

SECONDARY AMENORRHEA

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Definitions:

Primary amenorrhea is failure of menses to occur. It is relatively rare and usually presents to the pediatrician. Very occasionally, such a patient will present to USHS and should be referred to a gynecologist specializing in reproductive endocrinology or an endocrinologist. The 95th percentile for menarche in the US is 14.5 yrs.

Secondary amenorrhea is cessation of menses for at least 3-6 months in women who have previously had normal cycles. For women who have previously been on OC's, secondary amenorrhea is defined after 6 months absence of menses. For women previously taking depot medroxyprogesterone acetate or with prior oligomenorrhea, secondary amenorrhea is defined after 12 months cessation of menses or at least 6 cycle times.

The single most common cause of secondary amenorrhea in reproductive age group women is PREGNANCY! Always start your workup with a urine or serum beta-hCG.

Polycystic Ovary Syndrome can present as either primary or secondary amenorrhea. It is common in the reproductive age group and because of its importance, will be discussed separately.

Secondary amenorrhea with significant virilization (frontal balding, increase in size of shoulder girdle muscles, clitoromegaly [>2 cm], coarsening of the voice, acne, hirsutism) especially if recent in onset and rapidly progressive, suggests an adrenal or ovarian tumor. These patients should be referred to an endocrinologist or a gynecologist specializing in reproductive endocrinology.

The rest of this discussion of secondary amenorrhea assumes that the patient is neither pregnant nor postmenopausal nor has signs of significant virilization.

Investigation of Secondary Amenorrhea

The investigation of secondary amenorrhea does not often require extensive hormonal or imaging studies. The evaluation should be guided by a thorough history and physical examination.

Consequences of Secondary Amenorrhea

- Anxiety, altered self-image, loss of self-esteem
- Possible decrease in fertility
- If there is a lack of estrogen, hot flashes, night sweats, vaginal dryness, dyspareunia, decreased libido, severe premature bone loss
- There may be a life-time increase in cardiovascular disease secondary to lipid effects
- If unopposed estrogen, endometrial hyperplasia and increased risk of endometrial CA

Etiologies of Secondary Amenorrhea

1. Two possible etiologies:

- Cyclic production of gonadotropins is deficient; “central” etiology
- Ovary or uterus is unresponsive; “end organ” etiology

2. Defects can be at one of 4 levels

- Level 1: hypothalamic
- Level 2: pituitary/thyroid
- Level 3: ovarian
- Level 4: uterine

Level 1: Hypothalamic defects

- After pregnancy, the next most common reason for secondary amenorrhea is a failure of the LH surge, or hypothalamic amenorrhea.
- Basal secretion of FSH is low to normal but a defect in estrogen secretion or the amplitude or frequency of LH release keeps the midcycle surge in LH from occurring.
- Three categories of hypothalamic amenorrhea will be discussed:
 - 1) Mild defects
 - 2) Severe defects
 - 3) Athlete’s amenorrhea

Mild Hypothalamic Defects

➤ Mild defects are associated with:

- Mild psychological stress such as leaving home for college, starting medical school or internship, etc.
- Mild weight loss
- Increase in exercise
- No reason

➤ Basal estrogen secretion is intact so the endometrium is subjected to low levels of proliferation. A brief course of progesterone (Provera 10 mg/d x 5-10 d) will induce a

withdrawal bleed within a few days after finishing the medication. After the pregnancy test, a progesterone challenge is the single most valuable diagnostic test in secondary amenorrhea. The withdrawal bleed:

- Is a safe bioassay of FSH and estrogen levels
 - Confirms uterine responsiveness
 - Reassures the patient by restoring menstrual flow
- Make sure you have the patient sign a consent form before taking the Provera (USHS policy)
- Long-term therapy includes:
- Reassurance and education
 - If amenorrhea is prolonged, consider oral contraceptives or periodic Provera (q 6-8 weeks) to prevent unopposed estrogen stimulation. Beware of giving cyclic Provera in patients who are sexually active and not using a method of contraception.

