Hormonal Contraception

Introduction

Hormonal contraception is used by millions of women in the U.S. and Canada. There are a variety of contraceptive options for women including both oral and non-oral forms. Understanding the differences among these contraceptives is important to determine the best choice for a particular woman. This article discusses the rationale for picking one formulation over another in women with particular needs and concerns.

Combined Oral Contraceptives

Estrogen content. The estrogen in most COCs is ethinyl estradiol. The estrogen dose of COCs has decreased from as high as 100 mcg/day in early formulations to as low as 10 mcg/day in Lo Loestrin Fe (U.S. only). Some of the major risks of COCs were identified in studies evaluating older formulations containing more than 50 mcg of ethinyl estradiol; these safety concerns may not apply to newer formulations that contain 35 mcg or less of ethinyl estradiol.

Some people question the efficacy of lower estrogen COCs. One method of comparing efficacy of different contraceptives is the Pearl Index. The Pearl Index measures the number of pregnancies that would occur if the contraceptive was used by 100 women for one year. The newer lower dose ethinyl estradiol COCs were designed to improve safety, but this has come with a slight decrease in efficacy. For example, pills approved before 1970 (i.e., 50 mcg pills; “first-generation” pills) had a failure rate of <1 per 100 women-years of use (i.e., Pearl Index <1). The subsequently marketed 35 mcg pills (low-dose pills; “second generation” pills) had a Pearl Index of <1.5. In the only reported trial mentioned in the product information, the Pearl Index with Lo Loestrin Fe (U.S. only) for women 18 to 35 years was 2.92 pregnancies per 100 women-years of use. It is important to remember that this number was derived from one study, using carefully selected patients, and may not be indicative of “real life use.” In comparison, the Pearl Index for Loestrin 24 Fe (a pill containing 20 mcg of ethinyl estradiol, similar to Minestrin 1/20 in Canada) is 1.82. This number suggests that the 10 mcg-containing Lo Loestrin Fe is less effective than the 20 mcg-containing Loestrin 24 Fe.

Most women should start with a COC containing 20 mcg ethinyl estradiol plus an older progestin such as levonorgestrel or norethindrone because they have a good balance of safety and efficacy. A higher estrogen dose may be appropriate in special circumstances such as drug interactions due to induction of cytochrome P450 enzymes (carbamazepine, etc).

Progestin content. There are a number of different progestins used in today’s COC pills. These progestins are most commonly classified by their “generation” according to when the agents were marketed. First-generation progestins such as norethindrone, norethindrone acetate, ethynodiol, and lynestrenol (not available in U.S. and Canada) are potent and well tolerated. However, with the low doses used in COCs they tend to have a higher risk of unscheduled bleeding and spotting. Second-generation progestins include norgestrel and levonorgestrel. These agents are more potent than first-generation progestins and have a longer half-life. Usual doses of levonorgestrel are 0.15 mg compared with 0.5 mg or 1 mg of norethindrone, a first-generation progestin. Second-generation progestins have more androgenic (antiestrogenic) activity which may translate to an improved libido, but can also be associated with hirsutism, acne, or dyslipidemia. To mitigate these problems, third-generation progestins were introduced. Third-generation progestins include desogestrel, norgestimate, and gestodene (not available in U.S. and Canada). They have similar gestational activity as second-generation progestins, but are not associated with as much androgenic (antiestrogen) activity. This can be

More...
beneficial in patients with acne. However, these agents are associated with a slightly higher risk of thrombosis. Most recently, a fourth-generation progestin, drospirenone, was marketed. Drospirenone is different from the other progestins in that the parent compound is spironolactone. Drospirenone has some of the antimineralocorticoid and antiandrogen effects of spironolactone. As with the third generation progestins, concerns about the increased risk of venous thromboembolism have been raised (see Risk of Thromboembolism below).

In women who use a COC, the estrogen content or progestin content may need to be adjusted based on adverse effects they experience. Common COC complaints associated with adverse estrogenic, progestogenic, and androgenic effects of COCs are listed in Table 1.1,6

| Too much estrogen... | Nausea, breast tenderness, increased blood pressure, melasma, headache. |
| Too little estrogen... | Early or mid-cycle breakthrough bleeding, increased spotting, hypomenorrhea. |
| Too much progestin... | Breast tenderness, headache, fatigue, changes in mood. |
| Too little progestin... | Late breakthrough bleeding. |
| Too much androgen... | Increased appetite, weight gain, acne, oily skin, hirsutism, increased LDL cholesterol, decreased HDL cholesterol. |

Based on the predominant symptoms a woman is experiencing, the estrogen or progestin content can be adjusted. For example, in a woman complaining of excessive breast tenderness, a COC with less estrogen can be considered.

