BMJ Best Practice

Evaluation of primary amenorrhea

Straight to the point of care

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Summary

Amenorrhea is the transient or permanent absence of menstrual flow and may be subdivided into primary and secondary presentations, relative to menarche.[1]

- Primary amenorrhea: lack of menses by age 15 years in a patient with appropriate development of secondary sexual characteristics, or absent menses by age 13 years and no other pubertal maturation.
- Secondary amenorrhea: lack of menses in a non-pregnant female for at least 3 cycles of her previous interval, or lack of menses for 6 months in a patient who was previously menstruating. See Evaluation of secondary amenorrhea .

Although overlapping attributes exist between the two groups, the diagnostic approaches vary significantly. The prevalence of primary amenorrhea in the US is <0.1%, compared with 4% for secondary amenorrhea.[2] [3] Even when causes of primary and secondary amenorrhea overlap, the relative likelihoods for these etiologies may differ. For example, polycystic ovary syndrome (PCOS) may cause either primary or secondary amenorrhea, but presents usually as secondary amenorrhea. Many causes of primary amenorrhea are rare in the general population (e.g., Kallman syndrome). Conditions that may seem to be rare events generally may appear more commonly in this subgroup of adolescent girls presenting with primary amenorrhea.

Despite the low prevalence of primary amenorrhea, a prompt and comprehensive assessment by a specialist in reproductive medicine, or a clinician well-versed in adolescent development is warranted, as amenorrhea is often the presenting sign of an underlying reproductive disorder. A delay in diagnosis and treatment may adversely impact the long-term future of such patients. For example:[1] [4] [5] [6] [7] [8] [9]

- An adolescent with complete androgen insensitivity requires counseling about the eventual removal of gonads, because these patients carry a 14% to 22% risk of gonadal neoplasms, although malignancy is rare before the age of 20 years. Removal needs to be weighed up against preserving hormone function during puberty and considerations of any fertility potential.
- Premature ovarian insufficiency occurring at an early age affects bone density during a critical period for bone development.
- In young teens presenting with PCOS, obesity, and hyperinsulinemia; behavioral and dietary modifications may prevent subsequent metabolic syndrome.

THEORY

Etiology

Amenorrhea may result from pathology in any of the four distinct functional and structural components required for menstruation: the hypothalamus, the anterior pituitary, the ovaries, and the genital outflow tract. Within these components, six conditions account for most patients presenting with primary amenorrhea: polycystic ovary syndrome (PCOS), hyperprolactinemia, thyroid dysfunction, hypogonadotropic and hypergonadotropic hypogonadism, and anatomic abnormalities.[1] In general, primary amenorrhea accounts for a small percentage of pediatric or adolescent patient visits, even at highly specialized centers.

Researchers have found rare variants in genes associated with idiopathic hypogonadotropic hypogonadism in women with hypothalamic amenorrhea, suggesting that these mutations may contribute to susceptibility.[10] Ovarian failure causing primary amenorrhea can also be the result of damage from previous chemotherapy, radiation therapy, or surgery.[1] [7]

Some clinicians prefer to approach the patient with amenorrhea based on the presence or absence of a uterus and breast development (signaling estrogen production).[1] A classification system presented by the World Health Organization (WHO) in the 1970s divided patients into groups based on endogenous estrogen production, follicle-stimulating hormone (FSH) levels, prolactin levels, and hypothalamic-pituitary dysfunction.[11] This classification eliminates several diagnoses based on initial information. However, since this system was developed there have been many advances in the understanding of hormonal control of ovulation and improvements in assay methodology, and further workup is required to narrow down the diagnosis.

Group	Characteristics	Example
1	Low estrogen Low follicle-stimulating hormone No hypothalamic-pituitary pathology	Hypogonadotropic hypogonadism
2	Normal estrogen Normal follicle-stimulating hormone Normal prolactin	Polycystic ovary syndrome
3	Low estrogen High follicle-stimulating hormone	Gonadal failure

World Health Organization classification of amenorrhea

Created by BMJ Knowledge Centre

In 2021, the International Federation of Gynecology and Obstetrics (FIGO) introduced a three-layered system to categorize ovulatory disorders. The first tier, called HyPO-P (hypothalamus-pituitary-ovary), focuses on anatomy, categorizing disorders into four component groups: type 1: hypothalamic; type 2: pituitary; type 3: ovarian; and type IV: PCOS. The second tier provides more specific causes within the categories: Genetic, Autoimmune, Iatrogenic, Neoplasm; Functional, Infectious and Inflammatory, Trauma and Vascular; Physiological, Idiopathic, Endocrine (GAIN-FIT-PIE). The third tier includes specific diagnoses or disorders.[12]

Urgent considerations

(See **Differentials** for more details)

- Patients with secondary sexual development should be assessed for pregnancy.
- Patients with hyperprolactinemia or those diagnosed with hypogonadotropic hypogonadism and neurologic symptoms should undergo neuroimaging to rule out an intracranial neoplasm.[13]
- Patients with symptoms of rapid virilization should undergo prompt workup to rule out adrenal or ovarian tumors.
- Patients diagnosed with gonadal dysgenesis (Y chromosome on karyotype) and androgen insensitivity syndrome are at risk for gonadal tumors such as dysgerminoma or gonadoblastoma and should be counseled regarding removal of the gonads.[6] [14]
- Patients with obstructive anomalies that result in compression of the urethra can lead to urinary retention (e.g., hematometrocolpos, Herlyn-Werner-Wunderlich syndrome).

