MENSTRUATION-RELATED DISORDERS

1- DYSMENORRHEA

Dysmenorrhea is pelvic pain, generally described as cramping, that occurs during or just prior to menstruation. Primary dysmenorrhea is pain in the setting of normal pelvic anatomy and physiology, whereas secondary dysmenorrhea is associated with underlying pelvic pathology.

⇨ Etiology

Risk factors for dysmenorrhea include irregular or heavy menses, age less than 30, menarche prior to age 12, body mass index (BMI) less than 20 kg/m^2, history of sterilization or sexual abuse, and smoking. Causes of secondary dysmenorrhea may include endometriosis, pelvic inflammatory disease (PID), uterine or cervical polyps, and uterine fibroids.

⇨ Pathophysiology

In primary dysmenorrhea, elevated arachidonic acid levels in the menstrual fluid lead to increased concentrations of prostaglandins and leukotrienes in the uterus. This induces uterine contractions, stimulating pain fibers, reducing uterine blood flow, and causing uterine hypoxia.

⇨ Treatment

»» *Desired Outcomes*

Desired treatment outcomes are relief of pelvic pain, improved quality of life, and fewer lost days at school and work.

»» *Nonpharmacologic Therapy*

Nonpharmacologic interventions which diminish dysmenorrhea symptoms include topical heat therapy, regular exercise, transcutaneous electric nerve stimulation (TENS), and acupuncture. In addition, a low-fat vegetarian diet has been shown to lessen the intensity and duration of dysmenorrhea.

»» *Pharmacologic Therapy*

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are the treatment of choice for dysmenorrhea. By inhibiting prostaglandin production, they exert analgesic properties, decrease uterine contractions, and reduce menstrual blood flow.

Choice of one agent over another is based on cost, convenience, and patient preference. Most commonly used agents are naproxen and ibuprofen. Treatment with an NSAID

should begin 1 to 2 days prior to the start of menses or at the onset of dysmenorrhea and continued for 2 to 3 days or until pain resolves. A loading dose (twice the usual single dose) is recommended, followed by the usually recommended dose.

Combination Hormonal Contraceptives (CHCs)

CHCs improve mild to severe dysmenorrhea by inhibiting the proliferation of endometrial tissue and ovulation, thereby reducing prostaglandin secretion and menstrual blood volume.

Two to three months of therapy are required to achieve the full effect. Both standard (28-day) and extended cycle (91-day) therapies are effective for primary dysmenorrhea. Extended cycle regimens are considered first line for dysmenorrhea due to endometriosis. Additional benefits include contraception and improving acne.

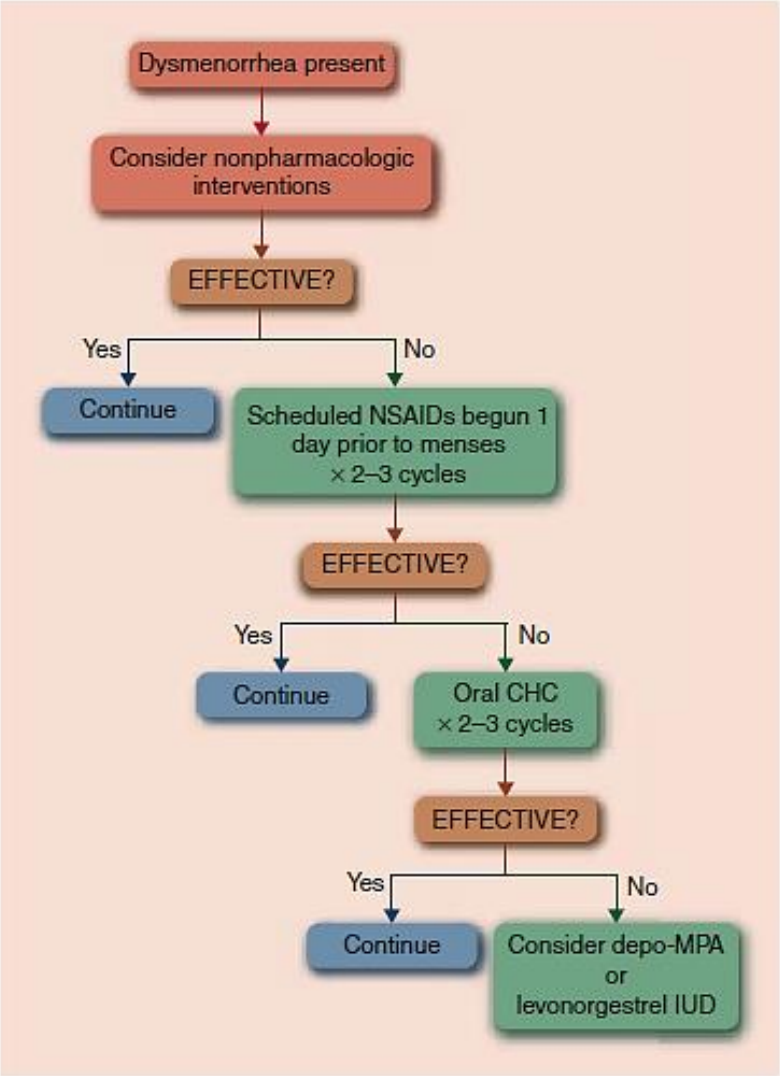

FIGURE 49–1. Treatment algorithm for dysmenorrhea. (CHC, combination hormonal contraceptive; IUD, intrauterine device; MPA, medroxyprogesterone acetate; NSAID, nonsteroidal anti-inflammatory drug.)

