Treatment of Amenorrhea

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Abstract

There are many different causes for amenorrhea. Having a systematic way to think about and work up the causes will help you diagnose the etiology. Causes of amenorrhea can be broken down into structural and endocrine categories. Structural causes are either due to congenital abnormalities such as those seen with primary amenorrhea or acquired, including cervical stenosis or Asherman syndrome. Endocrine causes are associated with dysfunction of the ovary, pituitary, or hypothalamus. Dysfunction of the ovary can be either due to chronic anovulation from polycystic ovary syndrome, obesity, thyroid dysfunction, or hyperprolactinemia. The other major cause of ovarian dysfunction is due to primary ovarian insufficiency/diminished ovarian reserve. Pituitary disorders can be endocrine or structural, with aberrant production of hormones or mass effect interrupting the normal hypothalamic-pituitary-ovarian (HPO) axis. Hypothalamic etiologies stem from congenital deficiencies such as Kallmann syndrome or dysfunction/failure from weight loss, heavy exercise, or emotional/psychological stress. The first visit with a patient should include a thorough history and physical exam. Initial labs such as urine HCG, TSH, prolactin, FSH, and estradiol are important for screening for the most common etiologies of amenorrhea. In addition, these also are the first step in assessing the status of the HPO axis in order to discover the underlying reason for amenorrhea.

Keywords

Amenorrhea • Anovulation • Primary ovarian insufficiency • PCOS • Müllerian anomaly

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1 Introduction

Amenorrhea, the absence of menses, is normal prior to menarche, after menopause, and during pregnancy and lactation (ASRM 2004). In the USA, the average age for the onset of menarche is approximately 12.3 years old, while the average age of menopause is 51.4 years old (Anderson et al. 2005; Kato et al. 1998). The absence of menses prior to or after these parameters must be investigated. Amenorrhea can be physiologic or pathologic, and its etiologies are best classified into endocrine or structural categories. The prevalence of amenorrhea is around 3–4% (Pettersson et al. 1973).

2 Primary Amenorrhea

Primary amenorrhea is defined by the following:

1. Absence of menses by age 15 regardless of the presence of normal secondary sexual characteristics (or up to 5 years after breast development if it occurs prior to age 10)
2. Failure to start breast development and menses by 13 years old (Table 1)

3 Secondary Amenorrhea

Secondary amenorrhea is defined by:

The absence of irregular menses for 6 month or the length of time equivalent to three prior menstrual cycles (i.e., 84 days for a 28-day cycle) (Table 2)

Table 1 Etiologies of primary amenorrhea

Chromosomal abnormalities	43%
Müllerian agenesis	15%
Constitutional delay	14%
Polycystic ovary syndrome	7%
GnRH deficiency	5%
Transverse vaginal septum	3%
Anorexia, weight loss, stress	2%
Pituitary disease	2%
Others: imperforate hymen, androgen insensitivity syndrome, pituitary tumor, congenital adrenal hyperplasia, hypothyroidism, CNS defect, Cushing's disease, craniopharyngioma	9% (~1% each)

An evaluation and workup may be warranted even if the above criteria are not met, such as evidence of not meeting pubertal milestones or having stigmata of disorders of sexual development.

The etiologies for amenorrhea can be broken down into different categories, which may guide provider workup. The World Health Organization (WHO) categorizes etiologies of amenorrhea into different groups (Table 3).

There are overlapping causes for primary and secondary amenorrhea; thus the general causes are broken down into the following:

1. Anatomic:
   (a) Genital outflow tract disorders
   (b) Congenital anomalies of the uterus
2. Endocrine: ovarian disorders
3. Endocrine: anterior pituitary disorders
4. Central nervous system disorders

4 History

The history taking should be thorough and tailored to the patient's presentation. Inquiring about pubertal milestones and a family history of delayed puberty is indicated in a girl or woman who presents with primary amenorrhea, has stigmata for Turner disease, or has not fully developed secondary sexual characteristics.

Clinicians should take an accurate account of patient's personal and/or childhood health as well as current physical, emotional, or psychological stressors. One should assess for lifestyle habits such as diet, exercise, and changes in weight. It is important to elicit symptoms of galactorrhea, virilization (balding, changes in dark hair growth, acne, or deepening of voice), or changes associated with thyroid dysfunction such as heat or cold intolerance, changes in bowel movements, and energy level. It is also necessary to inquire about any symptoms of brain mass such as headaches or visual changes. Lastly, but still importantly, a thorough medication list should be recorded.

Table 2 Etiologies of secondary amenorrhea

Ovarian dysfunction	40%
PCOS	30%
Primary ovarian insufficiency	10%
Hypothalamic amenorrhea	35%
Pituitary dysfunction	17%
Uterine adhesions	7%
Others: congenital adrenal hyperplasia, ovarian or adrenal tumor, hypothyroidism	1%

5 Physical Exam

Physical exam should include vital signs and body mass index. Providers should evaluate and document normal breast development, signs of virilization (hirsutism, acne), skin examination (evaluating for striae, pigmentation, vitiligo), and presence of stigmata of Turner syndrome (low hairline, webbed neck, shield chest, widely spaced nipple short stature).

6 Genitourinary Exam

The inguinal region should be palpated for any masses, and a careful genital exam should be performed, taking note of clitoral size; pubic hair tanner stage; the hymen (presence or absence); depth of the vagina; presence of the cervix, uterus,

Table 3 WHO classification for amenorrhea

Characteristic	Group I	Group II	Group III=
Estrogen	Low	Normal	Low
FSH	Low/normal	Normal	High
Prolactin	Normal	Normal	
Hypothalamus/ pituitary	No pathology		
Example	Hypogonadotropic hypogonadism	Polycystic ovary syndrome (PCOS)	Primary ovarian insufficiency (POI)

and ovaries; and any abnormalities. If a genital exam is not feasible (particularly in younger girls), then an abdominal ultrasound may be ordered to assess for the presence or absence of the uterus.

6.1 Normal Pelvic Anatomy

A patent vagina, visible cervix, and palpable uterus exclude congenital outflow abnormalities. This, however, does not exclude cervical stenosis or uterine synechiae (scarring). The latter two may be evaluated with sonohysterography or a hysteroscopy if indicated by the patient's history.

6.2 Abnormal Pelvic Anatomy

The embryology of the female genital tract involves:

1. Medial migration and midline fusion of the paramesonephric and müllerian ducts, which ultimately form the uterus, cervix, and upper vagina.
2. Urogenital sinus invaginates to form the lower vagina and introitus.

Abnormalities during formation of these structures can lead to imperforate hymen, transverse vaginal septum, and cervical atresia. Pelvic ultrasound can be ordered to better evaluate the genital tract and presence or absence of any organs.

7 Ovarian Function

If history and physical exam do not arouse suspicion for a genital tract abnormality, a hormonal workup must be initiated. The most common etiology for amenorrhea is ovarian dysfunction. Disorders include chronic anovulation or oligo-ovulation secondary to thyroid dysfunction, hyperprolactinemia, polycystic ovary syndrome, obesity, or primary ovarian insufficiency.

8 Laboratory Workup

The initial workup for someone with amenorrhea includes a urine human chorionic gonadotropin (hCG) to exclude pregnancy.

> Pregnancy is the most common etiology for secondary amenorrhea. Other laboratories to include in the workup are thyroid-stimulating hormone (TSH), prolactin (PRL), follicle-stimulating hormone (FSH), and estradiol (E2). The TSH and PRL are to evaluate for thyroid dysfunction and hyperprolactinemia.

The FSH and estradiol are to evaluate the state of the hypothalamic-pituitary-ovary axis. A cell blood count (CBC), chemistry panel, and a basic urinalysis can be ordered to exclude system disease.

8.1 Estrogen Measurement

Normal levels of estradiol are typically seen with anovulation. Low estradiol levels are seen in women with ovarian failure, hypothalamic dysfunction, or pituitary disorders. However, since estradiol levels normally fluctuate, a single normal or low level may not be sufficient to make a diagnosis. In addition, patients with primary ovarian insufficiency, pituitary dysfunction, or hypothalamic amenorrhea may regain intermittent ovarian function and sporadically ovulate and produce estradiol.

