

Missing menses

Amenorrhea in the Adolescent

Materials for Learners:

- Handout #1: Etiology of Amenorrhea (Figure 1), and Treatment Options (Table 1)
- Handout #2: Assessing Hirsutism - Ferriman-Gallwey Scoring Diagram (Fig. 4)
- Clinical Pearls
- Knowledge questions and answers
- References

Handout #1

Figure 1: Etiology of Amenorrhea

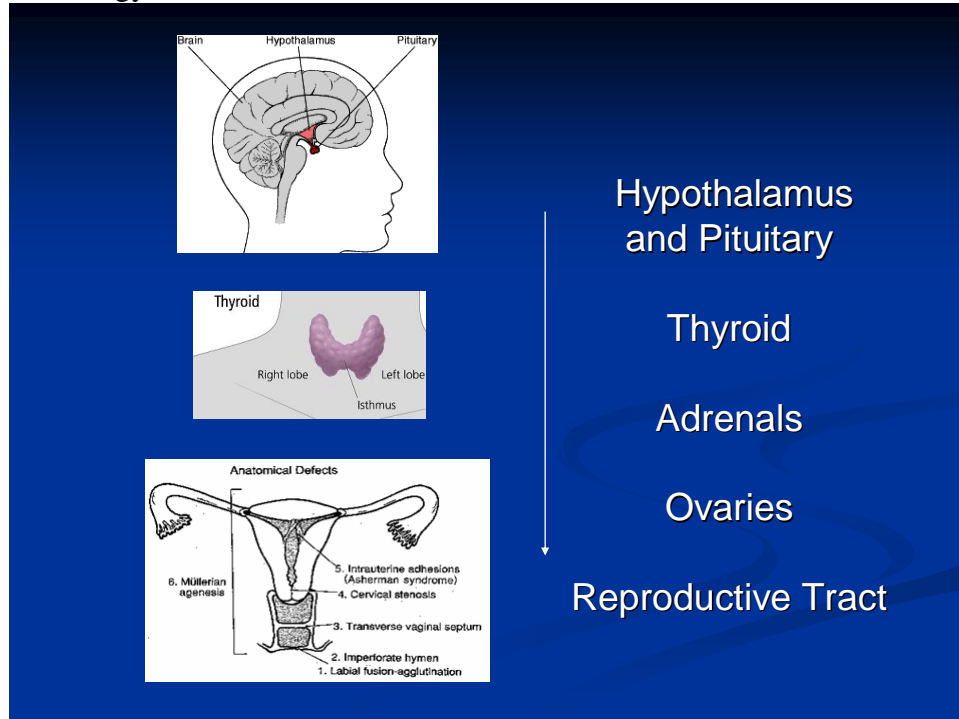


Table 1: Therapeutic options for polycystic ovary syndrome (PCOS)