**Phasic Pills**

Combined oral contraceptives were first developed as monophasic pills; biphasic and triphasic pills were later developed in order to reduce dose-dependent adverse effects of the progestin. More recently, a four-phasic pill (Natazia) was approved. Phasic pills were designed to more closely mimic fluctuations in estrogen and progesterone levels during the menstrual cycle. However, a recent Cochrane review was unable to determine if there is a difference in efficacy between monophasic and biphasic pills. In addition, based on the results of a single qualified study, the reviewers found no major difference in bleeding pattern between a monophasic pill (Loestrien) and a biphasic pill (Ortho-Novum 10/11). Another Cochrane review compared biphasic and triphasic pills. It found that cycle control was worse with a biphasic pill containing norethindrone (Ortho-Novum 10/11) than a triphasic pill containing levonorgestrel (Triphasil [no longer available]). The reviewers concluded that the choice of progestin is more important than the phasic formulation.8

**Extended and Continuous Regimens**

Combined oral contraceptives such as Seasonale and Seasonique provide active pills for 84 days followed by a 7-day pill-free interval, or 7-day low-dose estrogen, respectively. It is already common practice to eliminate the pill-free interval of a monophasic COC for two to three cycles to achieve an extended cycle (bi-cycling and tri-cycling). Four packets of a low-dose monophasic COC without the placebo pills will provide a regimen similar to Seasonale.1,6 Menstruation-related problems that may improve with an extended cycle regimen include menorrhagia, anemia, dysmenorrhea, endometriosis, and menstrual headache.1,6,9 A continuous regimen without a pill-free interval has been reported to decrease endometriosis-related menstrual pain inadequately relieved by a traditional cycle COC.9,10

There is only one true continuous use COC, Amethyst (U.S. only). Each tablet contains ethinyl estradiol 20 mcg and levonorgestrel 90 mcg. There is no pill free interval and women take an active pill every day. The effects of Amethyst can be replicated by continuously using an extended cycle COC. However, the long-term effects of extended use oral contraceptives are not known. Taking oral contraceptives continuously will expose the woman to one additional month of estrogen and progestin in the course of one year, increasing lifetime hormone exposure. The significance of this observation is not known, but is not thought to be harmful. Some women may prefer to have periodic withdrawal bleeding as reassurance that they are not pregnant.

**Hormonal Contraceptive Effectiveness**

The effectiveness of contraceptives is evaluated under two conditions, “typical use” and “perfect use.” Perfect use refers to use by couples who use the method consistently and correctly. Effectiveness values are much higher for perfect use, but may not be applicable to the general population. The table below summarizes the

More...
percentage of women who have an unintended pregnancy with the commonly used hormonal contraceptives.¹

<table>
<thead>
<tr>
<th>Hormonal Contraceptive</th>
<th>% unintended pregnancy during first year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Perfect use</td>
</tr>
<tr>
<td>No method</td>
<td>85</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
</tr>
<tr>
<td>(combined and progestin-only)</td>
<td>0.3</td>
</tr>
<tr>
<td>Ortho Evra</td>
<td>0.3</td>
</tr>
<tr>
<td>NuvaRing</td>
<td>0.3</td>
</tr>
<tr>
<td>Depo-Provera</td>
<td>0.2</td>
</tr>
<tr>
<td>IUS*</td>
<td>0.2-0.6</td>
</tr>
<tr>
<td>Implanon (Nexplanon)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*IUS = Intrauterine System

Breakthrough Bleeding

No pill is clearly better than the others for maintaining good cycle control. Breakthrough bleeding or spotting is common with all forms of COC, especially during the first three months of use.⁹ BLEEDING during the first three months does not indicate a lack of efficacy.¹⁰,¹¹ If bleeding persists, switching the type of pill may improve certain patterns of breakthrough bleeding (BTB).¹²,¹³ For example, if they are taking a COC with 10 mcg or 20 mcg of ethinyl estradiol, consider increasing the estrogen content. If a woman is already taking an OC with 30 or 35 mcg of ethinyl estradiol, consider changing the progestin or increase the progestin dose if they are using a progestin-only or multiphasic COC. In women taking a concomitant enzyme inducer such as phenytoin, a COC with a higher estrogen content may reduce breakthrough bleeding.¹⁰,¹¹

