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Approximately 50% of girls with congenital hypogonadotropic hypo gonadism, with or without anosmia, have a history of some degree of breast development, and 10% report one to two episodes of vaginal bleeding. Family studies suggest that genes identified in association with absent puberty may also cause delayed puberty, and recent reports have further suggested that a genetic susceptibility to environmental stresses such as diet and exercise may account for at least some cases of func tional HA, including in girls who present with primary amenorrhea. Although neuroanatomic causes of delayed puberty are considerably less common in girls than in boys, it is always important to rule these out in the setting of primary hypogonadotropic hypogonadism.

PART 12 Endocrinology and Metabolism ■ ■FURTHER READING Balasubramanian R, Crowley WF Jr: Isolated gonadotropin-releasing hormone (GnRH) deficiency. 2007 May 23 [Updated 2022 May 12], in GeneReviews [Internet]. Adam MP et al (eds). Seattle, WA, University of Washington, Seattle, 1993-2025. Available from: https://www.ncbi.nlm. nih.gov/books/NBK1334/. Brito VN et al: The congenital and acquired mechanisms implicated in the etiology of central precocious puberty. Endocr Rev 44:193, 2023. Cedars MI: Evaluation of female fertility-AMH and ovarian reserve testing. J Clin Endocrinol Metab 107:1510, 2022. Lippincott MF et al: HU206 constitutional delay of puberty and idiopathic hypogonadotropic hypogonadism: differential contri butions of common genetic variants. J Clin Endocrinol Metab 7:bvad114.1457, 2023. Louden ED et al: Genetics of hypogonadotropic hypogonadism: Human and mouse genes, inheritance, oligogenicity, and genetic counseling. Mol Cell Endocrinol 534:111334, 2021. Moore AM et al: KNDy neurons of the hypothalamus and their role in GnRH pulse generation: An update. Endocrinology 165:bqad194, 2023. Janet E. Hall, Anuja Dokras

Menstrual Disorders

and Pelvic Pain Menstrual dysfunction can signal an underlying abnormality that may have long-term health consequences. Although frequent or prolonged bleeding usually prompts a woman to seek medical attention, infre quent or absent bleeding may seem less troubling, and the patient may not bring it to the attention of the physician. Thus, a focused menstrual history is a critical part of every encounter with a female patient. Pel vic pain is a common complaint that may relate to an abnormality of the reproductive organs but also may be of gastrointestinal, urinary tract, or musculoskeletal origin. Depending on its cause, pelvic pain may require urgent surgical attention. Recent guidelines no longer recommend routine pelvic examination in asymptomatic, average-risk

women other than periodic cervical cancer screening. However, pelvic examination is an important part of the evaluation of amenorrhea, abnormal uterine bleeding, and pelvic pain. MENSTRUAL DISORDERS ■ ■DEFINITION AND PREVALENCE Amenorrhea refers to the absence of menstrual periods and is classified as primary if menstrual bleeding has never occurred in the absence of hormonal treatment or secondary if menstrual periods cease for 3–6 months. Primary amenorrhea is a rare disorder that occurs in <1% of the female population. However, between 3 and 5% of women

