Advanced Oral Contraceptive Regimens and Their Management

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ABSTRACT

Contraceptive pill regimens have gone through numerous changes and modifications to improve safety, compliance, and tolerability. Several generations of progestins were introduced, and their doses were adjusted over time. Four dosing regimens (monophasic, biphasic, triphasic and quadriphasic) have been introduced. These dosing regimens provide different hormonal doses at different stages of menstrual cycle. The 28-day cyclic (21 + 7) regimens are preferred because they result in better compliance than 21-day regimens. In the present review, we comprehensively describe the development of contraceptive pills, contraceptive doses, dose regimens, cyclic regimens, extended-cycle contraceptive pills, selection criteria of contraceptives, and emergency contraceptive pills. We also provide the FDA's guidelines for managing missed contraceptive pills to assist users in taking them safely and to avoid contraceptive failure. In conclusion, the literature suggests that the success of combined oral contraceptive pills depends on regular intake according to a prescribed routine.

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Since the 1960s, oral contraceptives have been prescribed to fertile women for preventing unwanted pregnancy. Numerous contraceptive methods and products can be used. Some of them are oral pills, intrauterine devices, transdermal patches, implants, surgical procedures, condoms, diaphragms, cervical caps, injections, vaginal rings, and vaginal spermicides.[1-3] The order of efficacy of contraceptive methods is presented in the **Figure**.[4] Large numbers of oral contraceptive products are available in the market, varying in dose strength, regimen, packaging, and hormone combinations. In the present review, we elaborate mainly on oral contraceptive pills (OCPs)—their dosage regimens, dosage strengths, compositions, and guidelines to manage missed pills—as well as emergency oral contraceptives.

Oral contraceptive pills are among the preferred contraceptive methods because they are easy to take, there is no pleasure interruption, no surgical procedure is required, there is no device-related discomfort, they can be discontinued easily if the couple is planning for pregnancy, and the method is highly effective when taken properly according to the regimen. Success of OCPs is almost 99% when taken regularly according to recommended regimens.[2] Compliance is the only major issue associated with OCPs and is considered to be responsible for cases of failure. Clinicians can play an important role in improving compliance by proper counseling of consumers about side effects, dose routine, and missed pill management, and can suggest backup plans in case of missed pills.[5-8] Various packaging and other methods such as wallet pill cards specifying days of the pills (Ovcon-50), colored pills (Ortho-Tri-Cyclen), shaped pills (Estrostep Fe), dial-pack dispensers (Ortho-Novum, Ortho-Cyclen), and click-case dispensers (Lybrel) have been developed to improve compliance.

Selection of the right contraceptive method/product requires making decisions, because the choice varies from person to person.[9] Several factors play important roles in the selection of contraceptives. A few of these factors are safety and side effects, health risks, simplicity of the method, user's

PRACTICAL IMPLICATIONS

Contraceptive pill regimens have gone through numerous changes and modifications to improve safety, compliance, and tolerability.

- Contraceptive pills should be taken according to a regular routine, and dose regimens should be followed strictly.
- Missed pills should be managed according to recommended guidelines.
- User-friendly packaging, which can improve compliance, is preferred.
- Nonhormonal contraceptive backup plans should be used for prescribed days when pills are missed.

compliance, user's experience, protection against sexually transmitted disease, success rate, pharmacoeconomic concerns, frequency of intercourse, lifestyle, age, product availability and access, sociocultural convictions, over-the-counter versus prescription products, cost, effects on regular periods, advice from partner, friends, or health professionals, advertising, interruption of pleasure, duration of contraception desired, duration of contraceptive effectiveness, mode of contraception (eg, reversible or irreversible), and so forth.[10-14] Mishell and colleagues updated the guidelines for oral contraceptive selection and recommended oral contraceptives as a first choice unless the consumer has some contraindication or intolerable side effects, or difficulty in taking pills regularly.[15]

LOW-DOSE AND ULTRA–LOW-DOSE ORAL CONTRACEPTIVES

The doses of contraceptives have been adjusted many times to reduce side effects. The doses of progestin or estrogen or both were reduced or shuffled. Combined oral contraceptive pills (COCPs) with higher estrogen content were discontinued (eg, Enovid, Ortho-Novum 10/21, Demulen 1/50, Ovcon-50, Preven). Estrogen content of currently available COCPs varies from 10 µg to 50 µg. The products containing 10 µg of estrogen are considered ultra–low- dose oral contraceptives (eg, Lo Loestrin Fe). Most of the marketed COCPs contain 20 µg to 35 µg of estrogen such as ethinyl estradiol (eg, Loestrin Fe 1/20, Loestrin Fe 1.5/30, Ovcon-35) (**Table**). The lower amount of ethinyl estradiol reduces the risk of thrombotic incidents and improves the safety for consumers.[17,18]

MONOPHASIC, BIPHASIC, TRIPHASIC, AND QUADRIPHASIC ORAL CONTRACEPTIVES

In addition to dose reduction, changing the dose regimen was another attempt to reduce the side effects caused by COCPs.[19,20] Since the 1960s, many dose regimens (monophasic, biphasic, triphasic, quadriphasic, and extended cycle) have been approved by the FDA as COCPs. There is no strong evidence to support the superiority of multiphasic oral contraceptives regimens (biphasic, triphasic, or quadriphasic) over monophasic regimens for birth control, and bleeding patterns.[21-23] Monophasic regimens (eg, Modicon-28, Yasmin, Desogen)provide a fixed hormone dose throughout the cycle. Most of the marketed COCP products are still monophasic (Table). Biphasic (eg, Lo Loestrin Fe), triphasic (eg, Ortho Tri-Cyclen, Ortho Tri-Cyclen-28, Ortho Tri-Cyclen-21, Ortho Tri-Cyclen Lo, Cyclessa, Estrostep Fe, Tri-Norinyl 28-Day, Ortho-Novum 7/7/7-28), and quadriphasic (eg, Natazia) regimens provide 2, 3, and 4 different doses, respectively, of estrogen, progestin, or both in a complete menstrual cycle. These regimens are designed to mimic the normal hormonal activity at different phases in the cycle to provide a better response along with fewer side effects, although they are quite complex and may pose compliance issues.

