

8

Amenorrhea

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INTRODUCTION

Amenorrhea means the absence of menstruation. Primary amenorrhea is the absence of menarche in a girl aged 16 years or older. Secondary amenorrhea is the absence of menses for 6 months in women with previously irregular cycles or 3 months in women with regular cycles (21–35 days)^{1,2}.

Menarche is the first menstrual period and starts after the development of secondary sexual characteristics: pubic and axillary hair and breast development (Tanner stages, Figure 1). The mean age of menarche is 13.5 years, but there exist huge differences between and within countries^{3,4}. Generally,

girls from rural areas in low-resourced countries are older at menarche than girls from urban areas. General living conditions, nutritional status, physical activity and genetic factors all influence sexual maturation and age at menarche⁴.

HISTORY TAKING

In primary amenorrhea

- Presence of secondary sexual characteristics. Are axillary and pubic hair present and is there breast development (see Tanner stages, Figure 1)? If no secondary sexual characteristics are present, there is usually a delay in puberty due to malnutrition (stunting), chronic childhood illness, excessive physical activity combined with reduced energy intake or the delay is constitutional.
- History of infections, especially encephalitis. Encephalitis and meningitis might have damaged the hypothalamus or pituitary.
- History of (abdominal) operations. Removal of the ovaries because of tumors, cysts or tubo-ovarian abscesses.
- Age of mother and older sisters at menarche. Late age at menarche is hereditary.
- Chronic (childhood) disease and/or history of major illness in past 3 years. Chronic debilitating disease can lead to anovulation through hypothalamic dysfunction.
- Cyclical abdominal pain. Together with an abdominal mass, this symptom could indicate a vaginal septum or imperforate hymen.
- Weight loss. Severe weight loss due to for example a chronic disease influences hypothalamic function.
- Hirsutism. A masculine distribution of body hair (breast, abdomen, face, thighs) and/or severe

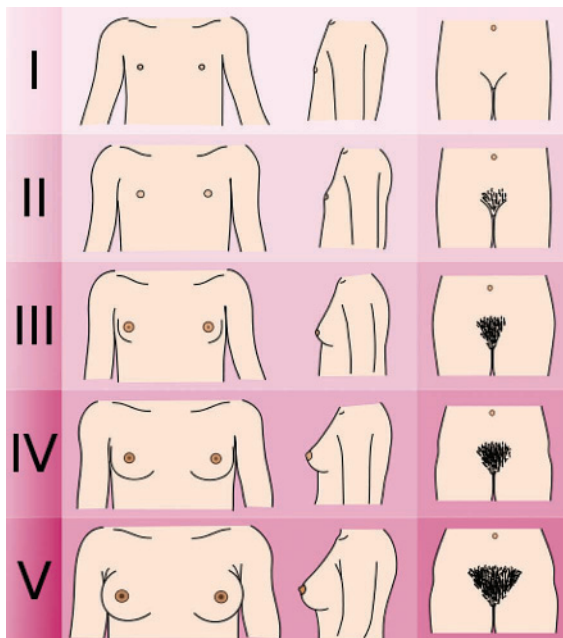


Figure 1 Tanner stages. Illustration by Michel Komorniczak

acne indicate androgen excess and is a symptom of polycystic ovary syndrome.

- Sexual relations (pregnancy). Question the girl sensitively about sex: does she engage in consensual sexual intercourse or is she a victim of sexual violence? Sexually transmitted infections (STIs), including HIV and pregnancy should be excluded.