Approach

Although history and physical examination frequently direct the clinician towards a working diagnosis, ancillary studies are often necessary. Most systemic disorders may be diagnosed with laboratory tests assessing neuroendocrine and ovarian function, and the majority of structural abnormalities are identified through pelvic examination or imaging studies.[1]

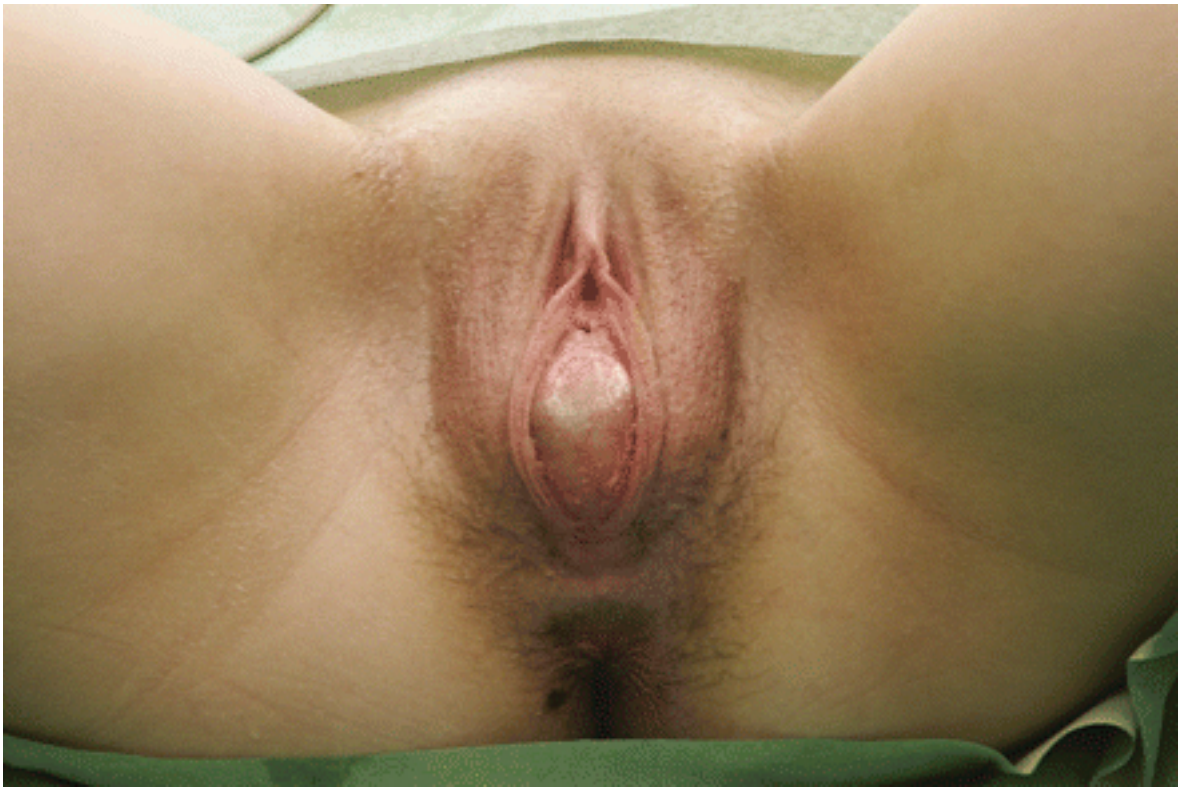
History

- The mean age of pubertal development aids in deciding the timing of an amenorrhea evaluation. Evaluation should take place with absent menstruation by age 15 years (if other pubertal development is noted), within 3 years of breast development, or with failure of breast development by age 13 years.[1] [15] [16] Thelarche ("breast budding") denotes previous or current estrogen production. Age of onset or lack thereof may be used to determine when to begin an assessment. Early pubarche (appearance of pubic hair) may be associated with development of polycystic ovary syndrome (PCOS).[17]
- Galactorrhea: hyperprolactinemia is more commonly associated with secondary amenorrhea.
- History of a traumatic head injury or central nervous system infection: a remote history may be elicited from the patient or parents.
- Headache/visual field changes: suggest a central nervous system tumor (e.g., craniopharyngioma).[18]
- Anosmia: suggests Kallman syndrome or a complete congenital gonadotropin-releasing hormone (GnRH) deficiency.[19]
- Chronic systemic illness: may present with fatigue, malaise, anorexia, and weight loss.
- Family history: height should be documented and compared with that of other family members. Short stature is suggestive of Turner syndrome or hypothalamic-pituitary disease.[20] A history of familial delayed puberty, in addition to onset of menarche in the patient's mother and female siblings, should be elicited.
- A diagnosis of functional hypothalamic amenorrhea should only be made after excluding anatomic or organic pathology. An inquiry into a patient's health status, eating habits, and body image is necessary. Poor nutritional status due to systemic illness, an eating disorder, and/or low body fat may result in hypothalamic dysfunction.[21] Emotional stress or extreme athleticism can also result in a similar phenomenon.[22] [23]

Physical examination

- The patient's weight and height should be measured. Shortened height may suggest a chromosomal abnormality. Patients with gonadal dysgenesis and hypoestrogenemia are at risk for shortened final adult height. Growth pattern should be documented and compared with that of first-degree relatives.
- On initial examination, careful attention should be given to male pattern baldness, deepening of the voice, wide distribution of terminal hair (male pattern), acne, or oily skin, suggesting hyperandrogenemia. These patterns may vary based on ancestry. If symptoms are slowly progressive, PCOS or non-classic congenital adrenal hyperplasia is possible. If acute and progressive, the patient may be harboring an androgen-producing tumor (ovarian or adrenal).
- Consider performing a neurologic examination to assess for neurologic findings such as peripheral vision changes, which suggests an intracranial mass impinging on the optic chiasm (e.g., pituitary adenoma, craniopharyngioma).