A trend of providing supplements with contraceptive regimens began in 1970s. The 7 inert pills of 28- and 91-days regimens are loaded with supplements, though these supplements do not prove any contraceptive potency.[24-26] Examples of such products are Loestrin 24 Fe (ferrous fumarate), Norquest Fe (ferrous fumarate), Beyaz (levomefolate calcium), Safyral (levomefolate calcium), and Estrostep Fe (ferrous fumarate).

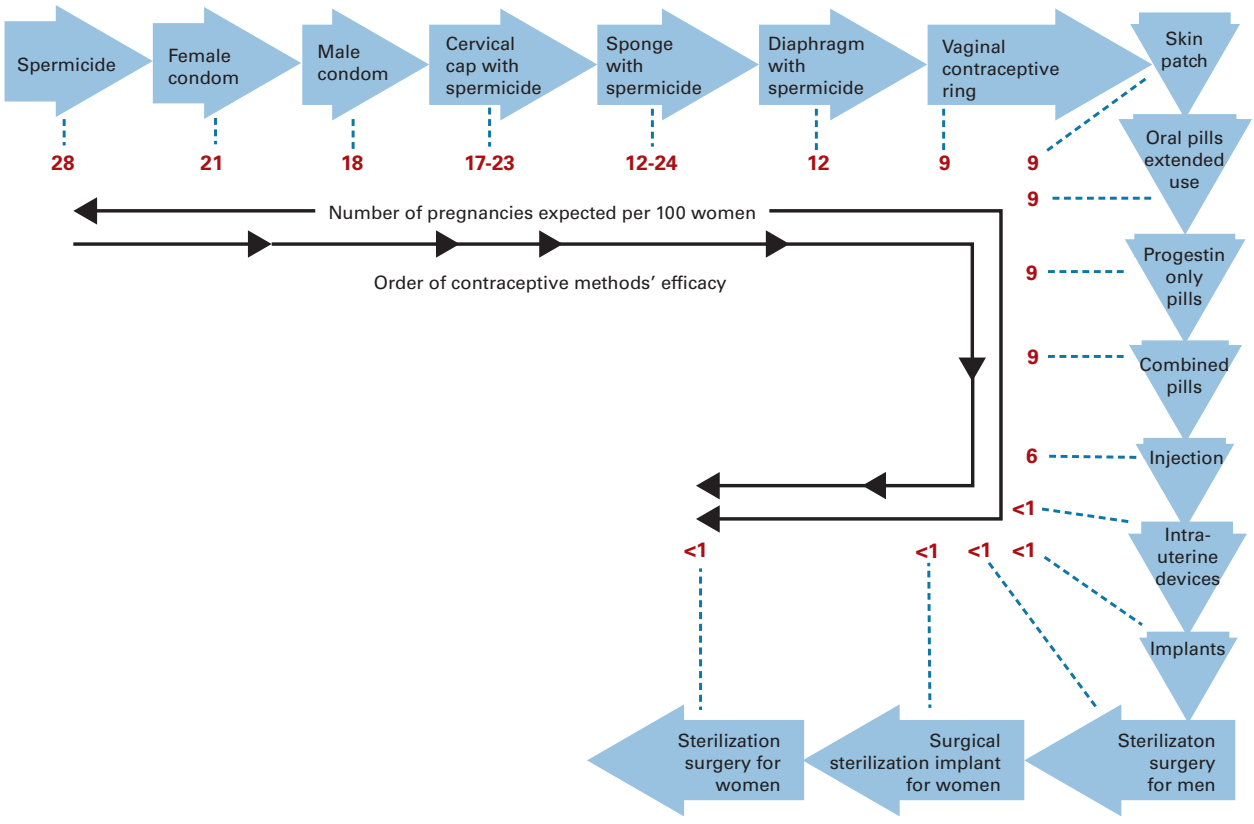
EXTENDED-CYCLE CONTRACEPTIVES

The extended-cycle contraceptives (eg, COCPs, implants, transdermal patch, vaginal rings) are used to prevent pregnancy as well as monthly bleeding by providing a continuous supply of hormones. Seasonique and Seasonale are COCPs approved for a 91-day extended cycle. The extended-cycle contraceptives are intended for women who want to avoid monthly bleeding because of travel, sports, vacations, parties, honeymoon, busy schedule, and so forth. Extended-cycle contraceptive regimens decrease the hormone-free period and reduce the scheduled bleeding episodes, as well as withdrawal symptoms such menstrual pain, headache, breast tenderness, bloating, cramping, and hypermenorrhea.[18,27,28]

EMERGENCY CONTRACEPTIVES

Most contraceptives are used before (eg, COCPs, implants, vaginal rings) or during (eg, condoms,

