Amenorrhea in Adolescents — Clinical Evaluation and Causes

See online here

The absence of menses in a woman is the definition of amenorrhea. Primary amenorrhea is defined as the absence of menses in a 16-year-old girl with secondary sexual characteristics or a 14-year-old girl without secondary sexual characteristics. Secondary amenorrhea is defined as the absence of menses for six consecutive months in a female with a previous irregular pattern of menstruation. If the menstrual cycle is regular, then secondary amenorrhea can be diagnosed in a female who does not have her menses for only three consecutive months.

Definition of Amenorrhea

Normal menses

- Menstruation is dependent on ovulation, estrogen, progesterone
- Average age of menarche is 12.7 years
- 2/3 girls experience menarche in genital tanner stage IV

Definition of primary amenorrhea

- No menarche by age 14 in absence of pubertal development
- No menarche by age 16 regardless of pubertal development

Definition and general characteristics of secondary amenorrhea

- Absence of menses for > 6 months in previously menstruating female
- Pubertal development normal
- Anovulatory cycles in young adolescents
- Disruption in HPO axis
    - Inadequate GnRH release
    - Inadequate LH, FSH release
    - Insufficient estrogen to stimulate LH surge and ovulation

Clinical Evaluation of Amenorrhea in Adolescents

It is currently recommended to start the evaluation process for amenorrhea in an adolescent who is 15 years old instead of 16 years old if she is showing normal secondary sexual characteristics development. Additionally, the clinical evaluation for amenorrhea **should be started in any girl who did not have her first menses five years after thelarche**.

History taking is of enormous value to the clinician as it can point towards the most probable cause of amenorrhea. Additionally, adequate history taking and physical examination are essential for the accurate definition of amenorrhea in the presenting adolescent. Family history is also important and one should specifically ask about the age at menarche for the girl's mother.

Primary amenorrhea
• Other signs of pubertal progression • Age of menarche in mother, sisters • Menstrual, gynecologic, pubertal problems in the family • Sexual activity • Abdominal pain or cramping • Diet and exercise habits • Underlying hormonal problems
Secondary amenorrhea
• Sexual activity • Eating behaviors • Competitive athlete/ excessive exercise • History of chemotherapy or pelvic radiation • Family history of menstrual or gynecologic problems • Psychotropic medications or illicit drugs • Underlying hormonal problems

The physical examination should focus on the **exclusion of the signs of systemic diseases** that are known to cause amenorrhea such as thyroid disorders. The gynecological examination is indicated to exclude an imperforate hymen. A bimanual rectal examination is indicated to exclude the absence of the uterus and a normal vaginal and uterine anatomy.

The first laboratory investigation to be ordered in an adolescent with primary amenorrhea is the **measurement of serum levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH)**. When FSH and/or LH are elevated, then the cause of amenorrhea is most likely related to primary gonads' disease. Low or normal FSH and LH levels indicate delayed puberty, pituitary dysfunction, or hypothalamic disorders.

The next step in the evaluation of the amenorrhoeic adolescent is to **perform an ultrasound scan of the abdomen**. Ultrasonography is helpful in assessing the ovaries

and the endometrium. When the ovaries appear abnormal, i.e. streak ovaries for example, then karyotyping is indicated. The most common chromosomal disorders that can cause primary amenorrhea including Turner Syndrome, androgen insensitivity syndrome and gonadal dysgenesis.