- Careful examination of the breasts to elicit galactorrhea should be performed in the event that prolactinoma is suspected.
- On speculum and bimanual exam, most structural anomalies are identified. The hymen must be assessed first. A blind vaginal pouch will be noted in patients with Mullerian agenesis, transverse vaginal septum, or androgen insensitivity syndrome (the latter along with inguinal hernias). The uterine cervix should be noted on examination. Internal examinations are not always possible and the clinician may need to proceed with imaging options or an examination under anesthesia.



Imperforate hymen

Lardenoije C, Aardenburg R, Mertens H. Imperforate hymen: a cause of abdominal pain in female adolescents. BMJ Case Reports 2009; doi:10.1136/bcr.08.2008.0722

Laboratory tests

All patients with primary amenorrhea, regardless of physical examination findings, should have preliminary laboratory studies drawn, including follicle-stimulating hormone (FSH), estradiol, thyroid-stimulating hormone (TSH), and prolactin. Based on these results, other tests are ordered.

Patients with secondary sexual development should be assessed for pregnancy. A karyotype is indicated for patients with primary amenorrhea and lack of secondary sexual development or those who are diagnosed with premature ovarian insufficiency (usually secondary amenorrhea).[7] [24]

- FSH: in concert with estradiol levels, gonadotropins help determine if amenorrhea is due to gonadal failure, hypothalamic dysfunction, or systemic or functional causes. FSH is more useful as a single test than luteinizing hormone (LH), and LH is not usually included in the initial investigations ordered.
- Serum estradiol: low levels are suggestive of either primary ovarian failure (along with elevated FSH) or suppressed hypothalamic function (low FSH).

- Serum prolactin: elevated levels of circulating prolactin (hyperprolactinemia), whether idiopathic or due to a pituitary adenoma, result in hypogonadotropic hypogonadism. For persistently elevated levels, neuroimaging is indicated to rule out intracranial neoplasm.[13]
- TSH: is indicated to rule out (primary) hypothyroidism, more commonly associated with secondary amenorrhea. Mild or subclinical hypothyroidism likely will not result in menstrual irregularities.[25] It is proposed that elevated thyrotropin-releasing hormone (TRH) stimulates prolactin secretion from the pituitary, suppressing FSH production.[26]
- Serum androgens: done for signs of hyperandrogenism. Androgens such as dehydroepiandrosterone sulfate (DHEAS) and free testosterone will be elevated in patients with PCOS, but higher levels are suggestive of an androgen-producing tumor and these patients should be referred for further investigation.[27] [28]
- Karyotype: helps to identify patients at risk for gonadal tumors, such as those with premature ovarian insufficiency (usually secondary amenorrhea), androgen insensitivity syndrome, or gonadal dysgenesis.[1][6] [14] A diagnosis of complete androgen insensitivity can be confirmed by a 46,XY karyotype, and a diagnosis of Turner syndrome by 45,X. Gonadal dysgenesis (streak gonads) can occur with normal XX and XY karyotypes.[1]

Physiologic tests and imaging

- Transabdominal or transvaginal ultrasound is performed if a pelvic examination is not possible. Ultrasound confirms normal anatomy and aids in the diagnosis of most structural abnormalities as well as the presence of an ovarian or adrenal tumor. Transvaginal is the preferred modality, if possible and appropriate, to evaluate endometrial thickness.
- MRI is the most effective tool for characterizing specific structural abnormalities and may prevent the need for surgical diagnosis. On MRI, Mullerian agenesis (Mayer-Rokitansky-Kuster-Hauser syndrome) or asymmetrical fusion defects of the Mullerian system (unicornuate uterus) can be identified as well as renal anomalies, which can occur in up to 30% of these patients.[29] A spine x-ray may reveal skeletal abnormalities, which have been reported in around 8% to 32% of patients with Mullerian agenesis.[30]
- If prolactin levels are significantly elevated, cranial MRI is indicated to rule out pituitary adenoma.[13]
- Bone density measurement may be indicated in selected patients.[24] Bone age is an additional test done for patients with delayed puberty.
- Audiometric and ophthalmologic testing is recommended in patients with Turner syndrome. A celiac screen is also useful in these patients.

Differentials overview

Common
Primary hypothalamic amenorrhea
Emotional/physical stress, eating disorder, or relative energy deficiency in sport (RED-S)
Constitutional delay
Malnutrition or chronic disease state
Kallman syndrome (hypogonadotropic hypogonadism)
Hyperprolactinemia
Polycystic ovary syndrome (PCOS)
Non-classic congenital adrenal hyperplasia
Turner syndrome or mixed gonadal dysgenesis
Mayer-Rokitansky-Kuster-Hauser syndrome (Mullerian agenesis)
Outflow tract obstruction, including imperforate hymen or transverse vaginal septum

Uncommon
Craniopharyngioma
Gonadotropin-releasing hormone (GnRH) receptor mutations
Post-encephalitis
Androgen-producing ovarian tumor
Androgen-producing adrenal tumor
XY gonadal dysgenesis (Swyer syndrome)
5-alpha-reductase deficiency
17-alpha-hydroxylase (CYP17) deficiency
Androgen insensitivity syndrome

