

**Amenorrhea**

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 initial history and physical examination would be as follows:

1. **Primary amenorrhea with sexual infantilism,**
2. **Primary amenorrhea with breast development and mullerian anomalies** (normal secondary sexual character),
3. **Amenorrhea and oligomenorrhea with breast development and normal mullerian structures.** this group includes disorders causing primary as well as secondary amenorrhea, oligomenorrhea, and the hyperandrogenic states.

**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. The presence of normal breast development confirms gonadal secretion of estrogen but not necessarily the presence of ovarian tissue. The presence of normal amounts of pubic and axillary hair confirms gonadal or adrenal secretion of androgens as well as the presence of functional androgen receptors.

1. **PRIMARY AMENORRHEA WITH SEXUAL INFANTILISM**
Patients with primary amenorrhea and no secondary sexual characteristics (sexual infantilism) display the absence of gonadal hormone secretion. The differential diagnosis is based on whether the defect is the result of a lack of gonadotropin secretion (hypogonadotropic hypogonadism) or an inability of the ovaries to respond to gonadotropin (hypergonadotropic hypogonadism due to gonadal agenesis or dysgenesis). The distinction can be made by the measurement of a basal serum follicle-stimulating hormone (FSH).

Hypogonadotropic Primary Amenorrhea and Sexual Infantilism

Patients with hypogonadotropic hypogonadism have low FSH levels, whereas patients with hypergonadotropic hypogonadism (e.g., gonadal dysgenesis) have elevated FSH levels in the menopausal range (>40 mIU/L).

Hypogonadotropic hypogonadism may be caused by lesions of the hypothalamus like craniopharyngioma or other central nervous system tumor or by functional disorders that result in inadequate gonadotropin-releasing hormone (GnRH) synthesis and release. Kallman syndrome is a rare genetic condition that is characterized by a failure to start or a failure to complete puberty. It is also accompanied by a lack of sense of smell (anosmia) Kallmann syndrome occurs due to a failure of the hypothalamus to release GnRH. Magnetic resonance imaging (MRI) or computerized tomography (CT) of the hypothalamic-pituitary area is recommended.

Hypogonadotropic hypogonadism resulting in primary...
amenorrhea and sexual infantilism may also be the result of lesions of the pituitary, including prolactin-secreting adenomas, or a general process of pituitary failure. These patients should be screened for other pituitary hormonal 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.

B\Hypergonadotrophic Primary Amenorrhea and Sexual Infantilism

Patients with hypergonadotropic hypogonadism have some form of failed gonadal development or premature gonadal failure and will have elevated FSH levels. These patients may have gonadal agenesis (the absence or early disappearance of the normal gonad). Examples in males who may appear to be female in some cases are 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 of gestation, they may have female external genitalia with or without ambiguity in addition to a lack of gonads, a hypoplastic uterus (secondary to absent secretion of antimullerian hormone), and rudimentary genital ducts.

Other individuals with hypergonadotrophic primary amenorrhea and sexual infantilism may have gonadal
dysgenesis, the presence of an abnormally developed gonad due to chromosomal defects. The differential diagnosis includes 45 XO (Turner syndrome), 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 for developing a gonadoblastoma (a benign germ cell tumor of the gonad) All patients with hypergonadotropic hypogonadism should have a karyotype performed. Because it is important to identify mosaicism,.

Patients with sexual infantilism may be treated to stimulate breast development by very gradually increasing estrogen doses. One commonly used regimen is to start with 0.3 mg conjugated estrogen every other day and slowly increase over 3- to 6-month intervals.

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

**Turner Syndrome**

The disorder is characterized by partial or complete loss (monosomy) of one of the X chromosomes. Individuals with Turner syndrome may benefit from growth hormone (GH) therapy, which can help to normalize height. Estrogen and progesterone replacement therapy will generally
promote puberty and the development of secondary sexual characteristics. Hormone replacement therapy is usually begun around 12-14 years of age. Replacement therapy must be continued until menopause.

Most individuals with Turner syndrome remain unable to conceive children. In vitro fertilization (IVF) with a donor egg and an implanted pregnancy is sometimes possible.

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**2 PRIMARY AMENORRHEA WITH BREAST DEVELOPMENT AND MULLERIAN ANOMALIES**

(normal secondary sexual characters)
Patients with primary amenorrhea, breast development, and some defect of mullerian structures fall into two categories: those with complete androgen insensitivity syndrome (AIS), formerly called testicular feminization, and those with mullerian dysgenesis or agenesis. The distinction between these two diagnoses can be made by the measurement of a serum testosterone level and determination of the karyotype.