Figure 1. Order of Contraceptive Methods' Efficacy (from left to right)



diaphragms) intercourse. Emergency contraceptives (EMCs) are used after unprotected sex or when a contraceptive method has failed.[31] Emergency contraceptives also are called "postcoital contraceptives" or "morning-after pills." Emergency contraceptives are used in cases of failed coitus interruptus, failed contraceptive methods (eg, diaphragm slipped out of place, breakage or misuse of condom during intercourse), sexual assault, consecutive missed contraceptive pills, and when no other contraceptive has been used. Emergency contraceptives act by preventing or delaying ovulation.[32,33] Sometimes, if the egg is fertilized by sperm, EMCs may prevent its implantation in the uterus wall.[33] Emergency contraceptives can be useful for the victims of sexual assault because undesired pregnancy can be avoided by taking the EMC pills within the recommended time period. Emergency contraceptive regimens recommend taking the pills as soon as possible within 3 to 5 days after unprotected intercourse.[34] In June 1996, the FDA Maternal and Reproductive Health Drugs Advisory Committee found that the use of EMCs pills within 72 hours of unprotected intercourse is safe and effective. The EMCs will also open a safe gate for women who are having intercourse less frequently (fewer than 4 times a month).[35] In such cases, unnecessary long- term exposure to combined contraceptives and extended contraceptive cycles can be avoided. Emergency contraceptives contain progestin in combination with estrogen (Yuzpe), progestin alone (Plan B), or antiprogestin (Ella). The Yuzpe method was the subject of a landmark study in the history of emergency contraception.[36] With the Yuzpe method, the combination of estrogen and progestin is used for emergency contraception, and a series of 4 contraceptive pills is taken.[37-39] The progestin-only EMCs were introduced as Plan B One-Step (single dose, 1.5 mg of levonorgestrel) and Plan B (2 doses, 0.75 mg of levonorgestrel).[34] Different EMC pills have different dosage regimens. The dose of Plan B One-Step should be taken within 72 hours, whereas in the case of Plan B the first dose should be taken within 72 hours and the second dose within 12 hours after the first dose. Plan B is available without a prescription, but the Yuzpe method requires a prescription. Ella

Table. List of Oral Contraceptive Pills Marketed in United States

No.	Brand Company Approval Year	Regimen	Product Strength
1.	**NORINYL 1+50 28-DAY** Watson Labs	28 days = 21 days active pills + 7 days inert pills	Mestranol; Norethindrone 0.05 mg; 1 mg Tablet; Oral-28
Excipients: lactose, magnesium stearate, povidone, and starch. Inert tablets: FD&C Yellow No. 6, lactose, microcrystalline cellulose, and magnesium stearate.			
2.	**MICRONOR** Janssen Pharmaceuticals	28 active pills, 1 pill daily.	Norethindrone 0.35 mg Tablet; Oral-28
Excipients: Corn starch, D&C Green No. 5, D&C Yellow No. 10, lactose, magnesium stearate, and povidone.			
3.	**NOR-QD** Watson Labs	28 active pills, one pill daily.	Norethindrone 0.35 mg Tablet; Oral-28
Excipients: D&C Yellow No. 10, FD&C Yellow No. 6, lactose, magnesium stearate, povidone, and starch.			
4.	**LOESTRIN FE 1/20** Warner Chilcott	28 days = 21 days active pills + 7 days inert pills	EE; Norethindrone Acetate 0.02mg; 1 mg Tablet; Oral-28
Excipients: acacia, compressible sugar, D&C yellow no. 10 aluminum lake, lactose monohydrate, magnesium stearate and pregelatinized starch. Inert tablet: crospovidone, ferrous fumarate, hydrogenated vegetable oil, NF Type I and microcrystalline cellulose.			
5.	**LOESTRIN FE 1.5/30** Warner Chilcott	28 days = 21 days active pills + 7 days inert pills	EE; Norethindrone Acetate 0.03mg; 1.5 mg Tablet; Oral-28
Excipients: acacia, compressible sugar, FD&C red no. 40 aluminum lake HT, lactose monohydrate, magnesium stearate and pregelatinized starch. Inert tablets: crospovidone, ferrous fumarate, hydrogenated vegetable oil, NF Type I and microcrystalline cellulose.			
6.	**NORINYL 1+35 21-DAY** Watson Labs	21 Days Regimen	EE; Norethindrone 0.035mg; 1 mg Tablet; Oral-21
Excipients: Magnesium stearate, povidone, maize starch, and lactose.			
7.	**NORINYL 1+35 28-DAY** Watson Labs	28 days = 21 days active pills + 7 days inert pills	EE; Norethindrone 0.035mg; 1 mg Tablet; Oral-28
Excipients: D&C Green No. 5, D&C Yellow No. 10, lactose, magnesium stearate, povidone, and starch. Inert tablet: FD&C Yellow No. 6, lactose, microcrystalline cellulose, and magnesium stearate.			
8.	**OVCON-50, 28-Day** Warner Chilcott	28 days = 21 days active pills + 7 days inert pills	EE; Norethindrone 0.05mg; 1 mg Tablet; Oral-28
Excipients: dibasic calcium phosphate, D&C Yellow No. 10 (aluminum lake), FD&C Blue No. 1 (aluminum lake), FD&C Yellow No. 6 (aluminum lake), lactose, magnesium stearate, povidone, sodium starch glycolate, starch (corn), and talc.			
9.	**LO/OVRAL-28** Wyeth Pharmaceuticals	28 days = 21 days active pills + 7 days inert pills	EE; Norgestrel 0.03mg; 0.3 mg Tablet; Oral-28
Excipients: cellulose, D&C Red 30, lactose, magnesium stearate, and polacrilin potassium.			
10.	**OVCON-35** Warner Chilcott	28 days = 21 days active pills + 7 days inert pills	EE; Norethindrone 0.035mg; 0.4 mg Tablet; Oral-28
Excipients: anhydrous lactose, dibasic calcium phosphate, FD&C yellow no. 6 aluminum lake, lactose monohydrate, magnesium stearate, povidone and sodium starch glycolate. Inert tablets: lactose monohydrate, magnesium stearate, and pregelatinized starch.			
11.	**BREVICON 28-DAY** Watson Labs	28 days = 21 days active pills + 7 days inert pills	EE; Norethindrone 0.035mg; 0.5 mg Tablet; Oral-28
Excipients: FD&C Blue No. 1, lactose, magnesium stearate, povidone, and starch. Inert tablets: FD&C Yellow No. 6, lactose, microcrystalline cellulose, and magnesium stearate.			