2- AMENORRHEA

Amenorrhea is the absence of menses. Primary amenorrhea occurs prior to age 15 in the presence of normal secondary sexual development or within 5 years of thelarche (if occurring before age 10). Secondary amenorrhea is the absence of menses for three cycles or 6 months in a previously menstruating woman.

⇨ Etiology

Unrecognized pregnancy is the most common cause of amenorrhea, therefore, a urine pregnancy test should be one of the first steps in evaluating amenorrhea. Amenorrhea not related to pregnancy, lactation, or menopause occurs in 3% to 4% of women. Additional causes of secondary amenorrhea include polycystic ovarian syndrome (PCOS), hypothalamic suppression, hyperprolactinemia, or primary ovarian insufficiency.

Amenorrhea is a potential side effect from using low-dose or extended oral CHCs and depot medroxyprogesterone acetate. Many women experience delayed return of menses after discontinuation of CHC. If spontaneous resolution of amenorrhea does not occur within 3 to 6 months following CHC discontinuation, evaluation for other conditions should be considered (like PCOS).

⇨ Treatment

»» *Desired Outcomes*

Treatment goals include restoring the normal menstrual cycle, preserving bone density, preventing bone loss, improving quality of life, and restoring ovulation, thus improving fertility. Amenorrhea attributable to hypoestrogenism (eg, premature ovarian insufficiency) can cause hot flashes and dyspareunia. In prepubertal females, the absence of secondary sexual characteristics and menarche may occur.

»» *Nonpharmacologic Therapy*

Nonpharmacologic therapy for amenorrhea depends on the underlying cause. Amenorrhea secondary to undernutrition or anorexia may respond to weight gain and psychotherapy. If excessive exercise is the culprit, exercise reduction is recommended.

»» Pharmacologic Therapy

Estrogen/Progestin Replacement Therapy

For most conditions associated with primary or secondary amenorrhea, estrogen treatment is recommended. To minimize risk of endometrial hyperplasia and cancer, progestin should also be given to women with an intact uterus. Estrogen's role is to reduce osteoporosis risk, stimulate and maintain secondary sexual characteristics, and improve quality of life. Conjugated equine estrogen and oral CHCs are examples.

Dopamine Agonists

In women with hyperprolactinemia who desire conception, dopamine agonists are an option. Dopamine agonists reduce prolactin levels and resolve amenorrhea. Additionally, they restore ovulation in 80% to 90% of women. The most commonly studied agents are bromocriptine and cabergoline.

Progestins

Progestins have long been used to induce withdrawal bleeding in women with secondary amenorrhea. Efficacy varies depending on the formulation used. Withdrawal bleeding occurs with intramuscularly injected progesterone and oral medroxyprogesterone acetate in 70% and 95% of patients, respectively. The usual dose of medroxyprogesterone acetate is 10 mg orally once daily for 7 to 10 days.

Insulin-Sensitizing Agents

Amenorrhea related to anovulation and PCOS may respond to insulin sensitizing agents (metformin).

Calcium and Vitamin D Supplementation

All patients experiencing amenorrhea should follow a diet rich in calcium and vitamin D to support bone health. Supplemental calcium and vitamin D (1200 mg/800 International Units per day) should be recommended for patients with inadequate dietary consumption.

