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Amenorrhoea

Objectives:

- → Define primary and secondary amenorrhea.
- → Explain the pathophysiology amenorrhea and identify the following types of primary amenorrhea.
  - → Amenorrhea with no breast development and sexual infantilism
  - → Amenorrhea with breast Development and mullerian anomalies
  - → Amenorrhea With breast development and normal mullerian structures
- → Explain the pathophysiology and identify the etiologies of secondary amenorrhea.
  - → Pregnancy.
  - → Hypothalamic causes.
  - → Pituitary causes.
  - → Ovarian causes.
  - → Uterine causes.
  - → Hyperandrogenism.
- → Describe the symptoms and signs of amenorrhea.
- → Outline a plan for investigation and management of amenorrhea.

- → Slides
- → Important
- → Golden notes
- → Extra
- → Doctor's notes
- → Previous Doctor's notes
- → Reference

Kaplan Video

Kaplan Video

Editing File

Normal Menstrual Function

Mechanism of Normal Menstrual Function:

→ **To have normal menstrual function the following is needed:**

1. Normal patient **communicating genital tract**.
2. Development of **endometrial lining** within the uterine cavity.
3. Normal endometrial development requires normal production of both **estrogen and progesterone** from a **normal ovary**.
4. Normal ovarian function requires normal **regulation by gonadotropins** (FSH - LH), by the anterior pituitary gland.
5. The release of FSH & LH is through the secretion of **GnRH hormone** produced by the hypothalamus.

1. Primary Amenorrhea

Definition:

01

No menstruation by the age of **14 years** accompanied by failure to grow properly or develop secondary sexual characteristics: no breast, no pubic or axillary hair.

02

No menstruation (periods) by the age of 16 regardless of the presence of normal development of secondary sexual characteristics.
Usually we wait for them to get menstruation without any intervention.

→ There is no need to stick to the above mentioned definitions if the patient presents with obvious abnormality e.g. Turners syndrome features or absent vagina.

Classification:

→ **Classification of primary amenorrhea can be done either by:**

- → Compartment and levels of affected organ (easier for work up).
- → Presence and absence of the breast and uterus.

1. Primary Amenorrhea

Classification:

A. ★ Compartment & Levels of Affected Organ: ★

	Abnormalities
Compartment I	*Outflow tract or uterine target organ* → **Mullerian agenesis:** → Absent uterus. → Absent vagina. → Transverse vaginal septum. → Imperforate hymen. → With the above abnormalities, the urinary system has to be evaluated.
Compartment II	***Disorders of the ovary*** → Gonadal dysgenesis. → Ovarian failure. → PCO.
Compartment III	*Disorders of the anterior pituitary* → Disorders of the anterior pituitary.
Compartment IV	*Disorders of CNS* → CNS disorders (hypothalamic factors).

B. Presence & Absence of Breast & Uterus:

	Breast Development Present	Breast Development Absent
Uterus Present	→ Consider secondary amenorrhea differential. → Hypothalamic cause → Pituitary cause → Ovarian cause → Uterine cause	→ Gonadal dysgenesis → 45,X → 46,X; abnormal X → Mosaic X → **Pure gonadal dysgenesis:** 46,XX or 46,XY → 17-Hydroxylase deficiency with 46,XX → Galactosemia
Uterus Absent	→ Müllerian agenesis → Androgen insensitivity syndrome	→ Hypothalamic or pituitary failure → Kallmann syndrome → CNS congenital defect → Hypothalamic-pituitary tumors → CNS infection → Physiologic delay → 17,20-Desmolase deficiency → Agonadism → 17-Hydroxylase deficiency with 46,XY

1. Primary Amenorrhea

Evaluation:

A. History Taking:

- → **Psychological disturbance & emotional stress:** hypothalamic - pituitary - expressive exercise.
- → **Nutritional history:** anorexia - bulimia - etc.
- → **Growth and development:** genetic disorders.
- → History of CNS diseases.
- → **History of galactorrhea:** hyperprolacturia.
- → History of acne & hirsutism.
- → **History of virilization:** chiromegaly or change in voice.
- → Cyclic lower abdominal pain.
- → Abdominal masses or swellings.

B. Physical Examination:

- → Weight and height.
- → General Examination.
- → Acne, Hirsutism.
- → Galactorrhea.
- → **Tanner staging:** breast + axillary and pubic hair.
- → Signs & symptoms of turner syndrome.
- → Abdominal exam.
- → External genitalia.

Diagnosis:

- → **17-Hydroxyprogesterone:** suspected congenital adrenal hyperplasia.
- → **Chromosomal analysis:** feature suggestive of a chromosomal problem.
- → **Imaging (US - MRI):** look for mullerian & renal abnormalities to be ruled out.

Clinical Approach:

- → How do we define primary amenorrhea? because age of menarche differs from girl to girl.
- → **History:**
  - → Does she have secondary sexual characteristics?
    - → Yes → a good sign.
    - → No → we worry.
  - → What brought her to the hospital? ask about abdominal pain, swelling, urine retention due to mass effect on bladder.
    - → **Characteristic of abdominal pain:** cyclic (like a period).
- → **Examination:** you must have a chaperone, also if it's a girl you need her mother in the room as well.
- → **Investigations**
- → **Anatomy:** upper 2/3 of vagina made from mullerian duct (common defect), lower 1/3 of vagina from urogenital tract.

1. Primary Amenorrhea

Clinical Approach:

→ There is a difference of opinion about the age at which primary amenorrhoea + secondary sexual characteristics should be investigated at 18 yrs. often suggested.
→ Provided the patient has developed normal secondary sex Characteristics and cryptomenorrhea imperforate hymen has been excluded.
→ While those patient with Primary amenorrhoea and sexual infantilism should be investigated at age of 15 years or 16 years (may be earlier).

Accurate, adequate history is essential to reach a firm diagnosis

→ Questioning to establish diagnosis of primary or secondary amenorrhoea.
  → Is the amenorrhoea is truly secondary? (*previous menses were actually steroid-induced*)

01 02 03 04

Careful physical examination aids in reaching a fairly firm provisional diagnosis

→ In minority, there is a need to go beyond simple outpatient investigation.
  → MRI in hyperprolactinemia to look for the uterus.
  → Laparoscopy in turner's syndrome to look for uterus.

Preliminary Evaluation:

→ **Are breasts present or absent?**
  → Physical examination → evaluate secondary sexual characteristics (**breast development** - axillary and pubic hair - growth).
    → Breasts are an endogenous assay of estrogen.
    → Presence of breasts → adequate estrogen production.
    → Absence of breasts → inadequate estrogen exposure.
→ **A uterus present or absent?**
  → US of the pelvis → assess presence of a normal uterus.

Based on Findings Regarding Breasts and Uterus:

→ Breasts present + uterus present:
  → **Differential diagnosis:**
    → Imperforate hymen.
    → Vaginal septum.
    → Anorexia nervosa.
    → Excessive exercise.
    → Possible pregnancy before first menses.
  → History and physical examination will identify the majority of specific diagnoses.
  → **Workup:** proceed as if for secondary amenorrhea.
→ **Breasts present + uterus absent:**
  → **Differential diagnosis:**
    → **Müllerian agenesis:** Mayer-Rokitansky-Kuster-Hauser syndrome.
    → **Complete androgen insensitivity:** testicular feminization.
  → **Workup:** testosterone levels + karyotype.
→ **Breasts absent + uterus present:**
  → **Differential diagnosis:**
    → **Gonadal dysgenesis: Turner syndrome**.
    → **HPO axis failure:** Kallman syndrome.
    → **Pituitary problems:** panhypopituitarism - craniopharyngioma - non-functioning pituitary adenoma - streak gonads.

1. Primary Amenorrhea

Disorder of Outflow Tract or Uterus:

1. Cryptomenorrhea:

→ Vaginal atresia or imperforate hymen → prevent menstrual loss from escaping.
→ Primary amenorrhoea in a teenage girl with normal sexual development.
  → Everything is fine, she is XX and has ovaries.
  → **Problem:** obstructed outflow → accumulated collection of blood → mass effect on bladder.
→ **Typical presentation to ER:** urinary retention - Hx of the same pain every month.

Features:

→ Intermittent abdominal pain.
→ **Possible difficulty of micturition (urinary retention):** multiple catheterizations before.
→ Palpable lower abdominal swelling (hematometra) presented as pelvic mass.
→ Bulging bluish membrane at lower end of vagina (hematocolpos).

Management:

→ **Incise membrane:** cruciate incision (diamond shaped).

2. Absence or Hypoplasia of Vagina:

→ Growth, develop, and ovarian function are usually normal.
→ Normal breast, pubic and axillary hair.
→ Uterus may be normal or rudimentary.
→ Renal anomalies (in 30%) or skeletal defects (in 10%) may be present.

Management:

→ Create a functional vagina by surgery or dilators.
→ If failed plastic surgery with skin graft.
→ She can be a biological mother but she can't carry the fetus and need a surrogate mother.

3. Testicular Feminization (Androgen Sensitivity):

→ Phenotype is woman but genotype is man (XY) → present testes.
→ Inherited by an X-linked recessive gene → familial.
→ **Result in:** absence of cytosol androgen receptor → no testosterone receptors.

Features:

→ Growth and develop are normal (may be taller than average).
→ Breasts are large but with sparse glandular tissue and pale areola.
→ Inguinal hernia in 50% of cases.
→ Scanty, or no axillary and pubic hair.
→ Labia minora underdeveloped.
→ Blind vagina, absent uterus, rudimentary fallopian tubes.
→ Testes in abd. or inguinal canal cryptorchid testes.
→ Normal levels of testosterone are produced.. But no response to androgens (endog. or exogen).
→ No spermatogenesis.
→ ↑ incidence of testicular neoplasia (50%) that's why it needs to be removed.

Diagnosis:

→ Diagnosed by chromosomal analysis.
→ With inguinal hernia.
→ With primary amenorrhea and absent uterus.
→ When body hair is scanty or absent.

Management:

→ These patients are female.
→ The gonads must be removed after puberty → then HRT started for bone and breast development.
→ Rare cases of incomplete test. feminization do occur → have variable degrees of masculinization

1. Primary Amenorrhea

Disorders of the Ovary:

1. Chromosomal Abnormalities:

→ Turner's syndrome (45 x 0) ⟶ gonadal dysgenesis.

Features:

→ **Amenorrhea:** primary, rarely secondary.
→ **Failure of secondary sex development:** no ovaries, breast, axillary or pubic hair.
→ Short stature and shield chest.
→ Webbing of neck.
→ ↑ carrying angle.
→ Coarctation of aorta.
→ **Renal collecting system defects:** look for it in case of genital anomalies.

Diagnosis:

→ **Streak ovaries present:**
  → **US:** she has a uterus & vagina.
  → **Laparoscopy:** streak ovaries present but no follicles.
→ ↑↑ **gonadotropins:** ↑ FSH & LH due to lack of -ve feedback.
→ ↓ estrogens.

→ Mosaic Chromosomal Pattern (e.g. XO/XX) ⟶ various degrees of gonadal dysgenesis and secondary amenorrhea had menses for a year + premature menopause / ovarian failure.
→ If Y-Chromosome is present in genotype ⟶ risk of gonadal malignancy makes gonadectomy advisable.

2. Gonadal agenesis:

→ Failure of gonadal develop, no other congenital abnormality.
→ **Phenotype:** female.
→ **Genotype:** XX 46.

3. PCOS:

→ Could be familial or obesity related.
→ Can cause both primary and secondary amenorrhea.
→ Mostly present with classical Stein-Leventhal syndrome (oligomenorrhea - obesity - hirsutism - infertility).
→ A substantial group will have secondary amenorrhoea with no obesity or hirsutism.

Diagnosis:

→ ↑ LH/FSH ratio (3:1), normally 1:1.
→ **Confirmation by laparoscopy:** enlarged glistening ovaries.
→ **USS:** at least 15 peripheral follicles "pearl follicles" +/- 50 volume (normal 7 - 8) , 4 cm (normal 2 - 3 cm), multicystic.

1. Primary Amenorrhea

Management:

→ Treat the cause according to each compartment:

	Abnormalities
Compartment I	*Outflow tract or uterine target organ* → Mullerian agenesis → counseling. → Imperforate hymen or transverse vaginal septum → surgery. → **Imperforate hymen:** move labia apart, you will see a blue bulge on examination → open an incision → blood flows (chocolate color). → Give certificate stamped from hospital for future purposes. → **Vaginal agenesis:** create a vagina with vaginal dilator.
Compartment II	*Disorders of the ovary* → **Gonadal dysgenesis:** → Testicular feminizing syndrome → surgical removal of gonads before the age of 30 to avoid malignant transformation. → Turners → HRT. → Ovarian failure → HRT. → **PCO:** → BCP or induction of labour. → Cyclic progestin.
Compartment III	*Disorders of the anterior pituitary* → Pituitary micro or macro ootenoma. → Micromedical bromocriptine. → Macro Medical / surgical.
Compartment IV	*Disorders of CNS* → Lifestyle modification. → Counseling. → Ovulation induction if pregnancy is desired → conservative measures.