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Table. List of Oral Contraceptive Pills Marketed in United States *(Continued)*

No.	Brand/ Company/ Approval Year	Regimen	Product Strength
12.	**MODICON 28** Janssen Pharms	28 days = 21 days active pills + 7 days inert pills	EE; Norethindrone 0.035 mg; 0.5 mg Tablet; Oral-28
Excipients: lactose, magnesium stearate and pregelatinized corn starch. Inert tablets: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized corn starch.			
13.	**LOESTRIN 21 1.5/30** Warner Chilcott	21 Days regimen	EE; Norethindrone Acetate 0.03 mg; 1.5 mg Tablet; Oral-21
Excipients: acacia, compressible sugar, FD&C red no. 40 aluminum lake HT, lactose monohydrate, magnesium stearate, and pregelatinized starch.			
14.	**LOESTRIN 21 1/20** Warner Chilcott	21 Days regimen	EE; Norethindrone Acetate 0.02mg; 1mg Tablet; Oral-21
Excipients: acacia, compressible sugar, D&C yellow no. 10 aluminum lake, lactose monohydrate, magnesium stearate and pregelatinized starch.			
15.	**ORTHO-NOVUM 1/35-28** Janssen Pharmaceuticals	28 days = 21 days active pills + 7 days inert pills	EE; Norethindrone 0.035 mg; 1 mg Tablet; Oral-28
Excipients: FD&C Yellow No. 6, lactose, magnesium stearate and pregelatinized corn starch. Inert tablets: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose , and pregelatinized corn starch.			
16.	**NORDETTE-28** Duramed	28 days = 21 days active pills + 7 days inert pills	EE; Levonorgestrel 0.03 mg; 0.15 mg Tablet; Oral-28
Excipients: cellulose, D&C Red 30, FD&C Yellow 6, lactose, magnesium stearate, and polacrilin potassium			
17.	**ORTHO-NOVUM 7/7/7-28** Janssen Pharmaceuticals	28 days = 21 (7+7+7) days active pills + 7 days inert pills	EE; Norethindrone 0.035 mg,0.035 mg,0.035 mg; 0.5 mg,0.75mg,1 mg Tablet; Oral-28
Excipients: White tablets: lactose, magnesium stearate and pregelatinized corn starch. Light peach tablets: FD&C Yellow No. 6, lactose, magnesium stearate and pregelatinized corn starch. Peach tablets: FD&C Yellow No. 6, lactose, magnesium stearate and pregelatinized corn starch. Inert green tablets: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized corn starch.			
18.	**TRI-NORINYL 28-DAY** Watson Labs	28 days = 21 (7+9+5) days active pills + 7 days inert pills	EE; Norethindrone 0.035 mg,0.035 mg,0.035 mg; 0.5 mg,1mg,0.5 mg Tablet; Oral-28
Excipients: Yellow green tablets: D&C Green No. 5, D&C Yellow No. 10, lactose, magnesium stearate, povidone, and starch. Blue tablets: FD&C Blue No. 1, lactose, magnesium stearate, povidone, and starch. Inert Orange tablets: FD&C Yellow No. 6, lactose, microcrystalline cellulose, and magnesium stearate.			
19.	**ORTHO-CYCLEN-28** Janssen Pharmaceuticals	28 days = 21 days active pills + 7 days inert pills	EE; Norgestimate 0.035mg; 0.25 mg & 0.035 mg; 0.25 mg Tablet; Oral-28
Excipients: FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized corn starch. Inert tablet: D & C Yellow No. 10 Aluminum Lake, FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose , and pregelatinized corn starch.			
20.	**Desogen** Organon USA Inc	28 days = 21 days active pills + 7 days inert pills	Desogestrel; EE 0.15 mg; 0.03 mg Tablet; Oral-28
Excipients: Vitamin E, corn starch, povidone, stearic acid, colloidal silicon dioxide, lactose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and talc. Inert green tablets: lactose, corn starch, magnesium stearate, FD&C Blue No. 2 aluminum lake, ferric oxide, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and talc.			