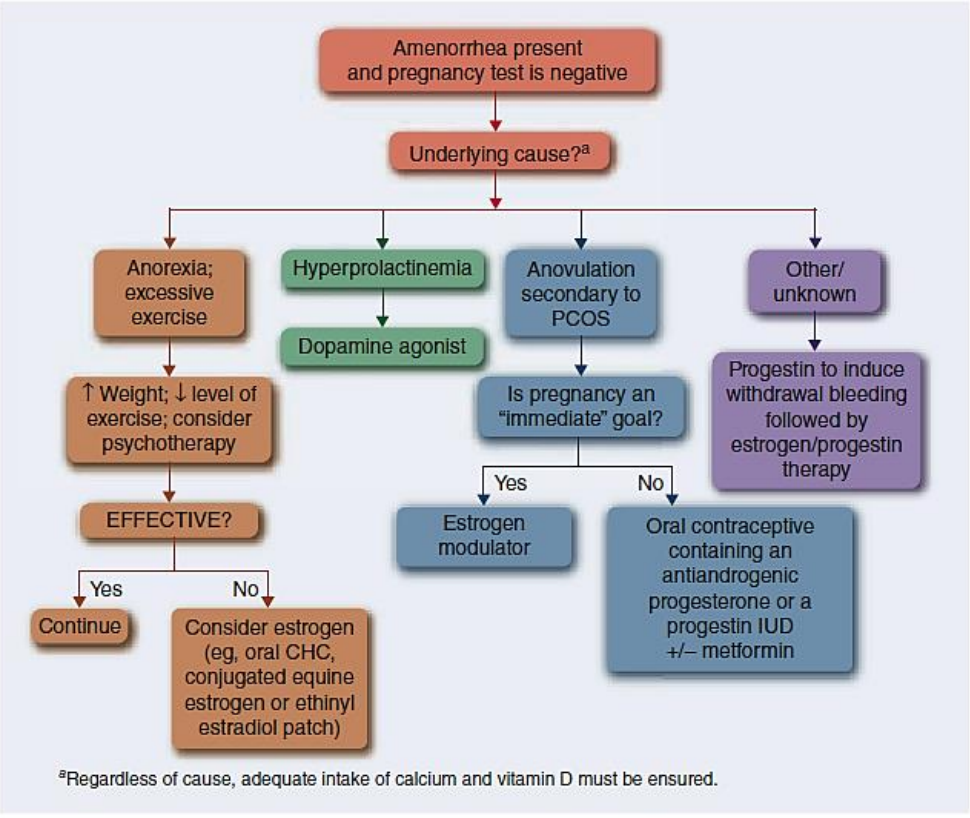

FIGURE 49–4. Treatment algorithm for amenorrhea. (CHC, combination hormonal contraceptive; IUD, intrauterine device; PCOS, polycystic ovarian syndrome.)

3- MENORRHAGIA

Menorrhagia describes prolonged menstrual bleeding (lasting greater than 7 days) or cyclic, heavy menstrual bleeding greater than 80 mL per cycle). It is difficult to quantify menstrual blood loss in clinical practice. Many women with less than 80 mL of blood loss seek medical attention with concerns of containment flow problems, unpredictable heavy flow, reduced quality of life, and other dysmenorrhea symptoms.

⇨ Etiology

Causes of menorrhagia can be divided into systemic disorders and reproductive tract abnormalities. Intrauterine pregnancy, ectopic pregnancy, and miscarriage are at the top of the differential diagnosis list for any woman presenting with heavy menses. Additionally, genital tract malignancies and infections may present with abnormal bleeding.

Systemic disorders include coagulation dysfunction such as von Willebrand disease and platelet function disorders. Hypothyroidism is also associated with heavy menses. Specific reproductive tract causes of menorrhagia are more common in older childbearing women, and they include fibroids, adenomyosis, endometrial polyps, and gynecologic malignancies.

⇨ Treatment

»» *Desired Outcomes*

Goals of therapy are to reduce menstrual blood flow, reduce risk of anemia, improve quality of life, and defer the need for surgical intervention.

»» Nonpharmacologic Therapy

Surgical interventions are reserved for patients nonresponsive to pharmacologic treatment and include endometrial ablation and hysterectomy.

»» Pharmacologic Therapy

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are first-line treatments for menorrhagia associated with ovulatory cycles. They are taken only during menses, and a 20% to 35% reduction in blood loss is reported in 75% of treated women. *This reduction is directly proportional to the amount of pretreatment blood loss.* They may also improve dysmenorrhea.

Combination Hormonal Contraceptives

CHCs are beneficial to women with menorrhagia who do not desire pregnancy. As with NSAIDs, *the reduction in blood loss is proportional to pretreatment blood loss.*

Progestins

Menorrhagia may also be treated with the levonorgestrel-releasing IUD, which consistently reduces menstrual flow by 75% to 95%, and after 12 months, 20% to 80% of women experience amenorrhea. Cyclic progestin therapy, either during the luteal phase or for 21 days of the menstrual cycle, reduces menstrual blood loss. The levonorgestrel IUD is more effective than oral norethindrone administered cyclically. Oral progestin therapy is considered a third line option.

Tranexamic Acid

Tranexamic acid reduces plasmin activity and tissue plasminogen activator. While an immediate-release product has been available for a long time, a modified-release product has recently become available. It has better gastrointestinal tolerability and gives women another non-hormonal option to manage menorrhagia. Additionally, it can be recommended for women with von Willebrand disease.

