The Challenges, Risks, and Benefits of Oral Contraceptives

Learning Objectives
After participating in this educational activity, participants should be better able to:

1. Identify the currently available oral contraceptives and their benefits and risks

2. Provide counsel to appropriate patients on emergency contraceptive products including their role in pregnancy prevention, efficacy, and safety

3. Create individualized plans to prescribe oral contraceptives for patients based on their needs, lifestyles, comorbidities, and reproductive plans
Introduction

42 year old female, Nancy, newly divorced, comes in to your primary care office to discuss options for birth control. She has two daughters, ages 16 and 12. Her ex-husband had a vasectomy after the birth of their youngest daughter so birth control was not an issue for her for the past 12 years. She is not currently sexually active, but wants to be prepared as she re-enters the dating world. She remembers taking an oral contraceptive pill years ago in her 20’s that had 21 pills of the same color for the first three weeks of the pack and then a different color the last week for the “placebo” pills. She would punch those out of the pill pack and throw them away. As she recalls, she was told to take the pill at night to prevent nausea and to take at the same time every evening to prevent break-through bleeding. One time she forgot to start on her new pack and had to wait until her next period to make sure she was not pregnant before starting her new pack; she remembers what a hassle that was. She asks: “Is it safe for me to take the birth control pill at 42 years old? I heard there are new ways of taking the pill so you don’t have to have a period every month; that sounds interesting, but is that safe? Also, a friend of mine said her doctor does not want her to be on the birth control pill after the age of 40 because it increases the risk of breast cancer and blood clots; is that true?”

Primary Care Clinicians need to be able to answer Nancy’s questions as well as other patient’s questions about oral contraceptive use. Many new formulations and new dosing schedules have emerged in recent years. Potential benefits and safety concerns need to be taken into account. Matching a patient’s profile with the best contraceptive product to address her needs is desirable. Our patients will benefit from our knowledge of current formulations of oral contraceptive products. In addition, being aware of how to counsel women needing emergency contraception is important.

Background

Despite advances in contraception options, almost half of all pregnancies are unintended and about half of these unintended pregnancies result in abortion.[1,2] In many cases, these women with intended pregnancies were using some form of contraception, but were using it incorrectly, inconsistently, or had stopped its use. Patient education by their primary care physicians regarding the correct use of contraception is critical. Selecting the optimal contraceptive method and regimen to meet a patient’s needs and lifestyle will increase patient satisfaction and compliance.

Contraception methods include hormonal oral contraceptive products, intrauterine devices (IUDs), hormonal transdermal patches, hormonal vaginal rings, hormonal subcutaneous pellets, diaphragms, and over the counter products such as condoms and spermicidal foams.

Case Study: Nancy

Nancy does not smoke, has no history of venous thrombosis or clotting issues, is not overweight, and is in overall good health. Her blood pressure is 110/70 and her exams including breast and pelvic exam are normal. Her menses are every 28-30 days, flow is moderate, and cramps are mild. You tell her the following (select the correct answer):

a. Hormonal oral contraceptive of any kind is not safe for her since she is over the age of 40
b. The progesterone-only contraceptive pill (POCP) would be safer than one containing estrogen
c. An intrauterine device would be safer for her
d. A combined oral contraceptive (COC) containing synthetic ethinyl estradiol and a progestin would be safe for her
In the absence of risk factors for cardiovascular events and in non-smoking, normotensive women, combined oral contraceptive pills containing both a synthetic estrogen and synthetic progesterone are safe for the majority of women in their 40’s.

You determine that a combined oral contraceptive pill is safe for Nancy. Options for dosing include all of the following EXCEPT:

- a. Extended-cycle contraceptive with 84 “active” pills followed by 7-days of low-dose estrogen pills
- b. **Continuous-cycle COC regimen with active pill for 6 months followed by 7 days of placebo**
- c. Extended-cycle contraceptive with 84 “active” pills followed by 7-days of placebo
- d. Continuous-cycle COC regimen with active pill every day for 1 year
- e. Low-dose COC with 10 mcg estrogen (ethinyl estradiol) with 24 “active” pills

The only current continuous-cycle COC is marketed under the brand name Lybrel®. It consists of 28 active hormone pills per pack and is taken continuously through the year. There is no current continuous COC for a 6-month period.