Turner Syndrome:

→ **Turner syndrome**
→ **Genetically:** 45 XO (this genotype represents 80%), mosaic.
→ **Characteristic:**
→ Streak ovary → fibrous.
→ Premature menopause.
→ Short status.
→ Webbed neck.
→ Cardiovascular symptoms & coarctation of aorta.
→ Widely spaced nipples.
→ ↓ estrogen.
→ ↑↑↑↑ (sky high) gonadotropin.
→ **Management:** if there is Y → risk of cancer → remove the gonads.

Testicular Feminization:

→ **Presentation:** Tall, choppy women with large breast & no period.
→ **Genetically:** XY → blind vagina (no uterus).
→ **Characteristic:**
→ Large breast, small areola (*not glandular tissue it's merely fat*).
→ Inguinal hernia because of testes (*suspect testicular hernia*).
→ Risk of cancer.
→ Gonadoblastoma.
→ Will grow to be a male.

2. Secondary Amenorrhea

Definition:

→ **Secondary amenorrhea:** 6 months if irregular, or 3 months if regular cycle of amenorrhea in previously menstruating women or absence of periods for at least the length of her previous 3 cycles.
→ **Secondary amenorrhea:** she had her period, but for some reason it disappeared.
→ **More common:** secondary amenorrhea
→ It could be physiological (pregnancy - menopause - lactational amenorrhea - prepubertal HPO axis not developed) or it could be pathological.
→ Always rule out physiological causes such as pregnancy (always think of pregnancy).
  → Prepubertal and post-menopausal conditions are to be excluded as physiological causes.

→ **Physiology of menstrual cycle:** hypothalamus → pituitary → ovaries → endometrium.
→ Hypothalamus produces GNRH → stimulate pituitary gland to produce FSH & LH → FSH stimulate follicles to grow → ↑ estrogen produced by granulosa cells → estrogen act on endometrium leading to proliferative phase → ↑ FSH reaches and start promoting ↑ LH → LH will cause ovulation of the oocyte forming corpus luteum → CL produce progesterone → progesterone will act on endometrium leading to secretory phase → if there's no pregnancy the CL will involute & ↓ progesterone → ↓ progesterone levels will cause the spiral arteries to constrict → endometrium lining will undergo necrosis and shedding → menstruation.

Etiology:

Reproductive tract:
- → Cervical stenosis
- → Asherman syndrome

Ovarian:
- → Primary ovarian insufficiency
- → Polycystic ovary syndrome

Pituitary:
- → Hyperprolactinemia
- → Pituitary adenomas
- → Sheehan syndrome

CNS:
- → Hypothalamic amenorrhea
- → Brain injury
- → Inflammatory or infiltrative process

Other endocrinopathies:
- → Hypothyroidism
- → Cushing syndrome
- → Late-onset adrenal hyperplasia

Causal Factors:

- → Surgical procedure (ie, LEEP, CKC)
- → Endometrial scarring
- → Idiopathic
- → Chromosomal abnormality
- → Autoimmune disease
- → Infection
- → Inappropriate gonadotropin secretion
- → Insulin resistance
- → Lactotroph hyperplasia ± prolactinoma
- → Drugs
- → Thyrotroph, corticotroph, or other hyperplasia
- → Postpartum hemorrhage
- → Stress - excessive exercise
- → Eating disorders - weight loss
- → Interruption of HPOA
- → Interruption of HPOA

2. Secondary Amenorrhea

Classification:

	Abnormalities
Compartment I	*Outflow tract or uterine target organ* → Asherman's Syndrome. → Cervical Stenosis. → Infection.
Compartment II	***Disorders of the ovary*** → PCOS. → Premature Ovarian Failure. → Premature Menopause. → Surgical Removal of the Ovaries. → Exposure to Chemo or Radiation. → Turner Mosaic. → Resistant Ovary Syndrome / Savage Syndrome.
Compartment III	*Disorders of the anterior pituitary* → **Pituitary Tumor:** micro or macro adenoma. → Sheehan's Syndrome. → Drugs. → Craniopharyngioma
Compartment IV	*Disorders of CNS* → Any severe uncontrolled medical problem can interfere with pituitary ovarian hypothalamic axis. → CNS disorders (hypothalamic factors). → Hypothyroidism. → Hyperthyroidism. → Renal failure.

2. Secondary Amenorrhea

Disorder of Outflow Tract or Uterus:

1. Asherman's Syndrome:

→ Intrauterine synechiae secondary to over curettage of the uterus removal of the regenerating layer of the endometrium.

→ Secondary amenorrhoea following destruction of the endometrium by overzealous curettage → multiple synechiae show up on "Hysterography".

→ Dilation and curettage D&C → obliterated functional layer of uterus.

→ Never use sharp curette in reproductive age women because of the fear of destruction of basal layer (regenerate layer of endometrium) → Asherman's syndrome.

Diagnosis:

→ History taking.

→ Hysteroscope.

→ Hysterosalpingography.

→ Sonography by US.

Management:

→ Under general anesthesia → breakdown intrauterine Adhesions through hysteroscope → insert an IUCD to deter reformation → hormone therapy (E2 + P).

2. Cervical Stenosis:

→ Caused by procedure such as dilation and curettage, LEEP and conization → injury & subsequent stenosis of cervix.

3. Infection:

→ Tuberculosis - Uterine Schistosomiasis.

→ Any post-op infection e.g., endometritis following a c-section.

Disorders of the Ovary:

1. PCOS

2. Premature Ovarian Failure

3. Surgical Removal of the Ovaries

4. Exposure to Chemo or Radiation

5. Turner Mosaic

2. Secondary Amenorrhea

Disorders of the Ovary:

6. Resistant Ovary Syndrome / Savage Syndrome:

- → Rare condition.
  - → No FSH receptors on the follicles.
- → Normal ovarian develop and potential.
- → ↑↑ FSH.

Management:

- → It may resolve spontaneously 3 - 5%.
  - → Hot flushes → treat with estrogen.

7. Premature Menopause:

- → No follicles.
- → **Ovarian failure due to:**
  - → **Autoimmune disease:** associated with addison's disease?
  - → **Viral infections:** such as mumps.
  - → **Cytotoxic drugs:** like chemotherapy
  - → **Tumor:** ovariectomy and chemotherapy
- → How to differentiate between resistant and premature?
  - → By histopathology.
    - → Follicles → resistant ovary syndrome.
    - → No follicles → premature ovarian failure.
  - → Not done nowadays because they have the same management so it will be useless.

Disorder of the Pituitary:

1. Pituitary Tumor:

- → Micro or macro adenoma → hyperprolactinemia → 🚫 ovulation.
- → Prolactin a a polypeptide hormone secreted by acidophil cells of the pituitary gland.
- → Hyperprolactinemia → 40% of women with hyperprolactinemia will have a pituitary adenoma.
- → Anterior pituirary fossa XR is necessary in all cases of amenorrhoea – particularly 20.

Features:

- → **In coned view (X-ray):**
  - → Erosion of clinoid process -Enlarge of pituitary fossa.
  - → Double flooring of fossa.
  - → If any of above features seen do CT scan or MRI + Assessment of visual fields looking for macro or micro adenomas.

Management:

- → **Bromocriptine (dopamine agonist):**
  - → Suppress prolactin secretion.
  - → Correct estrogen deficiency.
  - → Permits ovulation.
  - → ↓ size of most prolactinomas.
  - → **ADRs:** hypotension - dizziness.
- → **Surgical removal of tumor:**
  - → If extracellular manifestation (pressure on optic chiasma).
  - → If patient cannot tolerate or respond to medical treatment.

2. Secondary Amenorrhea

Disorder of the Pituitary:

2. Sheehan's syndrome:

→ Sheehan's syndrome → pituitary necrosis → insufficient 20 to postpartum hemorrhage.
→ Necrosis of anterior pituitary due to severe **PPH** (postpartum hemorrhage) **Pan – or partial hypopituitarism** (↓ FSH, LH, TSH)
→ A rare problem today, due to better obstetric care and adequate blood transfusion.

3. Drugs ↑ Prolactin:

→ Phenothiazines.
→ Methyldopa.
→ Metoclopramide.
→ Anti-histamines.
→ Oestrogens.
→ Morphine.

4. Craniopharyngioma:

→ Other intracranial tumor - nasal pharyngioma.

Diagnosis:

→ ↓ FSH & LH.
→ hypogonadotropic–hypogonadism.

Disorder of the Hypothalamus:

→ Same as primary amenorrhea.
→ Any severe uncontrolled medical problem can interfere with the pituitary ovarian hypothalamic axis and cause secondary amenorrhea.
  → Hypothyroidism, hyperthyroidism, renal failure, etc.
→ Commonest reason for hypogonadotropic secondary amenorrhoea.
→ Often associated with stress (migrants - young women when leave home - university student).
→ **Diagnosis:** by exclusion of pituitary lesions.
→ **Management:** hormone therapy or ovulation induction is not indicated unless patient wishes to become pregnant.

2. Secondary Amenorrhea

Clinical Approach:

→ There are multiple etiologies for secondary amenorrhea, which can be **classified by alterations in FSH and LH** levels:
  → **Hypogonadotropic → suggesting hypothalamic or pituitary dysfunction:**
    → Exercise/ Stress
    → Kallman's syndrome
    → Loss of weight
    → Sheehan syndrome
  → **Hypergonadotropic → suggesting ovarian follicular failure:**
    → Premature ovarian syndrome
    → Persistence ovarian syndrome
  → **Eugonadotropic → suggesting pregnancy, anovulation, or uterine or outflow tract pathology:**
    → Asherman's syndrome
    → Hyperprolactinemia

→ **Specific etiology:**
  → **Pregnancy:** first step is a β-hCG to diagnose pregnancy.
    → Most common cause of secondary amenorrhea.
  → **Anovulation:** no corpus luteum present to produce progesterone → no progesterone-withdrawal bleeding → unopposed estrogen endometrial stimulation.
    → **Causes:** PCOS - hypothyroidism - pituitary adenoma - ↑ prolactin - medications (antidepressants).
    → **Initially:** anovulatory patient will demonstrate amenorrhea.
    → **As endometrial hyperplasia develops:** irregular, unpredictable bleeding will occur.
  → **Estrogen deficiency:** no adequate estrogen priming → atrophic endometrium with no proliferative changes.
    → **Causes:** absence of functional ovarian follicles - hypothalamic–pituitary insufficiency.
  → **Outflow tract obstruction:** even with adequate estrogen stimulation and progesterone withdrawal, menstrual flow will not occur if the endometrial cavity is obliterated or stenosis of the lower reproductive tract is present.

Management:

→ Take proper detailed history to try and find out which compartment is the likely cause
→ Complete physical examination.
→ Pregnancy test, TSH, Prolactin level.
→ Treat the underlying cause.

Amenorrhea

Associations:

Weight Loss Associated with Amenorrhea:

- → A loss of > 10 kg is frequently associated with amenorrhoea.
- → In young women and teen age girls who became obsessed with their body image and starve themselves.
- → **Jogger's amenorrhoea:** frequently seen in women training for marathon racing, in ballet dancers and other form of athletes.
  - → **Causes:**
    - → Redistribution between proportion of body fat mass and body muscle mass.
    - → Mediated by exercise related changes in β-endorphins.
- → **Anorexia nervosa:** associated with secondary amenorrhoea (misnomer → no loss of appetite).

Amenorrhea and Anosmia:

- → Rare cause of amenorrhea of hypogonadotropic–hypogonadism (counterpart in males is Kallman's syndrome).
- → Absence of GnRH receptors.

Progesterone Challenge Test (PCT):

- → There is no evidence that estrogen and progesterone contraceptive pills predispose to amenorrhoea once pill taking is ceased.
  - → An irregular menstrual cycle frequently precedes pill taking.
  - → If this assumption of amenorrhoea being merely an after-effect of pill taking many cases of hyperprolactinemia will be missed (1:5).
  - → Premature ovarian failure will be missed in 1:10 cases.
  - → Once other causes are excluded, this type of amenorrhoea responds well to ovulation induction with Clomiphene citrate if pregnancy is desired.

Investigations:

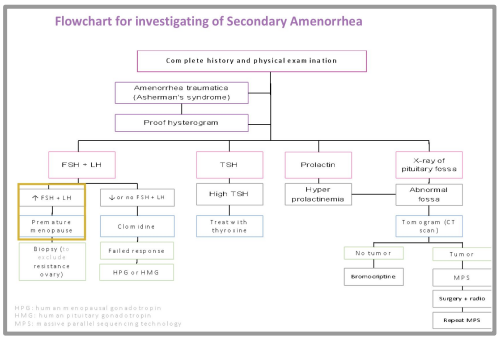
01

Serum prolactin level and TFT

02

Karyotyping

→ If chromosomal anomaly is suspected.
→ Chromosomal analysis is done if amenorrhea < 30 - 35 y.