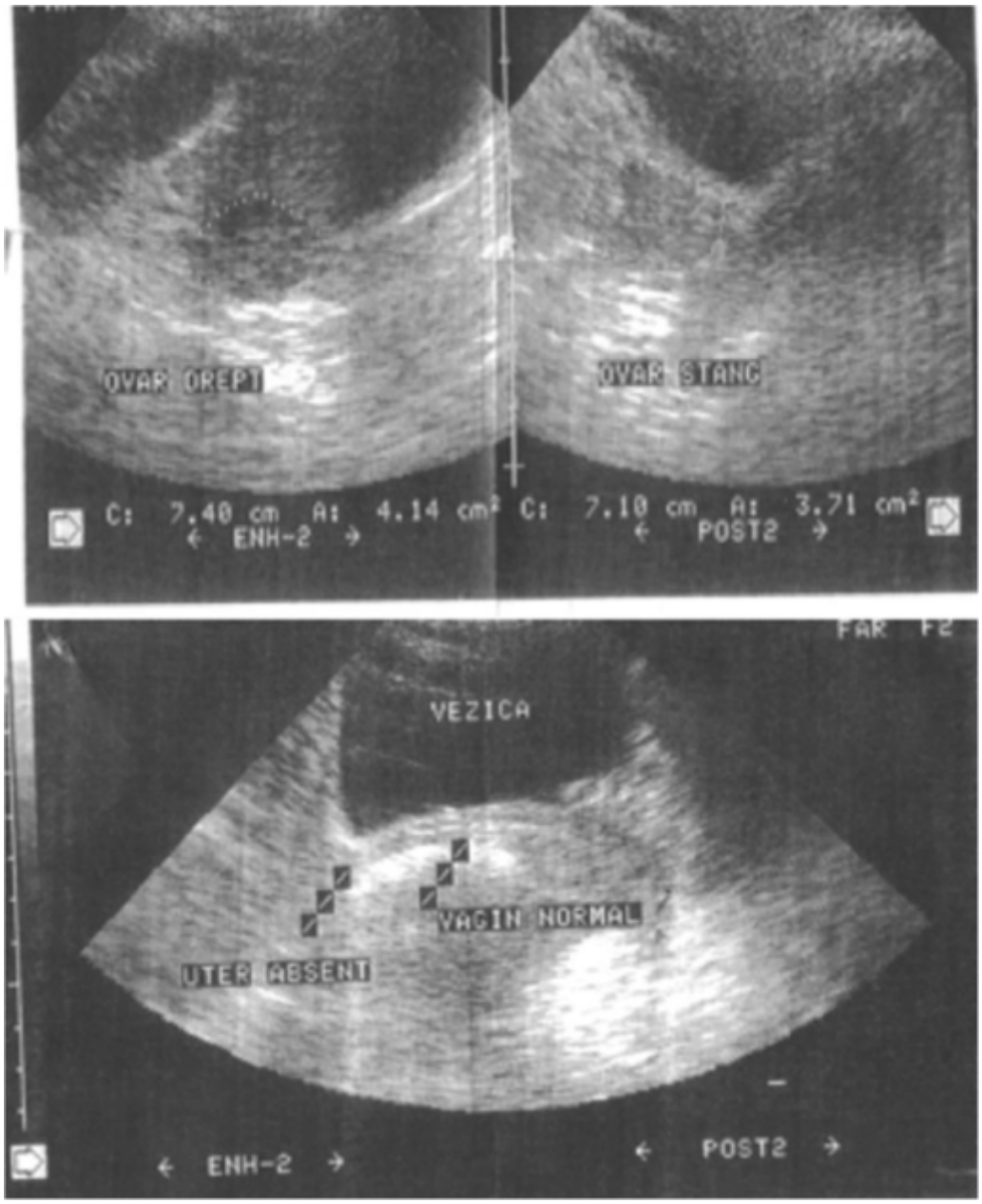

Image: "Pelvic ultrasonography images showing absence of the uterus, and the presence of both ovaries." by Piciu D, Piciu A, Irimie A – J Med Case Rep (2012). License: CC BY 2.0

An adolescent patient with secondary amenorrhea should get a **pregnancy test to exclude pregnancy**, the most common cause of secondary amenorrhea. The presence of acne, hirsutism, deepening of voice and clitoromegaly is suggestive of hyperandrogenism, another common cause of secondary amenorrhea.

Patients with secondary amenorrhea should get FSH, LH, testosterone, and dehydroepiandrosterone sulfate levels measured. Moderate elevation of testosterone and an LH/FSH ratio that is above 2 suggests polycystic ovary syndrome. **Dehydroepiandrosterone sulfate levels between 5 and 700 mg/dl indicate possible adrenal gland disorder** and require further diagnostic workup. When the levels of dehydroepiandrosterone sulfate are above 700 mg/dl, the diagnosis of late-onset

type congenital adrenal hyperplasia becomes very likely.

Progesterone challenge test

1. Administer oral medroxyprogesterone acetate for 5–10 days	
2. Look for withdrawal bleed after medroxyprogesterone cessation	
A positive response:	
⇓	⇓
Is any bleeding more than light spotting that occurs within 2 weeks after the progestin is given	Will usually occur 2–7 days after the progestin is finished
Interpretation	
Bleeding • Endometrium has been primed by estrogen • Patient likely has anovulation • Consider polycystic ovarian syndrome	No bleeding • Evaluate for hypothalamic-pituitary insufficiency • Consider outflow tract obstruction

Patients with secondary amenorrhea and no signs of hyperandrogenism should get their FSH, LH and thyroid stimulating hormone levels checked. Hyperprolactinemia due to a pituitary adenoma can also cause secondary amenorrhea in an adolescent.