8.2 Gonadotropin Measurement

Routine evaluation of serum FSH in conjunction with estradiol levels in amenorrhea can be helpful in assessing ovarian dysfunction. High levels of FSH are typically associated with either ovarian insufficiency or follicular depletion (i.e., diminished ovarian reserve). Low levels of estradiol production prevent negative feedback on the hypothalamus and thus increase release of FSH from the pituitary to stimulate estradiol production. Exceptions to this are highly unlikely, but include mutations in the LH

Table 4 Expected gonadotropin and estradiol levels in different ovarian disorders

Ovarian functional status	Serum FSH	Serum LH	Serum estradiol
Normal:	5–20 IU/L	5–20 IU/L	>40 pg/mL
Normal			
Chronic anovulation			
Hypogonadotropic hypogonadism:	<5 IU/L	< 5 IU/L	<40 pg/mL
Prepuberty			
Hypothalamic dysfunction			
Pituitary dysfunction			
Hypergonadotropic hypogonadism:	>20 IU/L	> 40 IU/L	<40 pg/mL
Primary ovarian insufficiency			
Diminished ovarian reserve			
Surgical menopause			

or FSH receptor, ectopic production of FSH by a tumor, or an enzyme deficiency leading to low or undetectable estradiol levels (aromatase or 17-alpha-hydroxylase). Given that LH production is similar to FSH, levels are not typically as helpful in assessing amenorrhea.

A low or normal FSH can signify a few different things. FSH can be low in the setting of functional ovarian follicles, anovulation, pituitary disease, or hypothalamic dysfunction. Above is a table with reference ranges and possible diagnoses (Table 4).

9 Endometrial Stripe on Ultrasound

Transvaginal ultrasound can be used to assess endometrial thickness, which reflects endometrial proliferation and may provide information regarding estrogen levels. A woman that is hypoestrogenic is more likely to have a thin endometrial stripe. In any woman with a prolonged history of anovulation, endometrial biopsy to exclude hyperplasia should be considered.

10 Progesterone Challenge

In addition to the initial workup with TSH and prolactin, a progesterone challenge can be performed. If a woman has sufficient circulating estrogen to build up her endometrium, the progestin challenge should induce menses. However, it is important to note that the sensitivity and specificity for assessing estrogen status with this test are low (Nelson 2009).

10.1 Positive Test

Positive tests are defined by bleeding 2–7 days after completing the progestin regimen. Of note, if a patient has a delay in her bleeding, approximately 14 days after the progesterone challenge, then this medication has either been an inadequate dose of progestin, there is an outflow obstruction, or less likely, the medication has triggered ovulation.

A positive test indicates normal circulating estrogen and anovulation (and confirms a patent outflow tract). Further evaluation is not necessary as long as the patient has a normal TSH and prolactin and the absence of galactorrhea.

In those with prolonged periods of anovulation, endometrial biopsy should be performed to exclude endometrial hyperplasia. Patients diagnosed with anovulation are recommended to have regular cyclic exposure to progestin therapy (or combined estrogen-progestin combination) to prevent constant estrogenic stimulation of the endometrium, which can lead to hyperplasia and malignancy over time.

Regimens for medical management for anovulatory patients include cyclic medroxyprogesterone 10–40 mg po daily 10–14 days every month. A combined estrogen-progestin contraceptive such as oral contraceptive pills, vaginal ring, or transdermal patch is also an option. Levonorgestrel IUD is an option for patients desiring a long-term contraception, requiring minimal effort after insertion. Etonogestrel implant and Depo-Provera injection are also additional options for contraception and progestin exposure.

10.2 Negative Test

If a patient only has a small amount of spotting after the progestin challenge, there is endogenous estrogen production, but this may indicate marginal levels and warrants further monitoring and possible workup.

> Complete absence of progestin withdrawal bleed indicates two possible disorders – Asherman syndrome or absence of estrogenization of the endometrium to induce proliferation.

Further workup is based on history – evaluation of the endometrial cavity for suspected Asherman syndrome and gonadotropin and karyotype workup for possible POI.

11 Normal Gonadotropin Levels

11.1 Ovarian Disorders Related to Chronic Anovulation

Normal serum FSH and estradiol are suggestive of chronic anovulation. The most common etiologies for this include polycystic ovary syndrome (PCOS), obesity, excessive exercise, ovarian aging, thyroid dysfunction, and hyperprolactinemia. Typically, anovulation secondary to excessive stress, whether it is emotional, physical, or nutritional, is a diagnosis of exclusion. However, a careful history and physical exam may support this diagnosis. Treatment of the underlying etiology is important. Addressing dietary, lifestyle, and behavioral issues may eventually lead to return of menstrual cycles.

11.2 Polycystic Ovary Syndrome (PCOS)

Polycystic ovary syndrome is the most common diagnosis for chronic anovulation. Based on recommendations from the Androgen Excess PCOS Society (Azziz et al. 2006), it is defined as:

1. Excess androgen activity
2. Chronic oligo- or anovulation and polycystic ovaries
3. Exclusion of other etiologies for excess androgen status

There are other definitions for PCOS, including the 2003 Rotterdam Criteria and the 1991 NIH criteria. All definitions are in agreement that the constellation of anovulation and androgen excess are the basis for the diagnosis of PCOS. Workup for suspected PCOS includes the typical amenorrhea workup (TSH, prolactin, HCG), along with serum testosterone, DHEAS, FSH, and LH to exclude other disorders. Given the increased risk for metabolic dysfunction, screening for dyslipidemia and glucose intolerance is also recommended with fasting lipid panel, fasting glucose, and 2 hour oral glucose tolerance test.

11.2.1 Endometrial Sampling

> If one is concerned for chronic anovulation in the setting of unopposed estrogen, endometrial sampling is indicated to exclude endometrial hyperplasia or malignancy.

Patients with PCOS, obesity, and long periods of anovulation are at the highest risk for disease (Aune et al. 2015). There are no studies

specifically examining endometrial thickness on pelvic ultrasound and associations with pathology in the premenopausal woman; thus clinical judgment is important in deciding who should have endometrial sampling.

In addition, periodic (cyclic) exposure to progesterone/progestin is important to prevent hyperplasia and malignancy.

In patients desiring pregnancy prevention options include, cyclic combined estrogen-progestin or progestin-only contraception options are OCPs, transdermal patch, etonogestrel/ethinyl estradiol vaginal ring, levonorgestrel IUD, etonogestrel implant, or medroxyprogesterone injection. In those not desiring pregnancy, cyclic progestin either monthly or every other month can be given.

11.3 Thyroid Dysfunction

A small proportion of patients with amenorrhea will have thyroid dysfunction without any other clinical symptoms. To assess for thyroid function, a TSH and free T4 are drawn together or free T4 can be drawn in the setting of an abnormal TSH. Primary hypothyroidism is associated with an elevated TSH and low free T4, and primary hyperthyroidism is associated with a low TSH and elevated free T4. An elevated TSH and normal free T4 define subclinical hypothyroidism. In the setting of infertility or menstrual dysfunction, it is recommended to treat the thyroid disorders, even in subclinical hypothyroidism (SCH) as many patients are diagnosed in their progression toward frank hypothyroidism.

11.4 Treatment

If someone is planning pregnancy, normalization of TSH levels to 0.1–2.5 mIU/L prior to pregnancy and during the first trimester and to 0.2–3.0 mIU/L in the second and third trimesters is indicated to minimize the potential neurological effects of hypothyroidism on the developing embryo and fetus (ACOG 2015).

Typical initial doses for the treatment of hypothyroidism are 1–2 mcg/kg orally daily (or 100 mcg daily for most) followed by rechecking TSH levels in 1 month and adjusting base on response (Garber et al. 2012). Levels may be checked after 2 weeks if the disease is severe. For women with SCH attempting conception, the American Society for Reproductive Medicine states there is good evidence for treating women with TSH >4 mIU/L to improve pregnancy and miscarriage rates and decrease risk of adverse neurodevelopmental outcomes. They also state there is insufficient evidence that treatment of SCH with a TSH between 2.5 and 5 mIU/L is associated with improved outcomes (ASRM 2015).

If there is a normal free T4 and a low TSH, serum triiodothyronine (T3) can be checked as an elevated value indicates hyperthyroidism, which must also be corrected. Methimazole 10–40 mg orally daily divided into two or three doses and propylthiouracil 50–150 mg daily divided into three times per day are both reasonable regimens (Garber et al. 2012). We recommend that an endocrinologist manage these medications.