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Table. List of Oral Contraceptive Pills Marketed in United States *(Continued)*

No.	Brand/ Company/ Approval Year	Regimen	Product Strength
21.	**ORTHO-CEPT** Janssen Pharmaceuticals	28 days = 21 days active pills + 7 days inert pills	Desogestrel; EE 0.15 mg; 0.03 mg Tablet; Oral-28
Excipients: colloidal silicone dioxide, corn starch, ferric oxide, lactose, hypromellose, lactose, polyethylene glycol, povidone, stearic acid, talc, titanium dioxide, and vitamin E Inert green tablets: FD&C Blue No.1 Aluminum Lake, ferric oxide, hypromellose, lactose, magnesium stearate, polyethylene glycol, pregelatinized starch, talc and titanium dioxide.			
22.	**ORTHO TRI-CYCLEN** Janssen Pharmaceuticals	28 days = 21 (7+7+7) days active pills + 7 days inert pills	EE; Norgestimate 0.035 mg,0.035 mg,0.035 mg; 0.18 mg,0.215 mg,0.25 mg Tablet; Oral-28
Excipients: White tablets: white tablets: Lactose, magnesium stearate, and pregelatinized corn starch. Light blue tablets: FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized corn starch. Blue tablets: FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized corn starch. Inert green tablets: D & C Yellow No. 10 Aluminum Lake, FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose and pregelatinized corn starch.			
23.	**ESTROSTEP Fe** Warner Chilcott	28 days = 21 (7+7+7) days active pills + 7 days inert pills	EE; Norethindrone Acetate 0.02 mg,0.03 mg,0.035 mg; 1 mg,1 mg,1 mg Tablet; Oral-28
Excipients: Calcium stearate; lactose; microcrystalline cellulose; and starch. Inert tablets: Microcrystalline cellulose; ferrous fumarate; magnesium stearate; povidone; sodium starch glycolate; sucrose with modified dextrins. Excipients: Polacrilin potassium, lactose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80 and FD&C Blue No.2 Aluminum Lake.			
24.	**Plan B** Teva Womens' Health	Emergency Contraceptive	Levonorgestrel 0.75 mg Tablet; Oral
Excipients: colloidal silicon dioxide, potato starch, gelatin, magnesium stearate, talc, corn starch, and lactose monohydrate.			
25.	**Cyclessa** Organon USA Inc	28 days = 21 (7+7+7) days active pills + 7 days inert pills	Desogestrel; EE 0.1 mg,0.125 mg,0.15 mg; 0.025 mg,0.025 mg,0.025 mg Tablet; Oral-28
Excipients: Vitamin E, pregelatinized starch, stearic acid, lactose monohydrate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, talc, yellow ferric oxide (in light yellow and orange tablets), and red ferric oxide (in orange and red tablets). Inert tablets: lactose monohydrate, corn starch, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, FD&C Blue No. 2 aluminum lake, yellow ferric oxide, and talc.			
26.	**YASMIN** Bayer Healthcare	28 days = 21 days active pills + 7 days inert pills	Drospirenone; EE 3 mg; 0.03 mg Tablet; Oral-28
Excipients: lactose monohydrate NF, corn starch NF, pregelatinized starch NF, povidone 25000 NF, magnesium stearate NF, hypromellose USP, macrogol 6000 NF, titanium dioxide USP, talc USP, and ferric oxide pigment, yellow NF. Inert tablets: lactose monohydrate NF, corn starch NF, povidone 25000 NF, magnesium stearate NF, hypromellose USP, talc USP, and titanium dioxide USP.			
27.	**ORTHO TRI-CYCLEN Lo** Janssen Pharmaceuticals	28 days = 21 (7+7+7) days active pills + 7 days inert pills	EE; Norgestimate 0.025 mg,0.025 mg,0.025 mg; 0.18 mg,0.215 mg,0.25 mg Tablet; Oral-28
Excipients: White tablets: Lactose, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, carnauba wax, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and purified water. Light blue tablets: FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, carnauba wax, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and purified water. Blue tablets: FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, croscarmellose sodium, microcrystalline cellulose, polysorbate 80, carnauba wax, hydroxypropylmethylcellulose, polyethylene glycol titanium dioxide, and purified water. Inert green tablets: FD & C Blue No. 1 Aluminum Lake, lactose, magnesium stearate, pregelatinized starch, ferric oxide, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, talc, and purified water.			

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Table. List of Oral Contraceptive Pills Marketed in United States *(Continued)*

