# Noncontraceptive Use of Contraceptive Agents

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## Educational Gap

**According to 2006–2008 National Survey of Family Growth data, 33% of adolescents ages 15 to 19 years using combined oral contraceptives do so solely for noncontraceptive reasons, mostly to alleviate problems and symptoms associated with menstrual periods. Consequently, it is necessary for physicians to become more knowledgeable of the known health benefits and noncontraceptive uses of contraceptive agents to enhance their treatment and care for adolescent patients. (1)**

## Objectives

**After completing this article, readers should be able to:**

1. **Identify medical conditions treatable with hormonal contraception.**
2. **Identify noncontraceptive benefits of contraceptive agents for adolescents.**
3. **Recognize conditions and diseases for which menstrual regulation or suppression can benefit adolescents, improve disease outcome, and enhance quality of life.**
4. **List the relative and absolute contraindications to the use of combined hormonal contraceptives.**
5. **Describe different contraceptive methods available for use.**

## Abbreviations

| | |
|---|---|
| CDC: | Centers for Disease Control and Prevention |
| CHC: | combined hormonal contraceptive |
| COCP: | combined oral contraceptive pill |
| FDA: | Food and Drug Administration |
| GnRH: | gonadotropin-releasing hormone |
| LNG-IUS: | levonorgestrel intrauterine system |
| NSAID: | nonsteroidal anti-inflammatory drug |
| PCOS: | polycystic ovary syndrome |
| PMDD: | premenstrual dysphoric disorder |
| PMS: | premenstrual syndrome |
| SCD: | sickle cell disease |
| vWD: | von Willebrand disease |
| vWF: | von Willebrand factor |

## Introduction

Recent data have revealed that more than 30% of adolescent girls use contraceptive agents solely for noncontraceptive reasons, typically to alleviate symptoms associated with menstrual periods but also for acne and endometriosis. (1) Most noncontraceptive uses of these agents are off-label; however, they have been deemed appropriate secondary to research and Cochrane review. This represents a change from historical trends in which contraceptive agents, specifically, oral contraceptive pills, were typically used by adolescents primarily for prevention of unintended pregnancy. In addition to this shift, another important change during the past decade has been the introduction of several new hormonal contraceptive agents. Not only has direct advertising to the public through various media increased public awareness of these newer methods, but marketing campaigns often highlight many of the noncontraceptive health benefits of these methods to increase use of the product. Because adolescents often are prescribed these newer contraceptive agents and are targets of such marketing campaigns, it is imperative for pediatricians to become more knowledgeable of their noncontraceptive indications and health benefits.

## Menstrual Regulation

Many adolescent girls have irregular menstrual periods. The most common cause of irregular menstruation is anovulatory bleeding secondary to immaturity of the hypothalamic-pituitary-ovarian axis. However, thyroid disorders,

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polycystic ovarian syndrome, and sexually transmitted infections are other common causes of irregular menstruation in adolescents.

Normal menstrual periods in adolescents usually occur every 21 to 45 days, with duration of flow between 3 and 7 days. Blood loss for each cycle is approximately 30 to 40 mL. Irregular menstruation is characterized by bleeding infrequently (oligomenorrhea) or too frequently (polymenorrhea). Variable menstrual cycle duration and/or menorrhagia (menstrual loss of >80 mL per cycle) or scanty menstrual flow may also occur. The presence of frequent, heavy menstruation often is the primary cause of iron-deficiency anemia in female adolescents, the incidence of which significantly increases when blood losses exceed 80 mL per cycle.

Combined hormonal contraceptives (CHCs), including the combined oral contraceptive pill (COCP), the contraceptive transdermal patch, and the contraceptive vaginal ring, can all be used to regulate menstruation. These agents are composed of estrogen in the form of ethinyl estradiol and various types of progestins, which are synthetic, orally active, progesterone-like hormones that also have androgenic and estrogenic properties. CHCs regulate menses by suppressing ovulation through inhibition of the gonadotropin-releasing hormone (GnRH) axis. Estrogen suppresses follicle-stimulating hormone and follicular development, whereas progestin prevents the luteinizing hormone surge in midcycle. Together, the hormones in CHCs inhibit ovulation and proliferative changes in the uterus, leading to endometrial thinning and atrophy with continued use.

There are many different formulations of hormonal contraceptive agents (Table 1). Most contain varying amounts of ethinyl estradiol, ranging from 10 to 35 $\mu$g with varying progestins. Low-dose COCPs (30–35 $\mu$g of ethinyl estradiol) are the most commonly used agents, given the lack of bone density protection associated with use of extremely low-dose COCPs (10–20 $\mu$g of ethinyl estradiol). Most COCPs consist of a 28-day pill pack with 21 days of active hormonal pills followed by 7 days of placebo pills; however, there are also formulations with a 28-day pill pack that consists of 24 days of active hormonal pills followed by 4 days of placebo or iron pills, as well as formulations that consist of 21 days of active hormonal pills only, allowing the patient to remain pill free during the week of vaginal bleeding. COCPs can be categorized either as monophasic, which contain a consistent amount of hormones within each pill, or multiphasic, which vary the amount of progestin or estrogen.

Most adverse effects of CHCs are minor. Adverse effects associated with the estrogen component include nausea, vomiting, headaches, breast tenderness, and changes in body weight. Adverse effects associated with progesterone include acne, weight gain, increased hair growth, and depression. More serious complications of the estrogen component of CHCs are deep venous thrombosis and arterial disease, such as myocardial infarctions and stroke; however, these complications are rare, especially within the adolescent age group. To decrease likelihood of adverse effects and serious complications, CHCs with lower doses of both estrogen (<50 $\mu$g of ethinyl estradiol) and progestins (varying doses, depending on the type of progestin) have been developed.

Most adolescents can be prescribed any of the CHCs safely; however, for adolescents with coexisting medical conditions, physicians should refer to guidelines developed by the Centers for Disease Control and Prevention (CDC), which outline the absolute and relative contraindications to contraceptive agent use (Table 2). (2) Using these guidelines, a physician can determine whether CHCs are appropriate given the patient's medical condition and, if necessary, prescribe another form of contraception. Another consideration is potential drug interactions with medications the patient is taking (Table 3). Physicians should always check for use of these medications when prescribing CHCs because concomitant use may be associated with decreased efficacy of either of these medications.