Another point of consideration is that hypothyroidism leads to elevated levels of thyroid-releasing hormone (TRH), which can stimulate prolactin production, causing hyperprolactinemia and possibly symptoms of galactorrhea. Elevated prolactin levels caused by hypothyroidism are typically less than 100 ng/mL. Also of note is that a longer duration of hypothyroidism can lead to decreasing levels of dopamine (inhibitory for prolactin production), and this can lead to unopposed stimulation of prolactin production by TRH. Treatment of hypothyroidism may correct hyperprolactinemia, with a slight lag in resolution of galactorrhea, over the course of months (Poretsky et al. 1986).

11.5 Hyperprolactinemia

Prolactin measurement is indicated in any amenorrhea workup. High levels may affect pubertal development; thus checking levels is even indicated in cases of primary amenorrhea. High levels of prolactin are thought to affect GnRH pulsatility, leading to decreasing levels of gonadotropins and hypogonadism. Mild elevations in prolactin levels (20–50 ng/mL) may be seen with stress, intercourse, and sleep, thus requiring repeat lab testing to establish a diagnosis of hyperprolactinemia. A fasting prolactin level can be drawn for accuracy, and if elevated (using the assay's reference range), imaging of the sella is recommended. MRI of the pituitary is recommended to exclude a mass, such as a prolactinoma or other tumor causing mass effect on the pituitary stalk, disrupting dopamine release. Other etiologies for hyperprolactinemia include hypothyroidism and medication. Medications that inhibit dopamine action or decrease levels, leading to hyperprolactinemia include (Molitch 2005):

- First-generation antipsychotics (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, thiothixene, trifluoperazine)
- Second-generation antipsychotics (paliperidone, risperidone, asenapine, ziprasidone, olanzapine, and less commonly clozapine, iloperidone, lurasidone, quetiapine)
- Tricyclic antidepressants (clomipramine, amitriptyline, desipramine)
- Selective serum reuptake inhibitor antidepressants (low risk – citalopram, fluoxetine, paroxetine, sertraline, fluvoxamine)
- Antiemetics (metoclopramide, prochlorperazine, domperidone) antihypertensive (methyldopa, verapamil)
- Opioid analgesics (methadone, morphine, etc.)

Other causes of prolactin elevations are physiologic: pregnancy, nipple stimulation, exercise, breast exams, and stress. Pathologic causes include lactotroph adenomas, hypothalamic or pituitary masses or disease affecting dopamine and prolactin, germline loss-of-function mutations of the prolactin receptor gene (*PRLR*), idiopathic elevated estrogen, and chronic renal insufficiency. Rare other causes of prolactin elevations include ectopic pituitary tissue found in the pharynx, bronchogenic carcinoma, renal cell carcinoma, gonadoblastoma, or even dermoid cyst/teratoma in the ovary.

11.6 Treatment

Stopping suspect medications and/or treating the underlying disease (i.e., hypothyroidism) should be done as indicated. Treatment for hyperprolactinemia is indicated in the following situations:

- Macroadenoma causing neurologic symptoms or abutting/invading the optic chiasm and cavernous and sphenoid sinuses
- Symptomatic hyperprolactinemia (galactorrhea) and hypoestrogenism (amenorrhea)
- Patients interested in conception

Treatment for symptomatic hyperprolactinemia is primarily done with dopamine agonists (Melmed et al. 2011). First-line treatment is cabergoline (0.25–1 mg by mouth twice weekly, with dose adjustments based on prolactin level). Cabergoline tends to have the best side effect profile. There is a slight increase in risk of valvular heart disease, but is uncommon in the doses used to treat hyperprolactinemia. Bromocriptine is second line (2.5–15 mg by mouth daily), adjusting for prolactin levels. Other medications not available in the USA include pergolide and quinagolide. The goals are to decrease the size of a microadenoma, improve symptoms related to hyperprolactinemia, and normalize menstrual function. If patients have hyperprolactinemia from a microadenoma and do not want to conceive or take dopamine agonists, combined oral hormonal contraception can be used. Further

treatment for hyperprolactinemia is discussed below.

Anatomical etiologies for amenorrhea can be associated with normal gonadotropins and are discussed in further detail below.

12 Elevated Gonadotropin Levels

12.1 Primary Ovarian Insufficiency

The presence of elevated gonadotropins is concerning for primary ovarian insufficiency (POI). This diagnosis is defined by oligomenorrhea or amenorrhea × 3 cycle lengths, elevated FSH >30–40 IU/L, and symptoms concerning for POI prior to age 40 (hot flashes, irritability, vaginal dryness). When suspicious for POI, a workup for chromosomal, genetic, and autoimmune etiologies is indicated.

12.2 Initial Workup

The initial basic workup for POI includes documenting elevated FSH values (two), TSH, and prolactin. When these confirm the diagnosis, a karyotype is indicated. Once POI is established either with normal or abnormal karyotype, hormone replacement therapy and monitoring of bone health via DEXA scan are recommended at least until age 50.

12.3 Genetic Abnormalities

Karyotype is the first step indicated in the workup for POI, especially if it occurs <30 years old. A karyotype will reveal deletions, mosaicism, and translocations. It is important to diagnose conditions such as Turner syndrome or mosaic, which have implications on cardiovascular, renal, and bone health. Further description regarding disorders of gonadal dysgenesis is discussed below.

Fragile X premutation and autoimmune etiologies are the next most common reasons for POI. Workup includes testing for *FMR1* premutation carrier status for fragile X and testing of anti-21-hydroxylase antibodies for autoimmune disease. More detail and workup of other etiologies for POI are listed below.

13 Low Gonadotropins

13.1 Hypothalamic Amenorrhea

Amenorrhea accompanied by low estradiol and low to normal gonadotropins is concerning for hypothalamic failure. MRI with contrast study of the sella is generally recommended in patients with hypothalamic failure. Below we detail clinical investigation, different etiologies, workup, and treatments for hypothalamic amenorrhea. Hypothalamic dysfunction is generally seen with low follicular level estradiol and low to normal gonadotropins accompanied by irregular menses or oligomenorrhea.

14 Specific Causes of Amenorrhea

14.1 Disorders of Amenorrhea by Compartment

I. Anatomical:
   (a) Asherman syndrome
   (b) Genital outflow tract disorders
   (c) Congenital anomalies of the uterus
II. Endocrine: ovarian disorder
   (a) Abnormal chromosomes
   (b) Normal chromosomes
III. Endocrine: anterior pituitary disorder
   (a) Prolactin tumors
IV. Central nervous system disorders
   (a) Anovulation
   (b) Weight loss/anorexia
   (c) Hypothalamic suppression
   (d) Hypothyroidism

Table 5 A list of outflow tract abnormalities causing amenorrhea

Acquired	Asherman syndrome
	Cervical stenosis
Congenital	Complete androgen insensitivity
	Imperforate hymen
	Transverse vaginal septum
	Müllerian agenesis

15 Anatomic Causes of Amenorrhea (Table 5)

15.1 Disorders of the Outflow Tract and Uterus

Physical exam and pelvic imaging can help characterize outflow tract disorders.

16 Asherman Syndrome

Asherman syndrome is defined as uterine synechiae and/or scarring, due to destruction of the functional lining of the uterus after uterine instrumentation. Clinically, it can present with amenorrhea, hypomenorrhea, dysmenorrhea, miscarriage, and/or infertility. Uterine synechiae typically form in the setting of infection and uterine scarring or postpartum curettage in the setting of hemorrhage or septic abortion (Berman 2008). Uterine artery embolization can also lead to ischemia of the endometrium and potentially Asherman syndrome (Davies et al. 2002). Uterine tuberculosis (TB) and uterine schistosomiasis can also cause endometrial damage, which can present similarly to Asherman syndrome. These are rare in developed countries but can be diagnosed with endometrial biopsy (TB) or testing for parasite eggs in urine, feces, or endometrium.