Primary amenorrhea	
Assess Tanner stage	Endocrinopathy or genetic disease
Growth parameters	Genital exam
• Low BMI can delay the onset of menses • Short stature (genetic or endocrine disorder)	• Hymenal opening: obstructed by a thin membrane • Enlarged clitoris: excess androgens • Tanner stage • Vaginal exam
Secondary amenorrhea	
Assess Tanner stage	Endocrinopathy
Growth parameters	Genital exam
• Weight • Height • BMI	• Clitoromegaly: excessive androgens • Bimanual exam: assess the uterus, ovaries
Skin exam for hirsutism, acne, striae, acanthosis nigricans	

Causes of Amenorrhea in Adolescents

The causes of amenorrhea in adolescents can be classified into anatomic defects of the outflow tract, primary hypogonadism, hypothalamic disorders, pituitary causes, other endocrine disorders and multifactorial causes.

Other causes of secondary amenorrhea

- Prolactinoma
- Hyperthyroidism
- Hypothyroidism
- Polycystic ovarian syndrome
- Late-onset congenital adrenal hyperplasia
- Virilizing tumor

Anatomic defects of the outflow tract

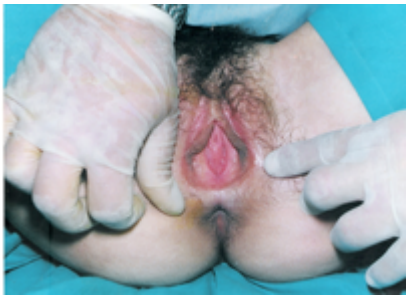

Image: “Vaginal agenesis, Mayer-Rokitansky-Küster-Hauser syndrome.” by Dr. Antonio Jose Marrero Ochoa. License: CC BY-SA 2.5

The most commonly identified anatomic defects of the outflow tract include **Mullerian agenesis, complete androgen resistance, intrauterine synechiae, imperforate hymen, transverse vaginal septum, cervical agenesis, cervical stenosis, and vaginal agenesis**. These causes result in primary amenorrhea except for intrauterine synechiae and cervical stenosis which cause secondary amenorrhea. These two conditions are very rare in adolescents.

Treatment of Mullerian agenesis is non-existent. Psychological support for the patient is essential. A neovagina might be created for a normal sexual experience in the future for the girl. If a remnant uterus is present and the patient complains of cyclic distress, surgical removal of the remnant uterus is indicated.

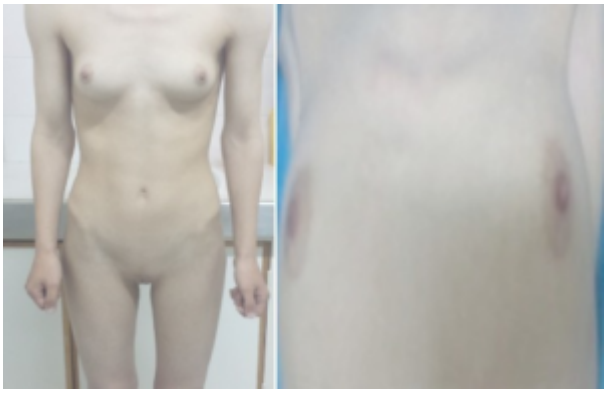

Image: “La patiente, morphotype féminin normal mais absence de pilosité pubienne et axillaire (Complete androgen insensitivity syndrome: report of two cases and review of literature).” [Complete androgen insensitivity syndrome: report of two cases and review of literature]. By Lachiri B, Hakimi I, Boudhas A, Guelzim K, Kouach J, Oukabli M, Rahali DM, Dehayni M – Pan Afr Med J (2015). License: CC BY 2.0

Girls diagnosed with complete androgen resistance syndrome also need psychological support, surgical intervention to create a neovagina and removal of the gonads due to the high risk of malignancy. Pregnancy is not possible in these two conditions and the only solution for fertility is a surrogate pregnancy.