Through artificial control of the menstrual cycle, CHCs induce monthly withdrawal bleeding, also known as a "pill period." For oral contraceptive pills, this is the week when no pills or placebo pills are taken instead of active hormonal pills. For the contraceptive patch and the contraceptive ring, this is the patch-free or ring-free week of administration. Because of the presence of a thinner, atrophied endometrium, both menstrual blood loss and menstrual period duration are decreased. Thus, the likelihood of iron-deficiency anemia is reduced in current users of CHCs.

Specific treatment protocols with CHCs can be used to regulate irregular bleeding in urgent clinical situations. In cases of menorrhagia without anemia, CHCs are typically dosed as they are for contraception: 1 pill daily or use of 1 patch weekly or vaginal ring per menstrual cycle. However, for acute episodes of menorrhagia with associated anemia, altered treatment is necessary. For such situations, high doses of COCPs (3 or 4 pills) help to stop bleeding quickly to prevent worsening anemia. Once bleeding has stopped, the high-dose COCP regimen should be tapered to 1 pill daily. A commonly used tapering regimen is to give 1 pill every 6 hours until the bleeding stops, then 1 pill 3 times per day for 2 days, 1 pill twice per day for 2 days, and lastly 1 pill daily until the anemia

## Table 1. Commonly Used Hormonal Contraceptive Agents

| Type | Estrogen | Progestin | Brand Names |
|---|---|---|---|
| Monophasic COCPs | 20 μg of ethinyl estradiol | 0.1 mg of levonorgestrel | Alesse[a] |
| | 20 μg of ethinyl estradiol | 1 mg of norethinedrone acetate | Loestrin Fe 1/20[b] |
| | 20 μg of ethinyl estradiol | 3 mg of drospirenone | Yaz[c] |
| | 30 μg of ethinyl estradiol | 0.15 mg of desogestrel | Apri,[d] Ortho-Cept[e] |
| | 30 μg of ethinyl estradiol | 0.3 mg of norgestrel | Lo/Ovral-28[f] |
| | 30 μg of ethinyl estradiol | 1.5 mg of norethinedrone acetate | Loestrin Fe 1.5/30[g] |
| | 30 μg of ethinyl estradiol | 3 mg of drospirenone | Yasmin[c], Ocella[d] |
| | 35 μg of ethinyl estradiol | 1 mg of norethinedrone | Ortho-Novum 1/35,[e] Nortrel 1/35[d] |
| | 35 μg of ethinyl estradiol | 0.25 mg of norgestimate | Sprintec,[d] Ortho-cyclen,[e] Mononessa[h] |
| | 35 μg of ethinyl estradiol | 0.4 mg of norethindrone | Ovcon-35[g] |
| | 20 μg of ethinyl estradiol | 1 mg of norethindrone acetate | Loestrin 24Fe[g] |
| | 10 μg of ethinyl estradiol | 1 mg of norethindrone acetate | Lo Loestrin Fe[g] |
| Triphasic COCPs | 20 μg/30 μg/35 μg of ethinyl estradiol | 1 mg of norethinedrone acetate | Estrostep Fe[g] |
| | 35 μg of ethinyl estradiol | 0.18 mg/0.215 mg/0.25 mg of norgestimate | Ortho Tri-Cyclen[e] |
| POPs | | 0.35 mg of norethinedrone | Micronor,[e] Nor-QD[h] |
| Extended-cycle COCPs | 30 μg/10 μg of ethinyl estradiol | 0.15 mg of levonorgestrel | Seasonique[b] |
| | 30 μg of ethinyl estradiol | 0.15 mg of levonorgestrel | Seasonale[d] |
| Vaginal ring | 2.7 mg of ethinyl estradiol, 15 μg of ethinyl estradiol released per day | 11.7 mg of etonogestrel, 120 μg of etonogestrel released per day | Nuvaring[i] |
| Transdermal patch | 0.75 mg of ethinyl estradiol, 20 μg of ethinyl estradiol released per day | 6 mg of norelgestromin, 150 μg of norelgestromin released per day | Ortho-Evra[e] |
| Implant | | 68 mg of etonogestrel, variable release rate | Nexplanon[i] |
| Injectable | | 150 mg of depot medroxyprogesterone acetate | Depo-Provera[j] |
| Intrauterine systems | | 52 mg of levonorgestrel, 20 μg of levonorgestrel released per day | Mirena[c] |
| | | 13.5 mg of levonorgestrel, 14 μg of levonorgestrel released per day | Skyla[c] |

COCPs=combined oral contraceptive pills; POPs=progestin-only pills.
[a]Wyeth Pharmaceuticals Inc.
[b]Duramed Pharmaceuticals Inc.
[c]Bayer HealthCare Pharmaceuticals.
[d]Teva Pharmaceuticals USA.
[e]Janssen Pharmaceuticals Inc.
[f]Akrimax Pharmaceuticals.
[g]Warner Chilcott Company Inc.
[h]Actavis.
[i]Merck & Co Inc.
[j]Pfizer Inc.

has resolved. Use of pills will be stopped to allow a withdrawal bleed when the patient is not anemic.

Another effective contraceptive used to treat menorrhagia in adolescents is a levonorgestrel intrauterine system (LNG-IUS). The CDC's US medical eligibility criteria for contraceptive use clearly state that intrauterine systems are safe and appropriate for nulliparous adolescents and older women. There are currently 2 LNG-IUSs on the market: Mirena (LNG-IUS-52 mg) (Figure 1) and Skyla(LNG-IUS-13.5 mg) (Figure 2). Both are T-shaped polyethylene devices with a steroid reservoir around the stem. Both contain the progestin levonorgestrel, which is released at a daily steady rate (Table 1). Mirena is approved by the Food and Drug Administration (FDA) for

