The Current Status of Oral Contraceptives: Progress and Recent Innovations

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Abstract

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.

Keywords

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

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

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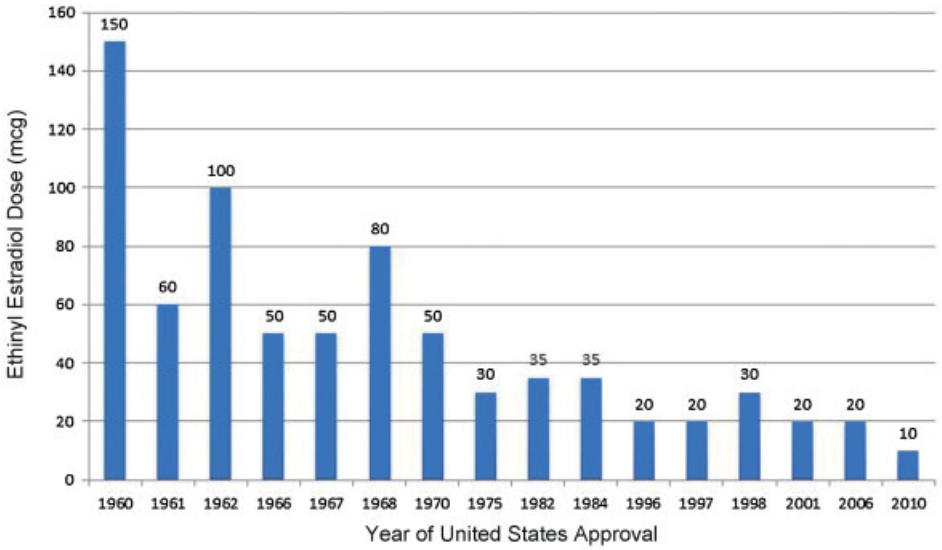

Fig. 1 Reduction in estrogen dosage in oral contraceptive products over time.

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,[6] 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.[7] 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.[8,9] 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.[1] 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 17B-estradiol.[10]

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 antiestrogenic 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.[1] 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.

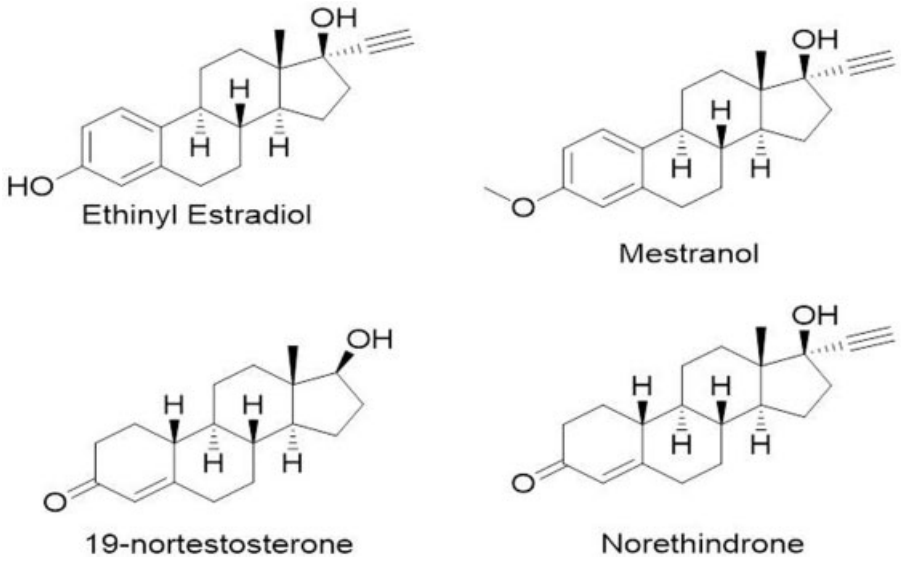

Fig. 2 Chemical structures of synthetic hormones.

