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Female hypogonadism: evaluation of the hypothalamic–pituitary–ovarian axis

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Abstract Female hypogonadism refers to deficient or abnormal function of the hypothalamic–pituitary–ovarian axis that clinically presents with menstrual cycle disturbances. Female hypogonadism can be due to a congenital or acquired cause, and the defect can be at the level of the hypothalamus, pituitary or ovary. A careful history, physical exam and selected laboratory testing can often determine the locus of the defect and whether it results from a structural or hormonal problem**.** Laboratory testing generally relies on basal hormone levels; however, timing of blood sampling in relation to menses is important to interpretation of the data.

Keywords Female hypogonadism · Amenorrhea · Hypopituitarism · Ovarian reserve testing

Abbreviations

FSH	Follicle stimulating hormone
LH	Luteinizing hormone
GnRH	Gonadotropin-releasing hormone
POF	Premature ovarian failure
PCOS	Polycystic ovarian syndrome
CAH	Congenital adrenal hyperplasia
DHEA-S	Dehydroepiandrosterone-sulfate
GPR54	G protein couple receptor 54
IHH	Idiopathic hypogonadotrophic hypogondadism
E2	Estradiol
HPO axis	Hypothalamic–pituitary–ovarian axis

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Definition of female hypogonadism

Female hypogonadism refers to deficient or abnormal function of the hypothalamic–pituitary–ovarian axis resulting in estrogen deficiency and menstrual cycle disturbances. Primary hypogonadism presents as a failure to undergo pubertal development with lack of breast development, other secondary sex characteristics and growth spurt. The vagina remains poorly estrogenized and deficient in cervical mucus [1]. In post-pubertal females, hypogonadism typically manifests as dysfunctional uterine bleeding or amenorrhea, defined as absence of menses. A careful history, physical exam and selected laboratory testing can often determine the locus of the defect, whether at the level of the hypothalamus, pituitary, or ovary. Such an evaluation will determine whether the disorder results from a structural, hormonal or combinatorial defect. This review will outline the differential diagnosis and evaluative testing approach to female hypogonadism.

Differential diagnosis of female hypogonadism: locus of the defect

Amenorrhea commonly results from a disorder of the ovary, a central defect related to pituitary or hypothalamic dysfunction. Primary ovarian disorders present with absent or irregular menses. Hormonal evaluation reveals low estradiol levels (below normative follicular phase ranges

for the assay employed) associated with elevated pituitary gonadotropins (follicle stimulating hormone (FSH) and luteinizing hormone (LH)) levels. Central hypothalamic or pituitary disorders may result from altered GnRH or gonadotropin secretion, and patients usually have inappropriately normal or low LH and FSH together with low estradiol levels. In each case, patients may present with oligo- or amenorrhea and symptoms and signs of estrogen deficiency (i.e. hot flashes, dyspareunia, or sleep disturbances).

Reproductive organ dysfunction

Amenorrhea may be caused by a primary problem of the female reproductive organs. A congenital absence of the uterus, cervix or vagina can cause amenorrhea with or without signs of estrogen deficiency. Scarring and fibrosis of the endometrial lining, after endometrial ablation or in Asherman's syndrome, following a dilatation and curettage, may also lead to secondary amenorrhea with normal estrogen levels [2].

Ovarian failure can be due to a congenital disorder presenting with failure of normal sexual development, or as an acquired ovarian defect resulting in estrogen deficiency. When the locus of the defect lies within the ovary, the FSH and LH levels are elevated, in response to the decline in sex hormone production from the ovary. Girls who fail to undergo sexual maturation due to an ovarian defect often have gonadal dysgenesis (Turner's Syndrome, XO). Patients with premature ovarian failure (POF) defined as ovarian failure prior to age 40, often present with oligo- or amenorrhea, elevated FSH and low estrogen levels with symptoms of hot flashes and vaginal dryness. Causes for POF include genetic, autoimmune, post-surgical and infectious [3]. Genetic etiologies that present post-pubertally include mosaic chromosomal disorders such as X0/XX. Autoimmune ovarian failure is common, occurring in 10–30% of cases [3]. There is often an association between and risk of other autoimmune disease such as autoimmune thyroid disease, pernicious anemia and/or Addison's disease [4]. Measurement of specific ovarian antibodies has not yet been clinically useful [3]. POF can also be caused by toxins, such as chemotherapy or radiotherapy or rarely, viral infections such as rubella [3]. Surgical menopause leads to an abrupt onset of estrogen deficiency.