## Table 2. Centers for Disease Control and Prevention Medical Eligibility Criteria for Combined Hormonal Contraceptive Use

| No Restrictions to Use (WHO Category 1) | Cautionary Use, Advantages Usually Outweigh Risks (WHO Category 2) | Relative Contraindications to Use (WHO Category 3) | Absolute Contraindications to Use (WHO Category 4) |
|---|---|---|---|
| Age <40 years | Smoking <35 years | Current or past history of deep vein thrombosis or pulmonary embolism with low risk of recurrence | Current or past history of deep vein thrombosis or pulmonary embolism with high risk of recurrence |
| Women >6 weeks post partum | Women 3–6 weeks post partum without risk factors for venous thromboembolism | Women 3–6 weeks post partum with risk factors for venous thromboembolism | Women <3 weeks post partum |
| Thyroid disorders | Lactation >1 month post partum | Lactation < 1 month postpartum | Surgery with prolonged immobilization |
| Minor surgery without immobilization | Major surgery without prolonged immobilization | Moderate hypertension (140–159/90–99 mm Hg) | Severe hypertension (>160/100 mm Hg) |
| Epilepsy | First-degree family history of deep vein thrombosis or pulmonary embolism | Severe hyperlipidemias | Hypercoagulability disorders (factor V Leiden, protein C deficiency, etc) |
| Varicose veins | Systemic lupus erythematosus with negative antiphospholipid antibody | Superficial thrombophlebitis | Systemic lupus erythematosus with positive or unknown antiphospholipid antibody |
| Postabortion | History of pregnancy-related cholestasis | History of cholestasis related to past combined hormonal contraceptive use | Known thrombogenic mutation |
| Viral hepatitis carrier | Gallbladder disease, asymptomatic or treated by cholecystectomy | Current or medically treated gallbladder disease | Liver disease (including severe cirrhosis, tumors, active viral hepatitis) |
| Nonmigrainous headaches | Migraine without aura | Current use of medications that decrease OCP efficacy | Migraine with aura |
| Severe dysmenorrhea | Inflammatory bowel disease without risks for deep vein thrombosis/pulmonary embolism | Inflammatory bowel disease with risks for deep vein thrombosis or pulmonary embolism | Current or past history of cerebrovascular event or disease |
| Heavy or irregular menstrual bleeding | Unexplained vaginal bleeding | History of breast cancer without recurrence for >5 years | Current or past history of ischemic heart disease |
| Family history of breast cancer | Cervical cancer | | Current breast cancer |
| Benign breast disease | Undiagnosed breast mass | | Vascular disease |
| Uterine fibroids | Uncomplicated valvular heart disease | | Complicated valvular heart disease |
| Pelvic inflammatory disease | Uncomplicated solid organ transplantation | | Complicated solid organ transplantation |
| HIV/AIDS | Uncomplicated diabetes mellitus | | Diabetes mellitus with complications |
| Antiretrovirals, nucleoside reverse transcriptase inhibitors | Antiretrovirals, nonnucleoside reverse transcriptase inhibitors | | |
| Sexually transmitted infections | Obesity | | |

*Continued*

Table 2. (Continued)

| No Restrictions to Use (WHO Category 1) | Cautionary Use, Advantages Usually Outweigh Risks (WHO Category 2) | Relative Contraindications to Use (WHO Category 3) | Absolute Contraindications to Use (WHO Category 4) |
|---|---|---|---|
| Malaria, schistosomiasis, tuberculosis | Rheumatoid arthritis | | |
| Thalassemia, iron-deficiency anemia | Sickle cell disease | | |
| Benign ovarian tumors | | | |
| Endometriosis, endometrial hyperplasia | | | |
| Depressive disorders | | | |
| Current use of most antibiotics, antifungals, or antiparasitics | | | |

HIV=human immunodeficiency virus; OCP=oral contraceptive pill; WHO=World Health Organization.

menorrhagia, effective for 5 years, and indicated in women of reproductive age who have had at least one child. Skyla, which is FDA approved for women under 18 years old, is a slightly smaller LNG-IUS effective for 3 years and indicated in both multiparous and nulliparous women of reproductive age, including adolescents under the age of 18. An LNG-IUS requires clinician insertion and removal; however, it is a highly effective form of contraception. Its low failure rate is attributable to lack of patient responsibility for administration or compliance other than having it inserted by a physician at onset of use, thereby creating a means of "forgettable" contraception.

The mechanism of action of the LNG-IUS involves thickening of cervical mucus and thinning of the endometrial lining. Consequently, there is a significant reduction in menstrual blood loss over time, which often progresses to amenorrhea. A study of young women with menorrhagia with low ferritin levels who had the Mirena LNG-IUS inserted found that after 12 months of use, 95% had increased ferritin levels, suggesting that when menstrual blood loss decreased, the iron stores returned to normal. (3) In addition, 58% became amenorrheic, providing additional evidence that LNG-IUS significantly reduces menstrual blood loss. Although the LNG-IUS is an excellent, well-tolerated contraceptive agent, its greatest disadvantage is intermenstrual bleeding and spotting in the first months of use.

## Table 3. Common Medications Which Adversely Interact with CHCs

| CHCs Decrease Efficacy | Decrease Efficacy of CHCs |
|---|---|
| Lamotrigine | Griseofulvin |
| | Rifampin |
| | Rifabutin |
| | Ritonavir |
| | Oxcarbazepine |
| | Phenytoin |
| | Barbiturates |
| | Carbamazepine |
| | Topiramate |
| | Felbamate |
| | Primidone |
| | St. John's wort |

### Hematologic Chronic Illness–von Willebrand Disease and Deficiency of Clotting Factors

Menorrhagia in adolescents is most commonly secondary to anovulation due to an immature hypothalamic-pituitary-ovarian axis; however, there are many coagulopathies that cause menorrhagia, such as von Willebrand disease (vWD) and deficiency of certain clotting factors. In fact, menorrhagia with severe anemia is a common presentation of vWD. Patients may also present with easy bruising, excessive bleeding at the time of surgical or dental procedures, or gastrointestinal or mucocutaneous bleeding.

In the normal clotting cascade, during menstruation, denuded endometrial glands and stroma are shed into the endometrial cavity, whereas intravascular fibrin-platelet plugs form to allow for hemostasis. In patients with vWD, through various mechanisms, abnormal von Willebrand factor (vWF) or decreased vWF in plasma impairs microvascular thrombosis and coagulation, resulting in menorrhagia and irregular uterine bleeding.

**Figure 1. Mirena Intrauterine System (levonorgestrel intrauterine system, 52 mg). Reproduced with permission from © Bayer HealthCare Pharmaceuticals Inc.**

The quality of life for patients with vWD and clotting factor deficiencies, whether genetic or acquired, may be significantly impaired by menorrhagia. Many miss school or work and report a reduction in other daily activities during menstruation. Use of CHCs in patients with a subtype of vWD characterized by partial quantitative defects in vWF (usually type 1) can suppress and regulate menses. Estrogen within the CHCs causes an elevation of plasma vWF, which decreases the frequency of menstrual blood loss and subsequent anemia.

Given the various consequences of menorrhagia in these patients, physicians should consider proactively starting CHC therapy when patients with vWD are Tanner stage 4 and perimenarchal to help manage menorrhagia from the start. This is especially useful if the patient's family members and/or siblings required transfusions with their first menstrual periods. If the patient is very short or the physician wants to maximize the growth, at Tanner stage 4, the physician can track patients every 3 to 6 months and prescribe CHCs as height progresses. With this kind of proactive approach, the patient's first menstrual periods do not need to be the cause of severe anemia.

