AMENORRHOEA

Amenorrhoea is the absence of menses in a woman of reproductive age. It can be primary or secondary. Secondary amenorrhoea is absence of periods for at least 3 months if the patient has previously had regular periods, and 6 months if she has previously had oligomenorrhoea. In contrast, oligomenorrhoea describes infrequent periods, with bleeds less than every 6 weeks but at least one bleed in 6 months.

Aetiology of amenorrhea in adolescents (from Golden and Carlson)

Type	Oestrogen-deficient	Oestrogen-replete
Hypothalamic	Eating disorders	Immaturity of the HPO axis
	Exercise-induced amenorrhea	
	Medication-induced amenorrhea	
	Chronic illness	
	Stress-induced amenorrhea	
	Kallmann syndrome	
Pituitary	Hyperprolactinemia	
	Prolactinoma	
	Craniopharyngioma	
	Isolated gonadotropin deficiency	
Thyroid		Hypothyroidism
		Hyperthyroidism
Adrenal		Congenital adrenal hyperplasia
		Cushing syndrome
Ovarian		Polycystic ovary syndrome
	Gonadal dysgenesis (Turner syndrome)	
	Premature ovarian failure	
		Ovarian tumour
	Chemotherapy, irradiation	
Uterine		Pregnancy
		Androgen insensitivity
		Uterine adhesions(Asherman syndrome)
		Mullerian agenesis
		Cervical agenesis
Vaginal		Imperforate hymen
		Transverse vaginal septum
		Vaginal agenesis

The recommendations for those who should be evaluated have recently been changed to those shown below. (adapted from Diaz *et al*)

Indications for evaluation of an adolescent with primary amenorrhea

1. An adolescent who has not had menarche by age 15-16 years
2. An adolescent who has not had menarche and more than three years have elapsed since thelarche
3. An adolescent who has not had a menarche by age 13-14 years and no secondary sexual development
4. An adolescent who has not had menarche by age 14 years and:
   (i) there is a suspicion of an eating disorder or excessive exercise, or
   (ii) there are signs of hirsutism, or
   (iii) there is suspicion of genital outflow obstruction

Pregnancy must always be excluded. The most common cause in adolescents is hypothalamic amenorrhoea (associated with anorexia nervosa, exercise, or chronic illness) followed by polycystic ovarian syndrome (PCOS). Oestrogen-deficient amenorrhea is associated with reduced bone mineral density and increased fracture risk, while oestrogen-replete amenorrhea can lead to dysfunctional

uterine bleeding in the short term and predispose to endometrial carcinoma in the long term. Administration of progesterone (Provera, 10mg orally per day for 7 days) to an adolescent girl after 2–3 months of secondary amenorrhea will prevent DUB (dysfunctional uterine bleeding) from occurring. Bleeding will occur 1-2 days after the Provera is ceased.