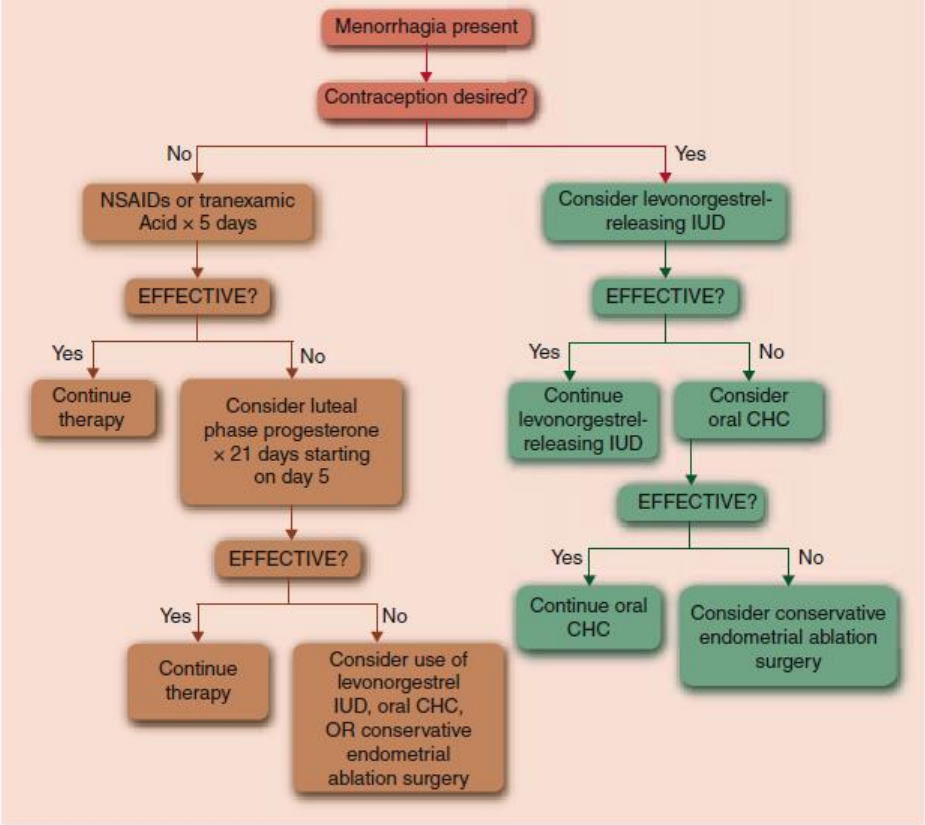

FIGURE 49–5. Treatment algorithm for menorrhagia. (CHC, combination hormonal contraceptive; IUD, intrauterine device; NSAID, nonsteroidal anti-inflammatory drug.)

4- PREMENSTRUAL SYNDROME

Premenstrual syndrome (PMS) encompasses both mood changes and physical symptoms. Symptoms may start up to 14 days before menstruation, although more usually they begin just a few days before and disappear at the onset of, or shortly after, menstruation. However, for some women, the beginning of menstruation may not signal the complete resolution of symptoms. Numerous studies have

demonstrated that this condition can cause substantial impairment of normal daily activity, including reduced occupational activity and significant levels of work absenteeism. The most severe form of PMS may be referred to as premenstrual dysphoric disorder (PMDD).

⇨ Etiology

PMS is not seen before puberty, during pregnancy or in postmenopausal women; therefore, the ovarian hormones have been implicated. The mineralocorticoids, prolactin, androgens, prostaglandins, endorphins, nutritional factors (e.g. pyridoxine, calcium and essential fatty acids) and hypoglycemia may be involved.

⇨ Symptoms

Symptoms occur 1–14 days before menstruation begins and disappear at the onset or shortly after menstruation begins. For the rest of the cycle, the woman feels well. Symptoms are cyclical, although they may not be experienced every cycle, and can be either physical and/or psychological.

Box 46.2 Diagnostic criteria for premenstrual syndrome (American College of Obstetricians and Gynecologists, 2000)

Patient reports one or more of the following affective and somatic symptoms during the 5 days before menses in each of three prior menstrual cycles.

Affective	Somatic
Depression	Breast tenderness
Angry outbursts	Abdominal bloating
Irritability	Headache
Anxiety	Swelling of extremities
Confusion	
Social withdrawal	

Symptoms relieved within 4 days of menses onset without recurrence until at least cycle day 13

Symptoms present in absence of any pharmacological therapy, hormone ingestion, or drug or alcohol abuse

Symptoms occur reproducibly during two cycles of prospective recording

Patient suffers from identifiable dysfunction in social or economic performance

Box 46.1 Summary of DSM-V diagnostic criteria for premenstrual dysphoric disorder (American Psychiatric Association, 2013)

One-year duration of symptoms which are present for the majority of cycles (occur luteal/remit follicular) as evidenced by prospective daily ratings during at least two consecutive cycles

Five of the following Criteria A symptoms (with at least one of those marked with an asterisk [*]) must occur during the week before menses and subside within days of menses.

1. Marked lability (e.g. mood swings)*
2. Marked irritability or anger*
3. Markedly depressed mood*
4. Marked anxiety and tension*
5. Decreased interest in usual activities
6. Difficulty in concentration
7. Lethargy and marked lack of energy
8. Marked change in appetite (e.g. overeating or specific food cravings)
9. Hypersomnia or insomnia
10. Feeling overwhelmed or out of control
11. Physical symptoms (e.g. breast tenderness or swelling, joint or muscle pain, a sensation of bloating and weight gain)

⇨ Treatment

»»General approach to treatment

The first step in the management of PMS is recognition of the problem and realization that many other women also suffer. Keeping a menstrual diary is useful

and will establish any link between symptoms and menstruation; this also will provide a cornerstone for diagnosis. After a few months, it will allow the patient to make predictions and help her deal with changes when they arrive.

»» Nonpharmacologic Therapy

Maintenance of good general health is important, especially with respect to diet and possible deficiencies. Dietary modifications that may be helpful include restricting caffeine and alcohol intake. Smoking can also exacerbate symptoms. Exercise may help, as may learning simple relaxation techniques. If fluid retention is a problem, then reducing fluid and salt intake may be of value. Increasing the intake of natural diuretics such as prunes, figs, celery, cucumber, parsley and foods high in potassium such as bananas, oranges, dried fruits, nuts, soya beans and tomatoes may all be useful. Hypoglycemia may also be involved in premenstrual tiredness, so eating small, protein-rich meals more frequently may help.