S. No.	Brand/ Company/ Approval Year	Regimen	Product Strength
28.	**SEASONALE** Duramed Pharmaceuticals	91 days = 84 days active pills + 7 days inert pills	EE; Levonorgestrel 0.03 mg; 0.15 mg Tablet; Oral
Excipients: anhydrous lactose NF, FD&C blue no. 1, FD&C red no. 40, hydroxypropyl methylcellulose USP, microcrystalline cellulose NF, polyethylene glycol NF, magnesium stearate NF, polysorbate 80 NF, and titanium dioxide USP. Inert tablets: anhydrous lactose NF, hydroxypropyl methylcellulose USP, microcrystalline cellulose NF, and magnesium stearate NF.			
29.	**ORTHO TRI-CYCLEN-21** Ortho McNeil Pharmaceutical	28 days = 21 (7+7+7) days active pills + 7 pill free days	EE; Norgestimate 0.035 mg,0.035mg,0.035 mg; 0.18 mg,0.215 mg,0.25 mg Tablet; Oral-21
Excipients: White tablets: lactose, magnesium stearate, and pregelatinized starch. Light Blue tablets: FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch. Blue tablets: FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch.			
30.	**ORTHO TRI-CYCLEN-28** Ortho McNeil Pharmaceutical	28 days = 21 (7+7+7) days active pills + 7 days inert pills	EE; Norgestimate 0.035 mg,0.035 mg,0.035 mg; 0.18 mg,0.215 mg,0.25 mg Tablet; Oral-28
Excipients: White tablets: lactose, magnesium stearate, and pregelatinized starch. Light blue tablets: FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch. Blue tablets: FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch. Inert green tablets: D & C Yellow No. 10 Aluminum Lake, FD & C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose and pregelatinized starch.			
31.	**SEASONIQUE** Teva Womens' Health	91 days = 84 days active pills + 7 days EE pills	EE; Levonorgestrel 0.03 mg,0.01mg; 0.15 mg,n/a Tablet; Oral
Excipients: Light blue-green tablets: anhydrous lactose, D&C yellow no. 10 aluminum lake, FD&C blue no. 1 aluminum lake, FD&C yellow no. 6/Sunset yellow aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, titanium dioxide and triacetin. Inert Tablets: anhydrous lactose, D&C yellow no. 10 aluminum lake, FD&C yellow no. 6/Sunset yellow aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polacrilin potassium, polyethylene glycol, polysorbate 80 and titanium dioxide.			
32.	**YAZ** Bayer Healthcare	28 days = 24 days active pills + 4 days inert pills	Drospirenone; EE 3 mg; 0.02 mg Tablet; Oral
Excipients: Betadex, lactose monohydrate NF, corn starch NF, magnesium stearate NF, hypromellose USP, talc USP, titanium dioxide USP, ferric oxide pigment, red NF. Inert tablets: lactose monohydrate NF, corn starch NF, povidone 25000 USP, magnesium stearate NF, hypromellose USP, talc USP, titanium dioxide USP.			
33.	**LOESTRIN 24 FE** Warner Chilcott	28 days = 24 days active pills + 4 days inert pills	EE; Norethindrone Acetate 0.02 mg; 1 mg Tablet; Oral
Excipients: acacia, lactose, magnesium stearate, starch, confectioner's sugar, and talc. Inert tablets: ferrous fumarate, microcrystalline cellulose, magnesium stearate, povidone, sodium starch glycolate, and compressible sugar.			
34.	**LYBREL** Wyeth Pharmaceuticals Inc	28 days = 28 active pills, one pill daily	EE; Levonorgestrel 0.02 mg; 0.09 mg Tablet; Oral
Excipients: Microcrystalline cellulose, lactose monohydrate, magnesium stearate, polacrilin potassium, hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide, polyethylene glycol 1450, montanic ester wax.			
35.	**LOSEASONIQUE** Teva Womens' Health	91 days = 84 days active pills + 7 days EE pills	EE; Levonorgestrel 0.02 mg,0.01 mg; 0.1 mg,N/A Tablet; Oral
Excipients: FD&C Yellow # 6 (Sunset Yellow) aluminum lake, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, corn starch, titanium dioxide and triacetin. Inert tablets: anhydrous lactose, FD&C Yellow # 10 aluminum lake, FD&C Yellow # 6 (Sunset Yellow) aluminum lake, hypromellose, magnesium stearate, microcrystalline cellulose, polacrilin potassium, polyethylene glycol, polysorbate 80, and titanium dioxide.			

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Table. List of Oral Contraceptive Pills Marketed in United States *(Continued)*

S. No.	Brand/ Company/ Approval Year	Regimen	Product Strength
36.	**PLAN B ONE-STEP** Duramed Pharmaceuticals	Single dose Emergency contraceptive	Levonorgestrel 1.5 mg Tablet, Oral
Excipients: colloidal silicon dioxide, corn starch, lactose monohydrate, magnesium stearate, potato starch, and talc.			
37.	**NATAZIA** Bayer Healthcare	28 days = 26 (2+5+17+2) days active pills + 2 days inert pills	Dienogest; Estradiol Valerate N/A,2 mg,3 mg,N/A,N/A; 3 mg,2 mg,2 mg,1 mg,N/A Tablet; Oral-28
Excipients: lactose monohydrate, maize starch, maize starch pre-gelatinized, povidone 25, magnesium stearate, hypromellose, macrogol 6000, talc, titanium dioxide, and ferric oxide pigment, yellow, or ferric oxide pigment, red.			
38.	**BEYAZ** Bayer Healthcare	28 days = 24 days active pills + 2 days inert pills	Drospirenone; EE; Levomefolate Calcium 3 mg,N/A; 0.02 mg,N/A; 0.451 mg,0.451 mg Tablet; Oral
Excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, talc, polyethylene glycol, ferric oxide pigment, red. Inert tablets: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, talc, polyethylene glycol, ferric oxide pigment, red, ferric oxide pigment, yellow.			
39.	**LO LOESTRIN FE** Warner Chilcott Co	28 days = 26(24+2) days active pills + 2 days inert pills	EE; norethindrone acetate 0.01 mg, 1 mg, Tablet; oral Ethinyl Estradiol: 10 mcg Tablet; oral Ferrous fumarate: 75 mg tablet; oral
Excipients: Blue tablets: Mannitol, microcrystalline cellulose, FD&C Blue No. 1 Aluminum Lake, sodium starch glycolate, magnesium stearate, povidone, vitamin E and lactose monohydrate. White tablets: Mannitol, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, povidone, vitamin E and lactose monohydrate. Inert brown tablets: ferrous fumarate, mannitol, povidone, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, sucralose and spearmint flavor.			
40.	**SAFYRAL** Bayer Healthcare	28 days = 21 days active pills + 7 days inert pills	Drospirenone; EE; Levomefolate Calcium 3 mg,N/A; 0.03 mg,N/A; 0.451 mg,0.451 mg Tablet; Oral
Excipients: lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose USP, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF, ferric oxide pigment, yellow NF, and ferric oxide pigment, red NF. Inert tablets: lactose monohydrate NF, microcrystalline cellulose NF, croscarmellose sodium NF, hydroxypropyl cellulose NF, magnesium stearate NF, hypromellose USP, titanium dioxide USP, talc USP, polyethylene glycol NF and ferric oxide pigment, yellow NF, and ferric oxide pigment, red NF.			
41.	**NORETHINDRONE AND ETHINYL ESTRADIOL AND FERROUS FUMARATE** Watson Labs Inc	28 days = 24 days active pills + 4 days inert pills	EE; Norethindrone 0.025mg; 0.8mg Tablet, Chewable; Oral
Excipients: D&C Yellow No. 10 aluminum lake, FD&C Blue No. 1 aluminum lake, FD&C Yellow No. 6 aluminum lake, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, spearmint flavor, sucralose and vitamin E. Inert tablets: ferrous fumarate, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, spearmint flavor and sucralose.			