In contrast to POF, other ovarian disorders can present with amenorrhea or oligomenorrhea in the presence of clinical and/or biochemical hyperandrogenism and variable patterns of gonadotropins. In these cases, the estradiol levels are usually normal. Hyperandrogenic anovulation may result from a variety of disorders including: polycystic ovarian syndrome (PCOS), ovarian tumors and obesity-induced hyperandrogenic anovulation. In addition, enzyme defects in the adrenal hormone synthesis resulting in congenital adrenal hyperplasia, or hyperfunctioning adrenal tumors can also present with anovulation in the presence of elevated androgens. Timed measurement of LH, FSH estradiol, testosterone, DHEA sulfate and 17 hydroxyprogesterone levels are useful to obtain for clarifying the correct diagnosis in the appropriate clinical setting.

Pituitary disorders that result in amenorrhea

Both genetic and acquired disorders cause hypopituitarism including: molecular mutations that resulting in one or more congenital pituitary hormone defects, pituitary and hypothalamic tumors, infiltrative or inflammatory disease and a recently appreciated association of pituitary dysfunction with traumatic brain injury. The incidence of hypopituitarism is 12–42 new cases per million per year, whereas the prevalence of pituitary insufficiency is 300–455 cases per million [5]. Patients with pituitary disease present with the typical signs and symptoms of hypogonadism in addition to the symptoms and signs of other associated pituitary hormonal insufficiencies. Gonadotropins (FSH and LH) and sex steroid hormone (estrogen and progesterone) levels are low. Other pituitary hormone deficiencies require dynamic testing (as outlined in other reviews in this series) for their diagnosis; however, testing for pituitary gonadotropin deficiency relies mainly on history, physical exam and baseline laboratory measurement of FSH, LH and estradiol.

Among the rare patients with genetic defects that result in hypopituitarism include those with mutations in the Pit-1 or Pou1F1 gene. Affected patients have deficiencies in GH, PRL, and TSH [6]. Mutations in other transcription factors important for pituitary development or differentiation have been identified that can lead to hypogonadism, such as defects in Prop1, Hesx1, and LHX3 [7]. Very rarely, mutations in the FSHβ and LHβ can lead to amenorrhea [8, 9].

Pituitary tumors cause symptoms related to mass effect, excess hormone secretion or hormone deficit. When pituitary hormone insufficiency occurs due to tumor compression of normal pituitary hormone production, growth hormone is often the first hormone to be deficient, then LH and FSH and later TSH and ACTH [10]. Most pituitary tumors are benign adenomas, but other lesions that reside in the hypothalamic/pituitary junction such as craniopharyngioma, Rathke's cleft cyst or rarely gliomas, meningiomas or chordomas may result in menstrual dysfunction [10]. Infrequently, metastasis from other tumors such as breast, lung or renal can result in hypogonadism associated with other hormonal deficiencies [11]. Metastasis will more often be associated with posterior hormone abnormalities such as diabetes insipidus, whereas primary

pituitary tumors will usually have only anterior hormone dysfunction [12].

Infiltration, inflammatory or destructive lesions in the pituitary may also lead to hypogonadotropic hypogonadism in females. Hemachromotosis, due to selective iron deposition in the gonadotropes is detected less frequently in women before menopause due to regular menstrual bleeding that protects against the iron overload and destruction of gonadotroph function until later in life [13]. Other infiltrative disorders of the pituitary include granulomatous diseases, such as sarcoidosis, tuberculosis and histiocytosis X [12]. Lymphocytic hypophysitis is due to a lymphocytic infiltration of the pituitary, usually present in patients during pregnancy or post partum, although it can occur at other times [14]. It is associated with other pituitary hormonal dysfunction, and the timing of the loss of gonadotrope function is later, with ACTH and TSH affected earlier, than generally observed in pituitary adenomas [14]. Some have postulated an autoimmune etiology, as patients frequently have other autoimmune diseases [12].

