The Current Status of Oral Contraceptives: Progress and Recent Innovations

Alexandra Golobof, MD1 Jessica Kiley, MD, MPH1

1 Section of Family Planning and Contraception, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Semin Reprod Med 2016;34:145–151

Abstract

Keywords
- oral contraception
- estrogen
- progestin
- extended-cycle oral contraceptive
- noncontraceptive benefits
- oral contraceptive regimen

Millions of women in the United States and abroad use oral contraceptive pills. These popular contraceptives are the most common reversible birth control method in the United States, and a wide variety of pills are available for prescription. Oral contraceptives provide safe and effective protection against pregnancy and offer several noncontraceptive benefits. Over the years, advances in the laboratory and knowledge gained through epidemiologic data promoted the development of new contraceptive preparations. Generations of oral contraceptives emerged over time, containing lower doses of estrogens and new and novel progestins. The current review discusses the clinical characteristics of oral contraceptives, with emphasis on basic pharmacology and the evolution of various contraceptive formulations and regimens.

History and Epidemiology

The development of the modern oral contraceptive pill was the culmination of the work of several chemists, biologists, researchers, and reproductive rights advocates. Early in the 20th century, experiments by Ludwig Haberlandt presented evidence that prevention of ovulation was linked to pregnancy prevention. Haberlandt first proposed a link between hormones and fertility in 1931. Russell Marker produced the first synthetic progestin molecule in his laboratory in 1939, and subsequently created a pharmaceutical company to produce the progestins used in the first contraceptive studies.1

A major scientific breakthrough occurred when Carl Djerassi discovered that modifying natural plant-based progesterone results in increased progestational activity, and the synthetic progestins norethindrone and norethynodrel were produced. The development of the earliest oral agents containing estrogen and progestins was spearheaded by George Pincus and physician John Rock, in concert with women’s rights advocates Margaret Sanger and Katherine McCormick.2

The oral contraceptive pill was introduced in the United States and Great Britain in 1957. It was initially marketed for treatment of gynecological conditions and menstrual irregularities, until 1960, when the first dedicated product, Enovid (Searle, Chicago, IL), was approved by the U.S. Food and Drug Administration (FDA) for contraception.3

Nowadays, the oral contraceptive is the most common reversible contraceptive method in the United States. Nearly 10 million of the 61 million U.S. women of reproductive age (15–44 years) use oral contraceptives.4 In 2012, an estimated 26% of all female contraceptive users relied on the pill for pregnancy prevention.5

The Modern Oral Contraceptive

The combined oral contraceptive (COC) pill has evolved over the years. Scientific advances generated better knowledge of the biochemical properties of steroid hormones and their physiologic effects, resulting in changes in hormone formulations and dosing.

Early formulations of the pill contained relatively high doses of estrogens. Initial formulations contained up to 500 μg of mestranol or up to 150 μg of ethinyl estradiol (EE). As the estrogen component is responsible for the major adverse
events and side effects associated with COC use, gradual decreases in estrogen dosing over the years resulted in a favorable safety profile, without sacrificing contraceptive efficacy or cycle control. While most pills in the 1960s and early 1970s contained 50 μg of EE, 80% of pills by the late 1980s contained lower doses, and the majority of current pills contain 20 to 35 μg (Fig. 1).

The estrogen and progestin types have also changed over time. Early pills contained mestranol, but over time EE replaced mestranol. Much current research focuses on the development of products using estradiol as the estrogen component, resulting in one recently marketed pill containing estradiol valerate. Similarly, the development of oral contraceptives saw marked changes in the progestin component. Products with new progestin types and changes in dosing were frequently introduced. These modifications resulted in the current complement of COC products available in the U.S. and world markets, with more than 100 choices available for prescription.

**Pharmacology**

The COC contains two components: an estrogen and a progestin. The majority of current COCs contain EE, or less commonly mestranol or estradiol valerate. Although estradiol is the most potent estrogen in the body, its potency and activity is largely reduced when ingested orally. EE contains an ethinyl group in the 17 position of the estradiol molecule, which increases its potency after oral administration. Mestranol is the 3-methyl ether of estradiol. Mestranol does not bind to estrogen receptors and must first be converted to EE for biologic activity. Both mestranol and EE differ from naturally occurring estradiol. Metabolism of these compounds varies between individuals, which may explain varying side effects experienced by women taking COCs.