In secondary amenorrhea

- Duration of amenorrhea and history of previous cycles. At what age did menarche start? Did the woman have a regular menstrual cycle (21–35 days) or was it irregular (<21 days or >35 days)? How long has she not menstruated?
- History of contraception. Has she used hormonal contraception? For how long? What type has she used? After stopping the combined oral contraceptive pill, a woman should regain her normal menstrual cycle. The use of long-acting depot medroxyprogesterone can delay the return to a normal cycle for up to 1 year.
- History of subfertility. Subfertility and amenorrhea are closely linked: around 20% of women with subfertility have amenorrhea. Women with subfertility are more likely to seek medical help (both in the formal and informal sector) and are prone to undergo curettage as ‘treatment’ which can damage the uterine cavity and lead to infection and adhesions (Asherman’s syndrome). They are also more likely to have had more sexual partners and therefore are at risk for HIV infection which in turn can cause amenorrhea.
- History of pelvic inflammatory disease (PID) and STIs. Infection of the uterus can cause intra-uterine adhesions and endometrial destruction.
- History of severe blood loss or shock after delivery. Pituitary necrosis due to severe postpartum hemorrhage (syndrome of Sheehan) causes lack of pituitary hormones like follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin. Failure to breastfeed is usually the first symptom followed by amenorrhea.
- Abdominal pain.
- Breastfeeding. (Exclusive) breastfeeding causes lactational amenorrhea by suppressing the production of LH and FSH by high levels of prolactin.
- Galactorrhea. In non-pregnant women leakage of milk from the breast can point to hyper-

prolactinemia causing amenorrhea. Galactorrhea combined with headache and/or visual disturbance may indicate a pituitary macroadenoma.

- Operations: dilation & curettage, abdominal operations including cesarean section. These operations can lead to intrauterine adhesions or cervical stenosis/adhesions.
- Fever after miscarriages, deliveries, cesarean section. Severe endo/myometritis or PID can destroy the endometrium, cause intrauterine or cervical adhesions.
- Chronic diseases, weight loss, night sweats, fever >1 month, diarrhea >1 month. HIV, tuberculosis, cancer, end-stage renal disease etc. cause a catabolic state with severe wastage. This influences hypothalamic function and causes amenorrhea.
- Hirsutism. A masculine distribution of body hair (breast, abdomen, face, thighs) and/or severe acne indicate androgen excess and is a symptom of polycystic ovary syndrome.
- Age of menopause in mother, older sisters. Age at menopause is usually hereditary.

INVESTIGATIONS

Physical examination

Always explain to the girl or woman what you are going to do and ask a girl if she wants someone she trusts present at the examination.

- Height and weight. Body mass index (BMI): weight (kg)/length × length (m). BMI <18 is underweight and BMI >30 is obese.
- Signs of malnutrition, tuberculosis, HIV/AIDS, chronic disease.
- Increased hair growth on the face, pubic region, abdomen and/or thighs.
- Secondary sexual characteristics (breast development and pubic and axillary hair).
- Breasts: leaking of milk spontaneously or after careful expression (see how to do that in Chapter 1).
- Abdominal examination: pregnancy, tumors.
- External genitalia: clitoris, hymen, hair growth. In a girl with primary amenorrhea look for a bulging hymen which indicates imperforate hymen.
- Speculum and pelvic examination (see Chapter 1) (if a girl/woman is not a virgin): atrophy, discharge, cervical abnormalities, cervical excitation, uterine size, pelvic mass.