03

Progesterone Withdrawal Test

→ **Example:** Provera (medroxy-prog).
→ Bleeding PV → reactive endometrium + patent outflow tract.

04

USS of Uterus & Ovaries

→ Useful to investigate & monitor treatment.

Progesterone Withdrawal Test

→ To check endogenous estrogen.
→ Normal PRL + no galactorrhoea → no need for further investigation for pituitary tumor/
→ Galactorrhoea → further evaluation of pituitary gland is necessary, regardless of level of PRL and menstrual pattern.
→ ↑↑↑↑ PRL (excluding stress) → radiology exam of pituitary to exclude tumors (must be repeated as it can be affected easily by other factors).
  → Abnormal X-Ray → visual fields assessment.
→ FSH & LH levels,especially if no withdrawal bleeding following progesterone challenge.
  → ↓ LH (< 5 IU/ml) → hypogonadotropic- hypogonadism.
  → ↑ FSH (> 40 IU/ml) on successive readings → premature ovarian failure or PCOS.
    → Irregular cycles → either PCOS or premature ovarian failure.
      → **PCOS:** irregular cycles ever since puberty.
      → **Premature ovarian failure:** normal regular cycles & suddenly become irregular & scanty.
        → < 35 years women → premature ovarian failure (menopause) → check karyotype, + Y → high risk of gonadal malignancy.

Management:

Pregnancy Test:
- → First step in management of secondary amenorrhea is to obtain a qualitative β-hCG test to rule out pregnancy.

Thyrotropin (TSH) Level:
- → If the β-hCG test is negative, hypothyroidism should be ruled out (TSH level)
- → ↑ thyrotropin-releasing hormone (TRH) in primary hypothyroidism → ↑ prolactin.
- → Hypothyroidism → **treatment:** thyroid replacement → rapid restoration of menstruation.

Prolactin Level

Progesterone Challenge Test (PCT):
- → Negative β-hCG + normal TSH & prolactin levels → administer either a single IM dose of progesterone or seven days of oral medroxyprogesterone acetate (MPA).
  - → **Positive PCT:** any degree of withdrawal bleeding is diagnostic of anovulation.
    - → Cyclic MPA is required to prevent endometrial hyperplasia.
    - → Clomiphene ovulation induction will be required if pregnancy is desired.
  - → **Negative PCT:** absence of withdrawal bleeding is caused by either inadequate estrogen priming of the endometrium or outflow tract obstruction

Estrogen–Progesterone Challenge Test (EPCT):
- → Negative PCT → administer 21 days of oral estrogen followed by 7 days of MPA.
  - → **Positive EPCT:** any degree of withdrawal bleeding is diagnostic of inadequate estrogen, an FSH level will help identify the etiology:
    - → ↑ **FSH:**
      - → Suggests **ovarian failure** (**premature menopause**).
      - → Occurs age <25 → could be **Y chromosome mosaicism** associated with malignancy → karyotype.
      - → **Savage syndrome or resistant ovary syndrome:** follicles are seen in the ovary by sonogram, though they do not respond to gonadotropins.
    - → ↓ **FSH:**
      - → Suggests **hypothalamic–pituitary insufficiency**.
      - → **Brain tumor** → CNS imaging study to rule it out.
    - → Positive EPCT → need estrogen-replacement therapy to prevent osteoporosis & estrogen-deficiency morbidity + cyclic progestins to prevent endometrial hyperplasia.
  - → **Negative EPCT:** absence of withdrawal bleeding is diagnostic of either an outflow tract obstruction or endometrial scarring (**example:** Asherman syndrome).
    - → Hysterosalpingogram (HSG) will identify where the lesion is.
    - → **Asherman:** result of extensive uterine curettage and infection- produced adhesions.
      - → **Treatment:** hysteroscopic adhesiolysis followed by estrogen stimulation of the endometrium + placing inflatable stent into the uterine cavity to prevent re-adhesion of the uterine walls.

439 Summary

Amenorrhea

Most topics are mentioned with more details in DSD & anomalies summary

Primary Amenorrhea	
Definition	• Absence of menses at 14 years of age in female individuals with no secondary sexual characteristics **OR** • Absence of menarche at 16 years of age despite normal development of secondary sexual characteristics

Etiology	• Anatomic anomalies: Outflow tract obstruction (cryptomenorrhea) with otherwise normal puberty:
	  ○ **Imperforate hymen**
	  ○ **Vaginal atresia**
	  ○ Transverse vaginal septum
	  ○ Müllerian agenesis: absence or hypoplasia of vagina
	• Receptor and enzyme abnormalities:
	  ○ Androgen insensitivity syndrome
	  ○ 5-alpha-reductase deficiency
	  ○ Congenital adrenal hyperplasia (CAH)
	• Hypergonadotropic hypogonadism:
	  ○ 46, XY gonadal dysgenesis
	  ○ Turner syndrome (XO)
	• Hypogonadotropic hypogonadism
	  ○ Kallmann syndrome
	  ○ **Sheehan syndrome**
	  ○ Pituitary tumors (e.g. pituitary adenoma)
	  ○ Other CNS tumors (e.g., craniopharyngioma)

Diagnosis
EXTRA!
	• Pregnancy test
	• Check for secondary sexual characteristics and anatomical anomalies (physical examination, pelvic ultrasound).
	  ○ Uterus **absent**: Perform **karyotyping** and serum **testosterone** to investigate for male/female genotype and androgen sensitivity.
	  ○ Uterus **present**: Test FSH and LH levels.
	  ■ Exclude imperforate hymen, vaginal atresia, and transverse vaginal septum.
	  ■ ↑ FSH: primary ovarian insufficiency (e.g., Turner syndrome, premature ovarian failure)
	  ■ Normal or ↓ FSH: constitutional growth delay, hypogonadotropic hypogonadism
	• If galactorrhea is present: Check prolactin and TSH levels.
	• If symptoms of hyperandrogenism are present:
	  ○ Check serum testosterone and dehydroepiandrosterone sulfate (DHEA-S).
	  ○ If high: Suspect an androgen-secreting tumor.
	• If blood pressure is high: Suspect congenital adrenal hyperplasia.

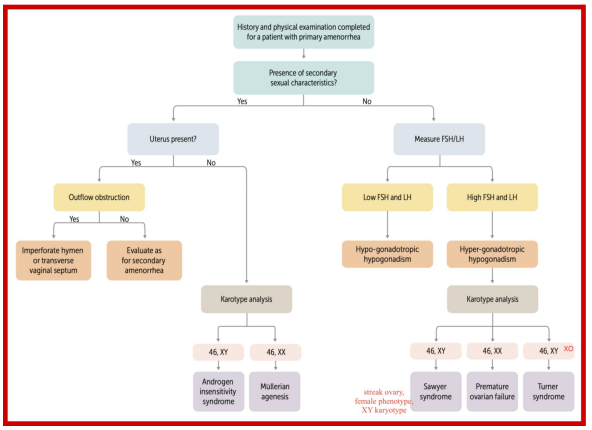
Secondary Amenorrhea	
Definition	• Absence of menses for more than 3 months in individuals with previously regular cycles, **OR** • Absence of menses for more than 6 months in individuals with previously irregular cycles

Etiology	• **Asherman's syndrome**
	• Polycystic ovarian syndrome
	• Hypothyroidism, hyperthyroidism
	• **Resistant ovary syndrome:** also known as savage syndrome OR **gonadotropin-resistant ovary syndrome**
	  ○ **Functional disturbance of the gonadotropin receptors despite normal ovarian function and development**
	  ○ Features:
	  ■ Secondary amenorrhea
	  ■ ↑FSH & LH
	  ○ Treatment: estrogen for hot flashes (if present), may resolve spontaneously
	• **Primary ovarian insufficiency: also known as premature ovarian failure** or premature menopause
	  ○ **Ovarian insufficiency before the age of 40 despite adequate gonadotropin stimulation**
	  ○ Etiology:
	  ■ Idiopathic (90% of cases)
	  ■ Genetic disorders associated with ovarian hypoplasia, (e.g., Turner syndrome, androgen insensitivity syndrome)
	  ■ Autoimmune diseases
	  ■ Smoking: major risk factor
	  ■ **Iatrogenic:** radiation and/or chemotherapy, prolonged GnRH agonist therapy, induction of multiple ovulation in infertility treatment
	  ○ Clinical features:
	  ■ Secondary amenorrhea or permanent cessation of menstruation
	  ■ Infertility or reduced fertility
	  ○ Diagnosis:
	  ■ ↑↑ FSH (> 30–40 mIU/mL); two samples at least 1 month apart
	  ■ > 3 months of menstrual irregularities in a woman under age 40
	  ○ Treatment: HRT
	Premature ovarian insufficiency (POI) is typically the end result of premature depletion of primordial follicles. However gonadotropin-resistant ovary syndrome could result in a similar clinical and laboratory picture with a more favorable outcome.
	• Functional hypothalamic amenorrhea: a dysfunction in the pulsatile secretion of GnRH. Etiology:
	  ■ Excessive exercise: e.g., in competitive athletes (also called exercise-induced amenorrhea)
	  ■ Reduced calorie intake (e.g., in eating disorders like **anorexia nervosa**)
	  ■ Stress
	  ■ Female athlete triad syndrome: menstrual dysfunction, calorie deficit, and decreased bone density in athletic female young adults or adolescents

Secondary Amenorrhea	

Etiology	• Pituitary disorders:
	  ○ Hyperprolactinemia: due to either:
	  ■ Prolactin-secreting Pituitary adenoma
	  • Presentation: milky discharge, bilateral temporal hemianopia, headache
	  • Treated by bromocriptine (dopamine agonist) or surgical removal of the tumor.
	  ■ Medications: phenothiazines, methyldopa, estrogens, metoclopramide
	  ○ Craniopharyngioma
	  ○ Cushing syndrome
	  ○ **Sheehan syndrome**
	  ■ **Etiology:** Usually occurs following postpartum hemorrhage, but can also occur even without clinical evidence of hemorrhage
	  ■ **Clinical features:** Amenorrhea, agalactorrhea, low BP, low sodium & glucose levels
	  ■ Diagnosis: low levels of pituitary hormones (pan or partial hypopituitarism) (include: GH, LH/FSH, ACTH, TSH, prolactin, ADH)
	  ■ Management: Replacing deficient hormones

Diagnosis	• Pregnancy test
	• If negative, obtain FSH, TSH, and prolactin levels.
	  ○ ↑ FSH: ovarian insufficiency
	  ○ ↑ TSH: hypothyroidism
	  ○ ↑ Prolactin
	  ■ Re-check history for medication intake (antipsychotics are the most frequent cause of medication-induced hyperprolactinemia).
	  ■ Perform brain MRI to evaluate for pituitary adenoma.
	• **Perform progestin challenge/progesterone withdrawal test: 10 days of progestin intake**
	  ○ Withdrawal bleeding induced: anovulation (e.g., PCOS, idiopathic anovulation, premature ovarian failure)
	  ○ No withdrawal bleeding (may indicate uterine anomalies or estrogen deficiency): test FSH levels.
	  ■ ↑ FSH: hypergonadotropic hypogonadism or ovarian failure
	  ■ ↓ FSH: combined estrogen and progesterone challenge
	  ■ Withdrawal bleeding induced: hypogonadotropic hypogonadism
	  ■ No withdrawal bleeding: endometrial or anatomical problem (e.g,. Asherman syndrome)
	  ○ If virilization is present: Check testosterone, DHEA-S, and 17-hydroxyprogesterone.
	  ■ Mild elevation: PCOS, congenital adrenal hyperplasia, Cushing syndrome
	  ■ Moderate-to-high elevation: androgen-producing tumor



Quiz

Question 1:

→ **A 17 year old presented to your clinic with amenorrhea. She has normal development. Which of the following supports diagnosis of cryptomenorrhea?**

A. Inguinal hernia
B. Cyclic abdominal pain
C. Webbing of neck
D. Short stature

Question 2:

→ **A 15 year old girl presented with inguinal hernia. Past medical history revealed amenorrhea. Physical examination shows scant pubic hair and blind vagina. What is the underlying mechanism for this presentation?**

A. Chromosomal abnormalities
B. Drug induced
C. Testicular feminization
D. Hypopituitarism

Question 3:

→ **Which of the following drugs can cause amenorrhea?**

A. Phenothiazines
B. Misoprostol
C. Warfarin
D. Gentamicin

Question 4:

→ **A 24 year old complains of amenorrhea and galactorrhea. She is not married. What investigation will you order?**

A. FSH
B. LH
C. TSH
D. PL

Question 5:

→ **In the previous question, how will you manage the patient?**

A. Medically with bromocriptine
B. Weight loss + metformin
C. Surgical removal of lesion
D. HRT + ovulation induction

1	2	3	4	5
B	C	A	D	A

Reference

CHAPTER 33

Amenorrhea, Oligomenorrhea, and Hyperandrogenic Disorders

DANIEL A. DUMESIC • JOSEPH C. GAMBONE

CLINICAL KEYS FOR THIS CHAPTER

- *Amenorrhea* literally means the absence of menses. As a menstrual disorder, amenorrhea is *primary* when menstruation has never occurred by the age of 16 years (or 14 years with the absence of breast development) and is *secondary* when menses has occurred at least once and then has been absent for at least 6 months.
- A more clinically useful classification of these menstrual disorders is to characterize them based on the initial presentation (history and physical examination) as (1) primary amenorrhea without evidence of secondary sexual characteristics (sexual infantilism), (2) primary amenorrhea with breast development and müllerian anomalies, or (3) secondary amenorrhea or oligomenorrhea with breast development and normal müllerian structures.
- The most common cause of primary amenorrhea is gonadal dysgenesis and/or agenesis (50% of cases). Secondary amenorrhea occurs most commonly with pregnancy and menopause (physiologic), followed by pathologic conditions such as hypothalamic-pituitary dysfunction, premature ovarian failure, hyperprolactinemia, and hyperandrogenism, such as polycystic ovarian syndrome (PCOS).
- Amenorrhea or oligomenorrhea with elevated androgens (hyperandrogenism) may result from adrenal, pituitary, or ovarian disorders, including tumors and functional problems with these tissues. Congenital adrenal hyperplasia, Cushing syndrome, PCOS, and the hyperandrogenic insulin resistance and acanthosis nigricans syndrome have adrenal and/or ovarian causes. Tumors of the adrenal glands and ovaries may cause excess androgen levels that can disrupt the menstrual cycle. Some tumors may be malignant, and all such tumors are managed surgically.
- PCOS is the most common endocrinologic disorder in women of reproductive age in developed countries. It has been recognized recently as a complex endocrinologic and metabolic syndrome that is diagnosed when at least two of the following three findings are present: (1) hyperandrogenism (either clinical or biochemical), (2) oligomenorrhea, and/or (3) polycystic ovaries by morphology. Not all women with PCOS have polycystic ovaries, and some women with polycystic ovaries do not meet the criteria for PCOS.

Amenorrhea, or the absence of menses, is a common symptom of several pathophysiologic states. This condition traditionally has been divided into **primary amenorrhea,** in which menarche (the first menses) has not occurred, and **secondary amenorrhea,** in which menses has been absent for 6 months or more. A more functional or clinical division of menstrual disorders based on the initial history-taking and physical examination is **(1) primary amenorrhea with sexual infantilism** (absence of secondary sexual development), **(2) primary amenorrhea with breast development and müllerian anomalies,** and **(3) amenorrhea or oligomenorrhea with breast development and normal müllerian structures.** The last group of disorders causes secondary, rather than primary, amenorrhea, including oligomenorrhea with and without hyperandrogenic states (Table 33-1).

Primary Amenorrhea

The diagnosis of primary amenorrhea is made when no spontaneous uterine bleeding has occurred by the age of 16 years. The workup should be initiated earlier if there is no evidence of breast development (thelarche) by age 14 years or if the patient has not menstruated (menarche) spontaneously within 2 years of thelarche. The presence of normal breast development confirms gonadal secretion of estrogen but not necessarily the presence of ovarian tissue. With androgen insensitivity, low levels of estrogen from the testicles may stimulate breast development in males (see Chapter 18). Normal amounts of pubic and axillary hair confirm gonadal or adrenal secretion of androgens as well as the presence of functional androgen receptors.

TABLE 33-1

CLINICAL CLASSIFICATION OF MENSTRUAL DISORDERS

Disorder	Notable Diagnostic Findings	Examples	Notable Clinical Features
Primary Amenorrhea with Sexual Infantilism			
Hypogonadotropic hypogonadism	Low FSH and LH, low estrogen; screening for other pituitary hormones is indicated; MRI of the hypothalamic and/or pituitary area is recommended	Central nervous system or pituitary tumor, constitutionally delayed puberty, Kallmann syndrome; rarely presents as secondary amenorrhea with late onset	Exclude serious causes before diagnosing constitutional delay (diagnosis of exclusion); anosmia/hyposmia with Kallmann syndrome
Hypergonadotropic hypogonadism	Elevated FSH and LH, low estrogen, karyotype indicated to rule out Y chromosome	Gonadal agenesis and/or dysgenesis (most common cause of primary amenorrhea), including Turner syndrome (45,XO) and pure gonadal dysgenesis (46,XX) or (46,XY)	May rarely present as secondary amenorrhea; streak gonads, short stature, and webbing of the neck with Turner syndrome
17-Hydroxylase (P450c17) deficiency	Low sex steroids (estrogens and androgens); a rare genetic disorder	Primary amenorrhea usually in 46,XX and female external genitalia in 46,XY	Hypertension and hypokalemia caused by mineralocorticoid excess (see Figure 33-1)
Primary Amenorrhea with Breast Development and Müllerian Anomalies			
Androgen insensitivity (46,XY)	Male levels of androgens in serum (which distinguishes androgen insensitivity from other müllerian anomalies)	Androgen insensitivity syndrome (formerly called *testicular feminization syndrome*)	Internal testicles, vaginal dimple, no uterus, and near-normal breast development with smaller areolae and/or nipples
Normal female karyotype (46,XX)	Female levels of androgens in serum	Anatomic defects resulting in outflow obstruction	Surgical correction possible in many, but not all, types
Imperforate hymen	Hematocolpos on abdominal ultrasound		Bulge at introitus, cyclic pain with absent vaginal bleeding
Transverse vaginal septum	Obstruction visible on MRI scan		Cyclic lower abdominal pain without menses, hematometra, decreased fertility potential
Cervical agenesis	Cervix absent on MRI scan		Hysterectomy likely
Müllerian agenesis and/or dysgenesis	Intravenous pyelogram or other renal imaging indicated	Mayer-Rokitansky-Küster-Hauser syndrome	Vaginal dimple only, absent uterus on rectal
Secondary (Rarely Primary) Amenorrhea and/or Oligomenorrhea with Breast Development and Normal Müllerian Structures			
Pregnancy	Positive pregnancy test		Always rule out first
Uterine defects	Intrauterine scarring visible on hysterosalpingogram	Asherman syndrome	Fertility problems
Hypoestrogenism	Low serum estrogen levels	Various types listed below	
Hypothalamopituitary dysfunction	Low FSH, LH, and prolactin; other hormone deficiencies should be ruled out	Excessive exercise (runner's amenorrhea); anorexia nervosa	Lean body mass; anorexia nervosa is primarily a psychiatric disorder with significant mortality (about 7%)
Premature ovarian failure	Elevated serum FSH, low serum estrogen, karyotype indicated if age <30 yr	Autoimmune premature ovarian failure	Age <40 yr
Hyperprolactinemia (serum estrogen level can vary)	Elevated serum prolactin	Pituitary adenoma, empty sella syndrome, primary hypothyroidism, drugs (for others, see Box 33-2)	Galactorrhea
Normal estrogen and amenorrhea and/or oligomenorrhea	Normal hormone levels	Mild hypothalamic amenorrhea: exercise, nutrition, stress, hypothyroidism	
Hyperandrogenism	Elevated androgens (variable)	Congenital adrenal hyperplasia, polycystic ovarian syndrome, HAIR-AN syndrome (for others, see Box 33-2)	Hirsutism, acne, insulin resistance, virilization in some severe cases

Modified from Gambone JC: Student manual, Los Angeles, 2003, David Geffen School of Medicine, University of California, Los Angeles.

PRIMARY AMENORRHEA WITH SEXUAL INFANTILISM

Patients with primary amenorrhea and no secondary sexual characteristics (sexual infantilism) display an absence of gonadal hormone secretion. The differential diagnosis is based on whether the defect represents a lack of gonadotropin secretion **(hypogonadotropic hypogonadism)** or an inability of the ovaries to respond to gonadotropin secretion **(hypergonadotropic hypogonadism caused by gonadal agenesis/dysgenesis).** The distinction can be made by measuring a basal serum follicle-stimulating hormone (FSH) level.

Hypogonadotropic Primary Amenorrhea and Sexual Infantilism

Patients with hypogonadotropic hypogonadism have low serum FSH levels, whereas patients with hypergonadotropic hypogonadism (e.g., gonadal dysgenesis) have elevated serum FSH levels in the menopausal range (>20 to 40 mIU/L, depending on the assay used). The measurement of serum luteinizing hormone (LH) is of limited additional diagnostic value. The absence of breast development is indicative of inadequate secretion of estrogen.

Hypogonadotropic hypogonadism may be caused by lesions of the hypothalamus or pituitary gland or by functional disorders that suppress gonadotropin-releasing hormone (GnRH) synthesis and release. Kallmann syndrome is an example of lesions in the hypothalamus causing hypogonadotropic hypogonadism, usually with anosmia (see Chapter 32 and Figure 32-6). Because patients with sexual infantilism caused by hypogonadotropic hypogonadism may have a craniopharyngioma or other central nervous system (CNS) tumor, magnetic resonance imaging (MRI) or computed tomography (CT) of the hypothalamic-pituitary area is recommended.

Hypogonadotropic hypogonadism resulting in primary amenorrhea and sexual infantilism may also be caused by lesions of the pituitary, including prolactin-secreting adenomas, or a general process of pituitary failure. These patients should be screened for other pituitary hormone deficiencies by testing for thyroid-stimulating hormone (TSH), growth hormone, and adrenocorticotropic hormone (ACTH).

Finally, apparent hypogonadotropic hypogonadism may actually represent constitutionally delayed puberty. This delay in the normal onset of puberty is generally attributed to undefined hereditary factors because there is commonly a history of late puberty in family members. Constitutional delay of puberty is a diagnosis of exclusion.

Hypergonadotropic Primary Amenorrhea and Sexual Infantilism

Patients with hypergonadotropic hypogonadism have some form of failed gonadal development or premature gonadal failure and have elevated serum FSH levels. These patients may have gonadal agenesis (the absence or early disappearance of the normal gonad). An example in males, who may appear to be female in some cases, is **pure gonadal dysgenesis,** or the **testicular regression syndrome.** These patients have an apparently normal 46,XY karyotype but lack testicular development. If fetal testicular regression occurs between 8 and 10 weeks' gestation, these individuals may have female external genitalia with or without ambiguity in addition to a lack of gonads, a hypoplastic uterus (secondary to absent secretion of anti-müllerian hormone), and rudimentary genital ducts (Swyer syndrome). Regression of the testes after 12 to 14 weeks' gestation results in variable development of male external genitalia. Anorchia or streak gonads occur with testicular regression syndrome.

Other individuals with hypergonadotropic primary amenorrhea and sexual infantilism may have gonadal dysgenesis, or an abnormally developed gonad caused by chromosomal defects. The differential diagnosis includes 45,XO (Turner syndrome), a structurally abnormal X chromosome, mosaicism with or without a Y chromosome, and pure gonadal dysgenesis (46,XX and 46,XY). Although most affected patients show no signs of secondary sexual characteristics, occasionally an individual with mosaicism or Turner syndrome will have sufficient ovarian follicular activity and secrete enough estrogen to cause breast development, menstruation, ovulation, and rarely even pregnancy.

In individuals with the presence of a Y chromosome, there is a risk of developing a gonadoblastoma (a benign germ cell tumor of the gonad) and eventually a dysgerminoma (a malignant germ cell tumor). All patients with hypergonadotropic hypogonadism should have a karyotype performed. Because it is important to identify mosaicism, a greater number of white blood cells (>35) should be karyotyped.

Rarely, some patients with primary amenorrhea and sexual infantilism have a defect of estrogen and androgen production. One example of this is 17-hydroxylase (P450c17) deficiency, which prevents the synthesis of these sex steroids (Figure 33-1). These individuals have hypertension and hypokalemia caused by mineralocorticoid excess. Other patients, such as those with a 46,XY karyotype and Leydig cell agenesis, may lack the cells necessary for sex steroid production. Because Leydig cells in the testes are responsible for producing testosterone, these individuals are born with female external genitalia.

Patients with sexual infantilism may be treated to stimulate breast development by administering

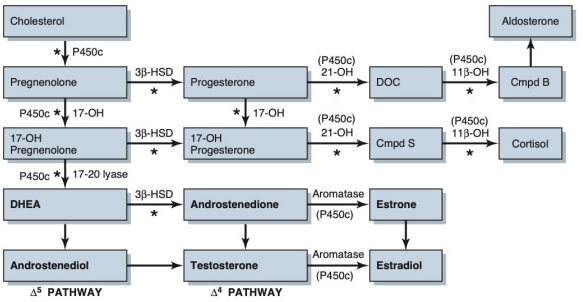


FIGURE 33-1 Diagrammatic representation of the steroid biosynthetic pathways. The *asterisks* denote specific enzyme defects that result in congenital adrenal hyperplasia. *Cmpd B,* Corticosterone; *Cmpd S,* 11-deoxycortisol; *DHEA,* dehydroepiandrosterone; *DOC,* deoxycorticosterone; *HSD,* hydroxysteroid dehydrogenase; *OH,* hydroxylase.

gradually increasing doses of estrogen. One commonly used regimen is to start with 0.3 mg of conjugated estrogen every other day and slowly increase the dose over 3- to 6-month intervals. This treatment should be guided by the presence or absence of mastalgia (breast tenderness) and the rate of breast development. The estrogen can safely be increased to 0.6 mg or more daily if necessary. Recently, skin patches that deliver 17β-estradiol (E2) in various comparable doses have been used.