experience at least 3 months of secondary amenorrhea in any specific year. There is no evidence that race or ethnicity influences the preva lence of amenorrhea. However, because of the importance of adequate nutrition for normal reproductive function, both the age at menarche and the prevalence of secondary amenorrhea vary significantly in dif ferent parts of the world. Abnormal uterine bleeding (AUB) has replaced the term dysfunc tional uterine bleeding and describes irregularities in the menstrual cycle involving frequency, cyclicity, duration, and volume of flow out side of pregnancy. A menstrual cycle typically occurs every 21–35 days, lasting between 4 and 7 days, with up to 80 mL of blood loss. Variations in any of these parameters constitutes a diagnosis of AUB, with up to one-third of women between menarche and menopause experiencing these symptoms. The acronym PALM-COEIN, which was developed to describe the etiologies for AUB, includes the structural causes (polyp, adenomyosis, leiomyoma [submucosal or other myoma], and malignancy and hyperplasia) and nonstructural causes (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, and not yet classified). Oligo- and anovulation are most frequently associated with polycystic ovary syndrome (PCOS). Primary Amenorrhea The absence of menarche (the first men strual period) by age 16 has been used traditionally to define primary amenorrhea. However, other factors, such as growth, secondary sexual characteristics, and the presence of cyclic pelvic pain, also influence the age at which primary amenorrhea should be investigated. Recent studies suggest that puberty is occurring at an earlier age, particularly in obese girls. However, it is important to note that these data reflect earlier breast development alone with minimal change in the age of menarche. Thus, an evaluation for amenorrhea should be initiated by age 15 or 16 in the presence of normal growth and secondary sexual characteristics; age 13 in the absence of secondary sexual character istics or if height is less than the third percentile; age 12 or 13 in the presence of breast development and cyclic pelvic pain; or within 2 years of breast development if menarche has not occurred. Secondary Amenorrhea or Oligomenorrhea Irregular cycles are relatively common for up to 3 years after menarche and for 1–2 years before the final menstrual period. In the intervening years, menstrual cycle length is ~28 days. Cycle-to-cycle variability in an individual woman who is ovulating consistently is generally +/− 2 days. Pregnancy should be excluded early in any evaluation of menstrual irregularity. However, many women occasionally miss a single period. Three months of secondary amenorrhea, or 6 months in women with previously irreg ular cycles, should prompt an evaluation, as should a history of inter menstrual intervals >35 or <21 days or bleeding that persists for >7 days. ■ ■DIAGNOSIS Pregnancy is the most common cause of amenorrhea and must be excluded in all cases, regardless of patient history. Evaluation of men strual dysfunction depends on understanding the interrelationships between the four critical components of the reproductive tract: (1) the hypothalamus, (2) the pituitary, (3) the ovaries, and (4) the uterus and outflow tract (Fig. 405-1; Chap. 404). This system is maintained by complex negative and positive feedback loops involving the ovar ian steroids (estradiol and progesterone) and peptides (inhibin B and inhibin A) and the hypothalamic (gonadotropin-releasing hormone [GnRH]) and pituitary (follicle-

stimulating hormone [FSH] and luteinizing hormone [LH]) components of this system (Fig. 405-1). Disorders of menstrual function fall into two main categories: disorders of the uterus and outflow tract and disorders of ovulation. Many of the conditions that cause primary amenorrhea are congenital but go unrecognized until the time of normal puberty (e.g., genetic, chromosomal, and anatomic abnormalities). All causes of secondary amenorrhea also can cause primary amenorrhea. Disorders of the Uterus or Outflow Tract Abnormalities of the uterus and outflow tract typically present as primary amenorrhea. In patients with normal pubertal development and a blind vagina,

– GnRH – LH FSH + Estradiol Progesterone FIGURE 405-1 Role of the hypothalamic-pituitary-gonadal axis in the etiology of amenorrhea. Gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus stimulates follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion from the pituitary to induce ovarian folliculogenesis and steroidogenesis. Ovarian secretion of estradiol and progesterone controls the shedding of the endometrium, resulting in menses, and, in combination with the inhibins, provides feedback regulation of the hypothalamus and pituitary to control secretion of FSH and LH. The prevalence of amenorrhea resulting from abnormalities at each level of the reproductive system (hypothalamus, pituitary, ovary, uterus, and outflow tract) varies depending on whether amenorrhea is primary or secondary. PCOS, polycystic ovarian syndrome. the differential diagnosis includes obstruction by a transverse vaginal septum or imperforate hymen; müllerian agenesis (Mayer-RokitanskyKuster-Hauser syndrome), which can be caused by mutations in the WNT4 gene, and androgen insensitivity syndrome (AIS), which is an X-linked recessive disorder that accounts for ~10% of all cases of pri mary amenorrhea (Chap. 403). Patients with AIS have a 46,XY karyo type, but because of the lack of androgen receptor responsiveness, those with complete AIS lack features of androgenization and have female external genitalia. The absence of pubic and axillary hair distinguishes them clinically from patients with müllerian agenesis, as does a testos terone level in the male range. The rare patient with 5α reductase type 2 enzyme deficiency has a similar presentation but undergoes viriliza tion at the time of puberty. Asherman’s syndrome presents as secondary amenorrhea or hypomenorrhea and results from partial or complete obliteration of the uterine cavity by adhesions that prevent normal growth and shedding of the endometrium. Curettage performed for pregnancy complications accounts for >90% of cases; genital tuberculo sis is an important cause in regions where it is endemic. TREATMENT Disorders of the Uterus or Outflow Tract Obstruction of the outflow tract usually presents as dysmenorrhea or lower abdominal cyclic pain with no menses. Evaluation of the patient includes a medical history, physical examination including a perineal examination, and ultrasound imaging. In many cases, a magnetic resonance imaging (MRI) scan can more accurately iden tify the reproductive tract anomaly prior to surgery. It is important that surgery be performed as soon as the diagnosis is made as the risk of endometriosis is increased with retrograde menstrual flow. Müllerian agenesis may require surgical intervention to allow sexual intercourse, although vaginal dilatation is adequate in some patients. In these patients, because ovarian function is normal, assisted reproductive techniques can be used with a surrogate