In a retrospective study of girls 9 to 18 years with vWD looking at treatment of menorrhagia with both low-dose COCPs vs desmopressin for a 6-month to 4-year period,

**Figure 2. Skyla Intrauterine System (levonorgestrel intrauterine system, 13.5 mg). Reproduced with permission from Bayer HealthCare Pharmaceuticals Inc.**

patients had significantly decreased menorrhagia with use of oral contraceptive pills. (4) No serious adverse events were reported with use. High-dose COCPs are not recommended secondary to the estrogen influence on coagulation factors. This treatment could increase adverse events, particularly thromboembolic events.

## Treatment for Perimenstrual Symptoms and Catemenial Conditions

Many patients may be affected by catamenial conditions, menstrual symptoms, or medical conditions, which are

exacerbated at the time of menses. Contraceptive agents can be useful in treatment of many of these conditions.

### Dysmenorrhea

Dysmenorrhea, defined as painful menstruation, is the most common gynecologic condition in adolescent girls, affecting 60% to 93%. Historically, dysmenorrhea has been one of the most common reasons contraceptive agents are prescribed for noncontraceptive indications. Although primary dysmenorrhea, defined as painful menses not due to any pelvic disease, is much more common during adolescence, dysmenorrhea secondary to pelvic disease (secondary dysmenorrhea) may also affect adolescent patients.

Although many adolescents experiencing dysmenorrhea do not seek medical care specifically for their symptoms, diagnosis and alleviation of dysmenorrhea are critical because the condition often is a cause of significant disability. Many adolescents miss school or work and also adjust their daily social and physical activities because of the pain experienced during menstrual periods.

The defining symptom of primary dysmenorrhea is midline, crampy, lower abdominal pain. It usually begins a couple days before or with onset of menses and lasts for 8 to 72 hours. Usually, pain is most intense on the first and/or second day of menstrual flow. Secondary symptoms of primary dysmenorrhea are more variable and may include breast tenderness, low back pain, diarrhea, bloating, headaches, mood lability, nausea, vomiting, and near-syncope. Symptoms associated with secondary dysmenorrhea are more varied and linked to the pelvic condition. The physical examination of a girl with dysmenorrhea is also variable and often dependent on the timeline of the patient's menstrual cycle. If the patient is close to or experiencing menstruation, mild to moderate suprapubic tenderness with normal bowel sounds may be present. At other times within the menstrual cycle, the physical examination findings may be unremarkable. A pelvic examination with bimanual examination is not usually required; however, an external genital examination should be performed on all girls regardless of sexual activity. Sometimes, a rectoabdominal examination to rule out a mass may be indicated to assess for a pelvic mass. Laboratory and radiologic workups are usually not necessary when history and physical examination provide sufficient evidence that primary dysmenorrhea is likely the inciting cause of pain.

Primary dysmenorrhea is caused by excess secretion of prostaglandins and leukotrienes, resulting in contractions of uterine muscle. Therefore, its treatment is linked to inhibition of these mediators. Nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase inhibitors that reduce the production of prostaglandins, are typically used as first-line treatment. If taken correctly before the onset of menstrual pain and continued appropriately, this class of medications relieves dysmenorrhea in up to 80% of adolescents. For those adolescents who do not experience complete relief with NSAIDs, CHCs may be used instead of or in conjunction with them. Hormones in CHCs act by suppressing ovulation and diminishing the endometrial lining of the uterus. Consequently, menstrual fluid volume decreases along with the amount of prostaglandins produced, which subsequently then reduces dysmenorrhea by decreasing uterine motility and uterine cramping. For patients with persistent dysmenorrhea, despite the use of oral contraceptives and NSAIDs, extended cycling of CHCs may be prescribed to decrease the number of menstrual periods and thus the occurrence of dysmenorrhea.

A Cochrane review of COCPs states that they may be helpful for dysmenorrhea; however, interpretation of the results is limited because of the variable quality of the randomized controlled trials studied. (5) Although this review reveals inconclusive data regarding COCP use for dysmenorrhea, clinical practice and other studies suggest that COCPs and other CHCs are effective treatment modalities for the treatment of primary dysmenorrhea.

## Other Catamenial Conditions

### Headaches

Many women experience headaches during menstrual periods. After dysmenorrhea, headaches are the most frequent menstrual-related symptoms. Usually, the headaches occur immediately before the onset of menses and possibly through the duration of menses. Numerous studies have documented the association between the onset of headaches and hormonal fluctuations, particularly estrogen. Headaches are thought to be triggered by the sharp decrease in estrogen levels immediately before menstrual flow. Physicians often attempt to treat headaches with traditional cycling of CHCs; however, because both estrogen and progestin levels decrease before a withdrawal bleed, women who use CHCs often are symptomatic during the hormone-free interval, but many have less severe headaches than if they were not taking CHCs.

Extended and continuous placebo-free CHC regimens have been used to decrease the number of hormone fluctuations and subsequently reduce the headaches experienced by patients. Such menstrual regulation has had tremendous quality-of-life implications for many women with headaches and has been found to be

associated with improvement in work productivity and involvement in activities. However, before initiating use of CHCs to treat headaches, a practitioner must be certain that the headache is not associated with an aura because use of CHCs in patients with migraines with aura are absolutely contraindicated as per CDC medical eligibility criteria guidelines for contraceptive use (Table 2). In addition, because the estrogen component of the CHCs may themselves cause headaches, patients should be counseled that if there is worsening of headaches or onset of new headaches after initiation of CHC use, they must contact their physician to be evaluated.

## Epilepsy

Many women with a medical history of epilepsy have severe seizures during menstruation. Catamenial epilepsy is described as the cyclical increase in seizures around the time of menses or at other phases of the menstrual cycle, usually during perimenstrual or periovulatory periods in normal ovulatory cycles and during the luteal phase in anovulatory cycles. The mechanism of these cyclical changes is thought to be secondary to the proconvulsant effect of estrogen and the anticonvulsant effect of progesterone. The cause of exacerbation of seizures during the middle of the menstrual cycle is likely linked to the surge of estrogen occurring before ovulation, which is unaccompanied by a comparable increase in progesterone. Contrasting this, it is a deficit of progesterone, which contributes to increased seizures during menstruation.