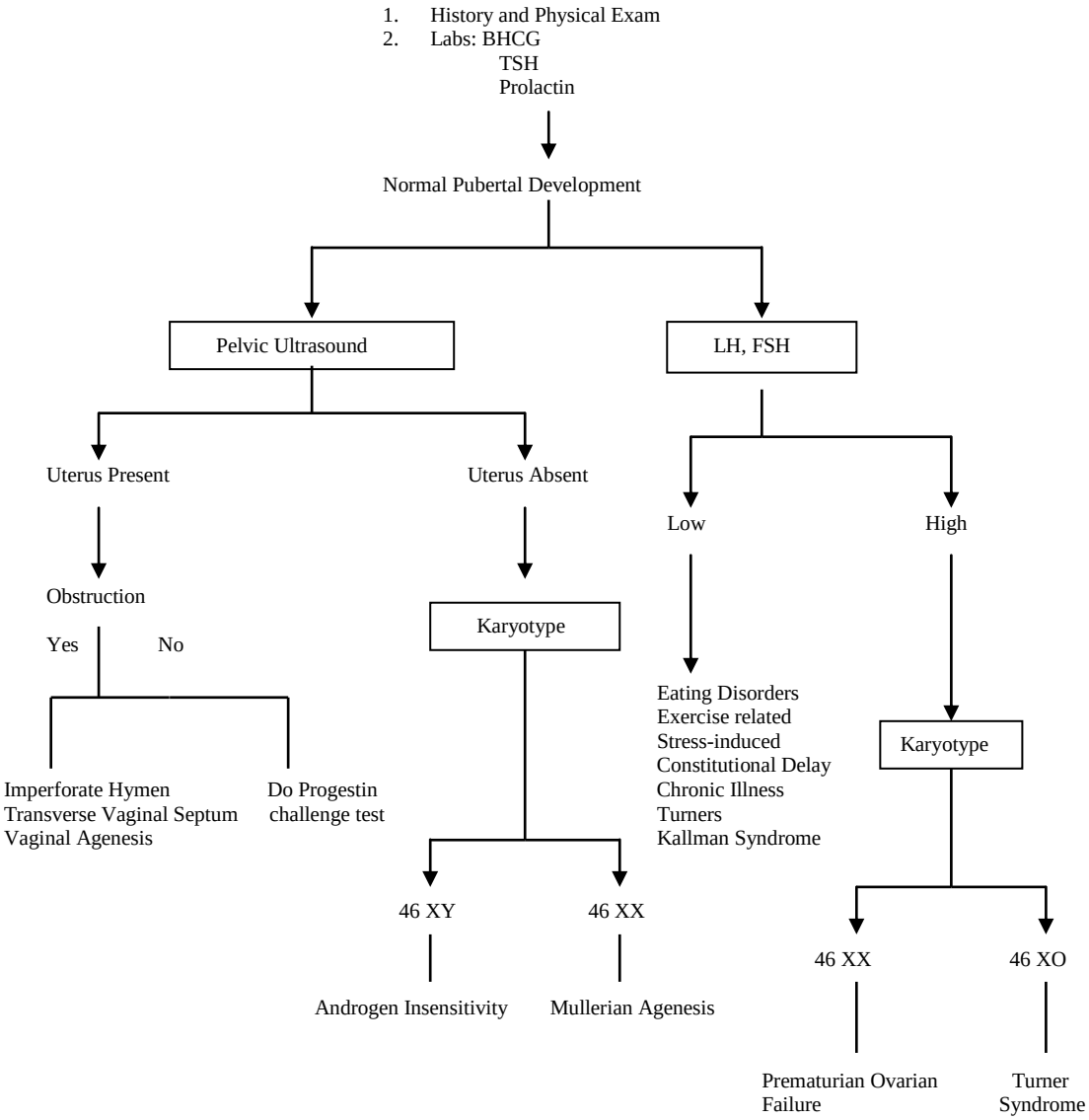
HISTORY
History of the development of secondary sex characteristics, sexual activity, evidence of psychological dysfunction or emotional stress, age of maternal menarche, family history of possible genetic anomalies or diabetes, the presence of galactorrhoea, symptoms of a thyroid disorder, weight loss or gain, hirsutism or menopausal symptoms should be sought.

EXAMINATION
Look at Tanner staging (any major discrepancy in Tanner staging of the breast and pubic hair development (e.g., Tanner V breast development in the absence of pubic hair or lack of breast development in the presence of adequate pubic hair) should arouse suspicion of a chromosomal abnormality such as androgen insensitivity (46,XY) or Turner syndrome), for stigmata of a chromosomal disorder, for signs of androgen excess (hirsutism, acne, alopecia), calculate BMI and perform an external genitalia examination.