Primary Secondary Hypothalamus 28% 36% Menstrual Disorders and Pelvic Pain CHAPTER 405 Pituitary 2% 15% Inhibin B Inhibin A Estradiol PCOS 8% 30% Ovary 43% 12% Uterus/outflow tract 19% 7% carrier. More recently, there have been a few cases of successful uterine transplantation in women with müllerian agenesis. AIS (Chap. 402) requires gonadectomy because there is risk of gonado blastoma in the dysgenetic gonads, although surgery is generally delayed until after breast development and the pubertal growth spurt. Estrogen replacement is indicated after gonadectomy,

and vaginal dilatation may be required to allow sexual intercourse. Disorders of Ovulation Once uterus and outflow tract abnor malities have been excluded, other causes of amenorrhea involve dis orders of ovulation. The differential diagnosis is based on the results of initial tests, including a pregnancy test, an FSH level (to determine whether the cause is likely to be ovarian or central), and assessment of hyperandrogenism (Fig. 405-2). HYPOGONADOTROPIC HYPOGONADISM Low estrogen levels in com bination with normal or low levels of LH and FSH are seen with anatomic, genetic, or functional abnormalities that interfere with hypo thalamic GnRH secretion or normal pituitary responsiveness to GnRH. Although relatively uncommon, tumors and infiltrative diseases should be considered in the differential diagnosis of hypogonadotropic hypo gonadism (Chap. 392). These disorders may present with primary or secondary amenorrhea. They may occur in association with other features suggestive of hypothalamic or pituitary dysfunction, such as short stature, diabetes insipidus, galactorrhea, and headache. Hypogo nadotropic hypogonadism also may be seen after cranial irradiation. In the postpartum period, amenorrhea occurs normally in association with breast feeding but may also be caused by pituitary necrosis (Shee han's syndrome) or lymphocytic hypophysitis. Because reproductive dysfunction is commonly associated with hyperprolactinemia from neuroanatomic lesions or medications, prolactin should be measured in all patients with hypogonadotropic hypogonadism (Chap. 392). Isolated hypogonadotropic hypogonadism (IHH) occurs in women, although it is three times more common in men. IHH generally pres ents with primary amenorrhea, although 50% have some degree of

Amenorrhea uterus and outflow tract Normal Karyotype + β-hCG Pregnancy – FSH PART 12 Endocrinology and Metabolism Normal/low Normal Hyperandrogenism ↑ testosterone hirsutism, acne Pituitary causes Hypothalamic causes R/o • 21 hydroxylase deficiency • Tumor PCOS FIGURE 405-2 Algorithm for evaluation of amenorrhea. β-hCG, β-human chorionic gonadotropin; FSH, follicle-stimulating hormone; GYN, gynecologist; MRI, magnetic resonance imaging; PRL, prolactin; R/O, rule out; TSH, thyroid-stimulating hormone. breast development, and ~10% report one to two menses. IHH is asso ciated with anosmia in half of women (termed Kallmann's syndrome). Genetic causes of IHH have been identified in ~50% of patients (Chaps. 403 and 404). Functional hypothalamic amenorrhea (HA) is a diagnosis of exclu sion of other causes of hypogonadotropic hypogonadism including chronic diseases (type 1 diabetes, celiac disease, hyperthyroidism, Cushing's syndrome) and use of opioids, glucocorticoids, or psychotro pic medications that increase prolactin levels. Functional HA is most commonly associated with conditions causing a mismatch between energy expenditure and energy intake and/or significant stress leading to increased corticotropin-releasing hormone (CRH), suppression of GnRH, and decreased thyrotropin-releasing hormone (TRH) input. Variants in genes associated with IHH may increase susceptibility to these environmental inputs, accounting in part for the clinical vari ability in this disorder. Metabolic and stress signaling is transduced to the reproductive axis, at least in part, through leptin signaling from the periphery and via hypothalamic kisspeptin, neurokinin B, and dynorphin control of GnRH. The diagnosis of HA generally can be made on the basis of a careful history, a physical examination, and the demonstration of low levels of gonadotropins and normal prolactin levels. Eating disorders, excessive exercise, and chronic disease must be specifically excluded. An atypical history, headache, signs of other hypothalamic dysfunction, or hyperprolactinemia, even if mild, neces sitates cranial MRI to exclude a neuroanatomic cause. Up to 10% of women with HA may have some features of PCOS (irregular menses, increased ovarian volume with polycystic appearing ovaries, higher anti-müllerian hormone [AMH] levels, and slightly elevated androgen levels). HYPERGONADOTROPIC HYPOGONADISM Ovarian failure is consid ered premature when it