**Oral Contraceptives: Available Options**

Oral contraceptives can be divided into two types:

1. Combination oral contraceptive (COC), containing a synthetic estrogen (ethinyl estradiol in most cases) and synthetic progesterone (progestin)
2. The “mini” pill or a progestin-only pill (POP) containing progestin only

When oral contraceptives were first introduced in the United States in the 60’s, the amount of ethinyl estradiol (EE) was commonly 50-80 mcg per pill. This higher dose of estrogen caused a higher risk of venous thrombosis and other cardiovascular events as well as a higher side effect profile including weight gain, nausea, breast tenderness, and headache; than current lower-dose formulations. In the years that followed, lower dose pills containing 20-35 mcg of ethinyl estradiol became popular. Dosing regimens changed from the traditional 21/7 pill packs to include triphasic and biphasic combinations. Recent developments include an oral contraceptive with only 10 mcg EE, 24/4 pill packs featuring 24 active pills with 4 placebo or iron pills, and extended COCs. There is a wide range of progestin options. To complicate our history taking in reviewing current contraceptive use, many generic oral contraceptives are also being used. The clinician may have difficulty in identifying the current hormonal amount if the patient provides only the generic name. Bringing in the pill pack for identification of the amounts and dosing regimen is highly recommended.
## Terminology

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<tr>
<th>Term</th>
<th>Description</th>
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<tr>
<td>Monophasic</td>
<td>All active pills in the pack contain the same amount of ethinyl estradiol and progestin</td>
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<tr>
<td>Biphasic</td>
<td>Two different strengths of active pills; vary in amount of EE or progestin</td>
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<tr>
<td>Triphasic</td>
<td>Three different strengths of active pills; most vary in amount of progestin</td>
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<tr>
<td>Cyclical</td>
<td>Active pill for 21-24 days followed by 4-7 days of placebo; allows for cyclical withdrawal bleed</td>
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<tr>
<td>Extended</td>
<td>Active pill for 84 days followed by 7 days of placebo or low-dose EE; allows for bleeding every 3 months</td>
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<tr>
<td>Continuous</td>
<td>All pills are active and no placebo; no scheduled withdrawal bleeding</td>
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<td>Add-Back Estrogen</td>
<td>Low-dose EE pills without progestin at end of combined active pill regimen; found in both triphasic and some extended formulations</td>
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<tr>
<td>High-Dose</td>
<td>Pill formulations containing greater than 35 mcg EE in each active pill</td>
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<tr>
<td>Low-Dose</td>
<td>Pill formulations containing 35 or less EE in each pill</td>
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<tr>
<td>Mini-Pill</td>
<td>Pill formulations containing only progestin and no estrogen</td>
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Almost all combined hormonal contraceptives contain ethinyl estradiol (EE) as the form of estrogen. Common dosage ranges from 20-50 mcg per pill; recently, a contraceptive pill with only 10 mcg EE has been introduced into the United States market. Progestins vary and are classified according to their steroid structure and introduction onto the market. They are commonly referred to as first, second, third generation, or fourth generation. Norethindrone is a first generation progestin, levonorgestrel and norgestrel as well as norgestimate are second generation, desogestrel is third generation, and drospirenone is fourth generation. The older (first- and second-generation) progestins have more androgenic activity while the newer (third and fourth generation) progestins have less androgenic activity. All progestins work to inhibit ovulation as well as cause the endometrium to become thin and the cervical mucus more resistant to sperm penetration. The addition of the ethinyl estradiol (EE) in the combined hormonal contraceptives helps to provide better cycle control. In general, the incidence of breakthrough bleeding increases as the dose of EE is reduced.