Differentials

Common

Primary hypothalamic amenorrhea

History	Exam	1st Test	Other tests
delayed development of secondary sexual characteristics	normal final adult height, prepubertal but normal external and internal genitalia, normal phenotypic female	»**serum hCG:** negative »**serum#follicle-stimulating hormone (FSH):** low to normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low Results are unreliable if patient is taking any form of hormonal therapy. »**serum#hyroid-stimulating hormone (TSH):** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31]	»**serum LH:** low High LH levels suggest alternate diagnoses. Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** prepubertal uterus with thin endometrial echo-complex »**MRI brain:** normal Performed if suspected Kallman syndrome. Also rules out structural or traumatic processes. »**dual energy x-ray absorptiometry (DXA) scan:** low bone density

Emotional/physical stress, eating disorder, or relative energy deficiency in sport (RED-S)

History	Exam	1st Test	Other tests
delayed development of secondary sexual characteristics, weight loss, anorexia, altered	normal final adult height, prepubertal but normal external and internal genitalia,	»**serum hCG:** negative »**serum FSH:** low to normal	»**serum LH:** low High LH levels suggest alternate diagnoses.

Common

Emotional/physical stress, eating disorder, or relative energy deficiency in sport (RED-S)

History	Exam	1st Test	Other tests
bowel habits, sleep disturbances, dry skin, depressed mood, prescribed medications	normal phenotypic female	All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31]	Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** prepubertal uterus with thin endometrial echo-complex »**MRI brain:** normal Performed if suspected Kallman syndrome. Also rules out structural or traumatic processes. »**dual energy x-ray absorptiometry (DXA) scan:** low bone density RED-S consists of disordered eating, amenorrhea, and low bone mineral density.

◊ Constitutional delay

History	Exam	1st Test	Other tests
delayed development of secondary sexual characteristics, longitudinal diagnosis (usually over months), family history of delayed puberty, normal subsequent pubertal development; difficult to distinguish from isolated gonadotropin deficiency	short normal adult height, normal but prepubertal external and internal genitalia, normal phenotypic female	»**serum hCG:** negative »**serum FSH:** low to normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low	»**serum LH:** low High LH levels suggest alternate diagnoses. Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** prepubertal uterus with thin endometrial echo-complex »**MRI brain:** normal

Common

◊ Constitutional delay

History	Exam	1st Test	Other tests
		Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31]	Performed if suspected Kallman syndrome. Also rules out structural or traumatic processes. »**dual energy x-ray absorptiometry (DXA) scan:** low bone density

Malnutrition or chronic disease state

History	Exam	1st Test	Other tests
delayed development of secondary sexual characteristics, weight loss, anorexia, altered bowel habits, dry skin	may have short childhood stature but normal adult height (if treated), normal but prepubertal external and internal genitalia, normal phenotypic female	»**serum hCG:** negative »**serum FSH:** low to normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients	»**serum LH:** low High LH levels suggest alternate diagnoses. Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** prepubertal uterus with thin endometrial echo-complex »**MRI brain:** normal Performed if suspected Kallman syndrome. Also rules out structural or traumatic processes. »**dual energy x-ray absorptiometry (DXA) scan:** low bone density

Common

Malnutrition or chronic disease state

History	Exam	1st Test	Other tests
		do not have to be fasting.[31]	

Kallman syndrome (hypogonadotropic hypogonadism)

History	Exam	1st Test	Other tests
delayed development of secondary sexual characteristics, anosmia; difficult to distinguish from constitutional delay	normal final adult height (if treated), normal but prepubertal external and internal genitalia, normal phenotypic female	»**serum hCG:** negative »**serum FSH:** low All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31]	»**serum LH:** low High LH levels suggest alternate diagnoses. Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** prepubertal uterus with thin endometrial echo-complex »**MRI brain:** absent olfactory bulb, possible hypoplastic olfactory sulci Rules out structural or traumatic processes. »**dual energy x-ray absorptiometry (DXA) scan:** low bone density

Hyperprolactinemia

History	Exam	1st Test	Other tests
galactorrhea (some patients), headache or visual disturbances (prolactinoma); may present with oligomenorrhea if	visual field deficit, normal phenotypic female, prepubertal external genitalia, incomplete development of	»**serum hCG:** negative »**serum prolactin:** elevated; >100 ng/mL is highly suggestive of prolactinoma	»**serum LH:** low to normal Prolactin has a suppressive influence on the

Common

Hyperprolactinemia

History	Exam	1st Test	Other tests
prolactin levels are not extremely elevated	secondary sexual characteristics	Persistently elevated levels warrant further evaluation to rule out primary hypothyroidism or prolactinoma. Testing should be performed mid-morning, but patients do not have to be fasting. Macroprolactinemia, caused by elevated levels of macroprolactin (biologically inert), should be evaluated by adding polyethylene glycol to the serum sample.[31] Mildly elevated levels may indicate another structural central nervous system lesion.[1] »**serum FSH:** low to normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low Prolactin has a suppressive influence on the hypothalamus, resulting in hypogonadotropic hypogonadism. Results	hypothalamus, resulting in hypogonadotropic hypogonadism. Results are unreliable if patient is taking any form of hormonal therapy. »**dual energy x-ray absorptiometry (DXA) scan:** bone density may be low Bone density measurement considered if hypoestrogenemia is prolonged. Any cause resulting in a lengthy hypoestrogenic state may result in bone loss.