Individuals with persistent hypogonadotropic hypogonadism who seek fertility require either human menopausal gonadotropin injections or pulsatile GnRH administered with an infusion pump. Patients with gonadal dysgenesis and 17-hydroxylase deficiency who have a normal uterus and cervix can achieve pregnancy only by in vitro fertilization (IVF) using donor oocytes.

PRIMARY AMENORRHEA WITH BREAST DEVELOPMENT AND MÜLLERIAN ANOMALIES

Patients with primary amenorrhea, breast development, and some defect of müllerian structures fall into two categories: (1) those with complete androgen insensitivity syndrome (AIS), formerly called *testicular feminization,* and (2) those with müllerian dysgenesis or agenesis. The distinction between these two diagnoses can be made by measuring serum testosterone and determining the karyotype.

Androgen Insensitivity Syndrome

Patients with complete AIS have a defect in the androgen receptor. Their karyotype is 46,XY, and they demonstrate male levels of testosterone, although usually on the lower side of normal. They may also have mildly elevated FSH and LH levels, due to the location of their testes within the abdominal wall or cavity (cryptorchidism). This location, with greater body heat, typically does not allow for normal male hormone secretion. Breast development (with nipples and areolae smaller than a normal genotypical female's) is caused by the testicular secretion of estrogens and by the conversion of circulating androgen to estrogens in the liver and elsewhere. **The testes of individuals with AIS secrete normal male amounts of anti-müllerian hormone (AMH); therefore, patients have only a vaginal dimple and no uterus.** Treatment should consist of gonadal resection to avoid neoplasia (i.e., gonadoblastomas and dysgerminomas) once puberty is complete. The creation of a neovagina when the patient is prepared for sexual activity is possible by surgical and nonsurgical methods. Psychological counseling is an important component of care for these patients.

Müllerian Dysgenesis or Agenesis

Patients with primary amenorrhea, breast development, and a 46,XX karyotype have serum levels of testosterone appropriate for females. This clinical diagnosis may be caused by müllerian defects that cause obstruction of the vaginal canal (e.g., an imperforate hymen or a transverse vaginal septum) or by the absence of a normal cervix and/or uterus and normal fallopian tubes. An imperforate hymen should be suspected in adolescents who report monthly dysmenorrhea in the absence of vaginal bleeding. Clinically, these patients often present with a vaginal bulge

Reference

and a midline cystic mass on rectal examination. Ultrasonography confirms the presence of a normal uterus and ovaries with a hematocolpos. These patients should be treated with hymenectomy.

Alternatively, females may present with similar symptoms, but without a vaginal bulge. When ultrasonography confirms a normal uterus and ovaries, **a transverse, obstructing vaginal septum or cervical agenesis should be suspected.** MRI is the diagnostic procedure of choice in these patients. If an MRI scan confirms a transverse septum, surgical correction is indicated. Surgical construction of a functional cervix is extremely difficult. In general, it is recommended that women with cervical agenesis undergo hysterectomy.

Finally, **rectal examination and ultrasonography may indicate the absence of a uterus, indicating müllerian agenesis or the Mayer-Rokitansky-Küster-Hauser syndrome.** This syndrome is characterized by a failure of the müllerian ducts to fuse distally and form the upper genital tract. These patients may have unilateral or bilateral rudimentary uterine tissues (analgens), fallopian tubes, and ovaries. It is uncommon for an individual to have functional endometrial tissue within the anlagen. On occasion, the ovaries are not visible on ultrasonography because they have not descended into the pelvis. In these cases, CT or MRI may reveal them well above the pelvic brim. **Currently, the pathophysiology leading to müllerian dysgenetic defects is not known.**

Creation of a neovagina can be accomplished by using one of two general approaches. **The Frank method of vaginal dilation** uses dilation of the vaginal pouch with vaginal forms (usually thermoplastic acrylic resin [Lucite] dilators) over the course of weeks to months. Alternatively, a **McIndoe vaginoplasty,** which involves the surgical creation of a neovaginal space using a split-thickness skin graft, may be performed. Both of these methods should be initiated and/or performed close to the time when the patient anticipates having vaginal intercourse.

Congenital anatomic abnormalities of the uterus or vagina, or both, are often associated with renal abnormalities such as a unilateral solitary kidney or a double renal collecting system, among others. **Therefore, for these patients, an intravenous pyelogram or other diagnostic radiographic study should be obtained to confirm a normal urinary system.**

Amenorrhea or Oligomenorrhea with Breast Development and Normal Müllerian Structures

Disorders in which the patient has breast development and a demonstrable cervix and uterine fundus on physical examination may cause primary as well as secondary amenorrhea, or they may present as oligomenorrhea (less frequent menstruation). Typically, women with oligomenorrhea have fewer than nine menstrual cycles per year.

All patients with menstrual bleeding disorders should be tested for pregnancy. Once pregnancy has been excluded, these individuals can be characterized as shown in Table 33-1. The initial history-taking should include questions about the timing of thelarche, pubarche, and menarche. The timing and development of the menstrual disorder (present since puberty or new), significant weight change, strenuous exercise activities, dietary habits, sexual activity, concomitant illnesses or complaints, abnormal facial or body hair growth, scalp hair loss, acne, and the presence or absence of hot flashes and vaginal dryness should be noted. A comprehensive list of medications and dietary supplements taken should be obtained.

In addition to a pregnancy test, the initial investigation of the amenorrheic patient should include a serum FSH level and a progestin challenge test. If the patient does not have withdrawal bleeding after receiving a progestational agent, significant hypoestrogenism or hyperandrogenism, a uterine defect, or pregnancy are all possible. Progestogens that are used include medroxyprogesterone acetate 5 to 10 mg/day orally for 5 to 14 days, norethindrone acetate 2.5 to 10 mg/day orally for 5 to 14 days, oral micronized progesterone 100 to 300 mg/day for 5 to 14 days, or progesterone in oil 50 to 100 mg intramuscularly. To evaluate the estrogenic status, some clinicians prefer to order a serum estradiol (E2) instead of the progestin challenge test.

UTERINE DEFECTS

Women who do not have withdrawal bleeding after a hormonal challenge test and who have a history of uterine instrumentation, particularly a dilation and curettage following vaginal delivery or pregnancy termination, may have Asherman syndrome (AS). This interesting syndrome is characterized by intrauterine scarring (synechiae), and patients with AS may have normal ovulatory cycles with cyclic premenstrual symptoms. Patients with AS should be evaluated by hysterosalpingography or sonohysterography. Hysteroscopic treatment with excision of the synechiae and normalization of the uterine cavity is the treatment of choice.

AMENORRHEA OR OLIGOMENORRHEA ASSOCIATED WITH HYPOESTROGENISM

The differential diagnosis for patients with amenorrhea associated with low serum levels of estrogen includes hypothalamic and/or pituitary dysfunction (hypothalamic amenorrhea), premature ovarian failure, or hyperprolactinemia. Women in the first group have low serum FSH and prolactin levels; women in the second group have high serum FSH and normal serum prolactin levels; and women in the third group have high serum prolactin and low serum FSH levels.

Hypothalamic-Pituitary Dysfunction

Patients with hypothalamic amenorrhea include women with severe weight loss, women engaging in excessive exercise resulting in low body fat, and women experiencing severe psychological stress. Also included are those women with physical wasting caused by severe systemic diseases such as disseminated malignancies and patients with pituitary or CNS lesions. In the most severe and life-threatening form of hypothalamic amenorrhea, women may have pituitary failure or anorexia nervosa. All patients with hypogonadotropic hypogonadism and hypothalamic-pituitary dysfunction should be evaluated for the status of the other pituitary hormones. Evaluation should also include MRI of the hypothalamus and pituitary gland to exclude neoplastic and other lesions if it is uncertain whether the patient has one of the functional disorders described above.

When hypothalamic-pituitary dysfunction cannot be resolved by identifying a modifiable underlying cause (e.g., excessive exercise), combination estrogen and progestin therapy, usually in the form of a combined oral contraceptive pill or E2 skin patches with oral progestins, should be prescribed to reduce the risk of osteoporosis. This therapy is also recommended to maintain normal vaginal and breast development. In patients with anorexia nervosa (AN), ovarian hormone therapy without weight gain will not totally prevent osteoporosis.

Premature Ovarian Failure

Premature ovarian failure **is defined as ovarian failure before the age of 40 years (see Chapter 35). When it occurs in patients younger than 30 years of age, ovarian failure may be caused by a chromosomal disorder. A karyotype should be performed to exclude mosaicism (i.e., some cells bearing a Y chromosome).** If cells with a Y chromosome are present, a gonadectomy to prevent malignant transformation is indicated.

Other causes of premature ovarian failure include ovarian injury as a result of surgery, radiation, or chemotherapy; galactosemia; carrier status of the fragile X syndrome; and autoimmunity. When premature ovarian failure is secondary to autoimmunity, other endocrine organs may be affected as well. Because there are no specific laboratory tests available to diagnose autoimmune ovarian failure, all patients with unexplained ovarian failure should be screened for diabetes (fasting glucose), hypothyroidism (TSH and free thyroxine [T_4]), hypoparathyroidism (serum calcium and phosphorus), and hypocortisolism (fasting morning cortisol or cortisol response to ACTH stimulation). It is not unusual for patients with premature ovarian failure to have episodes of normal ovarian and menstrual function. **Patients with premature ovarian failure require hormone therapy (estrogen and a progestin) to reduce the risk of osteoporosis.**

AMENORRHEA OR OLIGOMENORRHEA WITH HYPERPROLACTINEMIA AND/OR GALACTORRHEA

The principal action of prolactin is to stimulate lactation. Hypersecretion of prolactin leads to gonadal dysfunction by interrupting the secretion of GnRH, which inhibits the release of LH and FSH and thereby impairs gonadal steroidogenesis. The primary influence on prolactin secretion is tonic inhibition of dopamine input from the hypothalamus. Any event disrupting this inhibition can result in a rise in prolactin levels.

The consequences of hyperprolactinemia that are clinically significant include menstrual disturbances and/or galactorrhea. About 10% of women with amenorrhea have elevated serum prolactin levels, and serum prolactin should be measured in all cases of amenorrhea of unknown cause. Potential causes of elevated serum prolactin are noted in Box 33-1. Normal serum prolactin levels are under 20 ng/dL, depending on the

BOX 33-1

CAUSES OF ELEVATED PROLACTIN

- Pregnancy (10-fold increase from baseline)
- Excessive exercise
- Postprandial states
- Stimulation of the chest wall or nipple
- Medications
  - Metoclopramide
  - Phenothiazines
  - Butyrophenones
  - Risperidone
  - Monoamine oxidase inhibitors
  - Tricyclic antidepressants
  - Serotonin reuptake inhibitors
  - Verapamil
  - Reserpine
  - Methyldopa
  - Estrogens
- Craniopharyngiomas
- Granulomatous infiltration of the pituitary or hypothalamus
- Acromegaly
- Severe head trauma
- Prolactinomas
- Pituitary stalk compression
- Primary hypothyroidism
- Chronic renal failure
- Marijuana or narcotic use

laboratory used. In patients with prolactin-secreting tumors, levels are usually above 100 ng/dL. An elevated serum prolactin level should be confirmed by a second test, preferably with the patient in the fasting state, as food ingestion may cause transient hyperprolactinemia. At the same time that the repeat prolactin level is measured, a TSH level should be obtained to test for hypothyroidism because hyperprolactinemia may be seen in patients with primary hypothyroid conditions.

A biologically inactive complex of prolactin and immunoglobulin, called *big prolactin,* can produce a physiologically insignificant elevation. Hence, the presence of a clinical abnormality should initiate the decision to test for hyperprolactinemia. **If clinically significant hyperprolactinemia is not explained by primary hypothyroidism or drug use, CT or MRI of the sella turcica should be performed.**

Galactorrhea is the most frequently observed abnormality associated with hyperprolactinemia. The secretion of milk may occur spontaneously or only after breast manipulation. Both breasts should be examined gently by palpating the gland moving from the periphery to the nipple. To confirm galactorrhea, a smear may be prepared and examined microscopically for the presence of multiple fat droplets (indicating milk). **Besides galactorrhea, hyperprolactinemia frequently causes oligomenorrhea or amenorrhea.**

Prolactinomas

Pituitary adenomas may cause hyperprolactinemia, and they make up approximately 10% of all intracranial tumors. Their etiology is unknown. Prolactinomas can be divided into two categories: macroadenomas (≥10 mm in diameter) and microadenomas (<10 mm in diameter). This distinction is important because microadenomas are unlikely to cause new problems as a result of additional growth. About 50% of patients with hyperprolactinemia have radiographic changes in the sella turcica consistent with an adenoma. Most patients have normal or low baseline levels of FSH.