Results from clinical trials involving pyridoxine (vitamin B6) have shown conflicting results. However, some women do respond to pyridoxine and show improvement, particularly with respect to mood change, breast discomfort and headache. A typical dosage regimen would be 50 mg twice daily after meals or 100 mg after breakfast. The dose should not exceed 100 mg/day. Gastric upset and headaches have been reported at doses greater than 200 mg. High doses over long periods have also been associated with peripheral neuropathies. Pyridoxine should be commenced 3 days before symptom onset and continued for 2 days after menstruation has started.

Calcium supplementation has shown some activity in reducing emotional, behavioral and physical symptoms. In addition, vitamin D and magnesium nutritional status have been found to be compromised in women with PMS.

There is limited evidence that supplementation with γ-linolenic acid, found in evening primrose oil, gives relief from physical symptoms, especially breast tenderness.

»» Pharmacologic Therapy

Antidepressants

The selective serotonin reuptake inhibitors (SSRIs) using fluoxetine, sertraline, citalopram, fluvoxamine or paroxetine are becoming more popular in the treatment of PMS related depression because they are an effective first-line therapy for severe PMS, and the side effects at low doses are generally acceptable. It is possible that SSRIs increase allopregnanolone levels which enhances GABA-A function. Studies have also found that not only do SSRIs improve behavioral symptoms, but some improvement in physical symptoms has also been noted, and this is being reflected in the increased prescribing of SSRIs.

Combined oral contraceptives

Some women are helped by the combined oral contraceptives (COCs) pill because it prevents ovulation from taking place. The combination of ethinylestradiol with drospirenone is also available as an oral contraceptive and appears to be useful in the management of PMS.

Progestogens

Because of the lack of convincing trial evidence and the risk of side effects, the use of progestogens is no longer recommended.

Other Treatments

Bromocriptine stimulates central dopamine receptors, and thus inhibits the release of prolactin. It may be useful for breast tenderness and occasionally has beneficial effects upon fluid retention and mood changes. However, side effects would now be seen as far outweighing the benefits for this particular indication.

Improvements in tension, irritability, depression, headache and general aches and pains can be seen in some women who take prostaglandin synthesis inhibitors. Most of the available information centers upon the use of mefenamic acid at dosages of 250 mg three times a day 12 days before a period is due, increasing to 500 mg three times a day 9 days before the period and continuing until the third day of menstruation. Other inhibitors of prostaglandin synthesis are likely to be just as effective and may be associated with fewer side effects. Some experimental evidence, however, suggests that, in addition to being a COX inhibitor, mefenamic acid also has activity as an antagonist at PGE receptors; therefore, this may be useful if heavy menstrual bleeding is also a problem. For optimum effectiveness, this form of therapy should be started 24 hours before the onset of symptoms.

5- POLYCYSTIC OVARY SYNDROME

Polycystic ovary syndrome (PCOS) affects approximately 6% to 15%, or approximately 1 in 10, women of reproductive age, making it the leading cause of anovulatory infertility and the most common endocrine abnormality for this age group. Stein-Leventhal syndrome, polycystic ovary, polycystic ovarian disease, hyperandrogenic chronic anovulatory syndrome, and functional ovarian hyperandrogenism are common alternative terms for PCOS.

⇨ Diagnostic Criteria

An expert conference in Rotterdam sponsored by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine in 2003 concluded that the presence of two of these three features, after exclusion of related disorders, confirmed diagnosis of PCOS: (a) oligo-ovulation (infrequent or

irregular ovulation with fewer than nine menses/year)or anovulation, (b) clinical or biochemical signs of hyperandrogenism (clinical signs such as hirsutism, biochemical signs such as elevated testosterone levels), or (c) polycystic ovaries.

⇨ Pathophysiology

The pathophysiology of PCOS is complex. The primary defect in PCOS is unknown, but at least three potential mechanisms, acting alone or synergistically, appear to create the characteristic clinical presentation. These mechanisms include inappropriate gonadotropin secretion, excessive androgen production, and insulin resistance with hyperinsulinemia. A genetic basis for PCOS has been postulated, but its mode of transmission is unclear.

⇨ Clinical Characteristics

Common clinical signs of hyperandrogenism in PCOS include hirsutism, acne, and alopecia. Hirsutism, the most common of these characteristics, occurs in 60% to 75% of women with PCOS. Women seeking treatment for hirsutism may be evaluated for PCOS.

Ovulatory dysfunction in PCOS is typically described as oligo-ovulation or anovulation, presenting clinically as a woman with irregular menstrual cycles. Overall, 95% of women with PCOS and oligo-ovulation have menstrual dysfunction, usually oligomenorrhea or amenorrhea.

Obesity (defined as a body mass index [BMI] $\geq$30 kg/m^2) occurs in approximately 61% to 76% of women with PCOS. Central or abdominal obesity is the typical pattern.

⇨ Long-Term Complications

»» Impaired Glucose Tolerance and Diabetes

Studies have shown that women with PCOS have a higher prevalence of impaired glucose tolerance (IGT), gestational diabetes, diabetes, and insulin resistance compared with women without the syndrome.