Interest in developing a COC containing estradiol, instead of EE, began years ago. Researchers based this effort on the idea that estradiol, a naturally occurring estrogen, would confer fewer side effects and improve tolerability. Upon oral administration, estradiol valerate is a prodrug in which the valerate side chain of the molecule is cleaved to form 17β-estradiol and valeric acid. The estradiol is subsequently metabolized to estrone and estrone sulfate. One milligram of estradiol valerate is equivalent to 0.76 mg of 17β-estradiol.

The progestin component varies in formulation, bioavailability, dose, and dose-dependent response. The chemical structures of selected synthetic steroid molecules are shown in Fig. 2. Although all progestins included in COCs exert progestational activity, androgenic, estrogenic, and anti-estrogenic activities vary among the different progestins. The initial discovery of progestational properties occurred in 1951, when norethindrone was formed after removal of the 19-carbon from ethisterone, an orally active form of testosterone. The hormonal effect was converted from that of a steroid to a progestin. These progestational derivatives were designated as 19-nortestosterones, based on missing a carbon at the 19-position of the testosterone molecule. Derivatives of 19-nortestosterone were used in the first three generations of COCs. Commonly, authors refer to four “generations” of COC products, reflecting the progressive development of different groups of pills over time.

**First-Generation Combined Oral Contraceptives**

The earliest generation of pills contained the highest doses of estrogens. Products with 50 μg or more of EE fall into this category, in contrast to the “low-dose” COCs of subsequent generations—the typical modern pills containing 35 μg or less. The progestins contained in the first-generation pills were members of the norethindrone family: norethindrone, norethynodrel, norethindrone acetate, and ethynodiol diacetate. These well-characterized progestins are now common components of generic COC formulations. They have the lowest potency and are well tolerated.
Second-Generation Combined Oral Contraceptives
These pills are characterized by their low-dose estrogen content, 35 μg or less of EE, and use of levonorgestrel, norgestimate, or a norethindrone relative for the progestin component. The common second-generation progestins, norgestrel and levonorgestrel, are enantiomers of each other, and are more potent than earlier progestins. Owing to the increased potency, second-generation progestins tend to exert more androgenic activity and related side effects.

Third-Generation Combined Oral Contraceptives
Attempts to reduce the androgenic activity of earlier progestins resulted in the development of the next generation of progestins. The third-generation progestins include desogestrel and gestodene. Fewer androgenic effects are potentiated by increased stimulation of estrogen receptors. Potential clinical benefits include treatment of androgenic conditions such as acne, but controversy exists over the hypothetical concern for increased thrombotic risk with these agents.

Fourth-Generation Combined Oral Contraceptives
The fourth-generation progestins—drospirenone, nomegestrol acetate, and dienogest—are characterized by heightened antimineralocorticoid and antiandrogenic properties. Drospirenone is an analog of spironolactone and has biochemical and pharmacologic profiles similar to endogenous progesterone. Drospirenone has both antimineralocorticoid and antiandrogenic activity. Its antiandrogenic activity may lead to suppression of undesired symptoms, such as acne and hirsutism. Its antimineralocorticoid activity balances the aldosterone-stimulating effects of estrogen, thereby potentially reducing water retention and weight gain. As with the third-generation progestins, questions about potentially increased risks of thromboembolism are an area of controversy.

Dienogest is a progestin derived from 19-nortestosterone but differs in structure from other progestins in its class. The 17α-ethinyl group, typical of many 19-nortestosterone derivatives, is replaced by a 17α-cyanomethyl group in dienogest. Dienogest exerts a strong progestational effect on the endometrium, but unlike other 19-nortestosterone derivatives, it is characterized by overall antiandrogenic effects.

Mechanisms of Action
The primary mechanism of action of COCs is prevention of ovulation, achieved via suppression of the luteinizing hormone (LH) surge. Follicle-stimulating hormone (FSH) and LH are pituitary gonadotropins, produced by the anterior pituitary gland, which are responsible for hormone secretion from the ovary, and follicular maturation and release. Progestins inhibit ovulation directly by blocking gonadotropin-releasing hormone (GnRH) and suppressing the LH surge, preventing release of a dominant follicle. Additional effects of COCs include thickening of the cervical mucus, rendering it impassable for sperm; impairment of the motility of the fallopian tubes; and modification of endometrial histology.