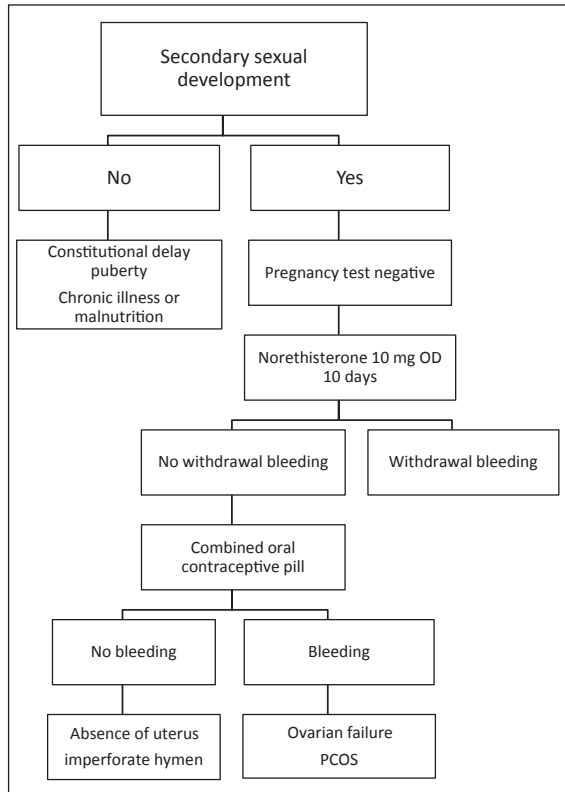


Figure 2 Diagnostic work-up of primary amenorrhea

- Ultrasound examination (see Chapter 1) (abdominal with full bladder or vaginal): uterus present, size of uterus, endometrium, ovarian size and presence of follicles, tubo-ovarian mass, cysts, free fluid? In a girl with primary amenorrhea specifically try to visualize the uterus as absence indicates a congenital defect or chromosomal disorder.

Additional investigations

- Pregnancy test
- Erythrocyte sedimentation rate, full blood count
- Urine analysis
- HIV test.

DIAGNOSTIC WORK-UP

Most laboratories in low-resource settings lack the facilities to measure FSH, estradiol, thyroid-stimulating hormone (TSH) and prolactin. These hormonal essays are routinely used in the diagnosis of amenorrhea in high-resource clinical settings. Therefore, this chapter will follow a more practical

and pragmatic approach to diagnose the cause of amenorrhea (Figures 2 and 3).

In the presence of secondary sexual characteristics, the first step is to exclude pregnancy. Then follows a progestational challenge test with norethisterone 10mg daily for 10 days. If the patient bleeds, the presence of a uterus with sufficiently prepared endometrium by estrogens and a competent outflow tract is confirmed. If the patient does not bleed, the next step is to give the combined oral contraceptive pill for one cycle which will cause a withdrawal bleeding when a uterus and a functional outflow tract are present. No withdrawal bleeding usually means there is a defect in the endometrium, uterus or outflow tract and further investigations should be directed towards assessing these.

CAUSES OF AMENORRHEA

See Table 1.

Disorders of the ovary

Gonadal dysgenesis

Gonadal dysgenesis can occur with normal XX and XY karyotypes, but the best known condition is Turner syndrome (45,X), whereby oocyte loss is accelerated. A typical girl with Turner syndrome has short stature, webbed neck, shield chest, cubitus valgus and prepubertal external genitals. Because the ovaries contain no primordial follicles, she will not ovulate and menstruate and is infertile. She has primary amenorrhea. Ultrasound examination can be helpful to diagnose this condition, but is difficult. It might show a small uterus with no endometrial lining and small ovaries with no primordial follicles. The progestational challenge test will cause no withdrawal bleeding, but the oral contraceptive pill will. (For more detailed information see <http://freebooks4doctors.com/fb/ENDOC.htm>)

Premature ovarian failure

Premature ovarian failure means the loss of primordial follicles before age 40 years and the woman will enter menopause prematurely. Women can experience hot flushes, night sweats and a dry vagina due to epithelial atrophy. Premature ovarian failure is usually idiopathic, but can be caused by radio- and chemotherapy, oophoritis or autoimmune disease. Although the chance for pregnancy is low, it does occur and patients who do not