occurs in women <40 years old and accounts for ~10% of secondary amenorrhea. Primary ovarian insufficiency (POI) has replaced the terms premature menopause and premature ovarian failure in recognition of the continuum of impaired ovarian

Abnormal Normal Abnormal • High premature ovarian insufficiency • Turner’s syndrome • Androgen insensitivity syndrome • 5α reductase deficiency History of uterine instrumentation • Müllerian agenesis • Imperforate hymen • Transverse vaginal septum • Cervical stenosis Normal prolactin FSH negative trial of estrogen/ progesterone Asherman’s syndrome function encompassed by this disorder. Ovarian insufficiency is associ ated with the loss of negative feedback restraint on the hypothalamus and pituitary, resulting in increased FSH and LH levels. FSH is a better marker of ovarian failure because of loss of negative feedback effects of both estradiol and the inhibins and because its levels are less variable than those of LH. AMH levels will also be low in patients with POI. As with natural menopause, POI may wax and wane, and serial measure ments may be necessary to establish the diagnosis. The presentation may include irregular menses or complete cessation of menses, hot flashes, and vaginal dryness. Once the diagnosis of POI has been established, further evaluation is indicated because of other health problems that may be associated with POI. Although POI is most commonly of unknown cause, it also occurs in association with a variety of chromosomal abnormalities (most often Turner’s syndrome), autoimmune polyglandular failure syndromes, and other rare disorders. Radiotherapy and chemotherapy may reduce ovarian reserve, with effects on both the oocytes and the supporting granulosa cells. New approaches, including ovarian, oocyte, and embryo cryopreservation, should be offered to women of repro ductive age prior to gonadotoxic chemotherapy or pelvic radiation treatment. The recognition that early ovarian insufficiency occurs in premutation carriers of the fragile X syndrome is important because of the increased risk of severe intellectual disability in male children with FMR1 mutations. Thus, follow-up testing should include a karyotype in all POI patients, serum anti-cortical and 21-hydroxylase antibodies (specific but not sensitive for subsequent adrenal insufficiency), thy roid function and thyroid peroxidase antibodies, FMR1 premutation screening, and assessment of bone mineral density. Ovarian biopsy is not indicated. Although the number of genetic causes of POI is increas ing, routine testing for mutations other than FMR1 is currently not recommended. Hypergonadotropic hypogonadism occurs rarely in other disor ders, such as mutations in the FSH or LH receptors. Aromatase defi ciency and 17α-hydroxylase deficiency are associated with decreased estrogen and elevated gonadotropins and with hyperandrogenism and

hypertension, respectively. Gonadotropin-secreting tumors in women of reproductive age generally present with high, rather than low, estrogen levels and cause ovarian hyperstimulation or dysfunctional bleeding. TREATMENT Hypo- and Hypergonadotropic Causes of Amenorrhea Amenorrhea almost always is associated with chronically low levels of estrogen, whether it is caused by hypogonadotropic hypogonad ism or ovarian insufficiency. Development of secondary sexual characteristics requires gradual titration of estradiol replacement with eventual addition of progestin. Hormone replacement with either low-dose estrogen/progesterone regimens or oral contracep tive pills is recommended until the usual age of menopause for bone and cardiovascular protection. In women with functional HA or anorexia nervosa, hormone replacement alone may not be suf ficient to restore or maintain bone density. A more long-term mul tidisciplinary approach including behavioral health professionals is essential. Patients with hypogonadotropic hypogonadism who are interested in fertility require treatment with both exogenous FSH and LH.