Common

Hyperprolactinemia

History	Exam	1st Test	Other tests
		are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal; may be elevated if hyperprolactinemia results from primary hypothyroidism »**MRI brain:** possible pituitary tumor »**pelvic ultrasound:** thin to variable endometrial echo-complex	

◊ Polycystic ovary syndrome (PCOS)

History	Exam	1st Test	Other tests
slowly progressive symptoms, obesity, hirsutism, acne, oily skin, weight gain, anovulatory cycles to amenorrhea	androgenic alopecia, acanthosis nigricans, increased waist-hip ratio	»**serum hCG:** negative »**serum FSH:** normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** normal to elevated Results from peripheral androgen conversion and decreased sex hormone binding globulin (influence of excess androgen). Results are unreliable if patient is taking any form of hormonal therapy.	»**free serum testosterone:** elevated Results are unreliable if patient is taking any form of hormonal therapy. »**2-hour oral glucose challenge:** possible hyperinsulinemia or abnormal glucose Assesses for hyperinsulinemia (30% risk) or type 2 diabetes mellitus (7% risk) in patients with PCOS.[32] [33] »**fasting serum lipid profile:** elevated triglycerides and LDL Patients with PCOS are at risk for hyperlipidemia and cardiovascular events.

Common

◊ Polycystic ovary syndrome (PCOS)

History	Exam	1st Test	Other tests
		»**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**serum 17-hydroxyprogesterone (17-OHP):** normal Fasting elevation confirms non-classic congenital adrenal hyperplasia (21-hydroxylase deficiency). »**serum dehydroepiandrosterone sulfate (DHEAS):** normal to elevated Marked elevations are suspicious for adrenal tumor (rapidly progressive signs of androgen excess) and require adrenal imaging. A history of persistent oligomenorrhea associated with clinical or biochemical hyperandrogenism may be sufficient for diagnosis, after other etiologies have been excluded.[28] »**total serum testosterone:** elevated; if >200 ng/dL, suspect ovarian hyperthecosis or	

Common

◊ Polycystic ovary syndrome (PCOS)

History	Exam	1st Test	Other tests
		androgen-producing tumor Well-standardized among differing laboratories; however, does not necessarily reflect the degree of clinical hyperandrogenism. Significant elevations suspicious for ovarian or adrenal tumor (rapidly progressive signs of androgen excess). Results are unreliable if patient is taking any form of hormonal therapy. A history of persistent oligomenorrhea associated with clinical or biochemical hyperandrogenism may be sufficient for diagnosis, after other etiologies have been excluded.[28] »**pelvic ultrasound:** may show polycystic ovaries Adolescents with PCOS may have polycystic type ovaries, but there is ongoing discussion as to the utility of ultrasound as a confirmatory diagnostic marker. Imaging may represent a more meaningful tool in older adolescents. Ovulatory	

Common

◊ Polycystic ovary syndrome (PCOS)

History	Exam	1st Test	Other tests
		dysfunction associated with hyperandrogenism may be sufficient after other etiologies have been excluded. »**serum LH:** elevated (LH:FSH ratio >2:1) Hypertrophy of ovarian stroma, resulting in ovarian androgen production. Due to pulsatile secretion of LH. Levels may not confirm or exclude PCOS. Results are unreliable if patient is taking any form of hormonal therapy.	

◊ Non-classic congenital adrenal hyperplasia

History	Exam	1st Test	Other tests
variable onset of symptoms; may have obesity; hirsutism, acne, deepening voice, male pattern hair growth or loss, oily skin, weight gain, anovulatory cycles to amenorrhea, history of premature pubarche	androgenic alopecia, increased waist-hip ratio, clitoromegaly	»**serum hCG:** negative »**serum FSH:** normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** normal to elevated Results from peripheral androgen conversion and decreased sex hormone binding globulin (influence of	»**free serum testosterone:** elevated Results are unreliable if patient is taking any form of hormonal therapy.

Common

◊ Non-classic congenital adrenal hyperplasia

History	Exam	1st Test	Other tests
		excess androgen). Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**serum 17-hydroxyprogesterone (17-OHP):** elevated fasting levels; a level >200 ng/dL in the follicular phase distinguishes this diagnosis from polycystic ovary syndrome The diagnosis is confirmed by an exaggerated response to high-dose adrenocorticotropic hormone (250 micrograms). »**serum dehydroepiandrosterone sulfate (DHEAS):** elevated Significant elevations are suspicious for adrenal tumor (rapidly progressive signs of androgen excess) and require adrenal imaging.	

Common

◊ Non-classic congenital adrenal hyperplasia

History	Exam	1st Test	Other tests
		»**total serum testosterone:** elevated; if >200 ng/dL, suspect ovarian hyperthecosis or androgen-producing tumor Well-standardized among differing laboratories; however, does not necessarily reflect the degree of hyperandrogenism. Significant elevations suspicious for ovarian or adrenal tumor (rapidly progressive signs of androgen excess). Results are unreliable if patient is taking any form of hormonal therapy. »**serum LH:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**serum progesterone:** a low level confirms follicular phase and helps rule out false elevation of 17-hydroxyprogesterone (17-OHP) Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** variable endometrial echo-complex	