Although COCPs have usually been found to be ineffective to improve seizure control, depot medroxyprogesterone acetate has been reported to have positive effects in decreasing the frequency of seizures in some women. Depot medroxyprogesterone acetate is progesterone derivative, which is administered intramuscularly at 3-month intervals at a dosage of 150 mg per injection. Its mechanism of action is via inhibition of ovulation at the hypothalamic level and via thickening and an increase of cervical mucus. Depot medroxyprogesterone acetate changes the endometrium so that it becomes more secretory and eventually atrophic. One major benefit of depot medroxyprogesterone acetate in these patients is that it usually does not adversely interact with antiepileptic medications as many COCPs do. Many antiepileptic medications decrease efficacy of COCPs, and concomitant use of COCPs with the antiepileptic medication lamotrigine can decrease lamotrigine's efficacy, thereby lowering a patient's seizure threshold (Table 3).

Although DMPA has many benefits, some significant adverse effects are associated with the method. Irregular bleeding and spotting usually occur during the first 6 to 9 months of receiving depot medroxyprogesterone acetate. Although heavy bleeding is rare, this is the most common reason the method is discontinued. In addition, other potential adverse effects include weight gain, headaches, depression, alopecia, fatigue, and osteopenia.

The negative effect of depot medroxyprogesterone acetate on bone mineral density has received significant attention, especially with regard to the adolescent population. Studies have found that depot medroxyprogesterone acetate significantly contributes to bone mineral density loss. This is probably due to the relative estrogen deficiency patients experience with depot medroxyprogesterone acetate. However, the changes are entirely reversible, and after discontinuation, bone density not only recovers, it also increases. When prescribing depot medroxyprogesterone acetate to adolescents, physicians should discuss the benefits and risks, as well as inform the adolescent and family of possible risk of bone loss. While patients are using depot medroxyprogesterone acetate, supplements of vitamin D (400 IU) and calcium carbonate (1300 mg) may be prescribed, as well as estrogen supplements if the patient is at high risk or has osteopenia.

## Premenstrual Syndrome

Premenstrual syndrome (PMS) is another common problem in menstruating women. It is characterized by a variety of symptoms, such as mood swings, mastalgia, food cravings, fatigue, irritability, and depression. The prevalence of PMS increases as the adolescent matures from menarche to more established ovulatory cycles. Symptoms of PMS are likely caused by cyclic hormonal fluctuations and hormonal-mediated fluctuations in neurotransmitters. Premenstrual symptoms may occur in more than 75% of menstruating women; however, PMS occurs in only 20% to 40% of women. To establish the diagnosis of PMS, patients' symptoms must be consistent with PMS, be relieved shortly after the onset of menses, and be associated with some impairment of daily activity.

Premenstrual dysphoric disorder (PMDD) is a severe form of PMS, which affects 3% to 8% of menstruating women. PMDD requires the presence of both affective (mood or emotional) and somatic (physical) symptoms. According to the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) criteria for PMDD, women must have at least 5 symptoms, including a mood problem, as well as substantial impairment in an activity of daily living. (6) These symptoms should be prospectively captured with a symptom log, which can be reviewed with the physicians.

CHCs are likely to alleviate the physical symptoms associated with PMS but do not significantly improve the emotional symptoms of PMS. However, a newer COCP with drospirenone and low estrogen (drospirenone, 3 mg, and ethinyl estradiol, 20 $\mu$g) has been approved by the FDA for treating PMDD and has been found to be more effective in treating these emotional symptoms than other CHCs. Most COCPs are derived from 19-nortestosterone; however, drospirenone is derived from spironolactone rather than 19-nortestosterone. Thus, drospirenone is an antimineralocorticoid progestin that may influence fluid balance and consequently prevent fluid retention, weight gain, bloating, and an increase in blood pressure seen in menstruating women. Serious adverse effects of drospirenone include the possibility of hyperkalemia in patients taking other drugs, which can increase potassium, and an increased risk of thromboembolic events when compared with COCPs that contain other types of progestin.

## Other Chronic Medical Conditions

### Sickle Cell Disease

Hormonal contraceptive agents also have noncontraceptive benefits effects on patients' with sickle cell disease (SCD). Many physicians are very concerned and cautious about potentially causing blockage of blood vessels and a subsequent bone pain crisis or promoting a thromboembolic event. Despite these concerns, it is safe to prescribe patients with SCD, who have not had a thromboembolic event, most contraceptive agents. Progestin-only contraceptive agents are preferred, and as CDC medical eligibility criteria guidelines state, there are no restrictions on use of progestin-only contraceptives and LNG-IUSs for SCD. (2) However, for those patients who will not use progestin only measures, the benefits of CHCs or the copper intrauterine device may outweigh the theoretical or proven risks of using these methods.

Multiple studies have revealed that depot medroxyprogesterone acetate contributes to a decrease in the frequency, severity, and duration of painful crises in female patients with SCD. The possible mechanism of action is progestin stabilizing the red blood cell membranes and making cells less prone to sickling, which causes the pain crises.

A recent Cochrane review supports these studies. It reported that depot medroxyprogesterone acetate is a safe contraceptive method in women with SCD, and that in addition to providing effective contraception, depot medroxyprogesterone acetate appears to reduce sickle pain crises. (7) With regard to CHC use in patients with SCD, many studies have not found an increase in pain crises or other complications of SCD disease among women who used CHCs.

### Rheumatoid Arthritis

There is no conclusive evidence in regard to a protective effect of contraceptives against rheumatoid arthritis; however, clinical practice has indicated that contraceptives may positively influence the severity and clinical course of rheumatoid arthritis.

## Menstrual Suppression

Many adolescent women require suppression or elimination of menstrual bleeding for a variety of reasons, ranging from personal preference to coexisting medical conditions. Menstrual suppression offers significant control over the menstrual cycle. Despite common belief, there is no scientific or medical basis of the need for intermittent use of hormonal contraception that allows for a monthly withdrawal bleed. Many patients taking CHCs with a 4- or 7-day break to allow for withdrawal bleeding (perceived period) often continue to have difficulties with other perimenstrual symptoms, such as dysmenorrhea, menorrhagia, headaches, bloating, and emotional lability, during the contraceptive-free interval. In addition, intermittent use of hormonal contraception has not been found to be any safer than using hormonal contraception continuously. To date, there are no long-term negative health consequences associated with menstrual suppression.