As they suppress ovulation, progestins serve as the main active ingredient in COCs. The estrogen component potentiates the action of the progestin by suppressing the FSH surge, which is necessary for recruitment of the dominant follicle. Estrogen also acts to stabilize the endometrial lining, reducing breakthrough bleeding and allowing favorable cycle control.

Progestin-Only Pills
The progestin-only pill, frequently called the “minipill,” is an oral contraceptive containing progestin alone, without an estrogen component. In the United States, the progestin-only pill contains norethindrone 35 μg. Progestin-only products composed of various other progestins, including desogestrel, levonorgestrel, and norethisterone, are available in Europe.

In contrast to the ovulation suppression imposed by COCs, the norethindrone-only pill exerts its major contraceptive action by thickening of the cervical mucus. Other effects include incomplete ovulation suppression through
gonadotropin inhibition and alteration of the endometrial environment. As they lack estrogen, progestin-only pills are suitable for women with contraindications to estrogen-containing products, including women with severe hypertension, history of venous thromboembolism, or history of stroke, who choose to use an oral contraceptive. The minipill is also commonly used by lactating women.

**Clinical Use of Oral Contraceptives**

The standard dosage cycle for COCs mimics a 28-day spontaneous menstrual cycle; 21 days of estrogen plus progestin, followed by 7 days of placebo (21/7 regimen). A woman takes a pill daily for 21 consecutive days, and then experiences withdrawal bleeding during the hormone-free week. Modifications of the traditional 21/7 regimen are now common. Extended-cycle formulations involve using active hormone pills for longer intervals, often 12 weeks, followed by a hormone-free week for withdrawal bleeding (84/7 regimen).

The major adverse events associated with COC use are venous thromboembolism, stroke, and myocardial infarction, all of which are rare. Commonly reported symptoms in COC users include breast tenderness, nausea, headache, weight gain, and nervousness, which are frequently nonspecific and often not actually attributable to the COC. COCs offer several noncontraceptive benefits, including cycle control, relief of dysmenorrhea, treatment of endometriosis, treatment of premenstrual syndrome or dysphoric disorder, improved acne and hirsutism, increased bone mass, amenorrhea, treatment of premenstrual syndrome or dysphoric disorder, treatment of endometriosis, and nervousness, which are frequently nonspecific and often not actually attributable to the COC.18

COCs offer several noncontraceptive benefits, including cycle control, relief of dysmenorrhea, treatment of endometriosis, treatment of premenstrual syndrome or dysphoric disorder, improved acne and hirsutism, increased bone mass, ovarian cyst suppression, and decreased risk of ovarian and endometrial cancers. Many women benefit from these effects, in addition to pregnancy prevention.19

**Contraceptive Effectiveness**

Contraceptive failure rates are defined as the percentage of users who will become pregnant over the course of 1 year. This rate is subdivided into "perfect use" and "typical use." Perfect use refers to the in vivo failure rates demonstrated when each method was taken correctly and consistently, and efficacy represents estimates reported in clinical studies. Failure rates demonstrated in clinical trials approximate perfect use.

In evaluating contraceptive effectiveness, the first-year failure rate with typical use is the clinically relevant measure. Typical-use pregnancy rates take into account when users fail to use a method consistently or use it incorrectly; this rate reflects use under "real-world" circumstances. Typical use does not imply that a contraceptive method was consistently used. As COCs require daily action by the user to take a pill, there is a pronounced difference between perfect-use and typical-use failure rates; these are 0.3 and 9%, respectively. The typical-use failure rate for the progestin-only pill is the same, 9%.20

**Recent Innovations**

Several major changes in COC products emerged over the past 60 years. These developments include lower estrogen doses, new progestin types, multiphasic formulations, extended-cycle regimens, and modified hormone-free intervals. New products tend to target better cycle control, reduction in the number of withdrawal bleeding episodes, improved compliance, noncontraceptive benefits, and potentially fewer adverse events.

**Lowered Estrogen Dose**

The dose of estrogen in COCs correlates with efficacy and adverse events. Risks of venous thromboembolism, a serious adverse event, increase with higher estrogen doses, whereas efficacy potentially declines with lower doses. First-generation COCs were associated with the greatest risks of hypercoagulability and cardiovascular adverse events. Manufacturers decreased estrogen dosages to minimize many potential adverse events, particularly thrombosis, without sacrificing contraceptive efficacy.