Severe Hypothalamic Defects

- Severe hypothalamic defects are associated with:
- Severely disturbed hypothalamic-pituitary axis
 - Basal estrogen secretion is low
 - There is no withdrawal bleed to progesterone challenge.
- Commonly seen in:
- Anorexia nervosa or other severe weight loss
 - Profound emotional stress
 - Strenuous exercise or musical training
 - Nutritional Deficiencies- not enough fat consumption
 - No apparent cause
- Correction of the underlying problem is required to correct the secondary amenorrhea
- If underweight, gain weight
 - Treat the eating disorder
 - Stress relief
 - Decrease in physical training

Athlete's Amenorrhea

- Young women in excellent physical condition often report oligomenorrhea or amenorrhea
- Luteal phase defects may contribute with subnormal progesterone secretion or actual shortening of the luteal phase
- Athlete's triad is the combination of:
- Eating Disorder and Excessive Exercise
 - Amenorrhea
 - Osteoporosis
- Appears severe but resolves with easing of contributing factors
- Fertility is not impaired

► Estrogen levels and bone density are lower than eumenorrheic peers and bone density may not be fully reversed by later resumption of menses. Therefore, these athletes may be risking long-range osteoporosis.

► Rx:

- Treat underlying eating disorder
- Decrease exercise
- If unwilling to do either of the above, consider oral contraceptives and calcium

Level 2: Pituitary Defects

1. Acquired gonadotropin deficiency

- 3 etiologies
 - 1) Postpartum necrosis of the pituitary (Sheehan's syndrome)
 - 2) Primary or metastatic tumor
 - 3) Granulomas
- FSH and LH are low
- No withdrawal bleed after progestin trial
- Ask about HA and look for visual field defects
- Measure estradiol, FSH, LH, prolactin
- CT or MRI

2. Hyperprolactinemia

- May be secondary to a hypothalamic defect or pituitary tumor
- Hypothyroidism as cause of hyperprolactinemia and enlarged pituitary gland
- *Accounts for 25% of cases or secondary amenorrhea!!!*
- Often secondary to microadenomas which are only revealed by CT or MRI (or too small to be imaged)
- Measurement of prolactin appears early in the diagnostic schema (see figure) because of the frequency of hyperprolactinemia in this population
- Excellent treatment is available

3. Empty Sella Syndrome

- Enlarged sella turcica not entirely filled with pituitary tissue
- Can be secondary to pituitary adenoma

Level 3: Ovarian Defects

- Primary ovarian failure is rarely seen in young women but is a cause of secondary amenorrhea. Occurs in women with Turner's Syndrome
- Other etiologies of acquired ovarian failure:
 - Autoimmune oophoritis, usually seen with other autoimmune disease such as adrenal or thyroid disorders
 - May be seen in women with myasthenia gravis or pernicious anemia
 - Mumps oophoritis (less common than orchitis)
 - Idiopathic premature ovarian failure
 - Follicular destruction produced by chemotherapy or radiation

- Estrogen levels are low
- No withdrawal bleed to progesterone
- FSH is high
- Refer to specialist for workup

Level 4: Uterine Defects

- Least common cause of secondary amenorrhea
- Found in patients with Asherman's Syndrome (those who have had severe endometritis, either postpartum or postabortion)
- Also found in patients who have had energetic endometrial curettage which has removed basal epithelial layers
- Found rarely in patients with chronic granulomatous disease
- Normal estrogen and gonadotropin levels
- No withdrawal bleed either after progesterone alone or after estrogen plus progesterone

Summary

Diagnosis

- Rule out pregnancy
 - History
1. Recent stress
 2. Drugs
 3. Symptoms of headache, visual defects, fatigue
 4. Symptoms of Estrogen Deficiency
 5. Galactorrhea, hirsutism, acne
 6. H/O obstetrical catastrophe

Physical Exam

- Measure height and weight
- Skin exam for signs of estrogen deficiency
- Skin for signs of hirsutism, virilization, acne

Labs

- UHCG
- Prolactin
- Thyrotropin
- FSH
- DHEA-S/testosterone if there are signs of hyperandrogenism

***** The above are just general guidelines please do not do excessive labwork secondary to cost to student health.**

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