### Going back to Nancy, here are some commonly used options for her:

1. Monophasic low dose cyclical EE 10-35 mcg pills with norethindrone as the progestin.
   - Brand names the clinician may be familiar with include:
     a. Loestrin® 1/20 (the 20 refers to the amount of EE; the 1 to the amount of progestin)*
     b. Loestrin® 1.5/30 (30 mcg EE in each active pill)
     c. Lo Loestrin® 1/10 (10 mcg EE in each active pill)
     d. Loestrin® 24 (the 24 refers to 24 active pills, 4 inactive; 20 mcg EE in active pills)
     e. Ovcon 35® (35 mcg EE in each active pill)
     f. Ortho-Novum® 1/35 (35 mcg in each active pill)
   - *Some include iron in the non-hormone pills and include Fe in the name such as Loestrin Fe 1/20, Loestrin Fe 1.5/30, and Lo Loestrin Fe 1/10
2. Monophasic low dose cyclical EE 20-35 mcg EE pills with drospirenone as the progestin. Brand names the clinician may be familiar with include:
   a. Yaz® (20 mcg EE in each active pill)
   b. Yasmin® (30 mcg EE in each active pill)

3. Extended-cycle oral contraceptives containing levonorgestrel as the progestin. Brand names the clinician may be familiar with include:
   a. Seasonale® (30 mcg EE in active pill; 84 active pills followed by 1 week placebo)
   b. Seasonique® (30 mcg EE in active pill; 84 active pills followed by 1 week 10 mcg EE pills)
   c. LoSeasonique® (20 mcg EE in active pill; 84 active pills followed by 1 week 10 mcg EE pills)

4. Continuous –cycle oral contraceptive
   a. Brand Name Lybrel® (20 mcg EE in all pills; .09 mg levonorgestrel as progestin in all pills)

5. Biphasic and Triphasic contraceptives
   a. Vary dose of EE in active pills (less common)
   b. Vary dose of progestin in active pill (more common)
   c. Common Name Brands include Mircette®, Ortho-Novum® 7/7/7, Ortho Tri-Cyclen®, Estrostep®

6. Progestin-only contraceptives
   a. Norethindrone as the progestin
   b. All contain 35 mcg progestin in each pill and no estrogen
   c. No placebo
   d. Monophasic
   e. Common Name Brands include Nor-QD®, Jolivette®, and Micronor®

The above formulations are commonly used ones, but there are many others not listed. For a more complete listing, the clinician may refer to the full Physicians’ Desk Reference (PDR).

**Case Study: Back to Nancy**

With so many options available for oral contraception, it may be useful to ask Nancy if she wants a more traditional cyclical type pill that allows for monthly withdrawal bleeding or would she prefer to use an extended or continuous type that would lessen her period frequency. The common side effects of spotting and unscheduled bleeding that can occur with the extended COCs needs to be explained to help her make her decision. Past experience with the pill may help guide this discussion and decision-making process. Unwanted estrogen-related side effects such as nausea and breast tenderness can be minimized with the lower 10-20 mcg EE options; however, there may be an increased risk of spotting compared to the 30-35 mcg EE options.

**Safety Issues**

Contraindications to the use of a combination oral contraceptive product include women with current or high risk of arterial or venous thrombotic disease, women with cancer including breast cancer that is estrogen or progestin-sensitive, and undiagnosed abnormal uterine bleeding. Smokers over the age of 35, women with migraine especially if associated with aura, history of deep venous thrombosis, uncontrolled hypertension, diabetes with vascular disease, and hypercoagulopathies put women at high risk of arterial or venous thrombotic disease. Hepatic disease or a hepatic tumor is also considered a contraindication for COCs.[3] There have been
conflicting reports on the restriction of COCs in women with migraine. A recent review article examined the current evidence regarding the effect of contraception on headache and migraine and concluded that there should be no restriction to the use of COCs for women with migraine without aura given the absence of other cardiac risk factors. Migraine with aura is associated with a twofold increased risk of ischemic stroke, but the absolute risk is low.[4] Therefore, the decision should be individualized for these women. Although ethinyl estradiol has been associated with increased risk of ischemic stroke, the risk is dose-dependent. Progestin-only formulations are considered safer for women with vascular disease, a history of venous thrombosis, a history of hepatitis, history of lupus, migraines, and for women who have multiple risk factors for cardiovascular disease.[5] Contraindications include breast cancer, undiagnosed abnormal vaginal bleeding, and liver tumors. In the past, progestin-only pills were not considered as effective as COCs, but recent data suggests their efficacy to be similar to COCs.[6]

Health Benefits
There are both short-term and long-term benefits with the COCs and POPs. Short-term benefits that become apparent within the first few months of use include improved mood including a reduction in Premenstrual Dysphoric Disorder (PMDD)[7], less acne[8], less dysmenorrhea[9], and less blood flow[10].