The clinical implications of the lowest-dose estrogen pills are unclear. While less estrogen is theoretically safer with respect to the risks of thrombosis and cardiovascular events, the actual incidence of these events in women using 20 μg EE pills has not been fully evaluated. The characteristics of COCs containing 20 μg EE with those containing more than 20 μg EE were compared in a recent Cochrane review.21 Failure rates were similar between groups. Users of 20-μg pills more often experienced abnormal bleeding (including irregular bleeding, breakthrough bleeding, and amenorrhea) and were more likely to discontinue trial participation earlier than anticipated.

An "ultra-low-dose" COC containing 10 μg EE was developed in an effort to further reduce estrogen-related adverse events. The regimen was 10 μg EE and 1 mg norethindrone acetate for 24 days, followed by 10 μg EE alone for 2 days, then placebo for 2 days, for a total of a standard 28-day cycle. The regimen was designed to improve efficacy and reduce breakthrough bleeding, as shortening the hormone-free interval from the usual 7 days has been proposed to confer these benefits.22 In an uncontrolled, open-label study, 1,683 women using this COC regimen were followed for 1 year. Pregnancy rates were low and comparable with perfect-use failure rates reported in most clinical trials of COCs. Breakthrough bleeding occurred in 52.7% of participants in cycle 2 of 13, and decreased to 36.4% in cycle 13. The discontinuation rate was 41.7%.23 Thus, although COCs with the lowest doses of EE may be theoretically safer, this idea has not been supported by data, and data suggest higher rates of bleeding pattern disruptions with these COCs.

**Extended-Cycle and Novel Dosing Regimens**

Elimination of withdrawal bleeding episodes in COC users has been practiced for years. Women with gynecologic disorders such as endometriosis and dysmenorrhea and premenstrual syndrome experience relief of symptoms when using the active pills daily and eliminating the placebo, hormone-free, inactive pills.24–26 Even in the absence of gynecologic problems, many women prefer to reduce the number of withdrawal bleeding episodes, for convenience or for other benefits such as better attendance at work and social events, and sparing the expense of feminine hygiene products.27,28
The development of dedicated products with extended-cycle (or continuous) dosing was popularized in the early 2000s. The FDA approved a new formulation in 2003, which delivers 30 μg ethinyl estradiol and 150 μg levonorgestrel, then placebo, in an 84/7 regimen. Various other extended-cycle regimens were subsequently introduced to the market (Table 1). Several clinical trials report similar efficacy and safety profiles between cyclic and extended-cycle regimens, and less menstrual pain, bloating, fatigue, and headache with extended-cycle pills. Breakthrough bleeding is fairly common with extended-cycle pills and improves over time. Long-term safety and the rates of serious adverse events for extended-cycle regimens compared with cyclic regimens have not been thoroughly evaluated, but current data suggest similar safety. As many women use oral contraceptives for the alleviation of menstrual symptoms and decreasing the number of withdrawal bleeding episodes, extended-cycle regimens offer a clinical benefit. However, the benefits of extended-cycle regimens do not necessarily require a dedicated product. Use of a standard 28-day COC formulation by taking only the 21 active pills continuously and omitting the inactive pills bestows the same effects.

Another modification of the traditional 28-day COC regimen is the shortening of the hormone-free interval. Rather than ingesting 21 days of active pills, followed by 7 days of inactive placebo (21/7 regimen), these regimens reduce the number of placebo days. Most commonly a 24/4 regimen, with 24 days of active pills and 4 days of placebo, these pills are designed to provide better ovarian suppression and potentially improve efficacy. A 24/4 formulation of 20 μg EE and 1 mg norethindrone was reported to have similar failure rates when compared with the same pill in a 21/7 regimen, and less scheduled and unscheduled bleeding. Similar low failure rates and high patient acceptability are reported for a 24/4 regimen of 20 μg EE and 3 mg drospirenone.