Imperforate hymen is a common cause of primary amenorrhea that can be easily diagnosed and managed. The surgical procedure of choice includes the removal of the hymeneal tissue in a triangular shape. This procedure allows for the commencement of menstrual blood flow in the future. Fertility is usually not affected.

Patients with a transverse vaginal septum will also present with primary amenorrhea. Surgical excision of the vaginal septum will restore the normal anatomy of the vagina and allow for normal menstrual blood flow.

Ashermann syndrome or intrauterine synechiae cause secondary amenorrhea. This disorder is uncommon in adolescents and is usually a consequence of postpartum endometritis.

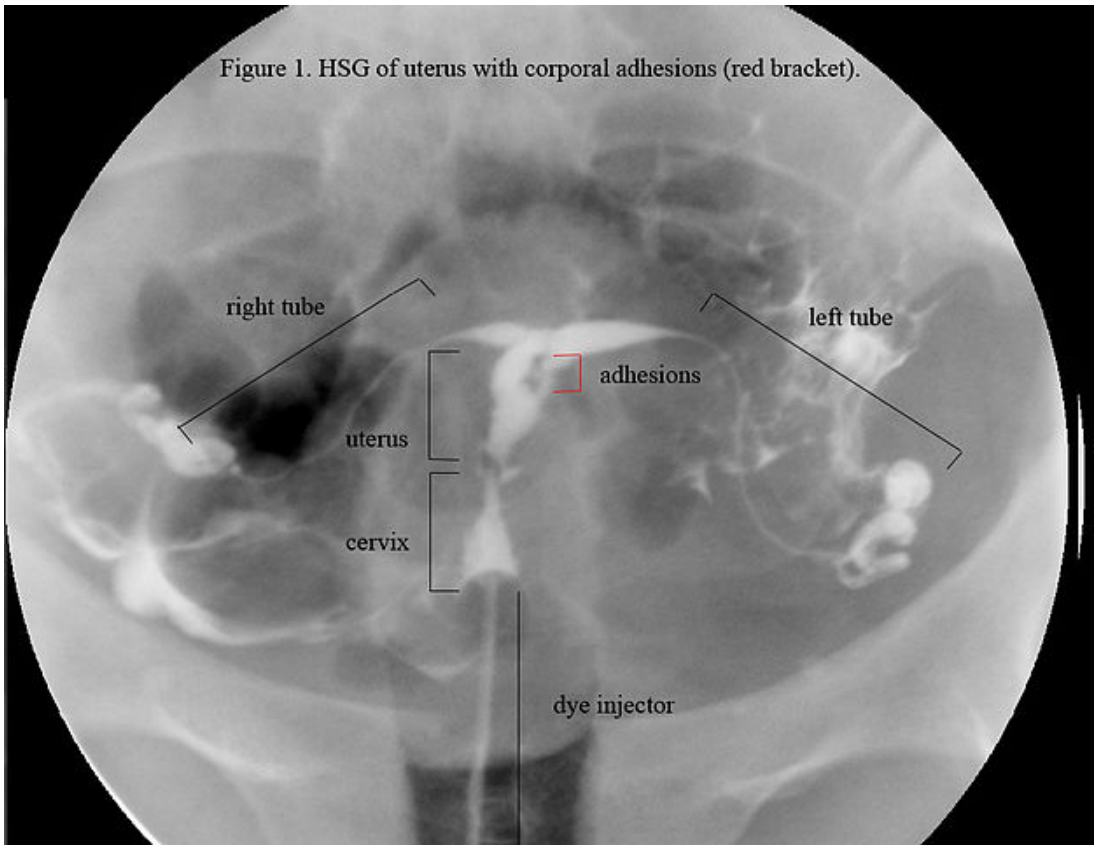

Image: “HSG view. Note: not the same uterus as in ultrasound or hysteroscopic view; this uterus appears to be T-shaped.” by Floranerolia. License: GNU Free Documentation License (GFDL)

Patients with incomplete cervical agenesis “cervical dysgenesis” might benefit from cervical canalization. On the other hand, the complete agenesis of the cervix is better treated with a hysterectomy.