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.[11]

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.[12,13]

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.[14] 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.[15] As with the third-generation progestins, questions about potentially increased risks of thromboembolism are an area of controversy.[16]

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-nortestoerone derivatives, is replaced by a 17α-cyanomethyl group in dienogest.[17] 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.[1,11]

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.[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 EE and 150 µg levonorgestrel, then placebo, in an 84/7 regimen.[29] 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 regimens 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.[30–32] 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.[33,34]

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.[35] Similar low failure rates and high patient acceptability are reported for a 24/4 regimen of 20 µg EE and 3 mg drospirenone.[36,37]

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.[38] 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)

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

Abbreviations: EE, ethinyl estradiol; EV, estradiol valerate.
[a]For 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.[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.[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,[7,10] and data suggest satisfactory cycle control and efficacy in the treatment of menorrhagia.[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,[42,43] and two pills are approved for treatment of premenstrual dysphoric disorder.[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).[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,[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 norethindrone 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.[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

1 Speroff L, Darney PD. Oral contraception. In: A Clinical Guide for Contraception. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011:19–166
2 Meldrum M. Women making contraceptive choices in 20th-century America. Lancet 2012;380(9837):102–103
3 Junod SW, Marks L. Women's trials: the approval of the first oral contraceptive pill in the United States and Great Britain. J Hist Med Allied Sci 2002;57(2):117–160
4 Jones J, Mosher W, Daniels K. Current contraceptive use in the United States, 2006–2010, and changes in patterns of use since 1995. Natl Health Stats Rep 2012;60:6
5 Daniels K, Daugherty J, Jones J. Current contraceptive status among women aged 15-44: United States, 2011-2013. NCHS Data Brief 2014;173(173):1–8
6 Gerstman BB, Gross TP, Kennedy DL, Bennett RC, Tomita DK, Stadel BV. Trends in the content and use of oral contraceptives in the United States, 1964-88. Am J Public Health 1991;81(1):90–96
7 Kiley JW, Shulman LP. Estradiol valerate and dienogest: a new approach to oral contraception. Int J Womens Health 2011; 3:281–286
8 Kiley J, Hammond C. Combined oral contraceptives: a comprehensive review. Clin Obstet Gynecol 2007;50(4):868–877
9 Speroff L, DeCherney A; The Advisory Board for the New Progestins. Evaluation of a new generation of oral contraceptives. Obstet Gynecol 1993;81(6):1034–1047