More recently traumatic brain injury is being recognized as a cause of hypopituitarism. Single or multiple pituitary deficits have been documented in up to two-thirds of affected patients with TB [15]. The HPO and growth hormone axes are the most commonly affected. At present there are no tests to discriminate between those patients who will have long term hypothalamic pituitary dysfunction and those with altered function due to the acute illness. Studies are still lacking to date as to the benefits of potential hormone replacement with growth hormone or sex steroid hormone in the acute period [15].

Hypothalamic dysfunction resulting in hypogonadism

Congenital disorders of the hypothalamic GnRH production cause failure of normal female reproductive development. Although more commonly seen in males, idiopathic hypogonadotrophic hypogonadism (IHH) also occurs in females. When presenting with anosmia, this is known as Kallmann Syndrome.

X-linked Kallmann Syndrome is caused by a mutation in Kal-1 which results in an abnormal anosmin protein, thought to be important in the scaffolding for GnRH neurons to migrate upon, during early development from the olfactory placode to the hypothalamus and causes the disorder in men [1]. There has been an explosion of new genes identified that are important for the normal development of the GnRH neuronal population and that, when mutated, result in IHH in women and men. Recently genetic mutations have been discovered that can lead to hypogonadotrophic hypogonadism with and without anosmia, such as FGFR1 and homozygous PROK2 and PROKR2 mutations [16–18]. Other defects have been described that are related to abnormal GnRH secretion from postmigratory GnRH neurons, such as mutations in the G protein couple receptor 54 (GPR54) leading to IHH [19, 20].

Acquired hypothalamic causes of central hypogonadism result from structural or functional defects that interfere with GnRH secretion. The former includes tumors such as craniopharyngioma, Rathke's cleft cyst and other less common CNS lesions. Radiation therapy can also have effects on GnRH secretion, as the hypothalamic releasing factors neurons are more radiosensitive than pituitary cells [21].

Hypothalamic amenorrhea or functional amenorrhea is a diagnosis of exclusion, due to an acquired defect in GnRH secretion [22]. Women with hypothalamic amenorrhea present clinically with oligo or amenorrhea together with low estradiol levels and low or inappropriately normal FSH and LH levels, abnormal weight loss, low body weight, and psychological or physical stressors can lead to deficient GnRH and gonadotropin secretion, resultant anovulation, estrogen deficiency, and oligo or amenorrhea [22].

Central inhibition by other hormonal dysfunction

In addition to direct effects of stress or nutritional deprivation to cause acquired hypothalamic amenorrhea, dysfunction of other hormones, such as prolactin, cortisol and thyroid hormone can have secondary effects on GnRH and LH to cause hypogonadism.

Prolactin

In women, tumors that secrete prolactin often present with amenorrhea well before any evidence of mass effect. The pathogenesis is a direct effect of PRL on episodic GnRH secretion, either by an induction of dopamine turnover inhibiting GnRH or increased endogenous opiate tone [7]. Patients have low or normal FSH and LH and low estradiol levels. Hyperprolactemia from non-pituitary causes such as medications has the same effect. Treatment of the elevated prolactin results in return of normal function of the HPO axis. If the medication cannot be discontinued, sex hormone replacement is recommended.

Cortisol

Hypercortisolism from stress, excessive exercise or endogenous or exogenous glucocorticoids also represses GnRH secretion and can result in hypogonadotropic hypogonadism. Elevated cortisol levels have been observed in amenorrheic runners [1]. Cortisol has direct effects on GnRH-induced LH pulse frequency. Women that present with Cushing's syndrome from a tumor causing hypercortisolism, usually have irregular menstrual cycles. As

they often have acne and hirsutism, it is important to keep Cushing's on the differential for women who present with these symptoms.