Common

Turner syndrome or mixed gonadal dysgenesis

History	Exam	1st Test	Other tests
may be detected prenatally; lack of pubertal development but variable spectrum of disease	stigmata of Turner syndrome: short stature, webbed neck, shield chest, cubitus valgus, low hairline, high arched palate, multiple pigmented nevi, lymphedema, short fourth metacarpal, cardiovascular anomalies, prepubertal external genitalia, lack of secondary sexual characteristics (all of these findings can present in a variable fashion; phenotype may vary along the entire spectrum of male-to-female disorders of sex development)	»**serum hCG:** negative »**serum FSH:** elevated (>25 IU/L) All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low to undetectable Results are unreliable if patient is taking any form of hormonal therapy. »**serum#TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**karyotype:** 45,XO or mosaic Presence of Y chromosome predisposes to gonadal tumors. »**pelvic ultrasound:** small uterus, streak gonads	»**serum LH:** elevated Results are unreliable if patient is taking any form of hormonal therapy. »**echocardiogram:** possible cardiac anomalies »**abdominal ultrasound:** possible renal anomalies »**serum lipids:** elevated »**thyroid function tests:** hypothyroidism or hyperthyroidism »**fasting glucose and HbA1c:** elevated »**liver function tests:** elevated »**audiometry:** may be abnormal »**ophthalmology testing:** may be abnormal »**IgA level and tissue transglutaminase IgA:** elevated in celiac disease

Common

◊ Mayer-Rokitansky-Kuster-Hauser syndrome (Mullerian agenesis)

History	Exam	1st Test	Other tests
normal-onset pubertal development (except menarche), inability to have vaginal intercourse	phenotypic female, postpubertal external genitalia with blind vaginal pouch, normal secondary sexual characteristics, syndactyly	»**serum hCG:** negative »**serum FSH:** normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**total serum testosterone:** normal female range Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** variable absence of Mullerian structures Occasionally shows obstructed, small rudimentary horn (active endometrium)	»**serum LH:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**MRI abdomen and pelvis:** renal anomalies (pelvic kidney, horseshoe kidney, unilateral renal agenesis) About 30% of patients will have a renal anomaly.[29] Pelvic anatomy is better defined than with ultrasound. »**karyotype:** 46,XX »**audiometry:** may be abnormal »**x-ray spine:** may reveal spinal abnormalities (e.g., scoliosis) Approximately 8% to 32% of patients will have skeletal anomalies.[30] »**echocardiogram:** possible cardiac anomalies

Common

◊ Mayer-Rokitansky-Kuster-Hauser syndrome (Mullerian agenesis)

History	Exam	1st Test	Other tests
		and normal ovarian characteristics.	

Outflow tract obstruction, including imperforate hymen or transverse vaginal septum

History	Exam	1st Test	Other tests
pubertal development with cyclic pelvic pain and lack of menses	either perirectal mass or bulging hymen (imperforate hymen) with hematocolpos; phenotypic female with adult secondary sexual characteristics	»**pelvic ultrasound:** imperforate hymen: blood within vagina, thickened tissue within the vagina (middle, upper), normal-appearing uterus and ovaries Imperforate hymen may be detected on pelvic examination.  *Imperforate hymen* *Lardenoije C, Aardenburg R, Mertens H. Imperforate hymen: a cause of abdominal pain in female adolescents. BMJ Case Reports 2009; doi:10.1136/bcr.08.2008.0722* »**MRI pelvis:** transverse vaginal septum; indicates location and thickness of septum for surgical repair	»**serum LH:** normal Results are unreliable if patient is taking any form of hormonal therapy.

Common

Outflow tract obstruction, including imperforate hymen or transverse vaginal septum

History	Exam	1st Test	Other tests
		More sensitive and confirmatory than ultrasound, ruling out other structural anomalies such as cervical agenesis and endometrial hypoplasia. »**serum hCG:** negative »**serum FSH:** normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31]	

Uncommon

Craniopharyngioma

History	Exam	1st Test	Other tests
headache, altered vision	neurodevelopmental delays, visual field defects, normal phenotypic female, prepubertal external genitalia, incomplete development of secondary sexual characteristics	»**serum hCG:** negative »**serum FSH:** low All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal to high (if the mass is compressing the pituitary stalk, prolactin may be elevated from dopamine disinhibition) Testing should be performed mid-morning, but patients do not have to be fasting.[31]	»**serum LH:** low High LH levels suggest alternate diagnoses. Results are unreliable if patient is taking any form of hormonal therapy. »**MRI brain:** sella and suprasellar space ranging from a few mm to >5 cm; hyperintense cystic component on T1 or T2 weighted images MRI with and without contrast is preferred. CT: partially cystic with solid components, calcifications. »**pelvic ultrasound:** prepubertal uterus with thin endometrial echo-complex

Gonadotropin-releasing hormone (GnRH) receptor mutations

History	Exam	1st Test	Other tests
spectrum of disorder may permit oligo-anovulation, difficult to distinguish clinically from isolated gonadotropin deficiency	normal phenotypic female, prepubertal external genitalia, incomplete development of secondary sexual characteristics, short stature	»**serum FSH:** normal to low All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient	»**serum LH:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** prepubertal uterus with

Uncommon

Gonadotropin-releasing hormone (GnRH) receptor mutations

History	Exam	1st Test	Other tests
		is taking any form of hormonal therapy. »**serum estradiol:** low (variable) Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31]	thin endometrial echo-complex »**pulsatile GnRH administration:** increased pituitary gonadotropin response

Post-encephalitis

History	Exam	1st Test	Other tests
previous infectious process, headache, altered vision	neurodevelopmental delays, visual field defects, normal phenotypic female, prepubertal external genitalia, incomplete development of secondary sexual characteristics	»**serum hCG:** negative »**MRI brain:** cerebral atrophy »**serum FSH:** low All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal	

Uncommon

Post-encephalitis

History	Exam	1st Test	Other tests
		»**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**serum LH:** low Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** thin to variable endometrial echo-complex	