In a study conducted in the Netherlands that used a telephone interview inquiring about women's attitudes toward changes in menstrual bleeding caused by COCPs and hormonal replacement therapy, adolescents aged 15 to 19 years indicated a desire for less painful and shorter menstrual bleeding significantly more often than reproductive-age women. (8) All women preferred decreasing the frequency of bleeding to less than once a month or completely eliminating menstrual periods altogether. When asked specifically about what bleeding frequency they would prefer if manipulated by COCPs, 72% of the adolescents stated never or less than once a month. Similar studies conducted in the United States have revealed comparable reactions. (9) Younger women, those already using birth control, low-income women, and women with severe symptoms during menstruation were those most receptive to suppression of menses.

A specific COCP (Seasonale, 150 $\mu$g of levonorgestrel and 30 $\mu$g of ethinyl estradiol) was introduced in 2003 and offers greater menstrual suppression than traditional COCPs. This COCP contains 84 days of active hormone tablets followed by 7 inactive pills, creating an extended

cycle of 91 days and giving the user only 4 withdrawal bleeds a year. Adverse effects, such as premenstrual symptoms, headaches, mood changes, and heavy or painful monthly bleeding due to hormone withdrawal, are reduced. In addition, patients using this COCP rarely have anemia secondary to infrequent withdrawal bleeding. Studies have reported that extended-cycle COCPs are effective, safe, and well tolerated.

If desired, more practical, or less costly for the patient, a physician can use any other 24- or 28-day formulations of monophasic COCPs to extend the patient's cycle. This extended cycle is achieved in a similar manner by simply advising the patient to take only the active hormone tablets within the pack continuously from pack to pack during an extended period, typically 3 months. When the patient finishes the active hormonal pills within the third pack, she can take the placebo pills to produce a withdrawal bleed.

Although COCPs are commonly used for extended or continuous cycling, the transdermal contraceptive patch is not an ideal choice for continuous cycling secondary to increased estrogen levels. Systemic estrogen levels are estimated to be 1.6 times higher in the transdermal patch than with the standard low-dose COCP. Studies have found that there is a possible increased risk of venous thromboembolism in patch users; therefore, extending cycling without a hormone-free interval is not recommended. On the other hand, extended and continuous cycling schedules that use the vaginal ring have been studied and found to be safe, tolerable, and effective. Results revealed an acceptable bleeding profile in most patients, reduction of pelvic pain, and a high continuation rate. There was no increase of thromboembolic events or increased endometrial hyperplasia. An adverse effect of the continuous use of the vaginal ring was some breakthrough bleeding and spotting; however, this is a common adverse effect of both traditional and extended or continuous cycling of many CHCs that adolescents should be counseled to expect. If breakthrough bleeding is bothersome to patients, they can be instructed to stop use of the pill for 4 days to allow a withdrawal bleed and then resume administration of the remaining pills. Bleeding and spotting tend to improve with continued use of CHCs, and most patients are willing to tolerate this to have fewer menstrual periods. A few of the conditions treated with menstrual suppression are discussed below.

## Patients With Physical and Mental Disabilities

Menstrual periods can be particularly difficult for both patients and caregivers of patients with physical or mental disabilities. Adolescents with such disabilities often have a high frequency of reported painful, heavy, and prolonged bleeding and behavior problems during menses. The disability can often make it challenging for patients or caregivers to maintain good hygiene during menstruation. Many families seek assistance from medical professionals for menstrual-related symptoms and request regulation and/or suppression to deliver more predictable and less frequent menstruation. Some families may request hysterectomy or permanent sterilization for such patients; however, this is often not a viable treatment for ethical and medical reasons. Therefore, patients with significant physical and/or mental disabilities may benefit from infrequent menstrual periods or induction of long-term amenorrhea by treatment with CHCs.

Long-term amenorrhea can be induced by extended CHC regimens; however, similar results can also be achieved with progestin-only medications. Depot medroxyprogesterone acetate is an agent frequently requested by patients and caregivers for menstrual suppression. Depot medroxyprogesterone acetate is an excellent agent for menstrual suppression because most patients usually achieve amenorrhea after the third or fourth dose, and it has few drug interactions. Another benefit of depot medroxyprogesterone acetate is that patients are not burdened with daily pill administration or weekly/monthly administration of the transdermal patch or vaginal ring. Lastly, with use of this method, estrogen is avoided, which could potentially be contraindicated in such patients or contribute to negative perimenstrual symptoms.

Immobility is fairly common in patients with physical and mental disabilities. Because of its negative effects on bone development, using depot medroxyprogesterone acetate presents a significant risk to these patients. Moreover, CHCs should not be used in girls who are immobile because of increased risk of deep vein thrombosis and subsequent emboli. Instead, progestin-only pills may also be used as an alternative to depot medroxyprogesterone acetate in patients with lack of or limited mobility. Another excellent alternative method is an LNG-IUS, which is progestin only and has a high rate of achieving amenorrhea with low risk to bone health. A limited number of studies support LNG-IUS use in adolescents with physical and mental disabilities. This method can reduce menstrual bleeding without adverse effects on bone health and only needs introduction or insertion every 5 years. Breakthrough menstrual bleeding, which is common during the first few months after insertion of the LNG-IUS, can be reduced by administering a 5- to 7-day course of NSAIDs to patients. Although Nexplanon is another progestin only form of contraception that one may consider using, it can be associated with episodic vaginal bleeding, so it may not be effective in achieving amenorrhea.

### Patients With Malignant Tumors

Contraceptive agents benefit adolescent girls with malignant tumors receiving chemotherapy. Many cancer patients must receive ablative or high-dose chemotherapy, which destroy the bone marrow until recovery of blood stem cells. Patients become pancytopenic, which results in severe morbidity secondary to their vulnerability to multiple diseases and infections. Growth factors help with recovery of white and red blood cell lines; however, thrombocytopenia is more difficult to treat because of a lack of an existing comparable platelet growth factor. These girls may subsequently experience bleeding from multiple body sites, including the uterus, resulting in menorrhagia. Often, such patients will require immediate blood products, such as platelets, packed red blood cells, and/or high-dose estrogen, to stop bleeding. To prevent these often emergency circumstances, pretreatment with depot medroxyprogesterone acetate, CHCs, or GnRH agonists has been used successfully to induce amenorrhea in such patients before the induction of the chemotherapeutic regimen. Progestin-only contraceptive agents are preferred over CHCs secondary to the potential adverse effects of estrogen on coagulation; however, given their higher rates of obtaining amenorrhea, GnRH agonists are usually chosen as first-line treatment in such clinical situations.