Initial workup for Asherman syndrome is done with sonohysterography. Diagnosis via hysteroscopy is the gold standard, as you can treat the adhesions at the same time. Hysteroscopic lysis of adhesions or removal of synechiae is recommended if this is identified, as consequences of Asherman syndrome include partial obstruction of functional endometrium leading to dysmenorrhea and outflow obstruction or infertility. For operative hysteroscopy, lysis of synechiae can be performed with scissors, cautery, myosure, or laser; however, scissors are associated with less postoperative adhesions (Yu et al. 2008). If there are severe adhesions obliterating the uterine cavity, concurrent laparoscopy or abdominal ultrasound guidance can be used to assist help in avoiding uterine perforation while completing the extensive resection. To prevent scar tissue reformation, a pediatric Foley catheter can be inserted, filled with 3 mL of fluid, sutured occlusion of outflow, and removed after 10 days. Alternatives can be placement of an intrauterine device, kept in place for 3 months, or insertion of hyaluronic acid, which is an adhesion barrier. Some practices routinely perform repeat hysteroscopy 10–14 days after treatment to visualize and treat any filmy adhesion reformation. If a Foley is inserted, broad-spectrum antibiotics should be given for 10 days (or for the duration of time the Foley catheter is in), such as doxycycline 100 mg orally twice daily. A comparison of Foley, IUD, and hyaluronic acid on retrospective review showed that Foley was associated with the least amount of adhesion reformation, followed by IUD and hyaluronic acid (Lin et al. 2013). Most physicians will also prescribe estrogen therapy for 4 weeks to stimulate endometrial proliferation. The regimen is 2.5 mg oral conjugated equine estrogen twice daily (or oral estradiol 4 mg twice daily), followed by progestin therapy (medroxyprogesterone acetate 10 mg po daily or norethindrone acetate 2.5 mg oral daily) during the last 10 days of estrogen therapy.

17 Cervical Stenosis

Cervical stenosis may be a result of scarring from surgery on the cervix for severe dysplasia such as a cold knife cone, laser, LEEP, or rarely cryotherapy. Presentation includes cyclic pelvic pain or light spotting instead of normal menstrual

flow. Treatment of this includes manual cervical dilation and occasionally temporary balloon catheter placement for 2 weeks to help decrease recurrence.

18 Androgen Insensitivity Syndrome

Androgen insensitivity syndrome (AIS) is also known as testicular feminization and is a disorder caused by a mutation in the androgen receptor (located on the X chromosome long arm), thus leading to end-organ insensitivity to androgen. Patients with AIS have a 46,XY karyotype and testes or gonadal remnants that may be intraabdominal, in the inguinal canal, or partially descended. During embryology, the presence of gonadal tissues results in the production of anti-müllerian hormone that blocks the formation of a uterus or fallopian tubes. Externally, these patients have a short, blind-ending vagina and no testicular or penile growth due to lack of androgen receptors. They will develop breasts secondary to estrogen derived from peripheral aromatase conversion of circulating testosterone to estrogen. On examination, these patients are sometimes called "super feminine" as they have scant or no pubic or axillary hair due to their androgen insensitivity, no facial hair, and often fully developed or large breasts.

> The most typical presentation in the adolescent period is complaint of primary amenorrhea (without cyclic pelvic pain due to the lack of müllerian structures)

Laboratory values will reveal elevated testosterone. Pelvic ultrasound will reveal lack of a uterus, cervix, or ovaries. Treatment for AIS includes options for vaginal reconstruction as seen for müllerian agenesis. Gonadectomy of residual gonadal tissue is recommended due to the increased risk of neoplasia, usually done after pubertal development occurs as tumors occur most commonly after puberty (Purves et al. 2008). In partial AIS, gonadectomy can be performed sooner to prevent virilization in a phenotypically appearing female.

19 Imperforate Hymen

Imperforate hymen may be caused by genetic factors, although it has not been well defined (Lim et al. 2003). The imperforate hymen can present in different ways, with the most common being cyclic pelvic or abdominal pain from buildup of menstrual blood in the adolescent period. It can also present with perineal pain or urinary retention from urethral obstruction. On physical exam, the vaginal orifice appears non-patent with a perineal bulge representing hematocolpos. An MRI should be obtained to rule out other GU tract abnormalities such as transverse vaginal septum as the treatment is different. In cases of imperforate hymen, menstrual buildup can lead to retrograde menstruation causing endometriosis as well as inflammatory changes in the pelvis.

Surgical treatment is recommended in the operating room with a goal to open the membrane and allow for tampon use and eventually sexual intercourse. The hymen is incised in a cruciate fashion at 2, 4, 8, and 10 o'clock. A vertical or U-shaped incision can be used as well. It is important to avoid making the incision too close to the vaginal mucosa as it may cause scarring, stenosis, and dyspareunia (Dominguez et al. 1997).

20 Transverse Vaginal Septum and/or Cervical Atresia

A transverse vaginal septum is caused by failure of canalization of the vaginal plate during embryogenesis. The septum is usually positioned between the upper one third and lower two third of the vagina. Symptoms of transverse vaginal septum may be similar to those of imperforate hymen

– cyclic pelvic pain and/or vaginal bulge or dimple detected in the adolescent age. Younger girls can present with mucocolpos. In some cases, microperforations allow bacteria to ascend causing pyohematocolpos. On physical exam, a vaginal bulge may be present from hematocolpos, but the position is different from the imperforate hymen as the imperforate hymen is located on the introitus, not the upper vagina. Pelvic ultrasound may be helpful to evaluate the uterus and adnexa, but MRI is a better study to help distinguish a septum from cervical atresia and to measure the size of the septum that aids in surgical planning (Reinhold et al. 1997). Dilators may be used preoperatively to thin the septum to facilitate removal. Removal is done with a vertical or "Z-plasty" incision to minimize scarring (Garcia 1967). We recommend that an experienced surgeon perform this procedure.

21 Müllerian Agenesis (Mayer-Rokitansky-Küster-Hauser Syndrome: MRKH)

Müllerian agenesis is the congenital absence of a vagina and variations of uterine development that includes bilateral or unilateral uterine horns, a hemiuterus, a midline uterus with no cervix, or a complete absence. Presentation of MRKH is usually primary amenorrhea in a girl or young woman with normal secondary sex features. In 10% or less of patients, there may be functional endometrium, and patients may present with cyclic pelvic pain. MRKH is thought to have a genetic component, as there are descriptions in the literature of familial cases with variable expression.

- Galactose-1-phosphate uridyl transferase gene mutations (GALT) have a higher prevalence in women with müllerian agenesis (Fedele et al. 1990).
- MRKH is associated with skeletal abnormalities and, in particular, the Klippel-Feil syndrome (low hairline, short neck, and pain associated with cervical vertebrae fusion) as well as VACTERL (vertebral anomalies, anal atresia, cardiovascular anomalies, esophageal atresia, renal anomalies, limb anomalies) (Rall et al. 2015).

The workup for MRKH includes karyotype to rule out androgen insensitivity syndrome and male pseudohermaphroditism, pelvic ultrasound (not mandatory – but can help evaluate remnant pelvic structures), and MRI. Given the association with renal and skeletal abnormalities, renal ultrasound and spinal x-rays should be ordered as well.

In certain candidates, there is a role for vaginal reconstruction surgery for sexual function. Different techniques exist, including the McIndoe (construction of neovagina using a skin graft), the Vecchietti operation (dissection of the vesicorectal space followed by internal stretching of the vaginal remnant), and laparoscopic modifications of the Vecchietti. Surgical candidates must be committed to using dilators post-procedure to maintain vaginal length and functionality. Fertility options include in vitro fertilization with oocyte retrieval and gestational surrogacy. More recently, uterine transplant has become a potential option, but remains experimental at this time (Jones et al. 2016).

22 Endocrine: Ovarian Disorders

22.1 Abnormal Chromosomes

22.1.1 Gonadal Dysgenesis

Gonadal genesis is the most common etiology for primary amenorrhea, making up to 30–40% of cases. It is caused by an X chromosome abnormality or defect in other genes involved in germ cell migration and/or organization. Patients have absent or incompletely formed gonads that are present as ovarian remnants. Some patients have a 46,XX karyotype, some 45,X. Turner syndrome is the most common etiology for gonadal dysgenesis.

- There is also a syndrome associated with gonadal dysgenesis and sensorineural deficit known as Perrault syndrome (Meyers et al. 1996).

22.1.2 Turner Syndrome

Turner syndrome is caused by the absence of one complete or partial copy of the X chromosome in some or all the cells. The karyotype of Turner syndrome includes monosomy (45,X), mosaicism (45,X/46,XY), partial monosomy (46X, del(Xp), or presence an isochromosome of two q arms (46, X,i(Xq)).