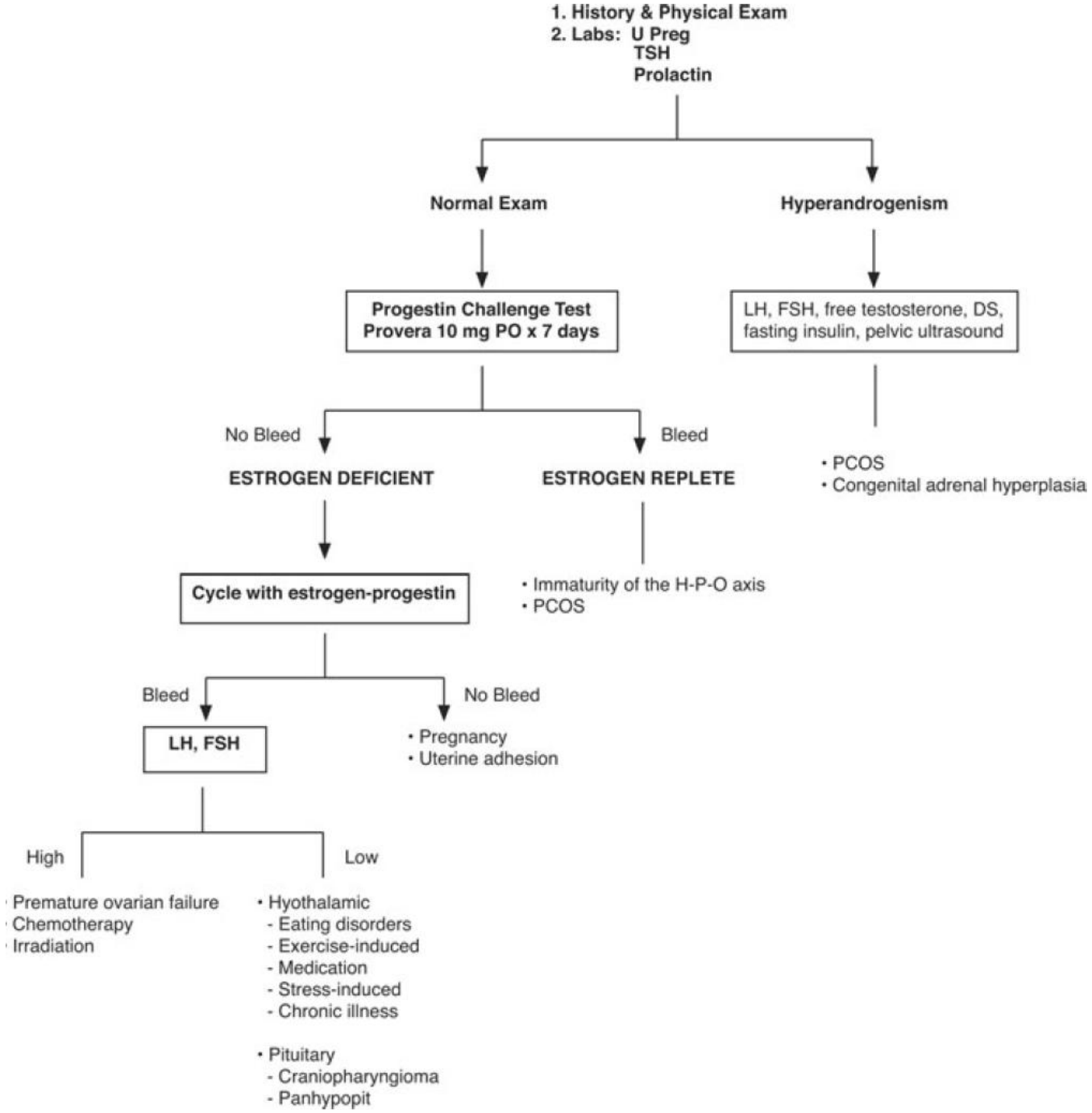
INVESTIGATIONS
These are divided into basic investigations which should be performed in all patients, and further investigations dictated by physical findings and history.
For all: FSH, LH, prolactin, TFT, pelvic US.
In hyperprolactinaemia a cranial MRI should be performed
If PCOS is suspected **(see PCOS fact sheet)** do testosterone, SHBG, free androgen index, androstenedione, and 17-OHP.

A progestogen challenge test is a means of evaluating the level of endogenous oestrogen and the competence of the outflow tract, and can be performed after the initial evaluation. A course of a progestational agent is administered (e.g. oral medroxyprogesterone acetate, 10 mg daily for 5 days). Within 2–7 days after completing the course, the patient should bleed. If she does, the presence of a functional outflow tract and a uterus lined by reactive endometrium sufficiently prepared by endogenous oestrogen is confirmed. Whilst the progestogen challenge test is very useful in determining hypo-oestrogenic states, there are rare conditions when withdrawal bleeding will not occur despite adequate levels of endogenous oestrogen. This can happen where the endometrium is decidualised in response to high levels of androgens (e.g. with polycystic ovaries), or high progesterone levels associated with a specific adrenal enzyme deficiency.

INVESTIGATION OF PRIMARY AMENORRHOEA



INVESTIGATION OF SECONDARY AMENORRHOEA



HYPOTHALAMIC AMENORRHOEA

Reduction in the frequency and possibly amplitude of GnRH pulses results in failure to stimulate sufficient synthesis and secretion of FSH and LH by the pituitary gonadotroph cells, leading to a degree of hypogonadal hypogonadism. Patients have low LH, FSH, and oestrogen levels with preserved LH and FSH responsiveness to GnRH.