Patients with POI can consider oocyte donation, which has a high rate of success in this population, although its use in women with Turner's syndrome is limited by increased cardiovascular risk in pregnancy. POLYCYSTIC OVARY SYNDROME The diagnosis of PCOS is made in adult women using the updated Rotterdam criteria (published in the 2023 international guidelines). These include irregular menses (<8 menses per year), clinical or biochemical hyperandrogenism (elevated total or free testosterone, modified Ferriman-Gallwey score >4–6 depending on ethnicity, see Chap. 406), and polycystic-appearing ovaries on ultrasound (≥20 antral follicles or ovarian volume ≥10 cm3 in at least one ovary) or elevated AMH. The presence of two of the three criteria will confirm the diagnosis, resulting in different phe notypes, namely, hyperandrogenic or non-hyperandrogenic. PCOS is a diagnosis of exclusion, and other etiologies for irregular menses and hyperandrogenism should be excluded (hypothyroidism, hyper prolactinemia, adrenal sources for hyperandrogenism). Diagnosis in adolescents may be difficult to establish, and it is recommended to wait at least 3 years after menarche before confirming the diagnosis. In adolescents, the diagnosis is based on irregular menses and hyper androgenism criteria only, as the ultrasound and AMH criteria are not established for this age group. Lean oligo-ovulatory patients with PCOS generally have high LH levels in the presence of normal to low levels of FSH and estradiol, although given the pulsatility of LH secre tion, a random serum LH/FSH ratio is not included in the diagnostic criteria. The prevalence of obesity is high in PCOS and significantly increases the risk of comorbidities including metabolic syndrome, type 2 diabetes, dyslipidemia, hypertension, and cardiovascular disease. Frequent anovulation results in irregular menses and increased risk of endometrial hyperplasia and endometrial cancer (two- to sixfold increased risk). Abnormalities in GnRH pulsatility result in elevated LH levels resulting in increased production of ovarian androgens. Insulin resistance, especially in skeletal muscle and adipose tissue, also contributes to increased insulin-stimulated ovarian androgen production. An alternate source of androgens, namely 11-oxygenated androgens, may also be elevated in this population. Genome-wide association studies in diverse populations and PCOS phenotypes have identified several loci (~19) associated with PCOS, and cluster analyses suggest the presence of reproductive and metabolic abnor malities. Symptoms generally begin in adolescence and are modified by obesity and age, such that by the fourth decade of life, most women with PCOS will have regular menses and normal serum androgens. There is a high prevalence of depression and anxiety disorders, as well as disordered eating and body image distress. PCOS is also associ ated with an increased risk of obstructive sleep apnea and metabolic

dysfunction-associated steatotic liver disease (MDSLD), independent of body mass index (BMI).

TREATMENT Polycystic Ovary Syndrome The first-line treatment of women with PCOS not attempting preg nancy is combined hormonal contraceptives to regulate menstrual cycles and decrease serum androgens by increasing sex hormone– binding globulin levels. Although serum androgens decrease by 2–3 months after initiating hormonal therapy, it may take longer to observe the beneficial effects on hirsutism and acne. Patients should be prescribed hormonal contraceptives containing the lowest effective dose of estrogen, either in a cyclic or continuous manner. If there is an inadequate response to hormonal con traceptives after 6 months for management of hyperandrogenic symptoms, antiandrogens, such as spironolactone and flutamide, can be considered (Chap. 406). Endometrial protection can also be achieved with the use of progestins (medroxyprogesterone acetate,10 mg, or Prometrium [progesterone], 200 mg daily for 10–14 days at least every 3 months, or a levonorgestrel intrauterine device [IUD]). All women with