**A\Androgen Insensitivity Syndrome**

Patients with complete androgen insensitivity syndrome have a defect in the androgen receptor. Their karyotype is **46 XY**, and they demonstrate male levels of testosterone, their testes are located within the abdominal wall or cavity (cryptorchic). This location, with greater body heat, typically does not allow for normal male hormonal secretion. Breast development (with smaller nipples and areolae than normal *genotypical females*) is caused by the testicular secretion of estrogens and by the conversion of circulating androgen to estrogens in the liver and elsewhere. The testicles of individuals with AIS secrete normal male amounts of antimullerian hormone; 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. Psychological counseling is an important component in the care of these patients.

**B\Mullerian Dysgenesis or Agenesis**

Patients with primary amenorrhea, breast development, and a 46 **XX** karyotype have levels of testosterone appropriate for females. This clinical diagnosis may be caused by mullerian defects that
cause destruction of the vaginal canal (e.g., imperforate hymen or a transverse vaginal septum) or by the absence of a normal cervix or uterus and normal fallopian tube'. An **imperforate hymen** should be suspected in adolescents who report monthly dysmenorrhea in the absence of vaginal bleeding. Clinical these patients often present with a vaginal bulge 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, women may present with similar symptoms **BUT** without a vaginal bulge. When ultra sonography 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 the MRI scan confirms a transverse septum, surgical correction is indicated.

Finally; rectal examination and ultrasonography may be a sign of the absence of a uterus indicating **mullerian agenesis or Meyer-Rokitansky-Kuster- Hauser syndrome**. This syndrome is characterized by a failure of the mullerian ducts to fuse distally and to form the upper genital tract. These patients may have unilateral or bilateral rudimentary uterine tissues, fallopian tubes, and ovaries. It is uncommon to have functional endometrial tissue.

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, these patients should have an intravenous pyelogram or other diagnostic study to confirm a normal urinary system.

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**Diagnosis of Primary Amenorrhea**
Amenorrhea and Oligomenorrhea with Breast Development and Normal Mullerian 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 may present as oligomenorrhea (menstrual cycles at greater than 35- to 45-day intervals).

All patients with menstrual bleeding disorders should be tested for pregnancy. 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 an FSH level and a progestin challenge test. Failure of the patient to have withdrawal bleeding after receiving a progestational agent indicates significant hypoes-trogenism or hyperandrogenism, a uterine defect, or pregnancy. The absence of a withdrawal bleed after the administration of a progestational agent due to a uterine defect can be ruled out by the presence of withdrawal bleeding following sequential estrogen and progestin therapy.

UTERINE DEFECTS(normal estrogen level)

Women who do not have withdrawal bleeding after 1 hormonal challenge test and who have a history of uterine instrumentation, particularly a dilation and uterine evacuation, following vaginal delivery or pregnancy termination may have Asherman's syndrome. This
interesting syndrome is characterized by intrauterine scarring (synechiae), and these patients may have normal ovulatory cycles with cyclic premenstrual symptoms. Patients with Asherman’s syndrome should be evaluated by hysterosalpingography or sonohysterography. The treatment of choice is hysteroscopic treatment with excision of the synechiae, followed by insertion of an IUCD with estrogen progesterone supplement for 3 months.

**AMENORRHEA AND OLIGOMENORRHEA ASSOCIATED WITH HYPOESTROGENISM**

The differential diagnosis for patients with amenorrhea associated with low levels of estrogen includes:

\h\hypothalamic-pituitary dysfunction (hypothalamic amenorrhea) have low FSH and prolactin levels.

\p premature ovarian failure have high FSH and normal prolactin levels.

\\hyperprolactinemia have high prolactin and low FSH levels.

\Hypothalamic-Pituitary Dysfunction

Patients with hypothalamic amenorrhea include women experiencing severe weight loss, women undergoing excessive exercise resulting in low body fat, and women experiencing severe psychological stress. Also included are women with severe systemic diseases such as disseminated malignancies and patients with pituitary or central nervous system lesions. In its most severe and life-threatening form, women may have pituitary failure or anorexia nervosa. All patients with hypothalamic-pituitary dysfunction should be evaluated for the status of the other pituitary hormones.
Sheehan’s syndrome
This term describes hypopituitarism that presents in the late postpartum period, and which is caused by haemorrhage and hypotension at the time of delivery. The hypotension results in avascular necrosis that affects the anterior pituitary more commonly than the posterior pituitary. Women most frequently present with failure of lactation and subsequent amenorrhoea, but they may have any feature of hypopituitarism including the more subtle features of hypoadrenalism and hypothyroidism.