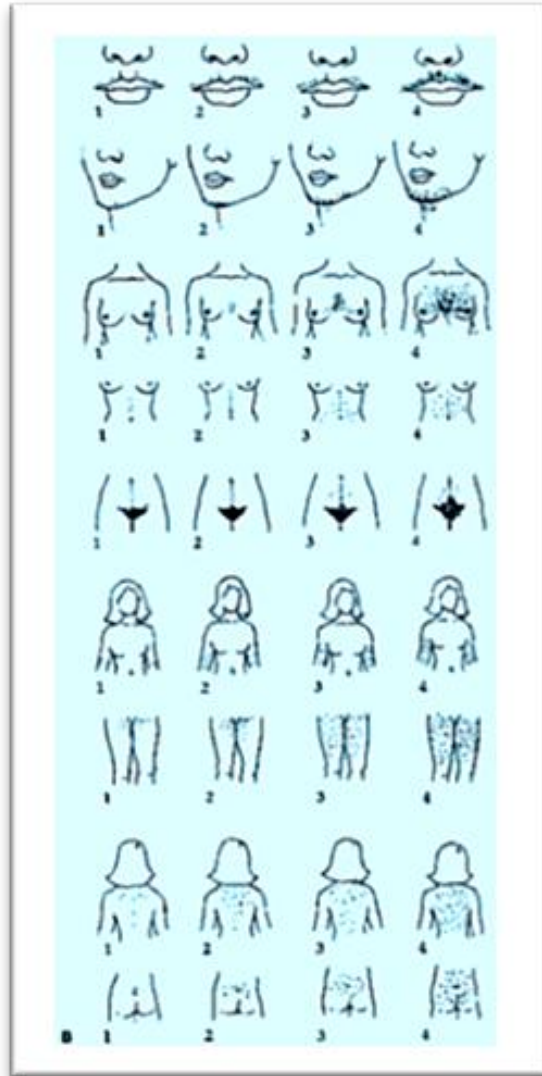
Chief complaint	First-line therapy ^a	Second-line therapy ^b
Oligomenorrhea	Estrogen/progestin	Metformin Progestins
Hirsutism, mild	Estrogen/progestin	Antiandrogen ^b Metformin
Hirsutism, moderate to severe	Estrogen/progestin <i>plus</i> Antiandrogen	Antiandrogen ^b
Overweight	Exercise/nutrition	Metformin <i>plus</i> Exercise/nutrition

- ^a Most medications, including oral contraceptives, are not specifically approved (i.e., are off-label) for PCOS.
- ^b Antiandrogens should be prescribed with estrogen/progestin contraceptives if there is any chance of pregnancy because of teratogenicity.

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Handout #2: Assessing Hirsutism



(Both Therapeutic Options for PCOS and Assessing Hirsutism reprinted with permission from S.J. Emans and M.R. Laufer, *Emans, Laufer, Goldstein's Pediatric and Adolescent Gynecology*, 6th ed. Lippincott, Williams & Wilkins; Wolters Kluwer, 2012)

The Ferriman-Gallwey system can be used to objectively assess hair growth. Clinicians score hair growth on a scale of 1 to 4 on multiple areas of the body; a score ≥ 6 indicates hirsutism.

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Clinical Pearls:

- Abnormal menses included those occur more frequently than every 21 days or less frequently than every 45 days (during early adolescence), or last longer than 7 days. Secondary amenorrhea is the absence of menses for > 3 months.
- The differential diagnosis for amenorrhea is broad but can be narrowed based on determination of primary versus secondary amenorrhea, and additional information gathered from patient history, growth charts, and physical exam.
- Pregnancy must be excluded in all adolescents with amenorrhea even those who deny sexual activity. Workup for amenorrhea should be tailored to each patient but in addition to urine HCG, at minimum, FSH, TSH, and prolactin levels should be ordered.
- There are multiple treatment options to address PCOS including lifestyle changes and pharmacologic options including hormones (estrogen/progestins or progestins), metformin, and/or anti-androgens.

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Knowledge questions:

1. *Which of the following statements is most correct?*

- a. Adolescents with amenorrhea secondary to acquired hypothyroidism are typically underweight for height.
- b. Laboratory abnormalities in amenorrheic patients with anorexia nervosa typically show elevated FSH and LH level, and normal estradiol.
- c. Patients with MRKH have a 46, XX karyotype but absent or rudimentary ovaries, fallopian tubes, uterus, cervix, and vaginal canal
- d. Rapid progression of hirsutism and virilization (temporal hair recession, deepening of voice, clitoromegaly) in an adolescent with amenorrhea should prompt an immediate workup for androgen-producing ovarian or adrenal tumor.

2. *Which of the following questions should be asked to help narrow the differential diagnosis?*

- a. How do you feel about your weight? Are you trying to lose weight? How?
- b. Are you sexually active? Have you ever had intercourse?
- c. Are you using birth control pills? Any other medications?
- d. All of the above.