Androgen-producing ovarian tumor

History	Exam	1st Test	Other tests
rapidly progressing symptoms, obesity, hirsutism, acne, deepening voice, male pattern hair growth or loss, oily skin, weight gain, anovulatory cycles to amenorrhea, history of premature pubarche	androgenic alopecia, clitoromegaly, increased muscle mass	»**serum hCG:** negative »**serum FSH:** normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** normal to elevated Results from peripheral androgen conversion and decreased sex hormone binding globulin (influence of excess androgen). Results are unreliable if patient is taking	»**free serum testosterone:** elevated Results are unreliable if patient is taking any form of hormonal therapy. »**MRI abdomen and pelvis:** ovarian mass

Uncommon

Androgen-producing ovarian tumor

History	Exam	1st Test	Other tests
		any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**serum 17-hydroxyprogesterone (17-OHP):** normal »**serum dehydroepiandrosterone sulfate (DHEAS):** normal Marked DHEAS elevations warrant adrenal evaluation. »**total serum testosterone:** elevated (>200 ng/dL) Results are unreliable if patient is taking any form of hormonal therapy. »**abdominal and pelvic ultrasound:** ovarian mass »**serum LH:** normal Results are unreliable if patient is taking any form of hormonal therapy.	

Uncommon

Androgen-producing adrenal tumor

History	Exam	1st Test	Other tests
rapid progression of symptoms, obesity, hirsutism, acne, deepening voice, male pattern hair growth or loss, oily skin, weight gain, anovulatory cycles to amenorrhea, history of premature pubarche	androgenic alopecia, clitoromegaly, increased muscle mass	»**serum hCG:** negative »**serum FSH:** normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** normal to elevated Results from peripheral androgen conversion and decreased sex hormone binding globulin (influence of excess androgen). Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**serum 17-hydroxyprogesterone (17-OHP):** normal »**serum dehydroepiandrosterone sulfate (DHEAS):** elevated Marked DHEAS elevations warrant adrenal evaluation.	»**serum LH:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**free serum testosterone:** elevated Results are unreliable if patient is taking any form of hormonal therapy.

Uncommon

Androgen-producing adrenal tumor

History	Exam	1st Test	Other tests
		»**total serum testosterone:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**MRI abdomen and pelvis:** adrenal mass	

◊ XY gonadal dysgenesis (Swyer syndrome)

History	Exam	1st Test	Other tests
lack of pubertal development	sexual infantilism with normal female phenotype (normal internal and external genitalia with lack of secondary sexual characteristics)	»**serum FSH:** elevated (>25 IU/L) All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low to undetectable Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**karyotype:** 46,XY Any permutation with a Y chromosome requires	»**serum LH:** elevated Results are unreliable if patient is taking any form of hormonal therapy.

Uncommon

◊ XY gonadal dysgenesis (Swyer syndrome)

History	Exam	1st Test	Other tests
		removal of gonads because these patients have up to a 30% chance of developing a gonadal neoplasm. Y chromosome in Swyer syndrome is dysfunctional, and so the streak gonads fail to produce Mullerian inhibiting substance, allowing for development of normal female internal genitalia. »**pelvic ultrasound:** small uterus, streak gonads	

◊ 5-alpha-reductase deficiency

History	Exam	1st Test	Other tests
peripubertal virilization (enlarging male external genitalia, male pattern hair growth, increased muscle mass, deepening voice)	prepubertal female phenotype, but may have had ambiguous genitalia at birth; at puberty, virilization occurs with masculine appearance secondary to testosterone (cannot form active metabolite, dihydrotestosterone, so small external genitalia and prostate)	»**serum FSH:** normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal	»**serum LH:** normal to slightly elevated Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** internal male genitalia are normal, and the testes are located in the labioscrotal pouch; external genitalia typically show severe perineoscrotal hypospadias and a blind vaginal pouch opening into the urogenital sinus or urethra

Uncommon

◊ 5-alpha-reductase deficiency

History	Exam	1st Test	Other tests
		Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**total serum testosterone:** normal male range Results are unreliable if patient is taking any form of hormonal therapy. »**karyotype:** 46,XY	

17-alpha-hydroxylase (CYP17) deficiency

History	Exam	1st Test	Other tests
presentation at puberty with lack of sexual development and menses	46,XX: sexual infantilism, hypertension; 46,XY: male disorders of sex development (lack of female internal genitalia, blind vaginal pouch, intra-abdominal testes)	»**serum FSH:** very high All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** low Decreased androgen production (lack of substrate) results in decreased aromatization to estrogen. Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal	»**serum LH:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**serum deoxycorticosterone:** elevated Mineralocorticoid excess results in volume expansion. »**CYP17 (progesterone substrate):** elevated »**serum progesterone:** elevated Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** 46,XY: lack of Mullerian

Uncommon

17-alpha-hydroxylase (CYP17) deficiency

History	Exam	1st Test	Other tests
		»**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**karyotype:** 46,XY or 46,XX	structures, possible intra-abdominal or inguinal gonads; 46,XX: underdeveloped Mullerian structures

Androgen insensitivity syndrome

History	Exam	1st Test	Other tests
normal timing of thelarche, minimal to no pubic hair growth, inability to have vaginal intercourse	phenotypic female, normal breast development with pale areolae, sparse pubic hair, blind vaginal pouch, palpable inguinal mass (testes), long arms, large hands and feet; incomplete syndrome may present with a range of ambiguous external genitalia (produce androgen after puberty)	»**serum hCG:** negative »**serum FSH:** normal All FSH assays have wide normative ranges, depending not only on cycle time but also on patient age. Results are unreliable if patient is taking any form of hormonal therapy. »**serum estradiol:** normal Results are unreliable if patient is taking any form of hormonal therapy. »**serum TSH:** normal »**serum prolactin:** normal Testing should be performed mid-morning, but patients do not have to be fasting.[31] »**karyotype:** 46,XY	»**serum LH:** elevated Results are unreliable if patient is taking any form of hormonal therapy.

