperforated hymen) and vaginal septum, clitoromegaly.

**Investigations:**

1.Pregnancy test: to rule out pregnancy although it causes secondary amen.

2. Pelvic Ultrasound: for the presence or absence of the uterus and ovaries, also to detect hematocolpos and hematometra

 3. CT scan and MRI for the abdomen, pelvis and brain

4. LH , FSH ,SHBG

5. Thyroid function test

6. Prolactin, estradiol, testosterone

7. Karyotyping to exclude XY female and turner

8.Progesterone challenge test: to induce withdrawal bleeding in females with functioning uterus.



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**Management is based on the aetiology, and the presence or absence of secondary sexual characteristics**

* **The presence of normal secondary sexual characteristics** should alert the clinician to the concept that **outflow tract obstruction** may be occurring. This is the most common cause of primary amenorrhoea in the presence of normal secondary sexual characteristics. It is simple to arrange for **pelvic ultrasound** to assess pelvic anatomy. Rarely we may need to use **MRI or CT scanning**. **If the uterus is absent** then **karyotype** should be performed and if this is **46XX** then the **Rokitansky syndrome** is the most likely diagnosis. If **46XY** the patient is **XY female**. **If the uterus is present** on ultrasound then there may be an associated Haematocolpos and haematometra and appropriate reconstructive surgery should be performed.

**If pelvic anatomy is normal assess**

* **Gonadotrophins & Prolactin levels**. This indicate hypothalamic cause for amenorrhoea, the so called **Constitutional delay.** In some cases **LH/FSH ratio** may be elevated in **PCOS.** If **Gonadotrophins** are elevated think of **Resistant ovary syndrome.** Elevation of **prolactin** indicates **Prolactinoma. Ovarian biopsy** if suspect Resistant ovary syndrome**. Histopathology** illustrating absence of oocytes. **CT or MRI imaging** **of pituitary fossa** if elevated serum prolactin levels ( **Microadenoma** ).

**Absent uterus:**

* Girl managed by special psychological counseling as she got problem regarding their future sexual activity & infertility.
* Vagina is created at appropriate time (Vaginoplasty ) by surgical or non- surgical way using vaginal dilators.
* Girl with XY Karyotype: Counseling over malignant potential of their gonads ( Gonadectomy ).

**Outflow obstruction:** Surgical management

* Imperforate hymen; cruciate incision of the hymen or hymenectomy.
* Transverse Vaginal Septum; Excision of the septum depending on its level within the vagina.
* **If constitutional delay**: and secondary sexual characteristics are complete no need to suggest any treatment apart from annual review until she has menstruation, some use COC pills to promote menstruation as this will reassure her that menstruation can occur.
* **If pituitary microadenoma:** then treatment is with Bromocriptine or Cabergoline, macroadenoma may necessitate surgery or radiotherapy.

**Absence of secondary sexual characteristics,** Assess **patient’s height:**

**If normal height for age:** assess & measure Gonadotrophins, either low or high.

-Low levels confirm Hypogonadotrophic Hypogonadism

-Elevated levels confirm & provoke clinician to perform Karyotyping.

* \*46XX: Mean Resistant Ovary Syndrome or Premature Ovarian Failure or Gonadal Agenesis.
* \*46XY: Mean XY Female will have 46XY Gonadal Agenesis or Testicular Enzymatic Failure.

**If short stature,** Do Gonadotrophins Measurement.

* If low; Intracranial lesion
* Or high; Turners Syndrome or Turners mosaic.
* Managemant: If Hypogonadotrophic Hypogonadism so hormone replacement therapy is indicated to induce secondary sexual characteristic development. Future need for ovulation induction as they will be infertile.

Oestrogen used alone for 2 years and then 2-3 years of gradual introduction of progestogens thereby establishing normal breast growth

**TURNER’S SYNDROME (45X AND MOSAICS)**

 This is probably the commonest abnormality in females involving the sex chromosomes. Although 1 in 2500 live-born girls are affected, most pregnancies with this abnormality miscarry, probably secondary to major cardiac defects.

**Physical abnormalities associated with Turner’s syndrome**

1. Growth failure: low birth weight and short stature;
2. ovarian failure: no secondary sexual development in most cases, occasionally secondary amenorrhoea in mosaicism;
3. inverted, widely spaced nipples, and shield chest;
4. webbed neck;
5. puffy hands and feet in babies due to lymphoedema;
6. low hairline;
7. cubitus valgus;
8. short fourth metacarpal;
9. high, arched palate, micrognathia and defective dental development;
10. renal dysgenesis;
11. left-sided cardiac malformations, coarctation of the aorta;
12. distortion of the Eustachian tube leading to otitis media;
13. nail dysplasia;
14. eye deformities.

 Intelligence is usually normal, but there is an increased risk of impairment of non-verbal skills, e.g. maths and visuospatial. The phenotypic abnormalities result in most cases being diagnosed in infancy and childhood. The girls are then usually referred to a gynaecologist after optimal growth potential has been achieved using growth hormone, for advice about long-term hormone replacement therapy (HRT). However, spontaneous pubertal development can occur, particularly in girls with mosaicism. In most girls, ovar­ian failure will have occurred early in life; although they have a uterus and vagina, they will not develop any secondary sexual characteristics without hormonal supplements.



**Treatment:**

 A low dose of oestrogen is given initially to encourage steady growth of the breasts; this is usually started after the age of 12 years as the administration of oestrogen promotes epiphyseal fusion, which stops further growth. The dose of oestrogen is gradu­ally increased over 2 years.

The uterus will respond to oestrogen therapy, so after 2 years it is necessary to add progestogens cyclically to produce regular endometrial shedding, or in a continuous combined regime to suppress endometrial development. HRT should be continued until at least the age of 50 years. Cryopreservation of ovarian tissue may be an option for future fertility, particu­larly for girls with mosaicism.

**There are a number of long-term health issues which affect women with Turner’s syndrome**:

1. hypertension; coarctation of the aorta; bicuspid aortic valve; dissecting aortic aneurysm; diabetes; hypothyroidism; coeliac disease;
2. sensorineural hearing loss; renal disease; eye problems – red–green colour blindness and increased risk of osteoporosis.

Premature mortality in women with Turner’s syndrome is three times higher than in the general population. After treatment with donor oocytes. Clinical pregnancy rates are reported to be comparable to those of other women with primary ovarian failure but there is an increased risk of com­plications including diabetes and hypertension in the preg­nancy, and delivery by caesarian section (CS) may be required because of the woman’s short stature.

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End of lecture