PCOS should be screened for obesity, hypertension, glycemic control, depression, and anxiety at the time of diagnosis and then at regular intervals. Overweight and obese women should also have a fasting lipid profile at the time of diagnosis. Lifestyle management should be recommended in all women with PCOS, and metformin should be considered for prevention of cardiometabolic risk factors in those with overweight and obesity (Chap. 420). Women with PCOS are at an increased risk of early miscarriage, gestational diabe tes, gestational hypertension, preeclampsia, and preterm birth. Lifestyle management and prepregnancy counseling should be offered prior to attempting pregnancy (Chap. 408). Letrozole, an aromatase inhibitor, is the first-line treatment for ovulation induc tion followed by clomiphene citrate, a selective estrogen response modulator, with or without metformin. Injectable gonadotropins can be used judiciously by experienced practitioners to induce monofollicular growth as PCOS increases the risk of hyperstimu lation. Metformin can be used as an adjunct with diet and exer cise for obese women with PCOS or for treatment of diabetes or impaired glucose tolerance, as in non-PCOS patients. However, metformin alone is not recommended for endometrial protection or treatment of hyperandrogenic symptoms, infertility, pregnancy loss, or prevention of gestational diabetes. Menstrual Disorders and Pelvic Pain CHAPTER 405 ■ ■PELVIC PAIN The mechanisms that cause pelvic pain are similar to those that cause abdominal pain (Chap. 16) and include inflammation of the parietal peritoneum, obstruction of hollow viscera, vascular disturbances, and pain originating in the abdominal wall. Pelvic pain may reflect pelvic disease per se but also may reflect extrapelvic disorders that refer pain to the pelvis. In up to 60% of cases, pelvic pain can be attributed to gastrointestinal problems, including appendicitis, cholecystitis, infec tions, intestinal obstruction, diverticulitis, and inflammatory bowel disease. Urinary tract and musculoskeletal disorders are also common causes of pelvic pain. APPROACH TO THE PATIENT Pelvic Pain As with all types of abdominal pain, the first priority is to iden tify life-threatening conditions (shock, peritoneal signs) that may require emergent surgical management. The possibility of preg nancy should be identified as soon as possible by menstrual history and β-human chorionic gonadotropin (β-hCG) testing. A thorough history that includes the type, location, radiation, and recurrence can help identify the cause of acute pelvic pain. Specific associations

with vaginal bleeding, sexual activity, defecation, urination, move ment, or eating should be specifically sought. Determination of whether the pain is acute versus chronic and cyclic versus noncyclic will direct further investigation (Table 405-1). However, disorders that cause cyclic pain occasionally may cause noncyclic pain, and the converse is also true. ■ ■ACUTE PELVIC PAIN Pelvic inflammatory disease (PID) refers to infection of the upper geni tal tract and may present with a spectrum of symptoms. In the acute setting, the most common presentation is bilateral lower abdominal pain of recent onset that may be exacerbated with sexual activity. Risk factors for PID include age <25 years and history of multiple sexual partners, sexually transmitted infections (STIs), or recent uterine pro cedures. However, any sexually active woman can be at risk for PID. PID associated with tubo-ovarian abscess or peritonitis may present with severe pain, fever, and peritoneal signs. Abnormal uterine bleed ing may occur in about one-third of patients. Cervical motion tender ness, uterine and adnexal pain, and vaginal discharge are common findings on pelvic examination. The presence of right upper quadrant pain is suggestive of perihepatitis (Fitz-Hugh–Curtis syndrome). PART 12 Endocrinology and Metabolism The diagnosis of PID is established based on symptoms and clinical examination and can be aided by a wet mount preparation of vaginal discharge and nucleic acid amplification tests for Chlamydia trachomatis and Neisseria gonorrhoeae. Of note, a presumptive clinical diagnosis is sufficient to prescribe treatment even in

the absence of positive test results, as PID can occur due to other vaginal and enteric pathogens. Pelvic imaging can be obtained based on symptoms, findings of the pelvic examination, or if there is lack of response to therapy. With public health efforts to control STIs, the incidence and severity of PID have declined in the United States and Europe; however, this is not the case in the developing world. Subclinical PID with its attendant risks of infertility and ectopic pregnancy remains a significant problem world wide. Public health and professional organizations recommend annual testing for C. trachomatis in all sexually active women <25 years old and both C. trachomatis and N. gonorrhoeae in all women at increased risk. Adnexal pathology can present acutely and may be due to rupture, bleeding, or torsion of ovarian cysts or, much less commonly, the fal lopian tubes. Rupture of an ovarian cyst may be diagnosed based on the acute presentation in a reproductive-age woman and pelvic ultrasound findings of a simple, collapsed or hemorrhagic cyst, with or without free fluid in the pelvis. Ovarian torsion typically presents as acute onset of unilateral, intermittent pain and is a diagnosis of exclusion unless absent blood flow to the ovary is demonstrated via Doppler ultrasound imaging. Neoplasms of the ovary or fallopian tube are much less com mon causes of acute pain. Ectopic pregnancy represents 1–2% of all pregnancies and most commonly occurs in the fallopian tubes. It may present with acute lower abdominal pain, hemodynamic instability, and peritoneal signs. The index of suspicion should be high in any reproductive-age woman TABLE 405-1 Gynecologic Causes of Pelvic Pain ACUTE CHRONIC Cyclic pelvic pain Mittelschmerz Dysmenorrhea Noncyclic pelvic pain Pelvic inflammatory disease Ruptured or hemorrhagic ovarian cyst, endometrioma, or ovarian torsion Ectopic pregnancy Endometritis Acute growth or degeneration of uterine myoma Threatened abortion Endometriosis Uterine fibroids Adenomyosis Pelvic adhesions Pelvic malignancy Vulvodynia Chronic pelvic inflammatory disease Tuberculous salpingitis History of sexual abuse Pelvic congestion syndrome