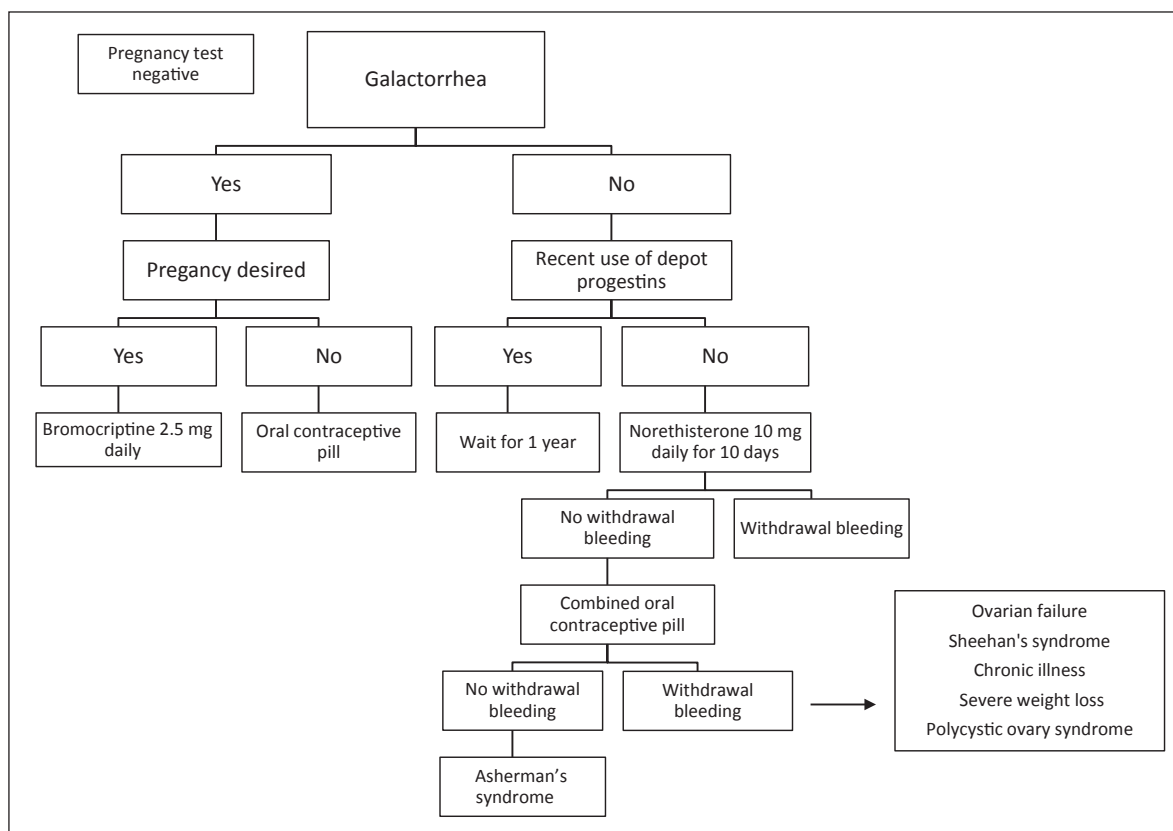


Figure 3 Diagnostic work-up of secondary amenorrhea

wish to become pregnant should be advised to use contraceptives, preferably the oral contraceptive pill to prevent osteoporosis. It is important to talk openly and repeatedly with the patient and if she allows, together with her partner, and counsel the couple on the low chances for pregnancy. These patients tend to visit a lot of different doctors and healers, and spend a lot of money on useless investigations and treatments, such as repeated curettage.

Disorders of uterus and outflow tract

Imperforate hymen

An imperforate hymen or vaginal septum is a rare cause of primary amenorrhea. Besides amenorrhea it presents with cyclical abdominal pain and an abdominal swelling sometimes in combination with acute urinary retention. The abdominal mass is the vagina or uterus filled with blood (hemato-colpos, hematometra). Examination of the vulva usually reveals a blue imperforate hymen bulging

from the vaginal introitus. Treatment is simple by making a cruciate, a circular or elliptical incision in the hymen and large amounts of chocolate-colored fluid will come out⁵. Prophylactic antibiotics should be given before surgery. After evacuation of blood, the edges of the hymen are excised to maintain an adequate opening⁵.