The most common causes are excessive weight loss, exercise, chronic illness, stress and medications. A number of rare hypothalamic space occupying lesions can present with amenorrhoea. Other tumours causing pituitary stalk compression prevent delivery of GnRH to the pituitary, again causing amenorrhoea. Kallman's syndrome describes a rare (1: 50 000) congenital absence of the development of GnRH neurons between the hypothalamus and pituitary. The condition may be sporadic or an autosomal dominant or X-linked recessive disorder, and may be seen in association with anosmia. Failure of the GnRH message reaching the pituitary prevents initiation of FSH and LH synthesis, with primary amenorrhoea and failure of sexual development.

PITUITARY CONDITIONS

Hyperprolactinaemia

Usually a result of a prolactin secreting tumour (macro or micro adenoma) and accounts for approximately 15% of secondary amenorrhoea and may present as primary amenorrhoea. Circulating concentrations of prolactin may also be moderately increased in polycystic ovary syndrome, SLE, rheumatoid arthritis, chronic renal failure, and hypothyroidism and by stress, leading to possible diagnostic confusion. Cannulated venous samples can be collected during bed rest if stress related hyperprolactinaemia is suspected. Pathological hyperprolactinaemia will be associated with amenorrhoea and, in most but not all cases, galactorrhoea. Bitemporal hemianopia should always be sought at first presentation, since it may indicate the need for urgent imaging of the pituitary to exclude an expanding macroadenoma.

Some macroadenomas, and most microadenomas will respond to drug therapy with dopaminergic agents such as bromocriptine and cabergoline. Bromocriptine is associated with a high incidence of gastrointestinal side effects. The more recent introduction of cabergoline has reduced GI side effects and allowed a less frequent and more convenient dosing regime. Resistant cases and some macroadenomas will
require hypophysectomy.

Craniopharyngioma

These are epithelial tumours arising from the craniopharyngeal duct in the sellar or parasellar region and can have an associated LH and FSH deficiency.

OVARIAN DISORDERS

PCOS

PCOS is common and can result in amenorrhoea or oligomenorrhea. In many, improvement of symptoms can result from weight loss. (see PCOS fact sheet).

Gonadal Dysgenesis

Gonadal dysgenesis refers to a number of conditions in which gonadal development is abnormal, leading to streak gonads. Oestrogen levels are low and levels of LH and FSH are markedly elevated. The most common form is Turner syndrome (45,X karyotype), but other forms do exist, such as pure gonadal dysgenesis (where the karyotype is normal) and Swyer syndrome (XY gonadal dysgenesis).

Primary Ovarian Failure

The ovary contains a finite number of primordial follicles, which form the woman's 'lifetime store' of potential ovulations. The number of primordial follicles in this pool varies from individual to individual, and can be depleted by medical interventions including chemo and radiotherapy. There is frequently a family history in such patients, or there may be manifestations of auto-immune disease leading to auto-immune oophoritis. Rarer causes include galactosaemia (even in treated patients), mumps oophoritis, Trisomy 21, female fragile X carriers, sarcoidosis .and Turner's syndrome mosaicism leading to early secondary amenorrhoea (girls with nonmosaic Turner's syndrome generally exhibit primary amenorrhoea).

Cessation of periods will be preceded by several years of irregular or more frequent menses, with hot flushes, sweats and other hypo-oestrogenic symptoms.

DISORDERS OF THE UTERUS AND VAGINA

Mullerian Anomalies

Failure of canalisation of the Mullerian duct at any level will result in primary amenorrhoea. The presentation will depend upon the level at which the tract is blocked. An imperforate hymen presents in a teenage girl with normal sexual development. She may also have intermittent abdominal pain, difficulty with micturition and a palpable lower abdominal swelling. Examination will reveal a bulging, bluish membrane at the lower end of the vagina. The treatment involves surgical incision of the membrane. If there is obstruction of the vagina or cervix at a
higher level associated with a normal functioning uterus this will be compounded by the painful distension of haematocolpos, haematometra or haemoperitoneum. In all cases surgery should be performed to re-establish continuity of the genital tract. MRI gives an accurate diagnosis.

Mullerian Agenesis

Primary amenorrhoea with no apparent vagina occurs due to a lack of Mullerian development. These patients have an absence or hypoplasia of the vagina. The uterus may be absent or abnormal (eg only rudimentary bicornuate cords present).
Ovarian function, growth and development are normal. The peripheral karyotype is normal 46, XX female in contrast to testicular feminisation.