Primary Hypogonadism

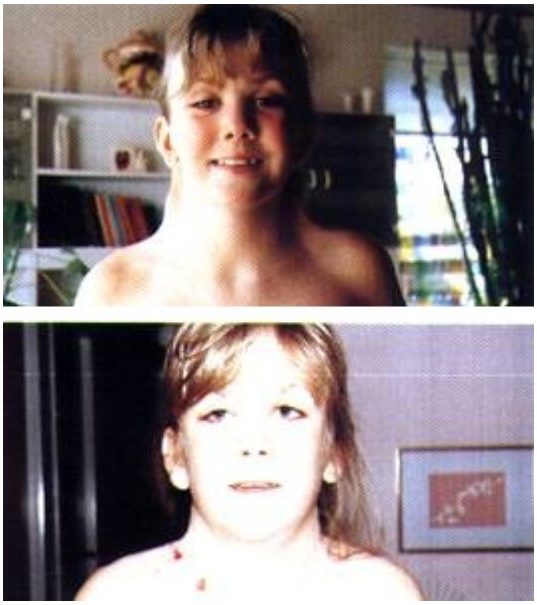

Image: “Girl with Turner syndrome before and immediately after her operation for neck-webbing.” By Johannes Nielsen. License: CC BY 2.0

The most common causes of primary hypogonadism include gonadal dysgenesis **“Turner syndrome, pure gonadal dysgenesis, and Swyer syndrome”**, gonadal agenesis, 17-hydroxylase deficiency, 17,20-Lyase deficiency, aromatase deficiency, idiopathic premature ovarian failure, secondary ovarian failure due to chemotherapy or irradiation, FSH receptor gene mutations, LH resistance, galactosemia or glycoprotein syndrome type 1.

Patients with gonadal dysgenesis are infertile and should get their gonads removed whenever possible. Adolescents with premature ovary failure should receive psychotherapy, estrogen replacement therapy, and infertility treatment. **Supplementary calcium and vitamin D should be administered** to adolescents who are diagnosed with premature ovarian failure. Approximately, 5 to 10 % of adolescents who are diagnosed with premature ovarian failure can achieve pregnancy without any intervention. In vitro fertilization of donor, oocytes are the only option for infertile adolescents with premature ovary syndrome who do not achieve conception naturally.

Hypothalamic causes of amenorrhea

Hypothalamic causes of amenorrhea include hypothalamic dysfunction due to stress, malnutrition or exercise. Kallmann syndrome and idiopathic hypogonadotropic hypogonadism, tuberculosis, syphilis, sarcoidosis, brain tumors, and chronic systemic illness can also cause hypothalamic dysfunction. The main cause of this condition is that the hypothalamus in the brain stops producing gonadotropin-releasing hormone (GnRH), the hormone that initiates the menstrual cycle in females.

Genetic, endocrine, nutritional, anatomic defects	
Ovaries not producing sufficient estrogen to proliferate uterine lining or induce ovulation	
⇓	⇓
Hypogonadotropic hypogonadism • Inadequate release of gonadotropins (LH, FSH) from pituitary	**Hypergonadotropic hypogonadism** • Inadequate ovarian response to gonadotropins
Anatomic problems with reproductive tract	

Image: by Lecturio
Absent uterus

Image: by Lecturio
Genital outlet obstruction

Stress, anorexia nervosa, and excessive exercise can cause secondary amenorrhea due to hypothalamic dysfunction. Treatment should focus on the restoration of normal nutrition and the administration of hormonal therapy. Transdermal hormonal therapy is preferred over oral hormone replacement therapy. Insulin-like growth factor 1 and leptin should be also administered to these patients.

Kallmann syndrome is a genetic disorder that is characterized by gonadotropin-releasing hormone deficiency plus anosmia. This condition usually causes primary amenorrhea. Hormone replacement therapy is needed to promote secondary sexual characteristics development and achieve regular menstrual bleeding. Calcium and vitamin D should be also administered. High dose gonadotropins or gonadotropin-releasing hormone pump can be used to achieve fertility.