Another clinical situation for which contraceptive agents can be beneficial is for girls with malignant tumors who are amenorrheic after radiation, chemotherapy, or bilateral oophorectomy. Lack of estrogen has consequences to bone health and may cause other symptoms, such as vaginal dryness. Estrogen replacement may be achieved by using CHCs.

## Treatment of Other Medical and Gynecologic Conditions

### Acne

Acne, a disorder of sebaceous glands of the skin, is another common condition that affects adolescents. It affects 40 million to 50 million people in the United States annually. Morbidity associated with acne and adverse effects of treatment can lead to both physical and emotional scars during a patient's lifetime.

The pathogenesis of acne is multifactorial. There can be an increased rate of sebum production, which results from an excess production of androgens from either the ovary or the adrenal glands. In addition, the sebaceous glands of many patients, particularly adolescents, are hyperresponsive to androgens. Consequently, the increased sensitivity to androgen results in secretion of excess amounts of sebum.

Testosterone levels in women using CHCs are reduced significantly through various mechanisms. Perhaps one of the strongest mechanisms of reduction is via suppression of ovulation. When ovulation does not occur, luteinizing hormone levels are suppressed, and androgen synthesis within the ovary and adrenal glands is significantly decreased.

Androgen bioavailability also is reduced by CHCs because ethinyl estradiol increases the level of the sex hormone–binding globulin, the protein that binds free androgens, which in turn increases binding of testosterone. Another way acne occurs is when testosterone is converted in the hair follicles and skin to dihydrotestosterone by the enzyme 5-$\alpha$-reductase. CHCs prevent this conversion by blocking androgen receptors and inhibiting 5-$\alpha$-reductase activity.

Androgen levels may be reduced by different degrees, depending on the type of CHC used. As stated previously, CHCs are composed of estrogen and various types of progestins. Progestins typically have progestational activity but also have varying levels of androgenic activity. CHCs that contain third-generation progestins, such as norgestimate, levonorgestrel, and drospirenone, have relatively greater affinity for progesterone receptors than for androgen receptors compared with older agents. Thus, theoretically, for treatment of acne, their ability to counteract the increased sebum production by the androgen-dependent sebaceous glands should be better than older contraceptive agents. Because of this benefit, many CHCs with these specific types of progestins, such as the triphasic (35 $\mu$g of ethinyl estradiol; 0.18 mg, 0.215 mg, and 0.25 mg of norgestimate; and 20 $\mu$g of ethinyl estradiol and 3 mg drospirenone) have been marketed, FDA approved, and used specifically for the treatment of acne. In addition, a triphasic COCP with varying degrees of estrogen has also been FDA approved and used for acne.

Although a few studies have found increased levels of sex hormone–binding globulin and decreased testosterone levels in women using COCPs with less androgenic progestins, in the Cochrane review studying the use of COCPs for treatment of acne, results revealed that all COCPs reduced acne lesion counts, severity grades, and self-assessed acne compared with placebo. (10) In addition, it stated that "the differences in the comparative effectiveness of COCPs containing varying progestin types and dosages were less clear and data was limited for any particular comparison." (10) Thus, the review provides evidence that all types of COCPs can be used by physicians for acne treatment with similar efficacy.

### Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is a condition characterized by chronic anovulation and hyperandrogenism. Clinical symptoms and signs of PCOS include irregular menstrual cycles, infertility, hirsutism, and acne.

In addition to anovulation secondary to immaturity of the hypothalamic-pituitary-ovarian axis and coagulation disorders, PCOS is a fairly common cause for irregular menstruation and acute episodes of menorrhagia in adolescent patients. The mechanism of PCOS involves increased androgen levels, which lead to anovulatory menstrual cycles. Anovulatory cycles result in unopposed estrogen exposure of the endometrium, which leads to endometrial thickening. When the endometrium eventually outgrows its blood supply, it begins to shed in an unpatterned way that is associated with irregular menstruation and often acute episodes of menorrhagia.

CHCs treat PCOS by increasing cycle regularity by delivering estrogen and progesterone in an orderly fashion, which restores synchrony to the endometrium. In addition, as mentioned above, CHCs suppress ovarian, adrenal, and peripheral androgen secretion through suppression of ovulation, increase of the levels of sex hormone–binding globulin, and inhibition of testosterone conversion. However, CHCs may not have any effects on the metabolic issues, which occur in PCOS.

### Structural Lesions

**OVARIAN CYSTS.** During development of the ovum during the menstrual cycle, small cysts may form around the egg while the egg is developing and moving. These cysts usually self-resolve, but some can persist, grow large, and/or become painful. It has become common clinical practice to prescribe CHCs to induce regression of ovarian cysts, but there is little evidence that supports this practice. Results of a Cochrane review revealed that COCPs did not cause ovarian cysts to regress faster: most self-resolved in 2 to 3 months. (11)

Although CHCs are likely not helpful in promoting ovarian cyst regression, historically, women taking CHCs are less likely to develop ovarian cysts compared with non-CHC users. This is secondary to CHCs' inhibition of ovulation, thereby preventing eggs from being released and resulting in a subsequent decrease in cyst formation. However, most studies with these findings were conducted with older higher-steroid dose COCPs. Recent data with newer lower-steroid doses do not show similar results because they have been found to have little effect on cyst formation.

**ENDOMETRIOSIS.** Endometriosis is the presence of endometrial tissue in sites outside the uterine cavity, most commonly the ovaries and peritoneum. The condition is frequently found in women with painful periods, dyspareunia, pelvic pain, and infertility. The mechanism of endometriosis is unclear; however, the most commonly accepted theory is that retrograde menstrual flow is involved with development of the condition. In addition to this theory, this condition is also thought to have a genetic component because it is found to occur more frequently in first-degree relatives of women with endometriosis.

Clinically, pelvic pain secondary to endometriosis may be associated with mild posterior uterine or cul-de-sac tenderness. The diagnosis of endometriosis is definitively made by visualizing the lesions on laparoscopy; however, current guidelines suggest that a laparoscopy is not always necessary before starting treatment. If the patient is experiencing significant symptoms of pain suggestive of endometriosis, then the condition can be empirically treated with COCPs. COCPs have been thought to down-regulate cell proliferation and enhance apoptosis in the endometrium of patients with endometriosis. COCPs have a few significant advantages over other hormonal treatments: they can be taken indefinitely, they offer long-term symptom control, and they are generally more acceptable to women than alternative hormonal treatments. The alternative (GnRH analogues) is limited to 6 months of use because of associated bone loss.