\/Premature Ovarian Failure

Premature ovarian failure is defined as ovarian failure before the age of 40 years. A karyotype is 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 from surgery, radiation, or chemotherapy; galactosemia; carrier status of the fragile X syndrome; and autoimmunity. 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 hormonal therapy (estrogen and a progestin) to reduce the risk for osteoporosis.

\/Amenorrhea and oligomenorrhea with hyperprolactinemia and 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, in turn, 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 galactorrhea

**Causes of elevated prolactin**

- Pregnancy (10-fold rise 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
  - Hypothyroidism
  - Chronic renal failure
  - Marijuana or narcotic use

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

D\Amenorrhea and Oligomenorrhea with Hyperandrogenism

Hyperandrogenism is the clinical manifestation of elevated levels of male hormones in women. Features may range from mild unwanted excess hair growth and acne to alopecia (hair loss), more extensive hirsutism, , masculinization and virilization. **Hirsutism is the presence of male-like hair growth caused by conversion of vellus to terminal hairs in areas such as the face, chest, abdomen, or upper thighs.** Signs of masculinization include loss of female body fat and decreased breast size. Virilization is the addition of temporal balding, deepening of the voice, and enlargement of the clitoris to any of the previous signs of excess male hormone. Androgens in women are normally produced in the ovaries and the adrenal glands. Hyperandrogenic disorders may be divided into functional and neoplastic disorders of the adrenal or ovary.
Diagrammatic representation of the steroid biosynthetic pathways.

**Hyperandrogenic Disorders**

In general, hyperandrogenic disorders can be attributed to excessive secretion of androgens by the ovaries, by the adrenals, or both.

**ADRENAL DISORDERS**

**Congenital Adrenal Hyperplasia**

Congenital adrenal hyperplasia (CAH) is a general term used to describe an assortment of disorders that arise from inborn glandular enzyme deficiencies associated with the overproduction of steroids. The most common cause of CAH is 21-hydroxylase deficiency. CAH represents a spectrum of disorders, ranging from the severe salt-wasting form (early onset), to simple virilizing CAH,. Alternatively the late onset) presents later in life, generally at the time of puberty or later. These patients (late onset) do not present with genital abnormalities, although they may develop hirsutism, acne, and menstrual and ovulatory irregularities. Because 21-hydroxylase is responsible for the conversion of 17-hydroxyprogesterone to 11-deoxycorticisol), a deficiency in 21-hydroxylase results in an excessive accumulation of 17-hydroxyprogesterone. As a result, this enzyme disorder is marked
by an elevated serum 17-hydroxyprogesterone level as well as increases in its metabolites androstenedione and testosterone. This disease is inherited as an autosomal recessive trait. CAH, are treated by the administration of glucocorticoids (e.g., 0.25 mg dexamethasone every other day at bedtime).

**Cushing's Syndrome**
Characteristic Cushinoid signs include truncal obesity, moon-like faces, hypertension, easy bruisability, impaired glucose tolerance, muscle wasting, osteoporosis, abdominal striae, and supraclavicular and cervical spinal fat pads. Other manifestations include hirsutism, acne, and irregular menses. This is a rare cause of menstrual dysfunction in women.

**Adrenal Neoplasms**
Adrenal tumors causing hyperandrogenism without symptoms and signs of glucocorticoid excess are rare.

**OVARIAN DISORDERS**

**Polycystic Ovary Syndrome**
Six to 10% of women of reproductive age have some form of PCOS. This syndrome is a chronic condition that has been defined as anovulation or oligo-ovulation with clinical or laboratory evidence of hyperandrogenism and without evidence of any other underlying condition

**Hyperandrogenic Insulin Resistance and Acanthosis Nigricans Syndrome**
HAIR-AN syndrome is characterized by extremely high circulating levels of insulin (>80 mU/mL basally or >500 mU/mL following an oral glucose challenge) due to severe insulin
resistance. Because insulin is also a mitogenic hormone, these extremely elevated insulin levels result in hyperplasia of the basal layers of the epidermal skin, leading to the development of acanthosis nigricans, a velvety, hyperpigmented change of the crease areas of the skin. In addition, because of the effect of insulin on ovarian theca cells, the ovaries of many patients with the HAIR-AN syndrome are hyperthecotic. Patients with this disorder can be severely hyperandrogenic and even present with virilization.

**Ovarian Neoplasms**

Androgen-producing ovarian tumors are extremely uncommon, and include Sertoli-Leydig, hilus, and lipoid cell tumors.
A diagnostic approach to secondary amenorrhea. (DHEA-S = dehydroepiandrosterone sulfate; FSH = follicle-stimulating hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.)