Glucose tolerance should be assessed in all women with PCOS using a fasting and 2-hour oral (75 g) glucose tolerance test. Routine screening for diabetes with an oral glucose tolerance test should be performed for all women with PCOS by the age of 30 years.

»» Metabolic Syndrome and Cardiovascular Risk

Approximately one-third to one-half of women with PCOS have metabolic syndrome. Metabolic syndrome is present when the patient exhibits any three of these symptoms: abdominal obesity (>40 inches in men and >35 inches in women), triglycerides greater than or equal to 150 mg/dL, low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women), blood pressure greater than or equal to 130/85 mm

Hg, and fasting glucose greater than or equal to 110 mg/dL. It is believed that insulin resistance and hyperandrogenism are contributing factors to metabolic syndrome in women with PCOS.
Compared with women without PCOS, women with PCOS are reported to have a higher prevalence of cardiovascular risk factors, including hypertension, dyslipidemia, and surrogate markers for early atherosclerosis (e.g., increased C-reactive protein concentrations).

»» Obstructive Sleep Apnea
Obstructive sleep apnea is cessation of breathing that occurs during sleep. Patients may not be aware that they are having the symptoms of sleep apnea, which include snoring and a gasping or snorting when breathing resumes. Insulin resistance appears to be a strong predictor of sleep apnea—more so than age, BMI, or the circulating testosterone concentration.

»» Endometrial Hyperplasia and Cancer
Chronic anovulation in women with PCOS results in an endometrium that is exposed to the prolonged effects of estrogen unopposed by progesterone. Therefore, PCOS is a risk factor for endometrial hyperplasia.

⇨ **Treatment**
»» ***Goals of Treatment***
The primary goals are to correct anovulation or oligo-ovulation and improve fertility, address hirsutism, maintain a normal endometrium, block the actions of androgens at target tissues, reduce insulin resistance and hyperinsulinemia, reduce weight, and prevent long-term complications.

»» Nonpharmacologic Therapy
Weight reduction programs designed for a modest weight loss (5%–10%) with the incorporation of fitness are effective in reducing metabolic disease, cardiovascular risk, and improving ovulatory potential. Weight reduction should be considered first-line therapy in all overweight or obese women with PCOS.

»» Pharmacologic Therapy
Combined Oral Contraceptives
Estrogen–progestin combination therapy with a COC is the treatment of choice for women seeking regularity in menstrual cycles and relief from hyperandrogenic symptoms. The estrogen component suppresses LH, resulting in a reduction of androgen production, and increases hepatic production of sex hormone binding globulin (SHBG), thereby reducing free testosterone. The progestins in various COCs

possess variable androgenic effects, so the choice of the COC may be considered to minimize androgenic exposure. The potential effects of COCs on insulin resistance, glucose tolerance, and lipids have been debated, do not appear to increase metabolic risk, and should be considered when choosing a progestin component.
Combined oral contraceptive therapy in PCOS should be initiated with a formulation that contains a low dose or very low dose of estrogen (≤35 mcg of ethinyl estradiol) and a progestin with low androgenic or antiandrogen properties. Most COCs manufactured today have low or very low estrogen doses. Desogestrel and norgestimate are progestins with low androgen potential, and drospirenone is an antiandrogen.

Metformin

Metformin inhibits hepatic glucose output, providing lower insulin concentrations and reducing androgen production in the ovary. Metformin also appears to influence ovarian steroidogenesis directly. Metformin is primarily used for IGT or T2D related to PCOS. Metformin has minimal effectiveness for hirsutism or acne and was found to have no benefit improving rate of miscarriage, fertility, or live-birth rates in anovulatory women with PCOS. Its routine use for treatment of infertility is not recommended. The most commonly used and most effective dose of metformin in PCOS is 500 mg orally 3 times daily. It should be titrated slowly to this effective dose; doses up to 2,000 mg daily or 2,550 mg daily may be necessary for individual circumstances.

»» Agents for Hirsutism

Spironolactone

Spironolactone acts by competitively inhibiting dihydrotestosterone (DHT) from interacting with its androgen receptor. This causes a decrease in activity of ovarian produced testosterone. Spironolactone reduces hair growth by 40% to 88%; however, it takes 6 to 9 months for improvement. The usual effective spironolactone dose is 50 to 100 mg orally twice daily for 6 to 12 months.

Finasteride

Finasteride is a type II 5α-reductase inhibitor, which decreases the conversion of testosterone to DHT. It provides an approximate 30% reduction from baseline for hirsutism. The dose of 5 to 7.5 mg orally daily typically takes 6 months for clinical improvement.

»» Agents for Ovulation Induction

Clomiphene Citrate

Clomiphene citrate induces ovulation via an antiestrogenic effect on the hypothalamus. GnRH secretion is increased, which increases LH and FSH

production. The increase in FSH concentrations causes appropriate follicle development and estrogen secretion, which produces a positive feedback on the hypothalamic–pituitary system to create a LH surge for ovulation. The usual initial dose of clomiphene citrate is 50 mg orally daily for 5 days, started on day 5 after a spontaneous or progestin-induced menses.