Uncommon

Androgen insensitivity syndrome

History	Exam	1st Test	Other tests
		X-linked recessive disorder resulting in defective androgen receptor. »**total serum testosterone:** normal male range Results are unreliable if patient is taking any form of hormonal therapy. »**pelvic ultrasound:** absent uterus; abdominal or inguinal testes Requires removal of gonads by age 20 years to avoid risk of malignancy.	

Key articles

- Practice Committee of the American Society for Reproductive Medicine. Current evaluation of amenorrhea: a committee opinion. Fertil Steril. 2024 Jul;122(1):52-61. Full text (https://www.fertstert.org/article/S0015-0282(24)00082-7/fulltext) Abstract
- American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Gynecology. ACOG Committee Opinion No. 605: primary ovarian insufficiency in adolescents and young women. Obstet Gynecol. 2014 Jul;124(1):193-7. Full text (https://journals.lww.com/greenjournal/fulltext/2014/07000/committee_opinion_no__605__primary_ovarian.36.aspx) Abstract
- Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2013 Dec;98(12):4565-92. Full text (https://pmc.ncbi.nlm.nih.gov/articles/PMC5399492) Abstract
- American College of Obstetricians and Gynecologists' Committee on Adolescent Health Care-Gynecology. ACOG Committee Opinion No. 728: Müllerian agenesis: diagnosis, management, and treatment. Obstet Gynecol. 2018 Jan;131(1):e35-42. Full text (https://journals.lww.com/greenjournal/fulltext/2018/01000/acog_committee_opinion_no__728__m_llerian.41.aspx) Abstract

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Images

Group	Characteristics	Example
1	Low estrogen Low follicle-stimulating hormone No hypothalamic-pituitary pathology	Hypogonadotropic hypogonadism
2	Normal estrogen Normal follicle-stimulating hormone Normal prolactin	Polycystic ovary syndrome
3	Low estrogen High follicle-stimulating hormone	Gonadal failure

Figure 1: World Health Organization classification of amenorrhea

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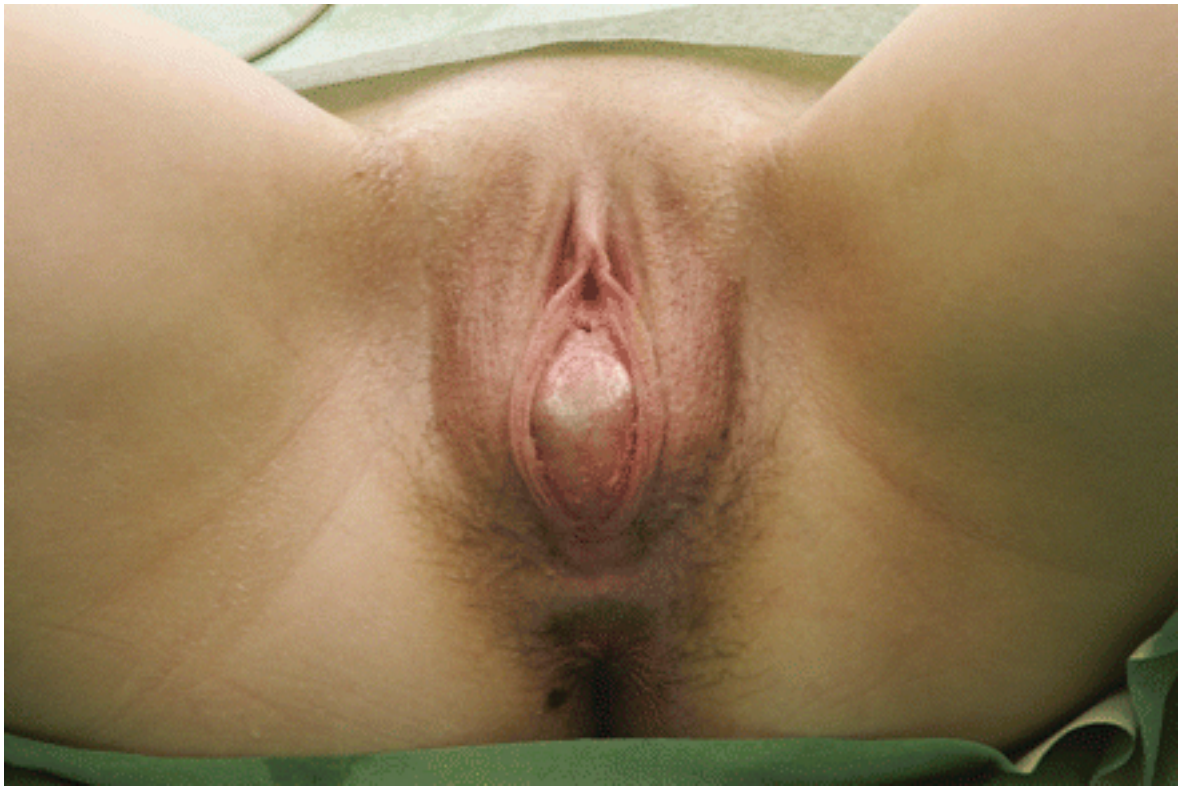

Figure 2: Imperforate hymen

Lardenoije C, Aardenburg R, Mertens H. Imperforate hymen: a cause of abdominal pain in female adolescents. BMJ Case Reports 2009; doi:10.1136/bcr.08.2008.0722

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BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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