Thyroid

Both hypo- and hyperthyroidism can have effects on the HPO axis, and menstrual irregularities are more common in this population when compared with healthy controls. Patients with hypothyroidism may present with heavy or irregular menses, as there are also direct effects on clotting factors influencing bleeding patterns [23]. Patients with hyperthyroidism will have shortened anovulatory cycles that can result in infertility. GnRH secretion patterns and sex hormone binding globulin levels are also directly affected by thyroid disorders, but random LH, FSH and E2 levels are often non diagnostic [23]. An elevated TSH with or without decreased FreeT4 will diagnose this condition, and thyroid hormone replacement will generally restore cyclical menses. There is also an association of autoimmune thyroid disease with infertility, but the effects of treatment with thyroid hormone on pregnancy outcomes is still being explored [23].

Evaluation of a woman with amenorrhea

History and physical

A detailed history and physical exam can often reveal the cause of hypogonadism. Questions should include birth and developmental history, timing and progression of puberty and growth curve, family history, onset of menarche and pattern of cycles, medication use as well as drug and alcohol use, weight changes, stress levels, and diet and exercise patterns. Clinicians should ask about the presence of other pituitary hormone dysfunction with questions about galactorrhea, headaches and symptoms of cortisol excess. Development of acne, hirsutism or concerns of virilization should be discussed.

A physical exam is performed to assess pubertal stage and development of secondary sex characteristic. Cranial nerve abnormalities and visual field changes should be assessed. A pelvic exam is performed to look for clitoromegaly and adequacy of estrogenization as well as palpation of the uterus and ovaries for any abnormalities.

Laboratory testing

Timing of hormonal testing

Optimally, hormone testing should be performed in the early follicular phase of the cycle (day 1–5 after onset of menses), if the patient is having menses (Figs. 1 and 2 describe the details of evaluating the patient with primary and secondary amenorrhea, respectively). Of course, pregnancy must be ruled out in any woman presenting with amenorrhea. If the patient is not having regular menses, but has sufficient estrogen, a 5–7 day course of progesterone (Provera 5–10 mg or Prometrium 100 mg bid) can be administered to induce a withdrawal bleed. Blood sampling then should be obtained within 1–5 days of the onset of menses. Measurement of blood hormone levels at random times in oligomenorrheic women or at various times within the normal cycle must be interpreted within the context of the changes that occur across the menstrual cycle. For example, FSH and LH levels drawn at the time of ovulation are often elevated as in menopause. However, the estradiol levels differ markedly. An elevated LH to FSH ratio is a normal finding in the luteal phase, but an abnormal finding in the follicular phase, often seen in patients with PCOS.

Gonadotropin measurements

Gonadotropin (FSH and LH) levels should be optimally obtained in early morning on day 1–5 after the onset of menstrual bleeding. In normal women, FSH and LH levels will be similar at this time of the cycle. Women with GnRH deficiency, hypothalamic amenorrhea and/or pituitary