Long-term non-contraceptive benefits include a statistically significant protection against endometrial, colorectal, and ovarian cancer.[11]

Case Study: Discussion with Nancy
After being given all options for oral contraceptive use, Nancy has decided to start on the COC that contains only 10 mcg EE in a 24/4 pill pack with 24 active pills followed by two pills with add-back estrogen followed by two iron containing pills. She is concerned about nausea and breast tenderness as well as long-term side effects of estrogen and likes the fact that this is the lowest dose estrogen-containing contraception. She understands the risks of COCs and agrees to return in 3 months to have her blood pressure checked and review how she is doing with her pills.

Emergency Contraception
After leaving the discussion with Nancy, you learn from your office that Melanie, a college student in your practice, has called frantically to ask about the “morning after” pill. She stopped her birth control pill this past fall after breaking up with her boyfriend and going to college. However, over this past weekend, she got back together with him, they had sex, and his condom broke. Her LMP was 2 weeks ago. Appropriate advice is (select the correct answer):

a. Emergency contraception (EC) requires a prescription from your office
b. EC must be taken within the first 72 hours after unprotected intercourse
c. EC consists of 4 tablets of EE taken as two tablets initially and then two 12 hours later
d. **EC is available without a prescription to all women 15 years and older**
e. Start back on her birth control pill immediately

Recent legislation passed making emergency contraception available without a prescription to females 15 and older. EC can be purchased in pharmacies and no parental consent or doctor’s prescription is needed. This legislation is for the single pill EC containing 1.5 mg levonorgestrel (LNG).
The use of emergency contraception has increased in recent years from more than 10% of women using it between 2006-2008 compared to just 4% in 2002.[12] There are more than 3 million unplanned or unintended pregnancies every year in the United States.[1,2] The use of emergency contraception could reduce this incidence of unintended pregnancies by 50% and this would translate into 1.5 million fewer unintended pregnancies.[13] Effectiveness of EC depends on the regimen used, as well as the time between unprotected intercourse and the emergency contraception treatment.[14]

Options currently available include a single pill containing 1.5 mg of LNG, a progestin.[15,16] LNG is marketed under the brand name of Plan B One-Step® and Next Choice One Dose™ and it should be taken within 72 hours of unprotected intercourse to be effective. A new EC is now available consisting of a progesterone agonist/antagonist as a single pill of 30 mg of ulipristal acetate (UPA). UPA is marketed under the name of ella® and requires a doctor's prescription. It can be effective up to 5 days after unprotected intercourse[17] and is at least as effective as LNG when used in the first 72 hours. Side-effects of emergency contraception include heavier menstrual bleeding, nausea, abdominal pain, fatigue, headache, dizziness, breast tenderness and a delay in menses. Contraindications for use include known or suspected pregnancy. If the subsequent menses is delayed by more than 1 week, pregnancy should be ruled out. Women who become pregnant or complain of lower abdominal pain after taking ella® should be evaluated for ectopic pregnancy.

Contrary to popular opinion, EC does not cause an abortion; rather, it works to inhibit/delay ovulation; interferes with fertilization of an egg; and may prevent implantation of a fertilized egg by altering the lining of the uterus. However, it does not stop the development of the fetus once implantation has taken place. It will not be effective if the woman is pregnant and the implantation has already taken place.

Summary
There are many oral hormonal contraceptive options available for women of childbearing age. The trend in recent years has been to decrease the amount of estrogen in the formulations while still maintaining efficacy. Lower dose formulations have a more tolerable side-effect profile and less risk of cardiovascular events. Extended and continuous options for delivery are now available making it possible for women to eliminate a monthly withdrawal bleed. Progesterone-only pills can be used in select women who cannot or should not take estrogen. Finally, for women who have unprotected intercourse, there are emergency contraception options that can be taken up to 5 days after the unprotected intercourse.

Clinicians who treat women of childbearing age need to be aware of all the options for oral hormonal contraception that are now available. Our women patients will appreciate our knowledge of the many choices available to them. With these options, we can help women select the option best suited for them given their existing health conditions, their needs, and their preferences.
References