(ulipristal acetate 30 mg; Lab HRA Pharma) provides a more flexible emergency contraceptive regimen; the regimen recommends 1 oral tablet as soon as possible within 120 hours (5 days) after unprotected intercourse or a known or suspected contraceptive failure. Emergency contraceptives are not abortifacient (ie, they do not terminate an existing pregnancy) and do not prevent pregnancy from acts of unprotected intercourse later in that menstrual cycle.[40,41] The emergency contraceptive kit (Preven) consists of 4 emergency contraceptive pills and a pregnancy test. The first dose of Preven should be taken as soon as possible; initially, 2 pills should be taken within 72 hours of unprotected intercourse, followed by the second dose of 2 pills 12 hours later.

CONTRACEPTIVE REGIMENS[16,39]

Most contraceptive regimens recommend 1 pill every day at an interval not exceeding 24 hours. The pill should

be taken as recommended at the same time each day, because the risk of pregnancy increases with each missed pill.[8,42] In medical conditions like vomiting or diarrhea, an extra pill can be taken from a spare pack or a backup contraceptive plan should be considered to avoid unwanted pregnancy.[43]

Combined oral contraceptive pill regimens can be started on either the first Sunday after the onset of menstruation (Sunday start) or on day 1 of menstruation (day 1 start). If menstruation begins on Sunday, the first pill should be taken on that day. During the first cycle, it is recommended that Sunday starters use a nonhormonal backup contraceptive plan for the first 7 days.[44-46] Day 1 starters do not require any backup contraceptive plan for first 7 days because the first 7 days of menstruation are considered to be a safe period.[44,47] If a day 1 starter begins the regimen later than day 1 of menstruation, then a nonhormonal contraceptive backup plan is recommended for first 7 days.[42] The nonhormonal contraceptive backup plan includes the use of birth control methods such condoms, diaphragms, and spermicidal gels.

Three contraceptive dosing regimens of 21, 28, and 91 days have been introduced. The 21-day dosing regimen provides 1 contraceptive pill daily for 21 days, followed by 7 pill-free days (see Table). The 28-day regimen was introduced to improve consumer compliance compared with the 21-day regimen. With the 28-day regimen, there is no need to count days between cycles because there are no off-tablet days. There are four 28-day regimens: 21 active + 7 inert pills, 24 active + 4 inert pills, 26 active + 2 inert pills, and 28 active pills. With the 21+7 regimen, 1 active pill is taken daily for 21 days, followed by 1 inert (hormone-free) pill daily for next 7 days (see Table). The inert tablets are provided to facilitate correct administration; consumers don't need to count days between cycles because there is no tablet-free day in whole cycle. With the 24+4 regimen, 1 active pill is taken daily for 24 days, followed by 1 inert (hormone-free) pill daily for next 4 days. Another 28-day regimen (Natazia) provides 26 (2 + 5 + 17 + 2) active pills and 2 inert pills. Lo Loestrin Fe provides 26 active pills (24 with norethindrone acetate and ethinyl estradiol, 2 with ethinyl estradiol) and 2 inert tablets. The 28-day regimens of Lybrel, Ortho-Micronor, and Nor-QD are different from other regimens because all 28 pills are active (norethindrone); 1 pill is taken daily for 28 days. The extended-cycle regimen of 91 days recommends 1 active pill daily for 84 days, followed by 1 inert or estrogen pill daily for next 7 days.

GUIDELINES TO MANAGE MISSED PILLS

Missed pills enhance the chance of contraceptive failure. Missed pills are managed on the basis of 4 criteria: (1) how many pills were missed, (2) at what stage pills were missed, (3) the progestin content of the missed pills, and (4) the dose regimen. In a 28-day (21+7) regimen, if 1 active pill is missed in the first, second, or third week of the cycle, take it as soon as remembered and take the next pill at the regular time (1+1 pill in a day). No backup contraceptive plan is required. If 2 active pills are missed in a row in the first or second week, take 2 pills on the day the pills are remembered and 2 pills the next day; thereafter continue the regular regimen. A contraceptive backup plan (nonhormonal birth control method such as condoms or spermicide) is recommended for next 7 days after restart of the missed pills if intercourse is planned for these days. If 2 active pills are missed in a row in the third week or if 3 or more active pills are missed in a row at any time, a day 1 starter should discard the remaining pills and start with a new pill pack that same day, and a Sunday starter should keep taking 1 pill every day until Sunday; on Sunday, she should discard the rest of the pills and start with a new pill pack that same day. A contraceptive backup plan (nonhormonal birth control method such as condoms or spermicide) is recommended for the next 7 days after restart of a new pill pack if intercourse is planned for these 7 days.[42] If any of hormone-free pills are missed in the fourth week, throw away the missed pills and keep taking 1 pill each day until the pack is empty. No backup contraceptive plan is recommended. After completion of the cycle, start a new pack on the same day.