Approximately 10–20% of Turner patients have spontaneous puberty, and 25% have spontaneous menses (Pasquino et al. 1997; Hadnott et al. 2011). Some patients may have spontaneous pregnancy as well, but may be at increased risk for chromosomal abnormalities in the offspring and/or miscarriage. Turner can also present as abnormal pubertal development and primary amenorrhea. Physical characteristics include short stature, webbed neck, widely spaced nipples, and shield chest. If a patient has mosaicism and a Y chromosome, the gonads may contain some testicular tissue and have an elevated risk for developing cancer, including gonadoblastomas, dysgerminomas, yolk sac tumor, and choriocarcinoma. Onset of germ cell tumors is typically less than 20 years old, with a cumulative risk of 7.9% by age 25 (Schoemaker et al. 2008).

Turner syndrome has implications on cardiovascular, renal, and bone health. Some of the associated cardiac anomalies are bicuspid aortic valve, coarctation, and other malformations (Cramer et al. 2014). Referral to cardiology is warranted with this diagnosis between 12 and 15 years old (or at diagnosis), and repeat echocardiogram is recommended every 5 years for any Turner patient. If the echocardiogram is abnormal, then echo is obtained more frequently, as determined by the cardiologist. In addition, a renal ultrasound should be obtained upon diagnosis and only repeated if abnormal (every 3–5 years). Turner patients have higher rates of thyroid dysfunction, and TSH and free T4 should be ordered on diagnosis and repeated every 1–2 years. Given the increased risk for metabolic dysfunction, hypertension, renal, and liver disease, labs including CBC, fasting glucose, fasting lipid profile, and chemistry panel (including creatinine and LFTs) are recommended every 2 years (Freriks et al. 2011). Other things to screen for are celiac disease (antiendomysial antibodies) as well as audiometry (to be followed every 10 years or more frequently if abnormal). For patients that are diagnosed early on, growth hormone treatment may help achieve more height.

22.1.3 Hormone Replacement Therapy

Patients with Turner are at risk for effects of hypoestrogenism, thus treatment with exogenous hormones is recommended. Therapy should start between ages 12 and 15 (allowing maximization of height). Dosing is 0.25–0.5 mg micronized estradiol or equivalent, increasing every 3–6 months depending on development of secondary sex characteristics. The goal is to complete tanner stage/sexual maturation after 3 years. Progestin therapy can be added with the first episode of vaginal bleeding for 1–2 years after onset of estrogen therapy to avoid unopposed estrogen exposure. Switch over to combination oral contraceptives ensures adequate estrogen treatment. Consideration of transdermal testosterone to reverse the often very low androgen levels is less frequent but is beneficial for muscle, bone, and skin. Turner patients may have infertility and may be candidates for in vitro fertilization with oocyte donation. Gestational surrogacy should be considered, as with the comorbidities, a high-risk pregnancy with an increased risk of death needs to be considered.

22.1.4 Swyer (46 XY Gonadal Dysgenesis)

Swyer syndrome is caused by a mutation of SRY (sex-determining region of the Y chromosome) and other mutations associated with testicular formation (desert hedgehog *DHH*, steroidogenic factor 1, *NR5A1*, *WNT4*, *DAX1*) (Das et al. 2011). Patients with Swyer syndrome have streak gonads, which do not produce androgens or antimüllerian hormone. This leads to a female phenotype and müllerian structures, as well as female external genitalia. Clinical presentation is usually primary amenorrhea and possibly delayed puberty. Upon diagnosis of Swyer syndrome, it is recommended that streak gonads be removed given the increased risk of malignancy in the

testicular portion of the gonads. The incidence of malignancy is up to 20–30% and includes gonadoblastoma, dysgerminoma, endodermal sinus tumor, choriocarcinoma, and embryonal carcinoma (Cools et al. 2006).

Exogenous hormonal therapy can be given for sexual maturation with a similar regimen for Turner syndrome. These patients will also have infertility, but can undergo in vitro fertilization with oocyte donation. There is no other special screening or health monitoring needed.

22.1.5 46,XX Gonadal Dysgenesis

Gonadal dysgenesis can also present with a normal 46,XX karyotype, due to some autosomal gene defects that encode for nucleic acid binding proteins and transcription factors involved in oogenesis (Simpson 2008). Patients may present with primary amenorrhea but will have normal height and sex characteristics.

22.1.6 Fragile X Premutations (FMR1)

It is recommended that women diagnosed with diminished ovarian reserve and primary ovarian insufficiency (cessation of normal ovarian function before age 40 years) should be screened for fragile X (ACOG 2006). The prevalence of POI in fragile X carriers lies somewhere between 10% and 20% (Davidson et al. 2000). In fact, some argue that any female should be screened, particularly when considering pregnancy as the sensitivity is high ~99% and there are implications to offspring health. This disease is a result of an *FMR1* gene mutation on the X chromosome at Xq27.3 leading to expanded CGG repeats. >40–55 CGG repeats indicate intermediate expansion, >55 to ≤200 repeats indicate fragile X (alphabetical X) premutation carrier status, and >200 repeats are considered the full mutation. In boys, clinical features encompass a wide range including developmental delay, intellectual disability, language, math, visuospatial, and attention deficits.

Physical findings range widely and may include relative macrocephaly, pale blue iris, strabismus, arched palate, mitral valve prolapse, joint hyperlaxity, hypotonia, and flexible flat feet. In females, full mutations can lead to milder effects on cognitive and behavioral development and intellectual disability. With the permutation, women can present with primary ovarian insufficiency, later onset of fragile x-associated tremor-ataxia syndrome, and milder cognitive deficits. Women with POI and the fragile X mutation should be counseled regarding the decreased fertility potential, as well as the possibility of passing the mutation onto their offspring. In vitro fertilization with preimplantation genetic diagnosis should be discussed with women as part of the counseling.

22.2 Normal Chromosomes

22.2.1 Autoimmune POI

About 3% of patients with POI will have concurrent diagnosis of adrenal insufficiency (Bakalov et al. 2002). If a POI patient has a normal karyotype, then workup for autoimmune etiologies for POI is warranted as the next step.

> Suspicion for autoimmune POI should be higher in a patient with a family history of autoimmune disease, or personal history, such as hypothyroidism, diabetes mellitus, pernicious anemia, myasthenia gravis, and hypoparathyroidism.

Although tests for anti-ovarian antibodies exist, these tests can be inconsistent, and there is no clear indication for testing given these findings (Novosad et al. 2003). Since a diagnosis of adrenal insufficiency would affect future medical management, testing for adrenal antibodies is reasonable. In fact, women that test positive for antibodies will have a 50% risk of developing adrenal insufficiency (Betterle et al. 1997). Anti-adrenal or 21-hydroxylase antibodies can be ordered to screen for the majority of causes for autoimmune POI, although defects in other steroidogenesis enzymes are rarer causes. Other screening labs include TSH, free T4, anti-

thyroperoxidase (TPO) antibodies, and a CMP to evaluate calcium, phosphorus, and fasting glucose. If there is a positive result for an adrenal antibody, providers should pursue confirmatory testing for adrenal insufficiency with ACTH stimulation test.

22.2.2 Other Etiologies for POI

Occasionally, the workup for POI will reveal normal karyotype, fragile X testing, and no evidence of autoimmune antibodies. There are other genetic defects that may contribute to POI, and next-generation sequencing to identify these potential mutations is being investigated but is not practiced routinely in the clinical setting. Mutations such as *FSHR*, *LHCGR*, *FOXL2*, *BMP15*, *STAG3*, *NOBOX*, *FIGLA*, and *STAG3* have been identified as nonsyndromic causes for POI. Advances are being made with new technologies like next-generation screening in identifying putative genes in POI (Fonseca et al. 2015).

22.2.3 Radiation

Radiation therapy (RT) may induce primary ovarian insufficiency, depending on the age, radiation dose, and radiation field. A later age of exposure, higher dose, and abdominal/pelvic radiation provide higher risk for POI. A dose of 2 Gy to the ovary will leave approximately 50% oocytes to survive (Wallace et al. 2003). Survivors after RT are at increased risk of POI and its subsequent long-term effects on bone and cardiovascular health. To decrease the risk of ovarian failure, ovarian shielding and surgical transposition of the ovaries prior to treatment are options. Success rates vary with radiation dose and field, as ovaries may be affected by scatter radiation or adjuvant chemotherapy. In patients who are anticipating undergoing radiation therapy, counseling for fertility preservation is important, particularly for IVF with oocyte or embryo cryopreservation. In prepubertal females, the only option that currently exists is ovarian tissue cryopreservation, which is experimental in nature and done primarily in the clinical setting.