Other Central Nervous System Lesions Affecting Prolactin

About 60% of pituitary adenomas do not produce prolactin, but may cause hyperprolactinemia by compression of the pituitary stalk. Another interesting lesion, **the empty sella syndrome,** is caused by a herniation of the subarachnoid membrane into the pituitary sella turcica through a defective or incompetent sella diaphragm. An empty sella may coexist with a prolactin-secreting pituitary adenoma. **Hypothalamic tumors** may also cause hyperprolactinemia by damaging the hypothalamus or by compression of the pituitary stalk, thereby interfering with the production or transport of dopamine. **Craniopharyngiomas are the most common of these lesions.**

Pharmacologic Agents Affecting the Secretion of Prolactin

A number of drugs may cause hyperprolactinemia and nonphysiologic galactorrhea (see Box 33-1). The mechanism of drug-induced hyperprolactinemia is secondary to reduced hypothalamic secretion of dopamine, depriving the pituitary of a natural inhibitor of prolactin release. When clinically indicated, patients with hyperprolactinemia caused by medications should be encouraged to discontinue the medication for at least 1 month. If hyperprolactinemia persists, or if the patient cannot interrupt the medication, a complete evaluation is indicated.

Miscellaneous Causes of Hyperprolactinemia

Patients with **acute or chronic renal failure** may have hyperprolactinemia because of delayed clearance of the hormone. These patients rarely require treatment other than for their renal failure. Patients with scars from previous chest surgery, including breast implantation, may have galactorrhea caused by **peripheral nerve stimulation.** Herpes zoster of the area including the breasts, as well as other forms of breast stimulation, can cause galactorrhea and sometimes hyperprolactinemia by the same mechanism. In about 3-5% of patients with galactorrhea and hyperprolactinemia, **primary hypothyroidism** is the underlying cause. These patients have a low serum free T_4 level. Consequently, they lack negative feedback on the hypothalamic–pituitary axis, resulting in increased secretion of thyrotropin-releasing hormone (TRH). TRH in turn stimulates elevated levels of TSH and prolactin. **Patients with primary hypothyroidism should be given T_4 replacement therapy.** Rarely, cancers such as bronchogenic carcinoma or hypernephroma can result in elevated prolactin levels.

Treatment of Galactorrhea and Hyperprolactinemia

The objectives of therapy for galactorrhea and hyperprolactinemia include the elimination of lactation, the establishment of normal estrogen levels, and the induction of ovulation when fertility is desired. The recommended forms of management are periodic observation, medical therapy, and surgery.

OBSERVATION. Periodic observation is indicated in normally menstruating women with galactorrhea who have either normal serum prolactin levels or idiopathic elevations of prolactin. **As long as the galactorrhea is not socially embarrassing and the patient has regular menses (confirming normal estrogen levels), there is no need to institute treatment.** Patients with oligomenorrhea who do not desire fertility should be treated with periodic progestins, or if contraception is needed, with hormonal therapy, to induce regular uterine bleeding. Failure to induce withdrawal bleeding with progestins is suggestive of hypoestrogenism. When verified by low serum levels of estradiol (<30 pg/mL) and a negative pregnancy test, cyclic hormone therapy (estrogen and a progestin) should be initiated**. Long-term treatment with bromocriptine** (for hyperprolactinemia) **in women with normal estrogen levels is not indicated.**

Observation can be extended to some women with radiologic evidence of a pituitary microadenoma (<10 mm in diameter). **Because the growth rate of microadenomas is slow, an annual measurement of serum prolactin is appropriate in patients with normal estrogen levels.** Macroadenomas (≥10 mm in diameter) require further evaluation by periodic pituitary scanning and possible treatment.

MEDICAL THERAPY. Patients with hyperprolactinemia may have galactorrhea and anovulation with resulting infertility. In more severe cases, they may be hypoestrogenic, which places them at risk for developing osteoporosis. **Anovulatory patients without tumors demonstrable by MRI and for whom the only issues are prevention of osteoporosis and menstrual cycle regulation may be treated medically with combination hormonal contraceptives.**

The ergot compounds bromocriptine and cabergoline act as dopamine agonists to reduce prolactin secretion and allow for the restoration of cyclic, physiologic estrogen secretion. Bromocriptine has a high initial incidence of side effects such as headache, nausea, and orthostatic hypotension. As a consequence, it should be started at a dose of 1.25 to 2.5 mg at bedtime and slowly increased in divided doses to tolerance and restoration of normal prolactin levels. Some patients tolerate bromocriptine better when it is given vaginally. Cabergoline is taken in twice-weekly doses beginning at 0.25 mg and increasing to a maximum of 1 mg twice weekly. It is better tolerated and more convenient to take than bromocriptine, but it is also more expensive.

Ninety-five percent of women without radiographic evidence of an adenoma require 5 mg/day of bromocriptine, whereas about 50% of patients with adenomas require higher doses to resume regular menses. **Bromocriptine normalizes the secretion of prolactin in about 80% of women with microadenomas, and it restores menses and fertility in over 90%.** Usually, menses resume and galactorrhea resolves after about 6 weeks of bromocriptine therapy in women without adenomas. If an adenoma is present, it takes another 3 or 4 weeks for bromocriptine to become effective. Return of ovulation requires an average of 10 weeks without a tumor and 16 weeks with a microadenoma. Restoration of normal menstrual cycles and pregnancy may occur without complete normalization of the serum prolactin level. Discontinuation of therapy usually results in the return of hyperprolactinemia, leading to galactorrhea and amenorrhea.

Patients with macroadenomas (≥10 mm in diameter) should undergo visual field testing and screening for other pituitary hormonal deficiencies. A repeat MRI scan is obtained 6 months after the full therapeutic dose of bromocriptine is reached. As long as shrinkage of the adenoma is demonstrated, bromocriptine therapy is continued. **Surgery should be performed for patients with significant visual field defects or symptoms that cannot be relieved by medical therapy.**

Bromocriptine therapy is usually discontinued as soon as a pregnancy is confirmed. The risk of symptomatic enlargement of a microadenoma during pregnancy is only about 1%. When a macroadenoma is confined to the sella turcica, it is unlikely to enlarge significantly during pregnancy. **If there is extension of a macroadenoma beyond the sella turcica, there is a 15-30% risk of enlargement during pregnancy.** If possible, these larger lesions should be debulked before conception, then bromocriptine treatment should be initiated. Pregnant patients with macroadenomas should have their visual fields evaluated in each trimester. **When abnormalities in visual fields develop, bromocriptine treatment should be reinstituted or increased and maintained for the rest of the pregnancy.** There is no increase in fetal malformations as a result of bromocriptine treatment, and the drug can be discontinued after the pregnancy to allow for breast-feeding. Cabergoline has not been adequately evaluated for use in pregnancy.

SURGERY. When surgery is required, the transsphenoidal route for microsurgical exploration of the sella turcica gives the best results. **Recurrence rates for microadenomas after surgery approach 30%, and the rate increases to 90% for macroadenomas. For this reason, medical management is preferred,** with surgery reserved for cases with expansion outside the sella turcica or for compressive symptoms, such as visual field defects. Women who do not tolerate pharmacologic therapy may need surgery. Fifty percent of patients followed for 5 to 10 years after successful resection of an adenoma have recurrence of hyperprolactinemia without radiologic evidence of a tumor.

Amenorrhea or Oligomenorrhea with Normal Estrogen Levels

Patients with amenorrhea or oligomenorrhea who consistently have normal levels of estrogen have a mild form of hypothalamic anovulation that may be caused by low body weight and exercise issues, psychological stress, recent pregnancy, or lactation. They may also have been treated with Depo-Provera or combined hormonal contraceptives in the recent past. **These**

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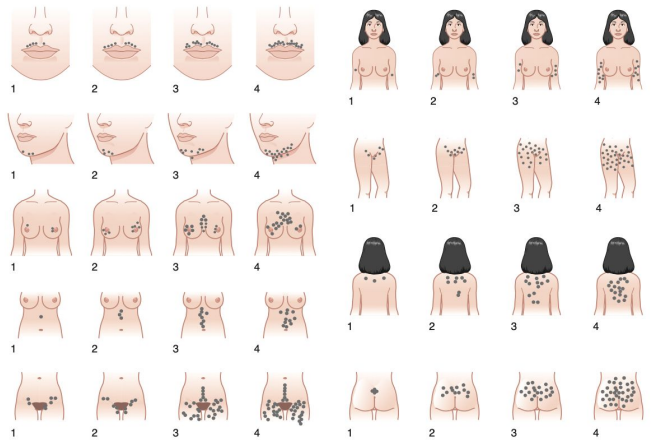

FIGURE 33-2 The Ferriman-Gallwey scoring system for hirsutism. (Adapted from Hatch R, Rosenfield RL, Kim MH, et al: Hirsutism: implications, etiology, and management. *Am J Obstet Gynecol* 140:815–830, copyright 1981, with permission from Elsevier.)

iatrogenic causes usually resolve spontaneously within 6 months. Some women with amenorrhea and/or oligomenorrhea and normal estrogen levels may have a subclinical androgen excess disorder, such as a mild form of polycystic ovarian syndrome (PCOS).

When contraception is not required in these anovulatory women and fertility is not desired, periodic progestin withdrawal to confirm normal estrogen levels and protect the endometrium is appropriate. When fertility is not desired, combination hormonal contraception is appropriate.

Amenorrhea or Oligomenorrhea with Hyperandrogenism

Hyperandrogenism is the clinical manifestation of elevated circulating levels of male hormones in women. **Features may range from mild, unwanted excessive hair growth and acne to alopecia (hair loss), hirsutism, and virilization.** *Hirsutism,* defined as excessive terminal hair appearing in a male-type pattern, represents exposure of hair follicles to androgen excess, either from a systemic origin and/or the local conversion of testosterone to the more potent dihydrotestosterone (DHT) by 5α-reductase in the hair follicle itself. Figure 33-2 illustrates a scoring system for hirsutism. ***Virilization*** **(masculinization) refers to the acquisition of male characteristics (i.e., temporal balding, deepening of the voice, and enlargement of the clitoris).** In females, it usually results from excessive male hormone production or exogenous hormone use. Signs of virilization also include defeminization or the loss of female body fat distribution (gluteofemoral fat deposits) and decreased breast size. Androgens in women are normally produced in the ovaries and the adrenal glands (see Figure 33-1). Therefore, hyperandrogenic disorders may be divided into nonneoplastic and neoplastic disorders of the adrenal glands or ovaries (Box 33-2).

NORMAL ANDROGEN METABOLISM

The formation of androgens results from the metabolism of cholesterol via the Δ^5 and Δ^4 pathways (see Figure 33-1). The stimulus for ovarian androgen production is LH.

BOX 33-2

HYPERANDROGENIC DISORDERS

Adrenal Disorders
- Late-onset congenital adrenal hyperplasia
- Cushing syndrome
- Adrenal adenomas and carcinomas

Ovarian Disorders
- Polycystic ovarian syndrome
- HAIR-AN syndrome
- Ovarian neoplasms
- Sertoli-Leydig cell tumors
- Hilar cell tumors
- Lipoid cell tumors

Idiopathic Hirsutism

HAIR-AN, Hyperandrogenic insulin resistance and acanthosis nigricans.

Approximately one-half of serum androstenedione originates from the ovaries, whereas the other half arises from the adrenal glands. Approximately 50% of testosterone arises from peripheral conversion of androstenedione, whereas 25% is secreted by the ovaries and an additional 25% by the adrenal glands. Dehydroepiandrosterone (DHEA) and its sulfate DHEA-S are primarily products of the adrenal glands and serve as markers for the secretion of adrenal androgens. **Most circulating androgens are bound to proteins, such as albumin and sex hormone–binding globulin (SHBG). In the bound form, androgens are biologically inactive, although weak binding of testosterone to albumin allows some of this testosterone to become bioavailable for tissue activity.** The free fraction (that which is unbound to SHBG or albumin and is available for target tissue activity) represents only about 1-2% of total circulating testosterone.

When androgens reach a target tissue, they are further metabolized, which results in more potent intracellular hormones. **Testosterone is converted (via 5α-reductase) to DHT, which possesses greater biologic potency.** The skin, particularly its pilosebaceous unit (PSU), is capable of this conversion and is the reason why hirsutism can be accompanied by oily skin and acne. Alternatively, testosterone may be aromatized to estrogen, thereby modifying its action. Unlike testosterone, DHT is a potent, nonaromatizable androgen that cannot be converted to estrogen.

Hyperandrogenic Disorders

In general, hyperandrogenic disorders can be attributed to excessive secretion of androgens by the ovaries, the adrenal glands, or both. In addition, the inadvertent or accidental use or abuse of androgenic drugs should always be considered as a possible source of androgen exposure and generally can be excluded by history-taking and clinical evaluation.