10 Palacios S, Wildt L, Parke S, Machlitt A, Römer T, Bitzer J. Efficacy and safety of a novel oral contraceptive based on oestradiol (oestradiol valerate/dienogest): a Phase III trial. Eur J Obstet Gynecol Reprod Biol 2010;149(1):57–62
11 Nelson AL. Combined oral contraception. In: Hatcher RA, Trussell J, Stewart F, eds. Contraceptive Technology. New York: Ardent Media; 2011:193–270
12 Burkman RT. Venous thromboembolism and oral contraceptives: current status and clinical implications. Treat Endocrinol 2002; 1(3):143–147
13 Shulman LP, Goldzieher JW, Minkin MJ, Sulak PJ, Thorneycroft I. Oral contraceptives and venous thromboembolic events. J Reprod Med 2003;48(4):306–307
14 Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception 2000;62(1):29–38
15 Batukan C, Muderris II. Efficacy of a new oral contraceptive containing drospirenone and ethinyl estradiol in the long-term treatment of hirsutism. Fertil Steril 2006;85(2):436–440
16 American Congress of Obstetricians and Gynecologists. . ACOG Committee Opinion #540. Risk of Venous Thromboembolism Among Users of Drospirenone-Containing Oral Contraceptive Pills, November 2012
17 Hoy SM, Scott LJ. Estradiol valerate/dienogest: in oral contraception. Drugs 2009;69(12):1635–1646
18 Grimes DA, Schulz KF. Nonspecific side effects of oral contraceptives: nocebo or noise? Contraception 2011;83(1):5–9
19 Kaunitz AM. Noncontraceptive health benefits of oral contraceptives. Rev Endocr Metab Disord 2002;3(3):277–283
20 Trussell J. Contraceptive failure in the United States. Contraception 2011;83(5):397–404
21 Gallo MF, Nanda K, Grimes DA, Lopez LM, Schulz KF. 20 µg versus >20 µg estrogen combined oral contraceptives for contraception. Cochrane Database Syst Rev 2013;8:CD003989
22 Hauck BA, Brown V. A primer on the hormone-free interval for combined oral contraceptives. Curr Med Res Opin 2015;31(10): 1941–1948
23 Archer DF, Nakajima ST, Sawyer AT, et al. Norethindrone acetate 1.0 milligram and ethinyl estradiol 10 micrograms as an ultra low-dose oral contraceptive. Obstet Gynecol 2013;122(3):601–607
24 Sulak PJ, Cressman BE, Waldrop E, Holleman S, Kuehl TJ. Extending the duration of active oral contraceptive pills to manage hormone withdrawal symptoms. Obstet Gynecol 1997;89(2):179–183
25 Shulman LP. The use of triphasic oral contraceptives in a continuous use regimen. Contraception 2005;72(2):105–110
26 Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. Fertil Steril 2003;80(3):560–563
27 Miller L, Notter KM. Menstrual reduction with extended use of combination oral contraceptive pills: randomized controlled trial. Obstet Gynecol 2001;98(5, Pt 1):771–778
28 Schwartz JL, Creinin MD, Pymar HC. The trimonthly combination oral contraceptive regimen: is it cost effective? Contraception 1999;60(5):263–267
29 Seasonale (Levonorgestrel/Ethinyl Estradiol Tablets). Current US Prescribing Information. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-544_SEASONALE_Prntlbl.pdf. Accessed October 22, 2015
30 Anderson FD, Gibbons W, Portman D. Safety and efficacy of an extended-regimen oral contraceptive utilizing continuous low-dose ethinyl estradiol. Contraception 2006;73(3):229–234
31 Anderson FD, Feldman R, Reape KZ. Endometrial effects of a 91-day extended-regimen oral contraceptive with low-dose estrogen in place of placebo. Contraception 2008;77(2):91–96
32 Teichmann A, Apter D, Emerich J, et al. Continuous, daily levonorgestrel/ethinyl estradiol vs. 21-day, cyclic levonorgestrel/ethinyl estradiol: efficacy, safety and bleeding in a randomized, open-label trial. Contraception 2009;80(6):504–511
33 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
34 Coffee AL, Kuehl TJ, Willis S, Sulak PJ. Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. Am J Obstet Gynecol 2006;195(5):1311–1319
35 Nakajima ST, Archer DF, Ellman H. Efficacy and safety of a new 24-day oral contraceptive regimen of norethindrone acetate 1 mg/ethinyl estradiol 20 micro g (Loestrin 24 Fe). Contraception 2007; 75(1):16–22
36 Anttila L, Bachmann G, Hernádi L, Kunz M, Marr J, Klipping C. Contraceptive efficacy of a combined oral contraceptive containing ethinyloestradiol 20 µg/drospirenone 3mg administered in a 24/4 regimen: a pooled analysis of four open-label studies. Eur J Obstet Gynecol Reprod Biol 2011;155(2):180–182
37 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
38 Berga SL. Metabolic and endocrine effects of the desogestrel-containing oral contraceptive Mircette. Am J Obstet Gynecol 1998;179(1):S9–S17
39 The Mircette Study Group. An open-label, multicenter, noncomparative safety and efficacy study of Mircette, a low-dose estrogen-progestin oral contraceptive. Am J Obstet Gynecol 1998;179(1): S2–S8
40 Krishnan S, Kiley J. The lowest-dose, extended-cycle combined oral contraceptive pill with continuous ethinyl estradiol in the United States: a review of the literature on ethinyl estradiol 20 µg/levonorgestrel 100 µg + ethinyl estradiol 10 µg. Int J Womens Health 2010;2:235–239
41 Jensen JT, Parke S, Mellinger U, Machlitt A, Fraser IS. Effective treatment of heavy menstrual bleeding with estradiol valerate and dienogest: a randomized controlled trial. Obstet Gynecol 2011; 117(4):777–787
42 Ebede TL, Arch EL, Berson D. Hormonal treatment of acne in women. J Clin Aesthet Dermatol 2009;2(12):16–22
43 Beyaz Prescribing Information. . Available at: http://labeling.bayerhealthcare.com/html/products/pi/fhc/Beyaz_PI.pdf. Accessed October 21, 2015
44 Yaz Prescribing Information. . Available at: http://labeling.bayerhealthcare.com/html/products/pi/fhc/YAZ_PI.pdf. Accessed October 21, 2015
45 Nelson AL. Comprehensive evaluation of Safyral(®) 2012. Womens Health (Lond Engl) 2012;8(6):619–633
46 Taylor TN, Farkouh RA, Graham JB, et al. Potential reduction in neural tube defects associated with use of Metafolin-fortified oral contraceptives in the United States. Am J Obstet Gynecol 2011; 205(5):460.e1–460.e8
47 Archer DF, Ahrendt HJ, Drouin D. Drospirenone-only oral contraceptive: results from a multicenter noncomparative trial of efficacy, safety and tolerability. Contraception 2015;92(5): 439–444