Absence of uterus or endometrium

In the Mayer–Rokitansky–Küster–Hauser syndrome there is no apparent vagina and the uterus is usually absent. Girls with this syndrome have normal growth and development and present with primary amenorrhea. The progestational challenge test and the combined oral contraceptive pill will cause no withdrawal bleeding. On examination of the vulva there is no vagina or a very shallow indentation. In most cases abdominal ultrasound will be able to establish the absence of a uterus. These girls will never be able to become pregnant. The patient herself can create a vagina by using vaginal

Table 1 Etiology of amenorrhea

<i>Disorders of uterus and vagina</i>	
Congenital (Müllerian abnormalities)	Imperforate hymen, transverse vaginal septum, vaginal agenesis/aplasia (Mayer–Rokitansky–Küster–Hauser syndrome, androgen insensitivity syndrome), cervical agenesis
Acquired	Asherman’s syndrome, cervical stenosis
<i>Disorders of ovary</i>	
Gonadal dysgenesis	Turner syndrome (45 X, mosaics), Swyer syndrome (46 XY), Perrault syndrome (with neurosensory deafness)
Premature ovarian failure	Idiopathic, injury (mumps, radiation, chemotherapy)
<i>Disorders of the pituitary</i>	
Pituitary tumors	Prolactinomas, other hormone-secreting tumors
Hyperprolactinemia	Hypothyroidism, psychotropic drugs, breastfeeding
Sheehan’s syndrome	
<i>Disorders of the central nervous system</i>	
Kallmann’s syndrome	Isolated gonadotropin deficiency (not able to smell, renal agenesis, neurological symptoms)
Dysfunctional	Nutrition-related (malnutrition, severe weight loss, eating disorder), exercise, stress
Use of medication	Anti-epileptics, hormonal contraception, antipsychotic drugs
Chronic diseases	HIV/AIDS, tuberculosis, malnutrition, sickle cell disease, liver cirrhosis, chronic kidney disease, cancer, major psychiatric disorders
Tumors	Craniopharyngioma
Infections	Tuberculosis, syphilis, encephalitis/meningitis, sarcoidosis
<i>Other</i>	
Polycystic ovary syndrome	
Other endocrine gland disorders	Hypo- and hyperthyroidism, ovarian tumors, adrenal hyperplasia, Cushing syndrome

dilators with increasing diameters. These should be applied with pressure to the vaginal orifice daily for 20 min.

Androgen insensitivity

Androgen insensitivity is the third most common cause of primary amenorrhea. The patient is a male pseudohermaphrodite: she has testes and a XY karyotype, but is phenotypically female. She has normal growth and development, although the breasts are abnormal (small nipples, less glandular tissue), underdeveloped labia minora, less deep vagina and no uterus. Body hair, axillary and pubic hair are absent or sparse. More than half of these women have inguinal hernias which contain the testes. Testes should be removed around age 16–18 years because cancer might develop. There is no withdrawal bleeding after the progestational challenge test or the combined oral contraceptive pill. An ultrasound should be able to establish the absence of a uterus.

Asherman’s syndrome

Asherman’s syndrome describes the destruction of the endometrium usually caused by forced or repeated curettage of the uterus in incomplete miscarriage or incomplete removal of the placenta after delivery. It can also occur after cesarean section, severe PID, infected abortion, severe endomyometritis or after severe obstructed labor with development of a vesico-vaginal fistula. Adhesions develop in the uterine cavity, the internal os and/or cervical canal. There is no withdrawal bleeding after the progestational challenge test and very minimal or no bleeding after the combined oral contraceptive pill. Hysterosalpingography (see Chapter 16 on subfertility) might help in the diagnosis, but hysteroscopy (see Chapter 1 on basic gynecological examinations) is the gold standard. If there is only stenosis or obliteration of the cervical canal, a cervical dilation might solve the problem. However, curettage as treatment of cavity adhesions should not be attempted because it can make

the situation worse. Hysteroscopy with adhesiolysis is the preferred treatment. In most studies an intrauterine device (copper IUD) or Foley catheter together with estrogen therapy is used to prevent recurrence of intrauterine adhesions, but no randomized controlled trials have been conducted to provide evidence for this management⁶.

Other causes

In areas where tuberculosis is endemic, genital tuberculosis can be the cause of amenorrhea and infertility. Diagnosis is made by culture of menstrual blood or endometrial biopsy. The physician should look for other signs and symptoms of tuberculosis. Treatment is with antitubercular therapy according to World Health Organization (WHO) guidelines⁷. Patients with genital tuberculosis have a poor prognosis regarding restoration of menstrual function and fertility, because of complete destruction of the endometrium⁸.