Risk of Thromboembolism

Thromboembolism is a rare, but severe, adverse effect associated with COC therapy. Until the mid 1990s, it was thought that venous thromboembolism was associated only with the estrogen component of oral contraceptives, and that the progestins did not contribute to the risk.¹⁴,¹⁵ Earlier studies showed that oral contraceptives containing high doses of ethinyl estradiol (50 mcg or more) were associated with a greater risk of thrombosis than those containing lower doses of estrogen (35 mcg of ethinyl estradiol).¹,¹³ However, with the introduction of newer generation progestins in combination oral contraceptive products, it was noted that there appeared to be a higher rate of thromboembolism than that seen in users of oral contraceptives containing estrogen and older progestins. Subsequent studies confirmed that the progestin also contributes to the thromboembolic risk.¹³,¹⁵

Controversial studies suggest that the relative risk of deep vein thrombosis is higher with pills containing drospirenone (Yaz, Yasmin, etc), compared with other progestins.¹ Six studies have been published which evaluate the relationship of drospirenone and venous thromboembolism.¹⁴,¹⁶⁻¹⁹ The results were mixed, with two showing no increased risk of venous thromboembolism and four showing an increased risk, although the magnitude of the increased risk was variable. The results of the newest study support the claims that drospirenone increases the risk of venous thromboembolism.

Questions about the safety of the transdermal patch Ortho Evra (Evra in Canada) and contraceptive ring (etonogestrel and ethinyl estradiol vaginal ring, NuvaRing), have arisen.²²,²³ Although the patch and ring do not contain drospirenone, there is concern that these newer contraceptive methods increase the rate of thromboembolism. It has been hypothesized that continuous, higher exposure to estrogen seen with Ortho Evra may increase thromboembolic risk.²² Although the exposure to estrogen is substantially lower with NuvaRing, it might still have a higher thrombosis risk. Using NuvaRing can cause a significant increase in sex hormone binding globulin. It is thought that the higher the levels of sex hormone-binding globulin, the higher the risk of thrombosis. The product labeling for both Ortho Evra (U.S.) and Evra (Canada) contains warnings about the thromboembolic risk.²⁴,²⁵

More...
Recent studies provide additional information to support the association of the contraceptive patch with venous thromboembolism and suggest that the etonogestrel/ethinyl estradiol vaginal ring may also increase the risk of thromboembolism.

For more information, see our PL Detail-Document, Hormonal Contraceptives and the Risk of Thrombosis.

Women with Coexisting Medical Conditions

When choosing a contraceptive for women with coexisting medical conditions, it is important to take these conditions into consideration. For example, in women with adequately controlled blood pressure or with systolic blood pressure 140 to 159 mmHg or diastolic blood pressure 90 to 99 mmHg, all contraceptives except estrogen-containing contraceptives can be considered. However, in women with systolic blood pressure 160 mmHg or greater, or diastolic blood pressure 100 mmHg or greater, a copper intrauterine system (IUS) is preferred. Alternatives include progestin-only oral contraceptives, implants, or levonorgestrel-releasing IUS. Estrogen-containing contraceptives and depot medroxyprogesterone should be avoided. See our PL Chart, Contraception for Women With Chronic Medical Conditions, for more information.

Obesity. Women who are obese present a number of clinical issues. The efficacy and safety of hormonal contraception in women who are obese are controversial. Some studies show a reduced efficacy in this population, while others do not. In addition, the concern of venous thromboembolism in a group of women who may already be at risk for clots is often highlighted. In general, for all forms of contraceptives, the benefits outweigh the risks and can be used. Heavier women have, at most, a slightly higher risk of pregnancy with hormonal oral contraceptives than normal weight women. However, the risk of venous thrombosis during pregnancy and in the peripartum period far outweighs the thromboembolism risk or slightly reduced efficacy with oral contraceptive use. Although some prescribers lean toward a contraceptive with 35 mcg of estradiol, there is no evidence that these higher dose pills are more effective than oral contraceptives containing lower amounts of estrogen. Pills containing 50 mcg of estrogen should be avoided because of the known increased risk of venous thrombosis, even in normal weight women. For more information, see our PL Detail-Document, Use of Hormonal Contraceptives in Obese Women.

