Protocol for diagnosis and management of Amenorrhea

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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 centers 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 for7 days
    - If the patient bleeds within one week after completing the progesterone challenge, this means that endogenous estrogen is available and the out flow tract is normal. Anovulation, 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 is present.

Second Step:

Necessary if tests administered in first step are negative.

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

Third Step:

Determine reason for lack of estrogen production. Follicle problem (axis 2) or gonadotropin 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 centers (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 hyperganadotropic 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 dysgenisis, 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-Hoauser 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 Dvaluation for Secondary Amenorrhea:

- Hyperprolactinemia is the cause of amenorrhea-galactorrhea syndrome. Serum prolactin level above 15 to20 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 (<50ng/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- Hyperandrogenisim
  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 tumor 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 hyperandrogenisim is directed toward patient’s goal (eg, relief of hirsutism, resumption of menses, fertility).
- Asher man’s syndrome needs hysteroscopic lyses of adhesions followed by long term oestrogen administration to stimulate regrowth of endometrial tissue.