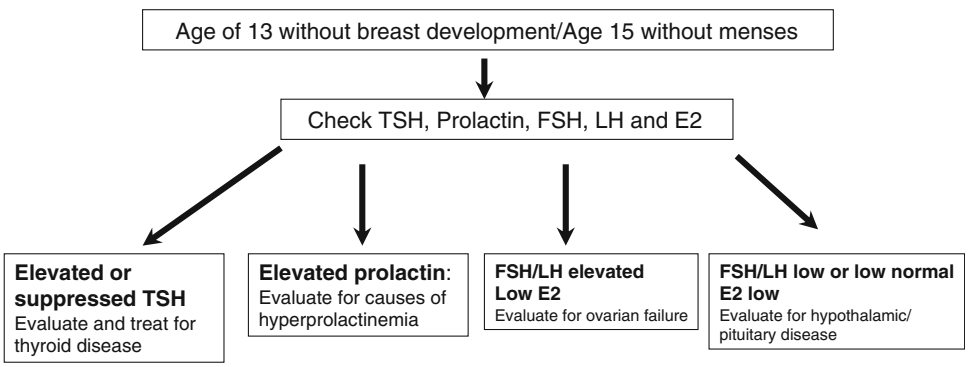

Fig. 1 Evaluation of delayed puberty/primary amenorrhea

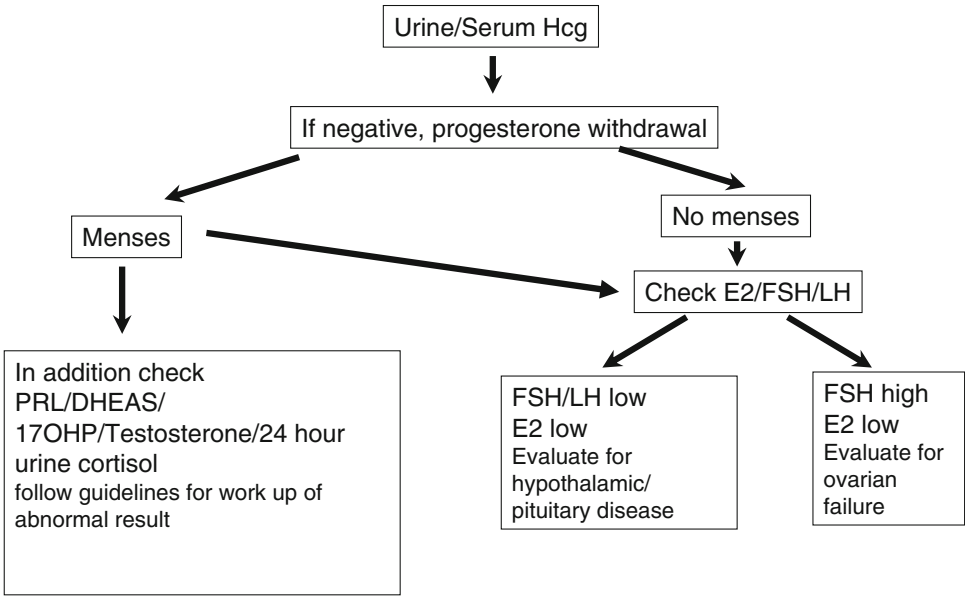

Fig. 2 Evaluation of secondary amenorrhea

disorders have low or inappropriately normal FSH and LH levels associated with low estradiol levels. An increased ratio of LH: FSH at this time is often observed in patients with PCOS. Elevated FSH, with or without LH and low estradiol levels, is suggestive of primary ovarian failure.

In evaluating primary amenorrhea, both delayed puberty and GnRH deficiency can both present with low FSH and LH [24]. Generally, the passage of time is the only way to distinguish between these two processes. The GnRH stimulation test, which can be helpful for the diagnosis of central precocious puberty, cannot reliably distinguish between acquired or genetic causes, or a hypothalamic compared to a pituitary locus of the defect.

Sex steroids

Estradiol is the major sex hormone measured to correlate with ovarian function. Estradiol levels vary markedly across pubertal development and then across the menstrual cycle. Thus, normative data is necessary to interpret the values. Ovarian failure is suggested by low early follicular phase levels together with an elevated FSH. Progesterone may be helpful as a marker of ovulation if measured during the mid luteal phase of the cycle. An elevated progesterone level around Day 20–24 indicates ovulation has occurred. A testosterone level is often measured to document hyperandrogenism in women with symptoms of acne, hirsutism or frank virilization. Markedly elevated testosterone levels are concerning for, but not diagnostic of, hormonally active ovarian or rarely adrenal tumors.

Although there is no one test that can predict success rate with assisted reproduction techniques, the goal is to identify women with declining ovarian function and low numbers of viable follicles to identify predictors of success and failure in IVF. Commonly used laboratory tests of ovarian reserve include early follicular FSH, basal estradiol, Inhibin A and B levels, and dynamic testing with Clomiphene citrate or gonadotropin analogs with measurement of ovarian response.

Since FSH with rises with menopause, early follicular FSH levels are frequently used as a masker of ovarian reserve. In a recent study of 3,519 women in a fertility clinic early follicular FSH levels of greater than 8 mIU/l were associated with a decreased probability of ongoing pregnancy [25]. The clomiphene citrate challenge test was initially described in 1987 by Navot et al. [26] with clomiphene 50 mg/day administered on days 5–9 of the menstrual cycle. FSH levels were obtained before and after administration (day 2–3 and then again day 9–11). An elevated FSH level correlated with diminished ovarian reserve [26]. Since clomiphene acts as an estrogen antagonist, gonadotropin levels increase during treatment. However, after cessation of the medication, levels should decrease, and thus, a continued elevation is thought to be a marker of diminished reserve [27]. In a more recent study, basal and day 10 FSH levels predicted success with a specificity of 100 for ongoing pregnancy with a result above 18IU/L, and the sensitivity was 25% [28]. Since the results often incorporate the day 3 levels, it has been debated whether the challenge tests add much additional information to early follicular phase FSH level alone [27].