Other regimens, using unique modifications to the traditional hormone-free interval, are also available. The regimens contain days of EE alone, with brief, 2-day placebo intervals. One early product of this type contained a regimen of 20 μg EE and 150 μg desogestrel for 21 days, then 2 days of placebo, followed by 10 μg EE for 5 days. Clinical trials reported high efficacy and safety and adverse event profiles similar to those of standard COC formulations. In the initial clinical studies, some cycle irregularities were reported, including absence of

Table 1 Oral contraceptive pill regimens with extended cycles or shortened hormone-free intervals (U.S. products)

<table>
<thead>
<tr>
<th>Brand namea</th>
<th>Manufacturer</th>
<th>Year approved</th>
<th>Estrogen type and dosage</th>
<th>Progestin type and dosage</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mircette</td>
<td>Organon (Roseland, NJ)</td>
<td>1998</td>
<td>EE 20 μg</td>
<td>Desogestrel 150 μg</td>
<td>Combined pill × 21 d Placebo × 2 d EE 10 μg × 5 d</td>
</tr>
<tr>
<td>Seasonale</td>
<td>Teva (North Wales, PA)</td>
<td>2003</td>
<td>EE 30 μg</td>
<td>Levonorgestrel 150 μg</td>
<td>Combined pill × 84 d Placebo × 7 d</td>
</tr>
<tr>
<td>Seasonique</td>
<td>Teva (North Wales, PA)</td>
<td>2006</td>
<td>EE 30 μg</td>
<td>Levonorgestrel 150 μg</td>
<td>Combined pill × 84 d EE 10 μg × 7 d</td>
</tr>
<tr>
<td>Lo-Seasonique</td>
<td>Teva (North Wales, PA)</td>
<td>2008</td>
<td>EE 20 μg</td>
<td>Levonorgestrel 100 μg</td>
<td>Combined pill × 84 d EE 10 μg × 7 d</td>
</tr>
<tr>
<td>Lybrel</td>
<td>Wyeth (Madison, NJ)</td>
<td>2007</td>
<td>EE 20 μg</td>
<td>Levonorgestrel 90 μg</td>
<td>Combined pill daily</td>
</tr>
<tr>
<td>Yaz</td>
<td>Bayer (Pittsburgh, PA)</td>
<td>2006</td>
<td>EE 20 μg</td>
<td>Drospirenone 3 mg</td>
<td>Combined pill × 24 d Placebo × 4 d</td>
</tr>
<tr>
<td>Beyaz</td>
<td>Bayer (Pittsburgh, PA)</td>
<td>2010</td>
<td>Same as Yaz, but each tablet contains levomefolate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LoEstrin 24 Fe</td>
<td>Actavis (Parsippany, NJ)</td>
<td>2006</td>
<td>EE 20 μg</td>
<td>Norethindrone acetate 1 mg</td>
<td>Combined pill × 24 d Iron tablet × 4 d</td>
</tr>
<tr>
<td>LoLoestrin</td>
<td>Actavis (Parsippany, NJ)</td>
<td>2010</td>
<td>EE 10 μg</td>
<td>Norethindrone acetate 1 mg</td>
<td>Combined pill × 24 d EE 10 μg × 2 d Iron tablet × 2 d</td>
</tr>
<tr>
<td>Natazia</td>
<td>Bayer (Pittsburgh, PA)</td>
<td>2010</td>
<td>EV 3, 2, 1 mg</td>
<td>Dienogest 2, 3 mg</td>
<td>EV 3 mg × 2 days EV 2 mg + dienogest 2 mg × 5 d EV 2 mg + dienogest 3 mg × 17 d EV 1 mg × 2 d Placebo × 2 d</td>
</tr>
</tbody>
</table>

Abbreviations: EE, ethinyl estradiol; EV, estradiol valerate.

aFor some formulations, brand name products are no longer available.
withdrawal bleeding and intermenstrual bleeding, which occurred in 5.5 and 12% of total cycles, respectively. \textsuperscript{39}

Some regimens deliver hormone continuously, without a hormone-free interval. Approved in 2008, one formulation provides 84 days of a low-dose, combined active pill containing 20 μg EE and 100 μg levonorgestrel. Instead of 7 days of placebo following the active pills, the regimen delivers 7 days of 10 μg EE. Existing studies reveal a similar efficacy and adverse effect profile compared with other extended-regimen oral contraceptives. Specifically, the unscheduled bleeding profile is similar to other extended-cycle oral contraceptives and improves with increasing duration of use. Although there is potential benefit from lower daily doses of hormonal exposure, the data are unclear if this specific regimen offers a lower incidence of hormone-related side effects or adverse events.\textsuperscript{40}