ADRENAL DISORDERS

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a general term used to describe a group of disorders that arise from inborn glandular enzyme defects that cause overproduction of the immediate steroid precursor of the specific enzyme deficiency. **The most common cause of CAH is 21-hydroxylase deficiency,** an autosomal recessive disorder that exhibits a spectrum of severity, ranging from the severe salt-wasting form, to simple virilizing CAH, to nonclassic CAH. **Both salt-wasting and simple virilizing CAH are called *classic* because symptoms (e.g., salt loss or ambiguous genitalia in female newborns) are present at birth or shortly thereafter.** Alternatively, the nonclassic form (also called *late-onset CAH*) presents later in life, generally at the time of puberty or later. These patients do not present with genital abnormalities, but rather develop hirsutism, acne, and menstrual and/or ovulatory irregularities. Clinical manifestations of 21-hydroxylase deficiency depend upon the degree of enzyme deficiency, which is determined in part by the type of 21-hydroxylase genetic mutation that occurs on chromosome 6.

Because 21-hydroxylase is responsible for the conversion of 17-hydroxyprogesterone to 11-deoxycortisol (compound S), 21-hydroxylase deficiency causes excessive accumulation of 17-hydroxyprogesterone as the immediate steroid precursor for this enzyme. Consequently, 21-hydroxylase deficiency is characterized by an elevated serum 17-hydroxyprogesterone level as well as increases in its Δ^4 metabolites androstenedione and testosterone (see Figure 33-1).

The disease is inherited as an autosomal recessive trait. In patients with a positive family history and in ethnic groups with a high risk for nonclassic CAH (e.g., Ashkenazi Jews, with a prevalence of 1 in 27; Hispanics, with a prevalence of 1 in 40; and Slavs, with a prevalence of 1 in 50), this enzyme deficiency can be excluded by obtaining a follicular (preovulatory) phase serum 17-hydroxyprogesterone level, preferably in the morning. A level less than 2 ng/mL rules out late-onset CAH.

Cushing Syndrome

Another major adrenal disorder that leads to excessive androgen production is Cushing syndrome or persistent hypercortisolism. **Characteristic signs of Cushing syndrome include obesity; increased fat over the face (moon facies), trunk, and cervicodorsal as well as supraclavicular regions; hypertension; easy bruising resulting from thinning of the skin; impaired glucose tolerance; muscle wasting of the upper legs and arms; osteoporosis; and purple abdominal striae.** Other manifestations include hirsutism, acne, and irregular menses. Mental disturbances include excessive euphoria, irritability, insomnia, and depression. The depression may occur because of excess cortisol action on the CNS limbic system. Cushing syndrome may arise from a cortisol-producing tumor of the adrenal glands or from an ACTH-producing pituitary adenoma (called *Cushing disease*). These disorders are rare causes of androgen excess in women.

Adrenal Neoplasms

Adrenal tumors causing hyperandrogenism alone without evidence of glucocorticoid excess are very rare. More commonly, adrenal tumors produce large amounts of both glucocorticoids and androgens, with the predominant adrenal androgen being DHEA-S.

OVARIAN DISORDERS

Polycystic Ovarian Syndrome

According to recent guidelines **(Rotterdam criteria),** PCOS is defined by the inclusion of **at least two of the following three features: (1) clinical or biochemical hyperandrogenism, (2) oligomenorrhea or amenorrhea, and (3) polycystic ovaries,** excluding other endocrine disorders that mimic PCOS. The various PCOS phenotypes vary in severity, with the classic PCOS form (i.e., clinical or biochemical hyperandrogenism with oligo-ovulation) having the most severe reproductive and metabolic abnormalities. **PCOS affects about 6-10% of women worldwide on the basis of classic PCOS criteria, and even more individuals on the basis of the new Rotterdam criteria,** making it one of the most common human disorders and the single most common endocrinopathy among women of reproductive age. The clinical symptoms of PCOS usually develop at the time of puberty. PCOS is more prevalent among family members (20-40% of first-degree female relatives affected) than in the general population (prevalence: 6-10%), suggesting that **genetic factors influence development of the syndrome.** Because adolescent girls may have some of the features of PCOS without having the disorder, it is recommended that all three of the Rotterdam criteria be met in them (see Chapter 32).

The hyperandrogenism of PCOS results from an overproduction of male hormones by the ovary and often from the adrenal gland. A common clinical sign of hyperandrogenism in PCOS is hirsutism. Visual assessment of hirsutism is valuable because most women with PCOS of white or black race demonstrate excessive hair growth, although **hirsutism is less likely in women who have used hormonal contraceptives for prolonged intervals** and for many East Asian women. Obesity per se is not necessarily intrinsic to PCOS. Rather, the worldwide prevalence of obesity in most female populations has increased over the past two decades, and hyperinsulinemia caused by obesity-related insulin resistance worsens the symptoms of PCOS.

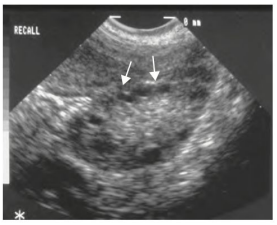

FIGURE 33-3 Transvaginal ultrasonogram of a woman with polycystic ovarian disease. The multiple subcapsular cysts, with their "string of pearls" appearance *(arrows),* are common in this syndrome.

In patients with PCOS, **ovarian hyperandrogenism, hyperinsulinemia caused by insulin resistance, and altered intraovarian signaling can disrupt follicular growth.** The consequent follicular arrest in PCOS is accompanied by menstrual irregularity, anovulatory subfertility, and the accumulation of small antral follicles within the periphery of the ovary, giving it a polycystic morphology (Figure 33-3). The ovarian stroma contains abundant theca cells that overproduce androgens. **Importantly, healthy women may also have polycystic-appearing ovaries, particularly in adolescence, when the ovaries normally contain a large number of follicles.**

LH hypersecretion increases serum LH levels in up to 70% of patients with PCOS, with elevated LH pulse amplitude and frequency inducing a two- to threefold elevation in circulating LH over FSH levels. Increased LH pulse frequency in PCOS, from enhanced hypothalamic GnRH pulsatile release, occurs as the result of reduced steroid hormone negative feedback on LH secretion from hyperandrogenism. As a result, **LH hypersecretion promotes ovarian hyperandrogenism in a feedforward mechanism, with androstenedione and testosterone undergoing peripheral aromatization to create tonic estrogen production without progesterone in the absence of ovulation.**

In women with PCOS, there is an association between hyperandrogenism and hyperinsulinemia because of insulin resistance. In approximately 60-70% of patients with PCOS, insulin sensitivity is impaired, leading to hyperinsulinemia. Consequently, the excessive amount of insulin perpetuates ovarian hyperandrogenism in several ways. The excess insulin stimulates the activity of CYP17A (cytochrome P450, 17A) in the theca cell. CYP17A is the enzyme responsible for androgen production in the theca cell. The excessive insulin also amplifies insulin-like growth factor 1 (IGF-1)–stimulated androgen production, elevating serum free testosterone levels through decreased hepatic SHBG production, which binds testosterone. Less binding results in more free testosterone. And finally, enhanced serum IGF-1 bioactivity results due to suppressed IGF-binding protein production. Thus, the physical manifestations of hyperandrogenism in PCOS may be dramatic in relation to the serum level of total testosterone.

Abdominal adiposity in women with PCOS preferentially worsens with weight gain, as does the prevalence of metabolic syndrome (elevated blood pressure and blood glucose with excess body fat around the waist). Metabolic syndrome, along with its underlying insulin resistance, occurs two to three times more frequently in women with PCOS than in age-matched controls, and it is 13.7 times more likely in PCOS women with the highest as opposed to the lowest BMI. **In the long term, the insulin resistance associated with PCOS may lead to an increased risk of cardiovascular disease,** most likely mediated through increased total and abdominal adiposity interacting with PCOS-related hyperandrogenism.

Women with PCOS also have a 2.7-fold increased risk of developing endometrial cancer. A major factor in this increased malignancy risk is the preceding development of endometrial hyperplasia caused by prolonged exposure to estrogen unopposed by progesterone in the absence of ovulation.

Hyperandrogenic Insulin Resistance and Acanthosis Nigricans Syndrome

The hyperandrogenic insulin resistance and acanthosis nigricans (HAIR-AN) syndrome is an inherited hyperandrogenic disorder of severe insulin resistance and is distinct from PCOS. HAIR-AN syndrome is characterized by extremely high circulating levels of insulin (>80 μU/mL basally and/or >500 μU/mL following an oral glucose challenge) caused by severe insulin resistance. Because insulin is also a mitogenic hormone, these extremely elevated insulin levels induce hyperplasia of the basal layers of the epidermal skin, leading to acanthosis nigricans, a velvety, hyperpigmented change in the creased areas of the skin (Figure 33-4). In addition, because of the effect of hyperinsulinemia on ovarian theca cells, the ovaries of many patients with the HAIR-AN syndrome develop hyperthecosis. Patients with HAIR-AN syndrome can be severely hyperandrogenic and present with virilization or severe, rapidly progressive hirsutism. In addition, these patients are at significant risk for dyslipidemia, type 2 diabetes mellitus, hypertension, and cardiovascular disease. These patients are particularly difficult to treat, although the use of long-acting GnRH analogs has been promising.

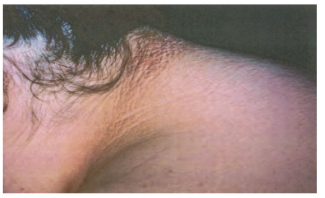

FIGURE 33-4 Acanthosis nigricans of the nape of the neck. These grayish brown velvety areas of the skin occur on the neck, groin, abdomen, or axillae and are markers of insulin resistance and hyperinsulinemia. (Courtesy Ricardo Azziz, MD, MPH, MBA, Cedars-Sinai Medical Center.)

Ovarian Neoplasms

Androgen-producing ovarian tumors are uncommon, occurring in only about 1 in 500 women with hirsutism. Ovarian tumors that produce androgens directly include **Sertoli-Leydig cell, hilus cell, and lipoid cell tumors.** Nevertheless, any large ovarian tumor (i.e., cystic teratomas, Brenner tumors, serous cystadenomas, and Krukenberg tumors) can produce androgens indirectly by causing hyperplasia of the surrounding normal stroma (see Chapter 20).

IDIOPATHIC HIRSUTISM

Some women exhibit mild to moderate hirsutism with normal ovulatory function and circulating androgen levels, a condition referred to as *idiopathic hirsutism.* This scenario may occur as a result of increased conversion of testosterone to the more biologically active DHT in the pilosebaceous units of the skin. Nevertheless, many conditions associated with hirsutism, including PCOS and CAH, have an inherited component, so hirsutism should be considered as a symptom of an underlying androgenic disorder in women until proven otherwise.

Evaluation of Patients with Signs of Hyperandrogenism

HISTORY

The evaluation of women with signs of androgen excess consists of diagnosing any serious underlying medical disease for which specific management may be necessary, assessing the emotional burden of hirsutism on the patient, and planning a personalized approach. **PCOS or late-onset CAH often initially appears during puberty and tends to progress slowly throughout**

Reference

adolescence into adulthood. Under these circumstances, the signs of androgen excess develop over the course of several years. In contrast, **neoplastic processes can occur at any time.** They most often arise years after puberty, and their manifestations appear abruptly. Progression is rapid, and these patients frequently present with recent onset of virilization. There is some overlap of symptoms between neoplastic and other androgen-related disorders in that 15% of patients with HAIR-AN syndrome can also exhibit signs of virilization, particularly severe hirsutism, temporal balding, and even clitoral enlargement.

PHYSICAL EXAMINATION

Patients should be asked about excessive facial hair, because they may conceal their hirsutism by waxing or electrolysis and may be too embarrassed to volunteer the information. The degree of hirsutism (see Figure 33-2), acne, or androgenic alopecia should be assessed. The thyroid should be palpated for any enlargement, and the breasts should be examined for galactorrhea. Any clinical evidence of Cushing syndrome should be noted. Acanthosis nigricans (see Figure 33-4) is a frequent marker of insulin resistance and hyperinsulinemia. A bimanual pelvic examination may reveal ovarian enlargement, with asymmetric ovarian enlargement accompanied by rapid onset of virilization suggestive of an androgen-producing tumor.

LABORATORY EVALUATION

It is important to test for elevated serum androgen levels in women with moderate or severe hirsutism or hirsutism of any degree when it is sudden in onset, rapidly progressive, or associated with menstrual dysfunction, obesity, or clitoromegaly.

On the basis of high-quality assay evidence, circulating total and free testosterone and DHEA-S are elevated in 50-75% of patients with PCOS. **Serum levels of DHEA-S above 7000 ng/mL or total testosterone in excess of 200 ng/dL raise suspicion of an adrenal or ovarian androgen-producing tumor, respectively. However, the best predictor of an androgen-secreting neoplasm is virilization,** which occurs with 98% of such tumors, regardless of circulating testosterone levels.