A new assay under investigation for its role in detecting early ovarian failure is anti Mullerian hormone (AMH) or Mullerian inhibiting substance (MIS). MIS is normally produced by ovarian granulosa cells, diminishes with age and is absent with ovarian failure at natural menopause. A

potential advantage is that a MIS level can be measured at any point during the menstrual cycle. Recently this test was compared to the clomiphene challenge test and had a sensitivity of 76% and specificity of 86% which were both lower than the clomiphene citrate challenge test [28]. Thus, although it may have some clinical utility in predicting response to gonadotropin therapy, at this time, it is not recommended for routine screening of ovarian reserve.

Other pituitary hormones

TSH should be done in all women with amenorrhea since both hypo and hyperthyroidism can lead to menstrual irregularities as mentioned earlier. A free T4 is needed if there is suspicion of pituitary disease. If the thyrotrophs are dysfunctional, the TSH will not be accurate to diagnose central hypothyroidism. Measurement of thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulin) can be used to screen for evidence of autoimmune thyroid disease. Prolactin should be tested in all women with amenorrhea, since, as mentioned above, prolactin directly inhibits GnRH-induced gonadotropin secretion to cause amenorrhea. Other pituitary testing should be performed based on the level of clinical suspicion for a pituitary or hypothalamic cause of amenorrhea.

Adrenal hormones

As discussed above, 24 h measurement of urine free cortisol should be ordered to evaluate for hypercortisolism that may induce menstrual cycle dysfunction. Conversely, a random serum cortisol of <3 μg/dL can diagnose adrenal insufficiency; however, a patient may have abnormal adrenal function with random cortisol levels within the normal range. An ACTH stimulation test as described in more detailed in another article in this series is employed to diagnose adrenal insufficiency.

An early follicular17 hydroxyprogesterone level may be obtained to evaluate for non-classical CAH. Some experts believe that this is widely under-diagnosed in the work up of women with irregular menses, acne and hirsutism [29]. The diagnosis can be made with a ACTH stimulation test for 17 hydroxyprogesterone with measurements for baseline and 30 or 60 min post cosyntropin infusion. Patients with non classical CAH have levels between 1,000 and 10,000 ng/dl [29].

DHEA-Sulfate, an adrenal androgen is measured instead of DHEA as an index of adrenal androgen production, as its half-life is longer and shows less variability throughout the day. Marked elevation in DHEA-S should prompt a search for a secretory adrenal tumor. Mild elevations in DHEA-S levels are often observed in women with PCOS.

Genetic testing

Karyotyping may be used to evaluate for gonadal dysgenesis or Turner's syndrome. This test is frequently employed as a work up for primary amenorrhea, but also when primary ovarian failure is diagnosed in women in early 1920s with no clear etiology.

Imaging

Pelvic ultrasound is usually done during the early follicular phase of the menstrual cycle to evaluate the anatomy, the endometrial stripe and ovarian follicles. The revised consensus on the diagnosis of PCOS in 2003 now include ultrasound criteria, however, this are still considered controversial as many women with normal menses and no clinical features of PCOS can have an ultrasound appearance of ovaries consistent with PCOS [30].

MRI of the pituitary is indicated if evidence of hypofunction or over-secretion of any pituitary hormones is found. Since the rates of incidental pituitary tumors are high in the general population, biochemical evidence of pituitary dysfunction must be present before imaging is obtained [31].

Conclusions

There are a variety of causes of female hypogonadism, with defects that can be congenital or acquired and can result from defects at the level of the ovary, pituitary or hypothalamus. A careful history and exam, together with selected basal and, in some cases, dynamic testing will usually determine the cause and direct treatment appropriately.

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