Aromatase Inhibitors

Letrozole is an aromatase inhibitor (AI) which blocks estrogen synthesis to directly affect hypothalamic–pituitary–ovarian function and increase pregnancy rates. Potential advantages of letrozole over clomiphene citrate include more physiologic hormonal stimulation of the endometrium, a lower multiple-pregnancy rate through single follicle recruitment, a better side-effect profile with fewer vasomotor and mood symptoms, and more rapid clearance which reduces the chances of periconceptional exposure.

Based on this information and its potential advantages over clomiphene, letrozole may become a first-line agent for ovulation induction in women with PCOS.

Other Agents

If the clomiphene or letrozole is not successful, dexamethasone 0.25 mg at bedtime can be used in combination with clomiphene.

6- ANOVULATORY BLEEDING

Anovulatory uterine bleeding (AUB) is irregular menstrual bleeding from the endometrium ranging from light spotting to heavy blood flow. *It includes noncyclic menstrual bleeding due to ovulatory dysfunction (AUB-O), including anovulation or oligo-ovulation. AUB-O is secondary to the effects of unopposed estrogen and does not include bleeding owing to an anatomic lesion of the uterus.*

⇨ **Etiology**

Anovulatory uterine bleeding is the most common form of noncyclic uterine bleeding. Anovulation results from dysfunction at any level of the hypothalamic-pituitary-ovarian (HPO) axis which can be due to physiologic life stages such as adolescence, perimenopause, pregnancy, and lactation or pathologic causes.

Anovulation also occurs at any time during the reproductive years due to a pathologic cause. The most common causes of nonphysiologic ovulatory dysfunction are PCOS, hypothalamic amenorrhea, hyperprolactinemia, and premature ovarian failure.

⇨ **Pathophysiology**

A normal ovulatory cycle includes follicular development, ovulation, corpus luteum development, and luteolysis. During the cycle, the endometrium proliferates and

undergoes secretory changes and desquamation. This is influenced by estrogen alone, then by estrogen and progesterone, and culminates with estrogen and progesterone withdrawal. Progesterone stops endometrial growth and stimulates endometrial differentiation. In anovulatory women, a corpus luteum is not formed, and the ovary does not secrete progesterone. Without progesterone, there is no endometrial desquamation or differentiation. Chronic unopposed estrogen causes endometrial proliferation. The endometrium becomes vascular and fragile, resulting in noncyclic menstrual bleeding. The endometrium may also become hyperplastic and progress to a precancerous state, increasing the woman's risk of endometrial cancer.
The most common pathologic cause of anovulation is PCOS.

⇨ **Treatment**

»» ***Desired Outcomes***

The desired outcomes of therapy are to stop acute bleeding, prevent future episodes of noncyclic bleeding, decrease long-term complications of anovulation (eg, osteopenia and infertility), and improve overall quality of life.

»» ***Nonpharmacologic Therapy***

Nonpharmacologic treatment options depend on the underlying cause. For all women with PCOS, weight loss may be beneficial. In women who have completed childbearing or who have failed medical management, endometrial ablation or resection, and hysterectomy are surgical options. The preferred procedure is unclear.

»» Pharmacologic Therapy

Estrogen

Estrogen is the recommended treatment for managing acute bleeding episodes. It promotes endometrial growth and stabilization. Given as a CHC, it has averted emergency surgery in 95% of patients. It should then be continued to prevent recurrent anovulatory bleeding. Long-term therapy with a CHC reduces the risk of endometrial cancer compared to unopposed estrogen therapy.

Medroxyprogesterone Acetate

Depot and intermittent oral medroxyprogesterone acetate suppresses pituitary gonadotropins and circulating androgens in women with PCOS. Furthermore, cyclic progesterone may benefit women older than 40 years with anovulatory bleeding.

Estrogen Modulators

If the goal is to induce ovulation, the treatment of choice is clomiphene citrate. It is approximately three times more effective than metformin at achieving live births.

Insulin-sensitizing Agents

Metformin improves insulin sensitivity and is recommended in women who cannot tolerate CHC and have IGT or type-2 diabetes mellitus. *In patients with PCOS, it is associated with reduced circulating androgen concentrations, increased ovulation rates, and improved glucose tolerance. Additionally, metformin may decrease cardiovascular risk and promote weight loss.* These improvements are attributed to the SHBG increase that occurs via increased insulin sensitivity.

7- ENDOMETRIOSIS

Endometriosis is a condition in which endometrial tissue is found outside the uterus. These so-called ectopic endometrial foci have been found outside the reproductive tract in the gastro-intestinal tract, the urinary tract and even the lungs.

⇨ Pathophysiology

The most commonly cited theory is that of retrograde menstruation or the flow of menstrual fluid, endometrial cells, and other debris backward through the fallopian tubes resulting in implantation in the peritoneal cavity. Once endometrial cells reach the peritoneum, stimulated angiogenesis (potentially by estrogen, among other factors) appears to be a determinant of the development and growth of lesions.

Also at this point, the lesion stimulates an immune response, triggering the activation of macrophages, as well as cytokine and growth factor release. Peritoneal lesions may contribute to more distant disease by spread via hematogenous or lymphatic routes, or even by movement owing to iatrogenic causes, such as cesarean sections and other forms of gynecologic surgery.

Genetics also play a role in the development of endometriosis. For first-degree relatives of women with severe endometriosis, there is a 6 times higher rate of developing endometriosis when compared with women who do not have affected relatives.