22.2.4 Chemotherapy

Chemotherapy can cause DNA damage in oocytes, leading to apoptosis, and accelerated depletion of the primordial follicle pool. Exposure to chemotherapy can predispose women to primary ovarian insufficiency. The type, duration, and age at exposure can influence the toxicity, with an increasing risk associated with an increasing age of exposure (Sonmezer and Oktay 2004). Studies have looked at GnRH agonists for ovarian protection during chemotherapy, with mixed results. This is not currently recommended for fertility preservation based on a recent systematic review; however, there are studies showing some benefit in the breast cancer population (Elgindy et al. 2015; Moore et al. 2016). Patients undergoing chemotherapy should be referred to a reproductive endocrinology and infertility specialist to discuss fertility preservation options, including in vitro fertilization with oocyte or embryo cryopreservation. Ovarian tissue cryopreservation is an option for prepubertal girls, which is still being investigated in clinical research trials.

> There are special ovarian stimulation protocols that are safe for women with estrogen-sensitive tumors.

22.2.5 Galactosemia

Galactosemia is an autosomal recessive disorder, where patients are unable to metabolize galactose due to galactose-1-phosphate uridyl transferase deficiency. Galactose metabolites may cause damage to germ cells migrating to the genital ridge in the developing embryo (Levy et al. 1984). Typically this diagnosis is made in young children or neonates due to developmental and growth delays or failure to thrive with milk intake.

22.2.6 Resistant Ovary Syndrome

This rare syndrome presents clinically with amenorrhea, possibly delayed puberty, elevated gonadotropins, and presence of ovarian follicles. The etiology may include defective or absence of

gonadotropin receptors or intracellular downstream signaling defects.

22.2.7 17-Hydroxylase Deficiency

This presents with delayed puberty (no sexual characteristics because sex steroid production is impossible), hypertension, hypokalemia, and elevated progesterone levels.

22.2.8 Follicular Development Failure

Genetic defects in follicular development may contribute to POI. Genes encoding for folliculogenesis, steroidogenic enzyme synthesis, gonadotropin receptor signaling, and intracellular signaling may contribute to some of the pathways not clearly defined leading to POI. Some of the genes include steroidogenic acute regulator enzyme (*STaR*) and aromatase (*CYP19A1*).

22.2.9 Counseling and Management of POI

POI patients should be counseled that they might still have intermittent ovulation and menses. Patients not interested in having children should use contraception. Patients desiring future fertility should be counseled that about 10% of women with POI have spontaneous conception and if they achieve a pregnancy, 80% will lead to a healthy live birth (Van Kasteren and Schoemaker 1999). The physician should discuss long-term outcomes and pregnancy chances with patients. Given that they are at higher risk for diminished ovarian reserve-related infertility, they should seek infertility guidance sooner than the 1 year of attempted conception and consider IVF with donor oocyte to improve their success rates.

One of the main adverse effects of POI is the elevated risk of developing osteopenia and osteoporosis (Gallagher 2007). Early menopause is also an independent risk factor for developing cardiac disease (Atsma et al. 2006). In addition, vasomotor symptoms, urogenital atrophy, and other associated findings with menopause may greatly affect quality of life. Treatment with exogenous estrogen therapy is recommended unless there is a contraindication. Treatment to achieve physiologic doses of estradiol (approximately 104 pg/mL or 382 pmol/L) should continue until at least 50 years old, after which women can be transitioned to menopausal level hormone therapy (Mishell et al. 1971) (Table 6).

Table 6 HRT regimens for premature ovarian insufficiency (higher doses in younger versus older)

Estrogen regimen options	Progestin regimen options
Transdermal estradiol 100–150 mcg daily (patch dosing 1 or 2× per week)	Oral medroxyprogesterone acetate 10–40 mg daily × 12 days per month
2 mg oral micronized estradiol daily	Micronized progesterone 200 mg daily for 10–12 days per month
1.25 mg oral conjugated equine estrogen daily	Combination products: conjugated equine estrogen 1–2 daily – 0.45/1.5 or 0.625 mg/2.5 mg
1.25 mg oral esterified estrogen daily	

22.2.10 Pituitary Disorders

In patients with low estradiol and low-normal gonadotropin levels, one must be suspicious for hypothalamic or pituitary failure. Imaging of the sella turcica is recommended to rule out any intracranial pathology. CT and MRI with a special view on the sella turcica are both reasonable options. MRI is the more sensitive imaging modality, provides the least radiation exposure, and can better characterize the sella and suprasellar regions and distinguish between solid tumors and vascular abnormalities, including hemorrhage. However, MRI can be lengthy and is much more expensive, so it is reasonable to pursue CT in certain contexts.

22.2.11 Pituitary Adenomas

Pituitary adenomas are largely benign and are the most common etiology for amenorrhea caused by a mass in the anterior pituitary. They are typically monoclonal (of one cell type) and may or may not be functional. They are classified as microadenomas if they are less than 10 mm and macroadenomas if they are greater than 10 mm. They may present with amenorrhea, galactorrhea, or neurologic symptoms such as headache and visual impairment, with the most common being bitemporal hemianopsia (from compression of the optic chiasm) or diplopia.

22.2.12 Lab Testing

In addition to imaging, laboratories are indicated to assess pituitary function as deficiencies may affect a patient's health.

If a patient has amenorrhea, the initial endocrine workup includes TSH, prolactin, FSH, and estradiol.

If there are findings of a macroadenoma on imaging, we recommend drawing a free T4 to distinguish between primary and secondary hypothyroidism, IGF-1 to evaluate for growth hormone deficiency, and morning cortisol drawn between 6am and 9am to screen for adrenal insufficiency.

- In the setting of low cortisol levels, ACTH stimulation test is indicated. Cosyntropin is administered (0.25 mg) IM or IV, with subsequent measurement of serum cortisol before and 60 min after mediation is administered. Normal levels post-administration are $\geq$15–18 μg/dl. Elevated basal cortisol may indicate Cushing's syndrome and requires further workup. Lack of response (i.e., if cortisol does not rise with cosyntropin administration) indicates that the adrenal gland is likely atrophic from chronic ACTH deficiency.

22.2.13 Gonadotroph Adenomas

Gonadotroph adenomas are typically nonfunctional and make up the majority of benign inactive adenomas in the pituitary. They often present with neurologic symptoms of headache and visual changes. Most patients have normal or low gonadotropin concentrations on workup. In rare cases, FSH-secreting tumors can cause spontaneous ovarian hyperstimulation syndrome. They may also cause ovarian cyst formation, amenorrhea, and premature breast development and bleeding in prepubertal girls. They mechanism for causing amenorrhea is through compression of the pituitary stalk, interrupting dopamine, leading to increased prolactin secretion. Gonadotroph adenomas may secrete a-subunit, and levels may be elevated on testing. There is no standard medical treatment for functional gonadotroph adenomas, and GnRH agonist has not been successful in downregulating FSH or LH in these cases.

Surgical treatment through transsphenoidal resection is an option, but it has its own risks and may potentially lead to removal of functional pituitary tissue.

22.2.14 Thyrotroph Adenomas

Functional thyrotrophs are rare and present with symptoms of hyperthyroidism. This includes fast heartbeat, palpitations, heat intolerance, nervousness, weight loss, hunger, insomnia, and more. They may also develop a goiter and have oligo- or amenorrhea, galactorrhea, and other neurologic symptoms. These patients will have a wide range of TSH levels and high levels of free T4 and T3, as well as elevated free a-subunit. Treatment is recommended and includes transsphenoidal resection and octreotide if there is persistent tumor (or sometimes is used preoperatively). Octreotide is a somatostatin analog and can reduce TSH levels.

22.2.15 Somatotroph Adenomas

Functional somatotroph adenomas lead to excess secretion of IGF-1 and lead to acromegaly. Symptoms and signs are typically gradual in onset and may include large hands and feet, enlarged jaw, deepening voice, fatigue, weakness, headache, and visual changes. IGF-1 level has diurnal variation and is age-specific. An oral glucose tolerance test can be used to diagnose acromegaly. Growth hormone levels will be low in normal individuals 2 h after 75 g glucose tolerance test (GTT) but in acromegaly will continue to be elevated ($>$0.3 ng/mL). The recommended treatment is transsphenoidal surgery that has good outcomes and leads to an 80–90% rate of resolution. If there is still a persistent functional tumor after removal, then octreotide is administered.