To exclude other disorders, measuring a **basal serum 17-hydroxyprogesterone level** is useful to exclude late-onset CAH due to 21-hydroxylase deficiency. A serum 17-hydroxyprogesterone level greater than 2 ng/mL requires an adrenal stimulation test to measure serum 17-hydroxyprogesterone before and 1 hour after intravenous infusion of the ACTH analog cosyntropin. If a 1-hour ACTH-stimulated serum 17-hydroxyprogesterone level exceeds 10 to 15 ng/mL, late-onset CAH is likely and can be confirmed by *CYP21* genotyping. Measurement of **serum prolactin and TSH levels** excludes hyperprolactinemia, with or without thyroid dysfunction. When Cushing syndrome is suspected, either a **24-hour measurement for free urinary cortisol** or an **overnight dexamethasone suppression test** should be performed. For the latter test, 1-mg dexamethasone is given orally at bedtime (11:00 pm), and serum cortisol is measured in an 8:00 am fasting specimen. Normal values are less than 5 µg/dL.

A pelvic ultrasound should be obtained to exclude any significant ovarian pathology. Androgen-secreting tumors of the adrenal gland can be detected by **CT or MRI.** If clinical or laboratory findings suggest an androgen-secreting tumor that cannot be located by these imaging techniques, **selective venous catheterization** may be performed to measure androgen levels in the venous blood from each adrenal gland and ovary, although this is not usually necessary.

A metabolic evaluation should be performed in patients with HAIR-AN syndrome or classic PCOS (particularly in those with a BMI >30 kg/m^2, lean with advanced age [>40 years], with a personal history of gestational diabetes, or with a family history of diabetes). Optimal screening for diabetes should include a **2-hour oral glucose tolerance test** because a 2-hour postprandial glucose level can be abnormal in the presence of a normal fasting glucose concentration. **Fasting serum lipid levels** also should be measured in these individuals.

TREATMENT OF HYPERANDROGENISM

Treatment should be guided by the nature of the underlying disease, the severity of clinical symptoms and signs, and the desires of the patient. **In the rare instance of an ovarian or adrenal neoplasm, surgical removal of the tumor is indicated.** In premenopausal women, unilateral salpingo-oophorectomy is sufficient for an ovarian tumor and preserves future childbearing potential. In postmenopausal women, the treatment is usually a total hysterectomy and bilateral salpingo-oophorectomy. **In patients with Cushing syndrome, treatment is surgical removal of the source of excessive cortisol or ACTH secretion** (adrenal or pituitary tumor).

PCOS is by far the most common ovarian abnormality causing hyperandrogenism, and its management depends on the patient's presentation and desires. **The initial therapy for hirsutism in patients with PCOS usually begins by suppressing ovarian androgen production with a combination oral contraceptive containing estrogen and a progestin.** Oral contraceptive therapy suppresses gonadotropins (both LH and FSH) and lowers circulating androgen levels, whereas its estrogen component stimulates SHBG production, which decreases free testosterone levels. There is no clinical advantage of one oral contraceptive over another.

A peripheral antiandrogen can be added to oral contraceptive therapy to treat hirsutism, regardless of the source of the excessive androgen. This therapy also may improve idiopathic hirsutism. An antiandrogen is combined with an oral contraceptive for synergism and to prevent conception, because an antiandrogen would block normal sexual differentiation in a male fetus if used during pregnancy.

The antiandrogen most commonly used to treat hirsutism in the United States is spironolactone. This aldosterone antagonist competes for testosterone-binding sites, thereby exerting a direct antiandrogenic effect in target tissues. In addition, spironolactone interferes with steroid enzymes and decreases testosterone production. Because this medication opposes the action of aldosterone, serum potassium levels may rise and should be monitored. Other drugs that block the binding of androgens to their receptor include **flutamide** and **cyproterone acetate,** whereas **finasteride** blocks the conversion of testosterone to its more potent metabolite, DHT. It may take up to 6 months to begin to observe a cosmetic improvement in hirsutism, and the maximum effect may not be seen for up to 2 years.

Eflornithine hydrochloride cream, an irreversible inhibitor of epidermal androgenic activity, can be applied topically to treat facial hirsutism. It requires twice-daily application for up to 8 weeks for improvement to be seen and may be associated with rash, stinging, redness, and acne.

Suppression of excessive androgenic action generally diminishes further hair growth, but does not cause disappearance of existing hair. **To obtain good cosmetic results, some local hair removal is usually required in addition to medical therapy.** Mechanical methods of hair removal include shaving, depilatory creams, electrolysis, and laser therapy and/or intense pulsed light. Plucking of individual hairs should be discouraged because of discomfort and the risks of scarring and folliculitis. Regardless of the method of hair removal used, pharmacologic therapy should be continued in women with hyperandrogenemia to minimize hair regrowth.

All patients with PCOS who have chronic anovulation are at increased risk of developing menstrual irregularity. With tonic estrogen production without progesterone exposure, anovulatory women with PCOS also are at increased risk of developing endometrial hyperplasia as a precursor of endometrial cancer. **Medical management of abnormal vaginal bleeding or endometrial hyperplasia consists of estrogen-progestin oral contraceptives, cyclic or continuous oral progestins** (i.e., 5 to 10 mg of medroxyprogesterone

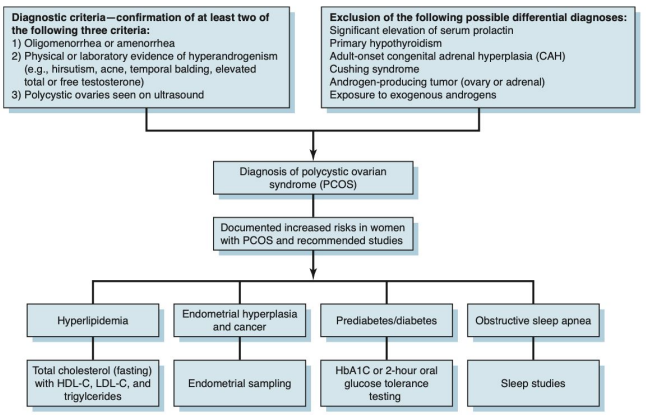

FIGURE 33-5 Algorithm for the diagnosis and investigation of patients with polycystic ovarian syndrome. *HbA1C,* Hemoglobin A1C; *HDL-C,* high-density lipoprotein cholesterol; *LDL-C,* low-density lipoprotein cholesterol.

acetate daily, 100 to 300 mg of micronized progesterone one to three times daily, **or 2.5 to 10 mg of norethindrone acetate daily), or a levonorgestrel-releasing intrauterine system (Mirena).**

INSULIN RESISTANCE AND POLYCYSTIC OVARIAN SYNDROME

Women with PCOS have a type of insulin resistance that is independent of, and additive with, that of obesity. Insulin resistance occurs in 50-70% of women with PCOS and in 95% of obese women with PCOS. Up to 40% of women with classic PCOS develop impaired glucose tolerance or type 2 diabetes mellitus by the fourth decade of life, with age and weight gain worsening glycemic control. **PCOS is associated with a four-fold increased prevalence of type 2 diabetes mellitus. Some patients with PCOS also may have several risk factors for cardiovascular disease, including increased abdominal adiposity, hypertension, hypertriglyceridemia, and low-density lipoprotein cholesterol levels and decreased high-density lipoprotein cholesterol levels.** Patients with PCOS with these findings should be counseled regarding weight loss, nutrition, exercise, and other lifestyle changes that will reduce their risk of developing diabetes mellitus and cardiovascular disease. In some cases, insulin-sensitizing agents such as **metformin** may be used to reduce insulin resistance and anovulation (see Chapter 34).

Controlling for body mass index, **women with PCOS are more likely to have sleep-disordered breathing and daytime sleepiness than healthy women,** which are additional risk factors for cardiovascular disease. Screening overweight and obese women with PCOS for symptoms of obstructive sleep apnea should be followed by polysomnography if necessary to make a definitive diagnosis. If obstructive sleep apnea is diagnosed, patients should be referred for appropriate therapy, including continuous positive airway pressure treatment. A flowchart for the diagnosis and investigation of patients with PCOS is shown in Figure 33-5.

Patients with adrenal hyperandrogenism, including late-onset CAH, can be treated with glucocorticoids (e.g., 0.25-mg dexamethasone every other day at bedtime). Many of these women, like those with PCOS, also require suppression of ovarian androgen secretion using combination oral contraceptives and antiandrogens.

CONGENITAL ABNORMALITIES OF THE VAGINA

Vaginal agenesis represents the most extreme instance of a vaginal anomaly, with total absence of the vagina except for the most distal portion that is derived from the urogenital sinus, which may appear as a dimple on the vulva. If the uterus is absent but the fallopian tubes are spared, the defect is **müllerian agenesis** or **Rokitansky-Küster-Hauser syndrome.** Isolated vaginal agenesis with normal uterine and fallopian tube development is rare, and is thought to be the end result of isolated vaginal plate malformation. The more common structural anomalies of the vagina include canalization defects such as **imperforate hymen, transverse and longitudinal vaginal septa, partial vaginal development, and double vagina.**

Imperforate hymen represents the mildest form of these canalization abnormalities. It occurs at the site where the vaginal plate contacts the urogenital sinus. After birth, a bulging, membrane-like structure may be noticed in the vestibule, usually blocking egress of mucus. If not detected until after menarche, an imperforate hymen may be seen as a thin, dark bluish or thicker, clear membrane blocking menstrual flow at the introitus (Figure 18-6, *A* and *B*). A similar anomaly, the **transverse vaginal septum,** is most commonly found

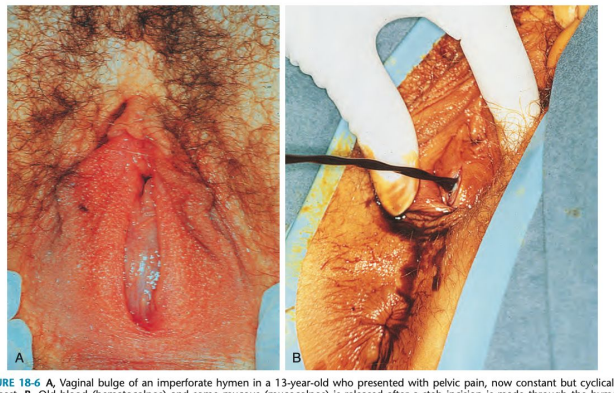

FIGURE 18-6 **A,** Vaginal bulge of an imperforate hymen in a 13-year-old who presented with pelvic pain, now constant but cyclical in the past. **B,** Old blood (hematocolpos) and some mucous (mucocolpos) is released after a stab incision is made through the hymen. (From McKay M: Vulvar manifestations of skin disorders. In Black M, McKay M, Braude P, et al, editors: *Obstetric and gynecologic dermatology,* ed 2, Edinburgh, 2003, Mosby, p 122.)

Reference

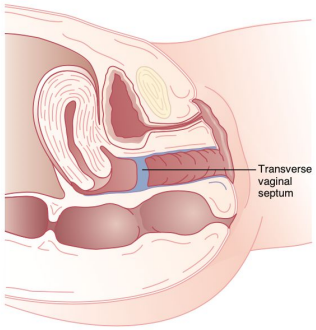

FIGURE 18-7 Illustration of a transverse vaginal septum.

at the junction of the upper and middle thirds of the vagina (Figure 18-7). Patients with an imperforate hymen or transverse vaginal septum usually have normal development of the upper reproductive tract.

A **midline longitudinal septum** may be present, creating a double vagina. The longitudinal septum may be only partially present at various levels in the upper and middle vagina, either in the midline or deviated to one side. In addition, a longitudinal septum may attach to the lateral vaginal wall, creating a blind vaginal pouch, with or without a communicating sinus tract. These septa are usually associated with a **double cervix** and one of the various duplication anomalies of the uterine fundus, although the upper tract is often entirely normal.

Adenosis of the vaginal wall consists of islands of columnar epithelium in the normal squamous epithelium. It is often located in the upper third of the vagina. The incidence of this finding is much higher in women exposed to diethylstilbestrol in utero.

Urethral diverticula are small (0.3 to 3 cm), sac-like projections that can be found along the posterior urethra in the midline of the anterior vaginal wall. They may or may not communicate with the urethra, and they may cause dyspareunia. Urethral diverticula can cause recurrent urinary tract infections (see Chapter 22).

ASHERMAN SYNDROME

Asherman syndrome is a condition where the endometrium is denuded and the endometrial cavity is filled with adhesions. Most commonly, the scarring results from curettage in high-risk settings, such as postpartum hemorrhage or septic abortion, although vigorous scraping under any circumstances can result in the loss of the endometrium and consequent adhesion of opposing myometrial surfaces. Endometrial ablation procedures are designed to deliberately destroy the endometrium and create such scarring. Subsequent bleeding disorders can range from irregular bleeding to amenorrhea depending on the amount of intrauterine scarring.

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