3. *You are seeing a 14 year old patient for primary amenorrhea. She began having breast development at 10 years of age but has never had a period. She has no significant past medical, family, or psychosocial history and takes no medications. Mom and older sister both had menarche at age 12. Review of systems is positive for abdominal pain that has been worsening over the past several months. She has a normal weight and height. Tanner V for both breast development and pubic hair distribution. External genital exam appears within normal limits including small hymenal opening. The remainder of her PE is normal with no significant findings. Which of the following is the most appropriate next step?*

- a. Reassure patient that no further workup is needed and would expect onset of menses within the next year.
- b. Counsel patient that she likely must gain weight before onset of menses can begin.
- c. Prescribe a course of medroxyprogesterone to induce a withdrawal bleed.
- d. Further assess patency, length and width of vaginal canal.

4. *Which of the following are considered co-morbidities of PCOS?*

- a. Impaired glucose tolerance
- b. non-alcoholic fatty liver disease (NAFLD)
- c. Elevated LDL and TG, decreased HDL
- d. all of the above

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Answers to Knowledge Questions

1. *Which of the following statements is most correct?*

Preferred response: D, “Rapid progression of hirsutism and virilization (temporal hair recession, deepening of voice, clitoromegaly) in an adolescent with amenorrhea should prompt an immediate workup for androgen-producing ovarian or adrenal tumor.”

Ovarian and adrenal tumors including Sertoli and Leydig cell tumors can present with rapid onset of hirsutism and virilization. In addition to checking testosterone, DHEAS levels, and early morning 17OHP levels, serum DHEA and androstenedione concentrations should also be checked. Testosterone levels >150 ng/dL may raise suspicion for of tumor, but level should be verified in a specialized endocrine laboratory. Ultrasound, CT or MRI is obtained for further evaluation if testosterone concentration is within the tumor range or rapid onset of virilization.

Adolescents with amenorrhea secondary to acquired hypothyroidism (and cortisol excess) are typically *overweight* for height, while those with poor nutrition including eating disorders, celiac disease, or inflammatory bowel disease are typically underweight for height. Laboratory abnormalities in amenorrheic patients with anorexia nervosa typically show suppressed FSH, LH level, and estradiol levels. Patients with MRKH have a 46, XX karyotype. The cervix, uterus, fallopian tubes, and upper 2/3rds of vaginal canal are often absent or not developed; however, they have normal ovaries and hormonal patterns.

2. *Which of the following questions should be asked to help narrow the differential diagnosis?*

Preferred response: D “All of the above.”

All of the above questions should be asked confidentially to help narrow the differential diagnosis. There are a multitude of medical problems associated with amenorrhea. Disordered eating behaviors, such as restricting and purging, and weight loss are risk factors for irregular menses.

All patients with amenorrhea should be asked whether they are sexually active. Clinicians should have a low threshold for pregnancy testing regardless of reported sexual history.

Multiple medications can induce amenorrhea including hormonal contraception such as depo-provera. Adolescents using low-dose COCs (20mcg EE) may also have amenorrhea or scant flow. Often times, adolescents may have obtained the method confidentially and family may not be aware. Drugs such as antipsychotics (e.g risperdal), phenothiazines, α methyl dopa, and protease inhibitors interfere with hypothalamic secretion of dopamine and may result in elevated prolactin levels and amenorrhea. A baseline prolactin level should be drawn before starting on these medications.

3. *Which of the following is the most appropriate next step?*

Preferred response: D. “Further assess patency, length and width of vaginal canal.”

Patient’s history (primary amenorrhea, abdominal pain, Tanner V pubertal development) raises concern for a genital anomaly despite a normal external exam. A patient with a transverse vaginal septum, or vaginal, cervical, or uterine agenesis typically have normal-appearing external genitalia. The most appropriate next step is to further assess for structural defects. A saline moistened cotton tipped applicator or Calgiswab should be gently inserted into the hymenal opening and slowly advanced. If there is a low septum or agenesis of canal, swab will not advance beyond 2 cm; a one finger examination of the vaginal canal will also allow assessment of length and width, along with palpation of cervix and uterus. Pelvic US can be obtained in patients not comfortable with an exam. For inconclusive ultrasound evaluations, and high level of suspicion for concern for structural lesions, MRI would be next step in assessment of pelvic organs.