There is a high association with other anomalies and appropriate investigations should be performed. The syndrome, often referred to as Mayer–Rokitansky–Kuster–Hauser syndrome, is the second most common cause of primary amenorrhea. It has been estimated to have a prevalence varying from 1 in 4,000 to 5,000 female births. Renal tract abnormalities (ectopic kidney, renal agenesis, horseshoe kidney and abnormal collecting ducts) are present in 30% of cases and skeletal abnormalities (mostly involving the spine) in 12%.

Androgen Insensitivity (Testicular feminisation)

It has an X-linked recessive inheritance. A blind vaginal canal is found with an absent uterus. The gonadal sex is male and the patient has testes and an XY karyotype, but the patient is phenotypically female, but with absent or sparse pubic and axillary hair. Growth and development are normal. They are often taller than average, and whilst breasts are large, glandular tissue is sparse, nipples are small and areolae are pale. Labia minora are usually underdeveloped.

The underlying condition is an androgen receptor defect. Thus circulating androgens are normal or slightly elevated, but the critical steps in sexual differentiation which require androgens fail to take place and development is totally female. The uterus, tubes and upper vagina are absent because anti-Mullerian hormone is present.

The testes may be intra-abdominal, but are often in an inguinal hernia. There is no spermatogenesis. The incidence of malignancy is high and the gonads should be surgically removed. However, this is best left until after puberty because tumours do not occur prior to this and development is achieved with endogenous hormones. This is in contrast to other cases where gonads with a Y chromosome should be removed as soon as a diagnosis is made. Following removal, oestrogen replacement therapy should be commenced.

Imperforate Hymen

Imperforate hymen occurs in 1 in 1,000 women. It may be diagnosed in childhood, but may also be missed and may present in adolescence with cyclic abdominal pain and primary amenorrhea. The typical physical finding is a bulging, bluish hymen, behind which is a blood-filled mass in the distended vagina (hematocolpos).

Transverse Vaginal Septum

A complete transverse septum occurs in approximately 1 in 80,000 women and is due to incomplete fusion of the mullerian duct portion of the vagina and the urogenital sinus component. The thickness and placement of the septum may vary: lower vagina, middle vagina, or upper vagina. Eighty to 90% occur in the middle or upper vagina, and the external genital examination appears normal. Though a

perforation in the septum is often present, patients may still present with amenorrhea and hematocolpos. Additionally, other malformations of the urological tract or rectum may be associated.

THYROID DISORDERS

Hypothyroidism

Although hypermenorrhoea or oligomenorrhoea are the more prevalent menstrual disorders, amenorrhea can also be seen and is thought to be due to increased prolactin secondary to raised TSH.

Hyperthyroidism

Patients with hyperthyroidism have rates of menstrual irregularities ranging from 20% to 60%, with rates of amenorrhea reaching up to 20%.

ADRENAL CAUSES

Congenital Adrenal Hyperplasia

CAH refers to a group of autosomal recessive disorders of steroidogenesis.
A number of enzyme deficiencies have been found, but more than 90% of cases are caused by deficiency of 21-hydroxylase. The two other major enzyme deficiencies are deficiencies of 11-beta-hydroxylase and 3-beta-hydroxysteroid dehydrogenase.
There are two major clinical forms of congenital adrenal hyperplasia, depending on whether the enzyme deficiency is complete or partial—the classic form and the nonclassic form. The classic form usually presents in infancy with salt wasting or ambiguous genitalia. It occurs in approximately one in 16,000 births. The nonclassic form is one of the most frequently seen autosomal genetic disorders and occurs in approximately 0.2% of the general population. This nonclassic form of congenital adrenal hyperplasia usually presents in childhood and is characterized by premature pubarche and in adolescence by hirsutism or amenorrhoea.

Cushing Syndrome

Cushing syndrome is caused by high circulating levels of cortisol. In adolescents, Cushing syndrome is most frequently caused by iatrogenic exogenous administration of corticosteroids. Other causes include hypersecretion of corticotropin by a microadenoma of the anterior pituitary (Cushing Disease); secretion of corticotropin by an adrenal tumour, or, occasionally, ectopic production of corticotropin by a nonpituitary tumour such as carcinoma of the lung.
The clinical findings are usually self-evident. Oligomenorrhoea and amenorrhea may be part of the clinical picture. The pathophysiology is direct suppression of the HPO axis.

REFERENCES

Golden NH and Carlson. JL; The Pathophysiology of Amenorrhoea in the Adolescent. Ann. N.Y. Acad. Sci. 1135: 163–178 (2008)

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