A recent Cochrane collaborative review supported the use of COCPs as an alternative treatment for the painful symptoms of endometriosis. (12) Other contraceptive methods to consider are continuously cycled COCPs, which have been reported to decrease menstruation-related pain symptoms. In addition, LNG-IUS, has been reported to effectively treat chronic pelvic pain associated with endometriosis compared with GnRH. The advantages of LNG-IUS are that it does not provoke hypoestrogenism and requires only one medical intervention for introduction of the device every 5 years.

**UTERINE FIBROIDS.** There is conflicting evidence regarding the effect of CHCs on uterine fibroids. However, a few studies have reported a reduced risk of development of uterine fibroids with COCP use. One study found that increased duration of COCP use was associated with increased protection and 10 years of use resulted in a 30% risk reduction. (13)

## Other Benefits of Contraceptive Agents

### Reduction of Cancers

**OVARIAN CANCER.** CHCs have the added benefit of reducing the risk of ovarian cancer via suppression of ovulation. Lack of ovulation decreases direct pituitary hormone effects on the ovarian epithelium, thereby decreasing injury and subsequent repair of the ovary. The likelihood of ovarian cancer is significantly decreased in women who have taken COCPs. The protective effect increases with duration of use of the COCPs and continues after discontinuing use of the COCPs. Both the older higher-dose pills (≥50 $\mu$g

of estrogen) and the newer COCPs with lower estrogen dosages (≤30 μg of estrogen) have been studied, and no difference in protective effect exists between high- and low-dose COCPs.

ENDOMETRIAL CANCER. CHCs also reduce the risk of endometrial cancer. The probable mechanism is via reduction of endometrial cell mitotic activity by the action of progestins. In addition, CHCs can reduce the risk of endometrial hyperplasia and endometrial cancer, resulting from unopposed estrogen exposure by regulating the cycle and stabilizing the endometrium. Studies have found that the amount of risk reduction depends on duration of use; however, this risk reduction can persist for many years after discontinuation of COCP use. Depot medroxyprogesterone acetate has also been found to decrease the risk of endometrial cancer for users.

COLON CANCERS. Colon cancer risk may also be reduced with CHC use. The mechanism of risk reduction is related to bile acid production. Progestins and exogenous estrogen may reduce bile acid production, and because bile acids act as promoters of colon carcinogenesis, CHCs can decrease their synthesis and subsequently decrease the risk of colorectal cancer. Previous studies have reported a risk reduction with high-dose COCPs; however, the evidence for use of low-dose COCPs is inconclusive.

### Reduction of Risk for Pelvic Inflammatory Disease

The risk of developing pelvic inflammatory disease is significantly decreased with use of CHCs and medroxyprogesterone acetate. Both these agents create progestin-associated thickening of cervical mucus, which impedes ascent of pathogens into the upper genital tract and uterine cavity. Multiple studies have found a reduction of risk and severity in patients that acquire pelvic inflammatory disease during COCP use. Those young women taking COCPs who develop pelvic inflammatory disease have a 60% decreased risk of hospitalization. (14) Among women with chlamydia, risk of pelvic inflammatory disease was 80% less than in those women not using the COCP; however, a similar association was not seen in women with gonorrhea. Protection is limited to current users; a patient's past use of COCPs does not exert a protective effect.

### Reduction of Benign Breast Disease

Fibrocystic change and fibroadenoma development are significantly reduced after 1 to 2 years of CHC use. Current CHCs users are at lowest risk, but there is a decreased risk of benign breast disease with increasing duration of use. The likely mechanism of action is inhibition of breast cell proliferation that normally occurs in the follicular phase of an ovulatory menstrual cycle. Because ovulation is suppressed with CHCs, breast cell proliferation is also decreased.

## Summary

- On the basis of strong research evidence, there are many noncontraceptive advantages to use of hormonal contraceptive agents in adolescent girls. (3)(4)(5)(7)(10)(11)(12)(13)(14)
- On the basis of research evidence and consensus, most of these agents are safe with minor adverse effects. (2)(3)(4)(5)(7)(10)(11)(12)(13)(14)
- On the basis of research evidence and consensus, through application of evidence-based approaches and proper counseling, pediatricians can use various contraceptive agents to treat several medical conditions and to help alleviate many of the undesired symptoms and complications associated with menstrual periods. (2)(3)(4)(5)(7)(10)(11)(12)(13)(14)
- On the basis of research evidence and consensus, these agents may be used in sexually active adolescents to simultaneously help prevent unintended adolescent pregnancies. (2)(3)(4)(5)(7)(10)(11)(12)(13)(14)

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1. What are the effects of combined hormonal contraceptives on the risk of cancer?
   A. Increased risk of endometrial cancer.
   B. Increased risk of ovarian cancer.
   C. Increased risk of colon cancer.
   D. No effect on either endometrial or ovarian cancer.
   E. Decreased risk of endometrial, ovarian, and colon cancer.

2. Which of the following statements accurately describe characteristics of a levonorgestrel intrauterine system?
   A. Newer products can be safely self-inserted by the patient.
   B. These products provide safe and reliable contraception for 3 to 5 years.
   C. These products reliably result in consistent, monthly menses.
   D. These products should not be used in nulliparous adolescents.
   E. These products are excellent for control of menorrhagia but are ineffective for contraception.

3. What is the primary mechanism of action of the combined oral contraceptive pill (COCP) in preventing pregnancy?
   A. Inhibition of ovulation and proliferative changes in the uterus.
   B. Inhibition of implantation of the fertilized ovum.
   C. Blocks the ability of sperm to penetrate and fertilize the egg.
   D. Increased proliferative changes in the uterus, leading to bleeding and spontaneous abortion.
   E. Direct spermicidal effect.

4. Which of the following is NOT a noncontraceptive benefit of COCPs?
   A. Treatment of menorrhagia.
   B. Treatment of dysmenorrhea.
   C. Treatment of premenstrual syndrome physical symptoms.
   D. Treatment of excessive menstrual bleeding in von Willebrand disease.
   E. Treatment of seizures.

5. Which of the following is true about the use of hormonal contraceptive agents in patients with sickle cell disease?
   A. The use of these agents is contraindicated in sickle cell disease.
   B. Progestin-only contraceptive agents are preferred.
   C. These agents substantially increase the rate of sickle cell pain crises.
   D. High-dose estrogen-progestin formulations are recommended.
   E. Depot medroxyprogesterone acetate should not be used in patients with sickle cell SS disease.

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