Patient should have further workup given she has not had menarche four years out from onset of secondary sexual characteristics. The patient is normal weighted, has fully matured, and has evidence of estrogen production on exam; there is no evidence at this time that she will need to gain additional weight. Before a course of medroxyprogesterone is tried, congenital or structural anomalies should first be ruled out.

4. *Which of the following are considered co-morbidities of PCOS?*

Preferred response: D. “all of the above”

There are multiple co-morbidities of PCOS that have been identified. PCOS increases lifelong risk of infertility, endometrial hyperplasia and cancer, irregular uterine bleeding, metabolic syndrome, impaired glucose tolerance and type 2 diabetes, hypertension, and abnormal lipid profiles. Liver dysfunction, particularly elevation of ALT, has been found in up to 30% of patients with PCOS in whom causes other than NAFLD were ruled out. Other obesity-related disorders are also common including obstructive-sleep apnea which increases future cardiovascular risk.

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References

1. Divasta A, Emans SJ. Amenorrhea in Adolescents. Emans SJ and Laufer MR (eds.) *Emans, Laufer and Goldstein's Pediatric and Adolescent Gynecology*, sixth edition in press Philadelphia: Lippincott, Williams and Wilkins; 2012
2. Divasta A, Emans SJ. Androgen Abnormalities in the Adolescent Girl. Emans SJ and Laufer MR (eds.) *Emans, Laufer and Goldstein's Pediatric and Adolescent Gynecology*, sixth edition in press Philadelphia: Lippincott, Williams and Wilkins; 2012
3. Treloar AE, et al. Variation of the human menstrual cycle through reproductive life. *Int J Fertil* 1967;12(1 Pt 2):77-126
4. American College of Obstetricians and Gynecologists and the American Academy of Pediatrics. Menstruation in girls and adolescents: Using the menstrual cycle as a vital sign. *Pediatrics* 118 (5) Nov 2006: 2245-2250
5. Wu T, et al. *Pediatrics* 2002;110(4):752.
6. Kaplowitz PB, et al. *Pediatrics* 2001;108:347.
7. Demerath EW, et al. *Am J Hum Biol* 2004;16:453.
8. American Academy of Pediatrics Committee on Adolescence, et al. *Pediatrics* 2006;118:2245-2250.
9. Economy KE, et al. *J Pediatr Adolesc Gynecol* 2002;15:101.
10. ACOG Technical Bulletin. *Int J Gynaecol Obstet* 1995;49(3):341-346.
11. Ferriman D, Gallwey JD. *J Clin Endocrinol Metab* 1961;21:1440-1447.
12. *Obstet Gynecol* 2009;114(4):936-949.
13. Wild RA et al. *J Clin Endocrinol Metab*. 2010;95(5):2038-49.
14. Ruchhoft EA, et al. *Fertil Steril* 1996;66(1):54-60.
15. Hoeger K, et al. *J Clin Endocrinol Metab* 2008;93(11):4299-4306.
16. Shapiro G, Evron S. *J Clin Endocrinol Metab* 1980;51(3):429-432.
17. Nestler JE, Jakubowicz DJ. *N Engl J Med* 1996;335(9):617-623.
18. Nestler JE, et al. *Fertil Steril* 2002;77(2):209-215.
19. Zadawski J, Duanif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. Oxford: Blackwell Scientific Publications;1992.
20. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Hum Reprod* 2004;19:41-47.
21. Azziz R, Carmina E, Dewailly D, et al. Position statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab* 2006;91:4237-4245.
22. Costello M, Shrestha B, Eden J, et al. Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. *Cochrane Database Syst Rev* 2007;(1):CD005552.