22.2.16 Corticotroph Adenomas

Cushing's disease is the most common manifestation of functional ACTH-secreting corticotroph adenomas. Clinically, high levels of cortisol lead

to the "Cushing's" phenotype of facial and central adiposity, abdominal striae, nuchal fat/buffalo hump, and some hyperpigmentation. Many of these patients will have amenorrhea, hirsutism, and acne. Different methods for diagnosis include 24 h urinary free cortisol, dexamethasone suppression test, and salivary cortisol test. With the overnight dexamethasone suppression test, 1.0 mg dexamethasone is given late (between 11pm and midnight), and serum cortisol is measured the following morning around 8am. Values of $\geq$1.8 mg/dl are abnormal. If one test is abnormal, we recommend a second test to validate the findings. Treatment for corticotroph adenomas is resection via transsphenoidal surgery, followed by radiation therapy for those that have persistently elevated cortisol after surgery. If radiation therapy fails, adrenalectomy is an option for definitive treatment, but has its own risks.

22.2.17 Lactotroph Adenomas (Prolactinoma)

Forty percent of pituitary adenomas are prolactinomas. They may spontaneously occur or be part of a syndrome called MEN1 (multiple endocrine neoplasia type 1), as a result of a *MEN1* mutation. Clinical manifestations include amenorrhea and galactorrhea, and in prepubertal patients severe cases may impair growth. Patients with prolactinomas have elevated prolactin levels, which tend to correlate with the size of the mass. If the adenoma is part of MEN1, patients can have hyperparathyroidism and hypercalcemia. Occasionally patients will have elevated IGF-1, since up to 10% of prolactinomas produce growth hormone.

Lactotroph microadenomas are common, rarely progress beyond 1 cm, and are typically not changed with medical therapy such as dopamine agonist. They often recur even if they are resected, but they often do not have any adverse health effects. Repeat imaging for microadenomas can be done at 1, 2, and 5 years after diagnosis. If there is no change in symptoms or mass size, then surveillance imaging can be discontinued.

If there is a presence of a macroadenoma and prolactin levels are $<$100 ng/mL, it is likely another type of secreting adenoma, and/or the macroadenoma is causing stalk compression and disruption of the dopamine regulation of prolactin. Commonly these tumors are associated with irregular menses or CNS symptoms, such as headaches or visual disturbances. Referral should be made to neurology and neurosurgery for further consultation and management. If a patient has a macroadenoma and prolactin levels $>$100 ng/mL, the diagnosis of prolactinoma is most likely. Growth of these tumors is typically slow but warrant management with an endocrinologist or reproductive endocrinologist, neurologist, and neurosurgeon for multidisciplinary management. If a patient is asymptomatic, long-term surveillance is reasonable, and repeat imaging should be done at 1/2, 1, 2, and 5 years. Any growth or CNS symptoms warrant treatment. In addition, endocrine screening of TSH, prolactin, IGF-1, and 24 h urinary cortisol or dexamethasone suppression test are recommended.

22.3 Treatment

22.3.1 Medical Therapy

Medical therapy for prolactinomas can be tailored to a patient's goals and is detailed above under hyperprolactinemia. If the patient does not desire pregnancy and does not have neurologic symptoms, she may use hormonal contraception for regulation of menses and pregnancy prevention. In patients desiring restoration of menses or desire pregnancy, the initial treatment for functional symptomatic prolactinoma is a dopamine agonist, which includes bromocriptine and cabergoline and is detailed above in the Sect. "11.5." Both bromocriptine and cabergoline are safe for conception and pregnancy and typically restore ovulation and menstrual function once prolactin levels resolve.

After initiating medication, prolactin levels should be checked 2–3 weeks later as they should normalize in weeks. Medical therapy may also work for symptomatic macroadenomas, but may take longer than the response seen with microadenomas. After initiation of treatment, repeating the MRI to assess size in macroadenomas after 3–6 months can help assess response. If a tumor is

stable in size during treatment, it may be a non-functional adenoma.

For microadenomas, the dose of dopamine agonist can be reduced after a year and even discontinued if the prolactin levels normalize for >2 years and repeat MRI is negative for an adenoma.

Macroadenomas: During therapy, a repeat MRI after 6 and 12 months of treatment is recommended. DA therapy can be reduced if the macroadenoma has decreased in size and the prolactin level is normal for >1 year. If the prolactin level is normal for 2 years and the MRI shows minimal or no evidence of tumor, the treatment can be reduced and possibly stopped. Levels and symptoms must still be followed for possible recurrence or regrowth.

22.3.2 Surgical Therapy

Transsphenoidal resection of macroadenomas is an option for large tumors (especially those seeking to get pregnant) or failure to respond to medical therapy. Incomplete resection is common; thus often patients may need further therapy.

22.3.3 Radiation Therapy

Radiation therapy is used for patients who underwent surgery for large macroadenomas with a persistent sizable tumor. Radiation therapy puts patients at risk for panhypopituitarism over 10 years after treatment (Snyder et al. 1986).

22.3.4 Fertility and Pregnancy

With dopamine agonist treatment, 80% of patients can achieve spontaneous ovulation and pregnancy (Kupersmith et al. 1994). The risk of microadenoma growth in pregnancy due to elevated estrogen levels is only 1–2%, and 5% will have some growth without symptoms. However, in patients with macroadenomas, growth and symptoms may occur in 15–20% (Molitch 1999). Dopamine agonist is discontinued during pregnancy, and it is not necessary to rechecking prolactin during pregnancy. If a patient develops neurologic symptoms secondary to an adenoma, a dopamine agonist can be safely given in pregnancy. Prolactin levels can be checked 2 months postpartum. DA therapy should not be given while breastfeeding. Reassuringly, there are no effects of breastfeeding on growth in micro- or macroadenomas. If patients are symptomatic when they deliver, they should not breastfeed as medical or surgical treatment may be indicated.

22.3.5 Empty Sella Syndrome

Empty sella syndrome occurs due to removal/destruction of a pituitary adenoma leading to filling of the sella with cerebrospinal fluid. In rare cases, it may present as a congenital finding. Asymptomatic patients who have elevated prolactin levels and an "empty sella" on MRI should have annual surveillance with prolactin and MRI.

22.3.6 Sheehan Syndrome

Sheehan syndrome is caused by ischemia of the anterior pituitary usually due to an acute blood loss such as that from postpartum hemorrhage. Clinically, it presents as difficulty with postpartum lactation, but may result in panhypopituitarism with endocrine deficiencies manifesting as fatigue, anorexia, weight loss, and amenorrhea. A laboratory workup to assess the pituitary function is important, including TSH, IGF-1, cortisol, and FSH/LH. Electrolytes should be checked as patients may concomitantly have hyponatremia. ACTH stimulation test should not be done until 6 weeks after initial event, as the adrenal gland may not have had chronic-deficient exposure to ACTH too soon after.

22.4 Infiltrative Lesions

22.4.1 Hemochromatosis

Hereditary hemochromatosis is caused by a mutation in the *HFE* gene, which encodes for a protein expressed on the cell surface that interacts with transferrin and affects regulation of iron levels. In hemochromatosis, serum iron levels will be elevated due to increased absorption in the gastrointestinal tract, and iron overload can lead to damage to different tissues/organs. Fasting transferrin saturation (serum iron: total iron binding capacity) will be >45%, and serum ferritin

>300 μg/L is an abnormal finding. Affected patients should be sent for HFE genotype. Sometimes, liver biopsy is performed to assist with diagnosis. Treatments include phlebotomy and chelation therapy.

22.4.2 Lymphocytic Hypophysitis

Lymphocytic hypophysitis is an autoimmune disorder that causes inflammation and damage to the pituitary. It most commonly occurs in pregnancy and postpartum and may be accompanied by hyperprolactinemia and hypopituitarism. Treatment may include transsphenoidal surgery, dopamine agonists, immunosuppression, or pituitary radiotherapy.