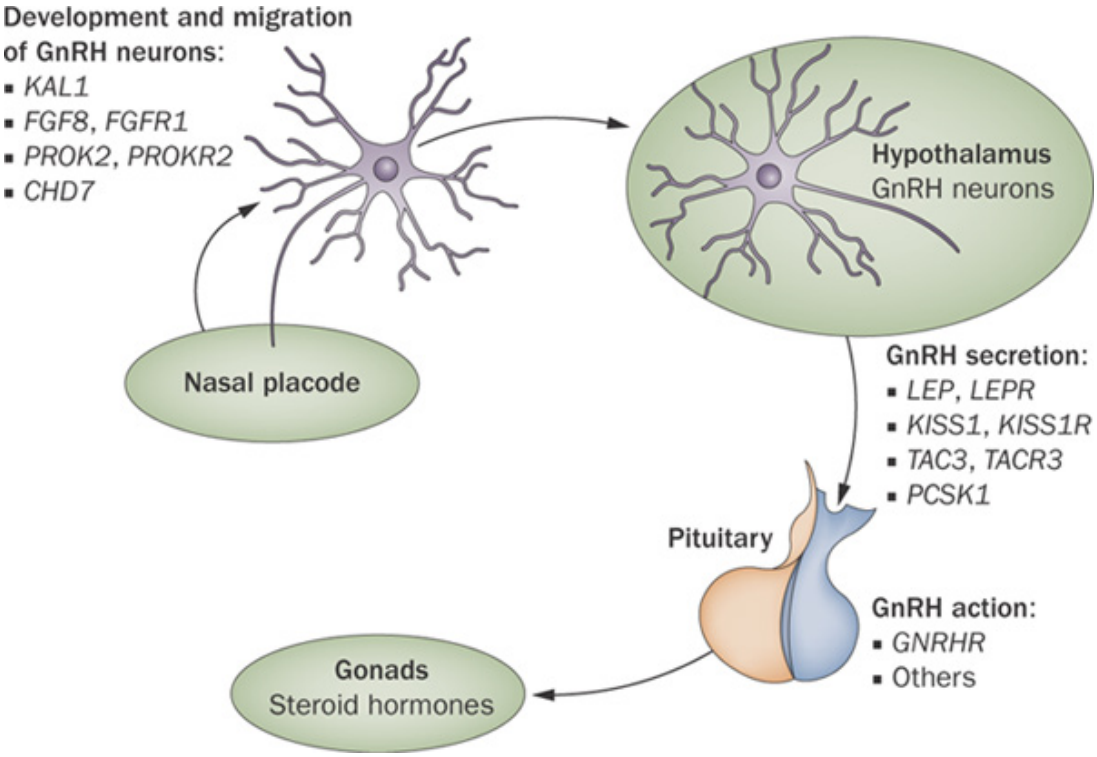

Image: "Genes involved in migration or activation of GnRH releasing neurones into the hypothalamus"by The genetic basis of idiopathic hypogonadotropic hypogonadism. The genetic and molecular basis of idiopathic hypogonadotropic hypogonadism Suzy D. C. Bianco & Ursula B. Kaiser Nature Reviews Endocrinology 5, 569-576 (October 2009).

Pituitary causes of amenorrhea

Hyperprolactinemia is the **most common cause of pituitary amenorrhea**. Prolactinomas, craniopharyngioma, metastatic tumors to the pituitary gland, empty Sella syndrome, arterial aneurysms, postpartum pituitary necrosis ‘Sheehan syndrome’, panhypopituitarism, sarcoidosis, and hemochromatosis can all cause amenorrhea due to pituitary gland hormonal dysfunction.

Treatment of hyperprolactinemia includes the administration of bromocriptine or cabergoline. Patients with hyperprolactinemia due to antipsychotic therapy should receive hormonal replacement therapy instead of dopamine receptor agonists for the management of their amenorrhea.

Multifactorial Causes of Amenorrhea

Polycystic ovary syndrome is characterized by secondary or primary amenorrhea, obesity, insulin resistance, hyperandrogenism, and infertility. Treatment should cover these aspects of the disease and not only the infertility part.

Exercise and eating a healthy diet are essential for weight loss, reducing the future risk of type 2 diabetes and managing the symptoms of hyperandrogenism. Oral contraceptive pills with an anti-androgenic progestin are the best option. Additionally, adolescents with polycystic ovary syndrome should receive metformin. Metformin helps with weight loss, neutralizes the hyperandrogenism state, and can help regulate the menstrual cycle. Additionally, metformin can achieve fertility.

References

Deligeoroglou, E., Athanasopoulos, N., Tsimaris, P., Dimopoulos, K. D., Vrachnis, N., & Creatsas, G. (2010). Evaluation and management of adolescent amenorrhea. *Annals of the New York Academy of Sciences*, *1205*(1), 23–32. http://doi.org/10.1111/j.1749-6632.2010.05669.x

Notes