Once endometrial tissue becomes implanted, hormones are necessary for their continued growth. As with intrauterine endometrium, the implants of endometriosis possess estrogen, progesterone, and androgen receptors. In general, estrogens stimulate the implants, whereas androgens or lack of estrogen results in implant atrophy. Because of their complex hormonal effects, progestins have variable effects on the implants. In addition, lesions also show high levels of estrogen biosynthesis, owing to abnormally increased aromatase activity, with a concomitant decrease in the inactivation of estrogen, resulting in high intralesional estrogen concentrations.

⇨ **Clinical Characteristics**

Location of Endometriosis and Associated Symptoms

Sites	Symptoms
Pelvic	
Cervix	Abnormal uterine bleeding
Ovaries	Dysmenorrhea
Peritoneum	Dyspareunia
Rectovaginal septum	Infertility
Uterosacral ligaments	Pelvic pain
Intestinal	
Abdominal scars	Intestinal obstruction
Sigmoid colon	Mid-abdominal pain
Small intestines	Nausea
	Painful defecation
	Rectal bleeding
Urinary Tract	
Bladder	Cyclic flank pain
Ureter	Hematuria
	Hydronephrosis
	Hydroureter

⇨ **Treatment**

»» ***Goals of Treatment***

The goals are to relieve symptoms and, if desired, to preserve or improve fertility.

»» ***Pharmacologic Therapy for Pain Management:***

Nonsteroidal Anti-inflammatory Drugs

NSAIDs, particularly those available as OTC products, are often the first medications that women try for relief of pain from endometriosis, often before they are officially diagnosed. NSAIDs may provide some relief of mild symptoms, particularly in women with endometriosis who have pain associated with the menses, and are an appropriate first choice for women with mild symptoms who do not desire contraception. They should not be the only therapy offered to patients with confirmed endometriosis.

Combined Hormonal Contraceptives

For women who do not receive pain relief from a trial of an NSAID, a reasonable next step for those women desiring contraception is the use of oral contraceptives because they are considerably better tolerated over the long-term versus other

hormonal options. They may be used alone or in combination with NSAIDs. OCs improves symptoms of endometriosis by inhibiting ovulation, decreasing hormone levels, and reducing menstrual flow, potentially to the point of amenorrhea. These mechanisms contribute to atrophy of endometrial implants. When used, the most appropriate regimen is continuous OC dosing, so that there is not a "placebo week" that allows for growth of endometrial implants.

Progestins

Similar to oral contraceptives, injectable progestins reduce symptoms of endometriosis by inhibiting ovulation, reducing hormone levels, and inducing endometrial atrophy. They may be particularly useful if estrogen use is contraindicated. Regimens used include oral medroxyprogesterone, depot medroxyprogesterone, or the levonorgestrel IUS.

Gonadotropin-Releasing Hormone Agonists

GnRH agonists (Nafarelin (Synarel), Leuprolide (Lupron), and Goserelin (Zoladex)) induce a pseudomenopausal state, resulting in relief of endometriosis symptoms. Because the GnRH agonists have a longer half-life than endogenous GnRH, their binding to GnRH receptors in the pituitary results in downregulation of the hypothalamic–pituitary–ovarian axis, decreasing release of FSH and LH, leading to low estrogen levels and amenorrhea.

Aromatase Inhibitors

Aromatase, the enzyme responsible for the synthesis of estrogens, is required for the conversion of androstenedione and testosterone to estrone and estradiol. Anastrozole and letrozole are type II AIs, binding reversibly to the enzyme to produce a beneficial effect on endometriosis symptoms.

However, early results suggest that their adverse effect profile, which includes flushes, myalgia, arthralgia, insomnia and decreased libido, is poorer than for the progestogens and oral contraceptives. Their use should be reserved at this time for those patients with severe endometriosis who have failed other therapies.

Danazol

Danazol, an androgenic drug derived from 17-ethinyl testosterone, also induces a pseudomenopausal state by increasing androgen levels and decreasing estrogen levels. It inhibits the enzymes involved in ovarian steroidogenesis and increases the metabolic clearance of estradiol. By creating a hypoestrogenic, hypoprogestogenic state, danazol causes anovulation, amenorrhea, and atrophy of endometrial implants.

Although effective at decreasing pelvic pain, danazol is poorly tolerated because of its significant side effects, which include weight gain, voice changes, edema, acne,

hot flashes, vaginal dryness, hirsutism, liver disease, and increased cholesterol; these occur in up to 85% of treated patients.

»» Nonpharmacologic Therapy for Pain Management:

Definitive Surgery

Definitive surgery, referring to total abdominal hysterectomy, bilateral salpingooophorectomy, and removal of all visible endometriosis, theoretically should eliminate the risk of recurrence of the disease. These procedures are not an option for many women with endometriosis who desire pregnancy in the future. It is invasive surgery, reserved for those patients whose pain is unresponsive to other therapies or to conservative surgery. Furthermore, removal of all endometriosis is difficult, and recurring pain is not uncommon.

Conservative Surgery

In contrast to definitive surgery, conservative surgery (involving ablation and removal of implants, and lysis of adhesions) preserves fertility and is commonly conducted during the initial diagnostic laparoscopy.