Schistosomiasis has also been described as a cause of Asherman's syndrome and the parasite can be found in urine, feces, menstrual blood or endometrium⁹. Treatment is with praziquantel.

Disorders of the pituitary

Hyperprolactinemia

Hyperprolactinemia¹⁰ is the cause of 1% and 15% of cases in primary and secondary amenorrhea, respectively. Breastfeeding, pituitary adenomas, primary hypothyroidism and psychotropic medication give rise to hyperprolactinemia. Amenorrhea develops because prolactin inhibits the pulsatile secretion of gonadotropin-releasing hormone (GnRH). Only one-third of women with elevated levels of prolactin have galactorrhea¹⁰. A progestational challenge test will be negative if estrogen levels are low, but the combined oral contraceptive pill will usually cause a withdrawal bleeding.

Adenomas of the pituitary gland are quite common: prolactinomas account for 50% of adenomas found at autopsies. Adenomas will only cause symptoms when they produce hormones [adrenocorticotropic hormone (ACTH), growth hormone, prolactin] or are >1 cm in diameter (headache and visual disturbances). Hyperprolactinemia caused by a prolactinoma needs treatment if a woman wants to conceive. Bromocriptine, a dopamine agonist, 2.5 mg once daily for several months will usually

restore ovulation and menstrual function (see Chapter 16).

Sheehan's syndrome

Sheehan's syndrome is caused by infarction and necrosis of the anterior pituitary gland after severe postpartum hemorrhage and shock. Panhypopituitarism is the most severe form of Sheehan's syndrome. The most frequent symptoms are failure to lactate and amenorrhea^{11,12}, but symptoms like chronic tiredness and lethargy can arise years later¹². Secondary adrenal insufficiency can lead to life-threatening conditions. The prevalence of Sheehan's syndrome might be higher in low-resource countries where access to and quality of obstetric care is poor and women with severe postpartum hemorrhage are treated late (of course, the prevalence might also be low, because women die of postpartum hemorrhage)¹³.

Disorders of the central nervous system

Specific hypothalamic disorders are extremely rare causes of amenorrhea. However, there exist more common conditions which influence GnRH pulsatility and cause hypogonadotropic amenorrhea. Psychological stress, severe weight loss, chronic illness, acute severe illness and strenuous exercise suppress GnRH. Women suffering from advanced HIV disease often present with amenorrhea. It is important to think of this cause of amenorrhea and counsel patients for HIV testing. Regular menstrual cycles will be restored with weight gain under highly active antiretroviral therapy (HAART) and a woman on HAART should be counseled about contraception.

Delayed puberty

The diagnosis of physiological delayed puberty can only be made when other causes of amenorrhea are excluded. Malnutrition and chronic illness cause delayed puberty and girls with these conditions are growth stunted and show no signs of secondary sexual characteristics^{14,15}.

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is present when two out of three criteria are present: oligo-amenorrhea, signs of hyperandrogenism (hirsutism, acne) and/or polycystic ovaries on ultrasound (12

follicles or more in one or both ovaries)¹⁶. Although obesity is not part of the criteria, many women with PCOS are overweight or obese. The exact pathophysiology of this syndrome is unclear, but the main problem is anovulation probably due to an intra-ovarian environment that is not conducive for development of a dominant follicle. Women with this syndrome respond with a withdrawal bleeding when given norethisterone because their endometrium has been stimulated by estrogens. This unopposed endometrial stimulation might be a risk factor for endometrial cancer and in women with no wish to conceive, the oral contraceptive pill should be advised. The oral contraceptive pill also has a positive effect on hirsutism when used for 9 months or longer. Weight loss in obese women can restore ovulation. Clomiphene citrate can be used for women who wish to conceive: start with 50 mg daily for 5 days to be increased to maximally 150 mg daily for 5 days (see Chapter 16 on subfertility).

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