With extended regimens like 28 (24+4) days, 28 (26+2) days, or 91 (84+7) days, if 1 active pill is missed in the first, second, or third week or if 2 pills are missed in a row in the first or second week, management is similar to that with the 21+7 day regimen. With a 28-day (24+4 or 26+2) regimen, if 2 active pills are missed in a row in the third or fourth week, or if 3 or more active pills are missed in a row at any time during the cycle, a day 1 starter should discard the remaining pills and start with a new pill pack that same day, and a Sunday starter should keep taking 1 pill every day until Sunday; on Sunday she should discard the rest of the pills and start with a new pill pack that same day. For both day 1 and Sunday starters, a backup plan is recommended. If 3 or more active tablets are missed in a row with the extended-cycle regimen, do not take the missed pills and keep taking 1 pill daily as directed until you finish the pack. A nonhormonal contraceptive backup plan is recommended for the first 7 days after restart of the normal schedule if intercourse is

desired for these 7 days. The extended-cycle regimen of Seasonique and LoSeasonique consists of 91 (84+7) active pills. The last 7 pills of these regimens contain ethinyl estradiol as the active substance. If any of these last 7 yellow pills is missed, discard the missed pill and continue with the regular regimen until the pack is finished. No backup plan is recommended.

Natazia and Lybrel have different guidelines to manage missed pills. Start the Natazia regimen on the first day of your menstrual bleeding by taking the first dark-yellow pill. A nonhormonal contraceptive backup plan is recommended for the first 9 days. If 1 Natazia pill is missed for more than 12 hours on days 1 through 17, take the missed pill immediately, then take your next pill at usual time (1+1) and follow the regular regimen. A nonhormonal contraceptive backup plan is recommended for next 9 days. If 1 pill is missed for more than 12 hours on days 18 through 24, discard the remaining pills, and take the day 1 pill from a new pack and continue with the regular regimen. A nonhormonal contraceptive backup plan is recommended for next 9 days. If 1 pill is missed for more than 12 hours on days 25 through 28, take the missed pill immediately and next pill of the day at the usual time (1+1), and then continue the regular regimen. No backup contraception is needed. If 2 pills are missed in a row on days 1 through 17, do not take the missed pill; instead, take the pill of the day when you notice that you missed the pill and continue the regular regimen. Use backup contraception for next 9 days. If pills for days 17 and 18 are missed, follow the instructions for days 17 through 25 instead. If 2 pills are missed in a row on days 17 through 25, discard all the remaining pills, take the day 3 pill from a new pack, and continue the regular regimen. Use backup contraception for next 9 days. If pills for days 25 and 26 are missed, then follow the instructions for days 25 through 28 instead. If 2 pills are missed in a row on days 25 through 28, discard all the remaining pills, start with a new pack on the same day or on the usual day a new pack is started, and continue with the regular regimen. No backup plan is required.

If 1 Lybrel is missed, take the missed pill as soon as remembered and next pill at regular time (1+1 pill); a nonhormonal contraceptive backup plan is recommended for 7 days. If 2 Lybrel tablets are missed in a row and remembered on the day of second missed pill, take 2 pills on the day you remember and then follow the regular regimen; a nonhormonal contraceptive backup plan is recommended. If 2 Lybrel tablets are missed in a row and remembered on the day after second pill is missed, take 2 pills on the day remembered and 2 pills the next day, followed by the regular regimen; a 7-day nonhormonal contraceptive backup plan is recommended. If 3 or more pills are missed in a row, do not take the missed pills, contact your healthcare provider for advice, and keep taking 1 pill every day; a 7-day nonhormonal contraceptive backup plan is recommended.

The regimens of Ortho-Micronor and NOR-QD are different from other conventional regimens because these products are progestin-only contraceptives and consist of 28 active tablets. If a regimen is started on a day other than first menstrual day, a nonhormonal contraceptive backup plan is recommended for next 48 hours. If a pill is taken more than 3 hours late or if 1 or more pills are missed, take the missed pills as soon as you remember and then follow the regular regimen at the right time. A nonhormonal contraceptive backup plan is recommended for next 48 hours.

FUTURE PERSPECTIVES

Over the years, several progestin and estrogen combinations have been approved for birth control. Numerous dose regimens and cyclic regimens have been provided to improve the safety and tolerability of contraceptive pills. Furthermore, attempts have been made to simplify the dosing schedule by introducing inert pills, marking days over pills pack (wallet card), differentiating pills by their color and shape, and using dispensers like a dial pack or click case. Still, there is room to improve patient compliance by developing a simple and flexible dosing schedule. Also needed are some other new combinations of estrogen and progestin that are free from thromboembolic adverse effects and safe for smokers and others. The simple, new, and safer dosing regimen should be included in the list of extended-cycle regimens, which are free from intermittent unscheduled bleeding. More user-friendly products like chewable pills or orally dispersible pills may also improve compliance because these products can be consumed without water.

CONCLUSION

Combined oral contraceptive pills are considered to be an effective birth control method when used regularly on a prescribed schedule, with missed pills being managed according to guidelines. The Sunday starters are advised to use a nonhormonal contraceptive backup plan for first 7 days if intercourse is desired. Nonhormonal contraceptive backup plans are also advised for 7 days when 2 or more pills are missed in a row and intercourse is desired in the 7 days after resuming the normal regimen. Introduction of 28-day (21+7, 24+4,

or 26+2) regimens and the use of a pill dispenser (dial pack, click case) improve users' compliance. Biphasic, triphasic, or quadriphasic dose regimens have not proven to be more efficacious than a monophasic regimen. Emergency contraceptive pills are recommended only the case of unprotected intercourse or when the regular contraceptive method fails. Emergency contraceptives are not recommended for routine use and are ineffective or less effective when used before or delayed more than 120 hours after sex.

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