presenting with abdominal pain or vaginal bleeding irrespective of cur rent use of contraception. Risk factors for an ectopic pregnancy include history of tubal disease, pelvic infection, tubal surgery, previous ectopic pregnancy, infertility, smoking, and current use of IUD, although a large proportion may have no risk factors. Rupture of the fallopian tube remains a life-threatening emergency; the incidence depends on access to care but is ~18% in developed countries. Diagnosis of an ectopic pregnancy can be established by assessing the patient’s menstrual his tory and symptoms, measuring a single or serial β-hCG levels, and performing pelvic ultrasound imaging. β-hCG levels typically double every 48 h in early first trimester, and 99% of viable intrauterine preg nancies are associated with an increase in hCG levels of at least 53% in

2 days. The discriminatory zone refers to β-hCG values above which the landmarks of a normal intrauterine pregnancy should be seen on ultrasound (1500–3000 IU/mL). Absence of an intrauterine pregnancy and presence of an adnexal mass or free fluid increase the likelihood of an ectopic pregnancy. Threatened abortion may also present with amenorrhea, abdominal pain, and vaginal bleeding with no cervical dilation in the setting of an intrauterine pregnancy with cardiac activ ity in the first trimester of pregnancy. Although more common than ectopic pregnancy, it is rarely associated with systemic signs. Uterine pathology includes endometritis, and less frequently, degenerating leio myomas (fibroids) present with acute pain. Endometritis often is asso ciated with vaginal bleeding and systemic signs of infection. It occurs in the setting of STIs, uterine instrumentation, or postpartum infection. TREATMENT Acute Pelvic Pain Treatment of acute pelvic pain depends on the suspected etiology but may require surgical or medical intervention. Immediate treat ment of PID is indicated upon diagnosis, even if the diagnosis is presumed or the symptoms are mild, due to long-term complica tions resulting in increased risk of ectopic

pregnancy and infertility. Treatment in patients eligible for outpatient management includes 250 mg IM ceftriaxone and a 14-day course of oral doxycycline 100 mg twice daily. If the presentation is acute with high fever, nausea, vom iting, severe abdominal pain, or presence of tubo-ovarian abscess, inpatient therapy is recommended (Chap. 141). Conservative man agement is an important consideration for ovarian cysts, if torsion is not suspected, to avoid unnecessary surgery and associated risks of reduced fertility due to cystectomy or adhesions. If surgery is performed, it is preferable to perform a cystectomy, removing the cyst wall and leaving the remaining ovary, in a reproductive-age woman. Combined hormonal contraceptives are recommended in women with a history of recurrent ovarian cyst formation. Surgi cal treatment may be required for ectopic pregnancies when the patient presents with acute pain, is hemodynamically unstable, or has signs of intraperitoneal bleeding. The choice of salpingectomy versus salpingostomy is based on patient’s presentation, desire for future child-bearing, and prior pelvic infections. Clinically stable women presenting with unruptured ectopic pregnancies may be appropriate for treatment with methotrexate, which is effective in ~90% of cases when multiple doses are used. Threatened abortion is managed conservatively even in the presence of a subchorionic hemorrhage. The treatment of endometritis is similar to PID. Pain from a degenerating fibroid, if visualized on pelvic sonography, can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs). CHRONIC PELVIC PAIN Chronic pelvic pain is a complex condition resulting from gyneco logic, urologic, or gastrointestinal organs and contributes to significant frustration and burden of disease. Common gynecologic conditions contributing to chronic pain are endometriosis, fibroids, adenomyosis, and adnexal pathology. In addition to a detailed history and physical exam, the evaluation of chronic pelvic pain typically includes a pelvic ultrasound. As causes other than those related to the female reproduc tive system are common, referral should be made to other specialists,

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