Migraine. Using hormonal contraception in women with migraines is another controversial area. The concern is the risk of stroke. However, guidelines support that women with migraines without aura can safely use COCs. Most menstrual migraine patients do not experience an aura, but a number of these patients also have migraines at other times of their cycle that may include an aura. Recent studies indicate that even in women with migraines with aura, COC may be safe and effective. This is especially true in women younger than 35 years who do not smoke and have normal blood pressure. However, caution is appropriate because strokes can be devastating, especially for young women. Guidelines continue to recommend avoiding COC in women with migraines with aura. The decision to use a COC in a woman with migraines with an aura should involve a discussion with the patient of the potential risks along with consideration of the potential benefits. Alternatively, use of a progestin-only contraceptive should be considered. For more information, see our PL Detail-Document, Combined Oral Contraceptives in Women with Migraines.

Perimenopausal women are another subset of women in whom selection of a contraceptive is challenging. In general, healthy, normal weight, nonsmoking women can use COC until menopause. Hormonal contraception can be used to help with vasomotor symptoms associated with perimenopause in addition to providing contraception. If women complain of vasomotor symptoms during their hormone-free days, a continuous or extended cycle product, or back-to-back low estrogen COC product to minimize the pill-free time can be tried.

Acne. Two triphasic formulations, Ortho Tri-Cyclen (Tri-Cyclen in Canada) and Estrostep (not available in Canada) and one monophasic extended-cycle pill, Yaz, are FDA-labeled for the treatment of acne. In Canada, Alesse, Tri-Cyclen, Yasmin, and Yaz are Health Canada-approved for acne. Although these are the only ones to officially carry this indication, other COCs also work. An estrogen-mediated increase in sex...
hormone-binding globulin levels may improve acne by decreasing free testosterone levels.\(^1\)

**Emergency Contraceptives**

Emergency contraceptives are contraceptives used after intercourse to prevent pregnancy. Before emergency contraceptives became commercially available, health care practitioners often prescribed high doses of commercially available COC pills containing ethinyl estradiol and either norgestrel or levonorgestrel (known as the Yuzpe regimen).\(^1\) More recently, products specifically approved for emergency contraception became available. These include ulipristal (** Ella**, U.S. only) and levonorgestrel (**Plan B, Next Choice**). Levonorgestrel can be administered as a single 1.5 mg dose or as two 0.75 mg levonorgestrel doses separated by 12 hours. In the U.S., both levonorgestrel products are available over-the-counter to those 17 years of age and older.\(^1\) In Canada, emergency contraception is also available without a written prescription from a physician. There is no age limit in Canada (http://planb.ca/faq.html).

Emergency contraceptives, while effective as a "morning after" contraceptive method, should not be used as a routine method of contraception. When used routinely, emergency contraceptives are less effective than other methods and may be associated with a greater incidence of adverse effects such as nausea and vomiting. Women should be counseled that repeated doses of progestin-containing emergency contraceptives expose them to progestin levels much higher than those found in daily contraceptives. Also, from an economic standpoint, routine use of emergency contraceptive products is likely more expensive than use of generic oral contraceptives or other forms of birth control.\(^1,3,4,5\) Women should use these agents only as a method of emergency contraception where there is concern about inadequate protection from a primary form of contraception. For more information see our **PL Detail-Document, Routine Use of Emergency Contraception...Is It Safe?**

---

Users of this PL Detail-Document are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

**Project Leader in preparation of this PL Detail-Document: Neeta Bahal O'Mara, Pharm.D., BCPS, Drug Information Consultant**

**References**


More...
22. December 8, and Risk Management Advisory Committee.

23. for Reproductive Health Drugs and the Drug Safety

24. document for joint meeting of Advisory Committee

25. FDA.

26. based on 142,475 women

27. Active Surveillance Study on oral contraceptives

28. levonorgestrel:

29. Risk of venous thromboembolism in women using oral

30. 2011;21:342:d2139

31. Risk of venous thromboembolism and the use of
dienogest- and drospirenone-containing oral

32. 2010:36:123-9

33. Seeger JD, Loughlin J, Eng PM, et al. Risk of

34. and other oral


37. Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism on users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. BMJ 2011;342:d2139