Introduced in 2010, estradiol valerate + dienogest is a COC formulation containing both a newly developed estrogen and progestin. Its unique regimen combines estradiol valerate with dienogest in a four-phasic dosing scheme designed to inhibit ovulation and minimize breakthrough bleeding. The 28-day formulation administers estradiol valerate alone 3 mg on days 1 to 2, estradiol valerate 2 mg + dienogest 2 mg on days 3 to 7, estradiol valerate 2 mg + dienogest 3 mg on days 8 to 24, estradiol valerate alone 1 mg on days 25 to 26, and placebo on days 27 to 28. Contraceptive efficacy is similar to that of traditional COCs,\textsuperscript{7,10} and data suggest satisfactory cycle control and efficacy in the treatment of menorrhagia.\textsuperscript{41}

**Selection of COC Formulations in Clinical Practice**

For some women, the primary indication for COC use is the treatment of a gynecologic or other medical disorder, and for others the noncontraceptive benefits of COCs are equally as important as the contraceptive effects. As a class, COCs offer relief of painful or irregular periods, alleviation of premenstrual syndrome, improvement of acne, as well as the benefits for cancer risk reduction, endometrial protection, and protection of bone mass. Some COCs carry specific FDA approvals for indications other than contraception. Currently, four products are approved for treatment of moderate acne vulgaris,\textsuperscript{42,43} and two pills are approved for treatment of premenstrual dysphoric disorder.\textsuperscript{43,44} While these pill formulations have documented efficacy in treatment of these conditions, prescribing clinicians should note that these products are potentially more costly, either due to brand name status or insurance company formulary requirements. Patients will likely derive similar benefits from generic pill formulations, despite not having the specific associated formal indications. Knowledge of the relative androgenicity of different progestin components may also impact COC selection.

An additional recent development includes COCs containing levomefolate, for the purpose of raising serum folate levels for prevention of fetal neural tube defects (NTD).\textsuperscript{43,45} The basis for the development of such formulations is that women may conceive quickly after discontinuation of an oral contraceptive, so folic acid supplementation in the pill could reduce the risk of fetal neural tube defects. The literature on the actual benefit is unclear. While one report suggests a theoretical benefit based on measurement of serum folate levels and mathematical assumption about neural tube defect risk reduction,\textsuperscript{46} no published research documents the presence or magnitude of a reduced incidence of neural tube defect in women using folate-containing COCs.

Progestin-only pills offer a contraceptive alternative for women with contraindications to estrogen. Traditional progestin-only formulations containing desogestrel or norethidrone are associated with suboptimal bleeding profiles or strict requirements to scheduled dosing requirements (little flexibility if a pill is missed). Recently, a progestin-only oral contraceptive containing drospirenone was proposed. Drospirenone 4 mg is administered for 24 days, followed by a 4-day placebo interval. An open-label, noncomparative, multicenter trial reported good cycle control, few adverse events, and contraceptive efficacy similar to COCs.\textsuperscript{47}

**Conclusion**

Oral contraception plays an important role in women’s health care. Historically, the development of COCs involved complex events in scientific discovery, societal changes, social progress, and women’s rights. Against a background of rapidly evolving social and political landscapes, many changes in the development of COC have occurred in the past 60 years.

Contraception is critically important to women, families, and society. Oral contraception is particularly important, as it is a popular, accessible, and reversible method. A vast array of COC options are available, and the choice of COC depends on patient characteristics, noncontraceptive benefits, and the prescriber’s understanding of the pharmacologic basis behind the clinical characteristics of each pill.

**References**

7. Kiley JW, Shulman LP. Estradiol valerate and dienogest: a new regimen offers a lower incidence of hormone-related side effects or adverse events.


23 Edelman A, Micks E, Gallo MF, Jensen JT, Grimes DA. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. Cochrane Database Syst Rev 2014;7:CD004695


27 Anttila L, Kunz M, Marr J. Bleeding pattern with drospirenone 3 mg+ethinyl estradiol 20 mcg 24/4 combined oral contraceptive compared with desogestrel 150 mcg+ethinyl estradiol 20 mcg 21/7 combined oral contraceptive. Contraception 2009;80(5):445–451


