Protocol for diagnosis and management of Amenorrhea

Definitions:

♦ **Primary Amenorrhea:**
  - No period by age 14 years and no growth and development of secondary sexually characteristics.
  - No period by age 16 years regardless of presence of normal development and secondary sexually characteristics

♦ **Secondary Amenorrhea:** Cessation of regular menstruation for more than three cycle interval or more than six months total.

**Evaluation of the amenorrheic patient.**

Menstrual function involves a four step interrelated system with negative feedback to higher centres from Axes 2 and 3. Disorders are divided into four axes, depending on the step that fails to function properly.

Axis 1: Disorders of the outflow tract, patency and continuity (endometrium, cervix and vagina).
Axis 2: Disorders of the ovary
Axis 3: Disorders of the anterior pituitary
Axis 4: Disorders of the CNS/ hypothalamus

**First step:**

♦ H&P
♦ Pregnancy test
♦ TSH level
♦ Progesterone challenge test (PCT):
  - 10 mg progesterone daily for 7 days
  - If the patient bleeds within one week after completing the progesterone challenge, this means that endogenous oestrogen is available and the out flow tract is normal. An ovulation, an axis 2 disorder, is established.
  - If the patient does not bleed, then further investigation is necessary to determine if an Axis 1, 3, or 4 disorders are present.

**Second step:**

Necessary if tests administered in first step are negative.

♦ Oestrogen and progesterone challenge test:
  - 1.25mg oestrogen daily for 21 days with the addition of 10 mg progesterone for the last 5 days
o If the patient does not bleed within 2 days after completing the progesterone, an outflow tract problem is present.
o If the patient bleeds, disorder may be axis 2, 3 or 4.

**Third step:**
Determine reason for lack of oestrogen production. Follicle problem (axis 2) or gonadotropine problem (axis 3 or 4) can be present. FSH and LH assay is recommended.
Key point: When gonadotropins (FSH or LH) are low, the problem is at the higher centres (hypothalamic/pituitary); when the gonadotropins are high, the problem is in the ovary/follicle.

**Fourth step:**
Determine the cause of hypogonadotropic or hypergonadotropic state.
If the patient is hypogonadotropic, axis 3 and 4 are involved. If the patient is hypergonadotropic and younger than 30 years karyotype determination is necessary. The presence of Y chromosome is indication for gonadectomy.

**Specific diagnostic evaluation for primary amenorrhea:**
- If there is no breast and FSH level is elevated probable diagnosis is gonadal dysgenesis, karyotype should be obtained. With 46 xy gonadectomy is mandatory.
- If the uterus is absent. FSH is normal and testosterone is within normal range, the probable diagnosis is mullarian agenesis (Mayer-Rokitansky-Kuster-Hoauer syndrome).
  If testosterone is in the male range the probable diagnosis is androgen insensitivity syndrome (testicular feminization). Will need karyotype determination. If there is Y chromosome material gonadectomy is mandatory.
- If FSH is normal and both uterus and breast are present, than the work up should focus on the secondary amenorrhea.
- Hyperprolactinemia and PCOS are the rare causes of primary amenorrhea, will discuss in evaluation of secondary amenorrhea.
Specific diagnostic evaluation for secondary amenorrhea:

- Hyperprolactinemia is the cause of amenorrhea- galactorrhea syndrome. Serum prolactin level above 15 to 20 ng/ml is considered abnormality high in women in reproductive age.
  - Serum prolactin level should be measured at least twice before MRI particularly in women with borderline high level (<50 ng/ml). All patients with hyperprolactinemia should be screened for thyroid disease because hypothyroidism can cause hyperprolactinemia.

- PCOS is a common etiologic factor for amenorrhea; the minimal criteria for the diagnosis are two out of three of the following:
  1. Hyperandrogenism
  2. Oligomenorrhea or amenorrhea
  3. Polycystic ovaries on ultrasound

- A high level of testosterone or DHEA-S may solidify the diagnosis of PCOS or may raise question of an androgen secreting tumour of ovary or adrenal gland. CT imaging or ultrasonography of the ovaries can be helpful.

- Asherman syndrome should be suspected in women with secondary amenorrhea and history of uterine infection or D&C for an obstetrical complication. Hysterosalpingography or ideally Hysteroscopy will confirm the diagnosis.

Management:

- All women with primary amenorrhea should be counselled regarding its cause treatment, and their reproductive potential.

- Psychological counselling is important in patients with absent mullarian structure or a Y chromosome.

- Presence of Y chromosome is indication for gonadectomy.

- HRT is considered in women with gonadal failure.

- In functional hypothalamic amenorrhea cause correction is recommended.

- An advance in assisted reproductive technology has now made it possible for many women with primary amenorrhea to participate in reproduction.

- A dopamine agonist Bromocriptine will correct hyperprolactinemia.

- Treatment of hyperandrogenism is directed toward patient’s goal (e.g., relief of hirsutism, resumption of menses, fertility).

- Asher man’s syndrome needs hysteroscopic lyses of adhesions followed by long term oestrogen administration to stimulate re growth of endometrial tissue.