22.4.3 Hypogonadotropic Hypogonadism:

The constellation of amenorrhea, normal imaging, low estradiol, and low or normal gonadotropins may be classified as hypothalamic amenorrhea. This diagnosis can be made after excluding other potential etiologies for amenorrhea.

22.5 Hypothalamus

22.5.1 Hypothalamic Amenorrhea

Factors associated with functional hypothalamic amenorrhea (FHA) include low body weight, decreased nutritional intake and/or eating disorders, excessive or frequent exercise, and emotional stress. Sometimes it is found in patients with none of the above. In FHA excessive stress or malnutrition is thought to alter the GnRHI pulsatility, leading to no or low gonadotropin production or release of gonadotropins with decreased functional activity. Increased levels of endorphins, corticotrophin-releasing hormone, ACTH, and cortisol cause a decrease in the amplitude and frequency of GnRH. Often, alterations in diet, lifestyle, and life stressors can reverse FHA and lead to resumption of menses.

22.5.2 Eating Disorders

There are ranges of eating disorders that can lead to amenorrhea.

Anorexia nervosa is an eating disorder with DSM-5 diagnostic criteria:

1. Restriction of energy intake relative to requirements leading to significantly low body weight in the context of age, sex, developmental trajectory, and physical health
2. Intense fear of gaining weight or becoming fat even through underweight
3. Disturbance in the way which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight

Anorexia can result from restriction of calories and binging/purging with the use of laxatives/diuretics. Physical exam and laboratory findings may include lanugo (thin hair covering body), bone density loss, anemia, renal failure, and amenorrhea.

Patients have low FSH, LH, estradiol, IGF-1, and leptin. Cortisol levels may be elevated, and thyroid studies are often normal. Treatment involves intensive nutritional, medical, and cognitive behavioral therapy. Patients may require hospitalization for severe electrolyte derangement and dehydration.

Bulimia nervosa has DSM-5 diagnostic criteria and is defined as:

1. Having recurrent episodes of binge eating in which large amounts of food are consumed in a discrete amount of time (<2 h) and a sense of lack of control over eating.
2. Recurrent inappropriate compensatory behavior in order to prevent gaining weight (i.e., purging).
3. Binge eating and compensatory behaviors both occur at least 1×/week for at least 3 months.
4. Self-evaluation is influenced by body shape and weight.
5. Disturbance does not occur exclusively during episode of anorexia nervosa.

Patients with bulimia may have electrolyte imbalances, tooth and gum decay, chronic

constipation/irregular bowel movements, and renal insufficiency.

22.5.3 Exercise

The combination of intense exercise, low body fat, and weight loss leading to a negative energy balance can lead to amenorrhea. The degree of amenorrhea is associated with the intensity of exercise. Running, gymnastics, and dance are activities where lean body mass is valued but is associated with higher rates of amenorrhea. In exercise-induced HA, decreased GnRH pulsatility and impaired gonadotropin release are thought to stem from adrenal activation (cortisol and CRH), endogenous opioid release after exercise, and decreased circulating leptin levels. Workup of HA should include the general workup for amenorrhea – HCG, LH, FSH, prolactin, and TSH. In suspected cases of exercise-induced amenorrhea, vitamin D levels and DEXA scan should be ordered. Generally blood results include normal TSH and prolactin levels, along with low-normal levels of gonadotropins and hypoestrogenism.

The "female athlete triad" refers to women with menstrual dysfunction, low calorie intake, and low bone density. The hypoestrogenism from HA leads to decreased trabecular bone density and can predispose women to stress fractures. In addition, weight-bearing activity does not negate the negative effects of low estrogen on bone health. Lifestyle changes including increasing nutritional intake and decreasing exercise intensity provide the best benefits toward improving bone density and restoration of menstrual function. Exogenous hormonal therapy may be indicated in cases of osteopenia where lifestyle changes do not improve bone density or the patient does not wish to engage in lifestyle changes. Supplementation with calcium (1,000–5,000 mg per day) and vitamin D (1,000–2,000 IU per day) is encouraged but not sufficient to restore and maintain bone density if hypoestrogenism is not corrected. In addition to effects on bone, hypoestrogenism may predispose women to higher levels of total cholesterol, triglycerides, and LDL. For patients seeking pregnancy who do not have resumption of menses after lifestyle changes, gonadotropin use for ovulation induction may be necessary.

22.6 Congenital GnRH Deficiency

GnRH deficiency is a genetic cause of hypothalamic amenorrhea. It can be inherited in autosomal dominant, autosomal recessive, and X-linked fashions. The majority of etiologies are sporadic, but many patients will have a family history of delayed puberty or infertility. Below are the different etiologies for GnRH deficiency.

22.7 Kallmann's Syndrome

Kallmann's syndrome is a disorder characterized by congenital GnRH deficiency and anosmia (or hyposmia). It is believed to arise from genetic mutations that affect GnRH neuronal migration to the ventral hypothalamus as well as olfactory neuron migration. Anosmin, an amino acid cell adhesion protein encoded by KAL1, is improperly expressed, leading to defunctory migration. FGFR1 mutations are autosomal dominant and are loss-of-function mutations, affecting signaling of fibroblast growth factor. The different genes include fibroblast growth factor-1 receptor (*FGFR1* – autosomal dominant), KAL gene (*Kal1* – X-linked), *FGF8*, *PROKR2*, *KAL3*, *KAL4*, and *KISS1*. Patients typically present with primary amenorrhea and delayed growth/puberty, but there are variations in severity. A unique finding in Kallmann's syndrome is that patients do go through adrenarche and thus have normal pubic hair. They have some DHEAS production and small amount of adrenal androgen and estrogen production. Patients may have other findings such as clef palate or lip, syndactyly, and other genitourinary anomalies.

The following labs can be drawn, and these cutoffs are typically found in GnRH deficiency: estradiol <20 pg/mL, FSH and LH low (<4–5 IU/L each), and normal pituitary function (TFTs, cortisol, IGF1, and imaging findings w/o evidence of pituitary mass).

22.8 GnRH Receptor Mutations

There are several mutations that inactivate the GnRH receptor gene, affecting GnRH binding, transport, etc. The clinical presentation ranges from puberty delay to not having development of secondary sex characteristics. Other genes involved include *GnRHR*, *GnRh1*, *TAC3*, *TAC3R*, *CHD7*, and *Semaphorin 3A*.

We recommend treatment of GnRH deficiency with hormone replacement therapy. The regimen depends on the severity and current age of the patient and includes bone age, height percentile, predicted adult height, and desired psychosexual outcomes. The goal is to help achieve secondary sex characteristics, build bone and muscle mass, and sustain/restore fertility. Treatment with oral or transdermal estradiol starting at low doses will initiate breast development. The dose is gradually increased to complete sexual maturation once breast development and a reasonable height are attained. After this, long-term combination oral contraceptives or replacement therapy to 50 and possibly beyond is recommended.

22.8.1 Dosing

Transdermal: 0.08–0.12 mcg estradiol per kg body weight.

Oral CEE: 0.3 mg per day up to 1.25 mg per day.

Once menses initiates, then addition of cyclic progestin therapy is indicated to protect against endometrial hyperplasia.

Patients with GnRH deficiency desiring fertility will need exogenous gonadotropins in order to induce ovulation.

23 Conclusion

The basic workup for amenorrhea includes hCG to exclude pregnancy, followed by TSH, and prolactin in nonpregnant women. FSH can be checked to evaluate the hypothalamic-pituitary axis. The most common reason for amenorrhea is ovarian dysfunction. With a normal FSH, PCOS, thyroid dysfunction, and hyperprolactinemia are the most common reasons for abnormal menses. High gonadotropins are concerning for primary ovarian insufficiency. The most common etiologies for this are genetic, and karyotype and fragile X should be evaluated in the initial step, followed by an autoimmune workup. In patients with a low FSH, a hypothalamic etiology must be evaluated and imaging obtained to rule out pituitary mass. In patients with low BMI weight loss, stress, or vigorous exercise, hypothalamic amenorrhea is common. Congenital outflow abnormalities can be detected with a physical exam and pelvic ultrasound and are seen with primary amenorrhea. In patients with a history of uterine instrumentation, Asherman should be suspected and can be evaluated with sonohysterography or hysteroscopy.

24 Cross-References

- ▶ Hyperprolactinemia, Galactorrhea, and Pituitary Adenomas
- ▶ Workup and Management of Polycystic Ovary Syndrome

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