



Contraceptives, Oral Therapeutic Class Review (TCR)

March 15, 2016

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, digital scanning, or via any information storage or retrieval system without the express written consent of Magellan Rx Management.

All requests for permission should be mailed to:

Magellan Rx Management
Attention: Legal Department
6950 Columbia Gateway Drive
Columbia, Maryland 21046

The materials contained herein represent the opinions of the collective authors and editors and should not be construed to be the official representation of any professional organization or group, any state Pharmacy and Therapeutics committee, any state Medicaid Agency, or any other clinical committee. This material is not intended to be relied upon as medical advice for specific medical cases and nothing contained herein should be relied upon by any patient, medical professional or layperson seeking information about a specific course of treatment for a specific medical condition. All readers of this material are responsible for independently obtaining medical advice and guidance from their own physician and/or other medical professional in regard to the best course of treatment for their specific medical condition. This publication, inclusive of all forms contained herein, is intended to be educational in nature and is intended to be used for informational purposes only. Send comments and suggestions to PSTCReDitor@magellanhealth.com.

March 2016

Proprietary Information. Restricted Access – Do not disseminate or copy without approval.
© 2004-2016 Magellan Rx Management. All Rights Reserved.

MagellanRx
MANAGEMENTSM

OVERVIEW

Hormonal oral contraceptives (OCs) are available in various dosage forms for prevention of pregnancy and are available as either a combination of estrogen and progestin (combination OCs) or progestin alone. Products differ in the specific hormones they contain and how these hormones are dosed throughout the cycle (hormone phases) resulting in several product options. The various hormone combinations and phases in which they are dosed create products that produce different cycle lengths and physiological effects. Traditional OCs are administered daily for 21 days, followed by a hormone-free week during which menstruation occurs. Extended cycle products (e.g., 91 day cycle) delay or completely eliminate the break in hormone use and may be desirable to women who wish to avoid menstruation.¹

Selection of the most appropriate product for a patient may depend on the desired phases of hormones, cycle length, associated product risks, side effect profile, and tolerability. Hormones vary in their venous thrombosis risk, an important point to consider when selecting a product.² In addition, some OCs have additional indications or components; for example, certain products are approved for the treatment of acne vulgaris and several products contain iron. In general, it is recommended that a product with the least amount of hormone that is associated with a low failure rate (pregnancy during use) is prescribed, and that new patients are started on products containing estrogen 35 mcg or less.³

The primary mechanism of action for combination OCs is suppression of ovulation. The progestin component prevents the luteinizing hormone (LH) surge required for the release of the ovum. Secondarily, progestin thickens cervical mucus and decreases tubal motility, creating a more difficult passage for sperm. The progestin also acts to thin the endometrium, resulting in tissue that is less receptive to implantation. The estrogen stabilizes the endometrium providing for an acceptable cycle control and bleeding profile. Estrogen also contributes to efficacy by inhibiting the release of follicle-stimulating hormone (FSH) from the pituitary which inhibits the development of a dominant follicle and thus potentiates inhibition of the LH surge.⁴

Progestin-only OCs, also known as the “mini pill”, contain lower doses of progestin than the combination OCs. Their primary mechanism is to thicken cervical mucus. Ovulation may be suppressed in 50% of cycles. Secondary mechanisms include the thinning of the endometrium and slowing sperm motility as described above.⁵ When used with perfect adherence, combined OCs have a 0.1% failure rate. However, the failure rate is 5% to 8% with typical use, and higher in adolescent females, due to non-compliance.⁶ With perfect compliance, progestin-only OCs have a first-year failure rate of about 0.5%.⁷

Estrogen Component

The majority of OCs contain the synthetic estrogen ethinyl estradiol, and the dose varies across products from 20 mcg/day to 50 mcg/day. There are products still available that contain mestranol, the estrogen used in many of the original OCs. Mestranol is an inactive prodrug of ethinyl estradiol which is metabolized in the liver to ethinyl estradiol.⁸ Estradiol valerate is a prodrug of estradiol, the naturally occurring estrogen. The biologic effect of 2 mg of estradiol valerate is similar to 20 mcg of ethinyl estradiol. This estrogen is contained in the 4-phasic OC, Natazia®.⁹

Progestin Component

There are currently 9 different progestins contained in OCs. The progestin in an OC is the primary differentiator among different OCs. They are commonly referred to as first through fourth generation progestins based on when they were introduced into the market. The older first generation agents include norethindrone, norethindrone acetate, and ethynodiol diacetate. Second generation progestins include norgestrel and its active isomer, levonorgestrel. Third generation agents are norgestimate and desogestrel and the fourth generation agents are drospirenone and dienogest. Progestins vary in their progestational, estrogenic, antiestrogenic, and androgenic activity. Drospirenone differs somewhat from the other progestins because it is derived from spironolactone and retains some of the anti-mineralocorticoid and antiandrogen effects of the parent compound.^{10,11}

The first generation progestins are generally well tolerated but are associated with spotting and breakthrough bleeding. The second generation drugs are more potent progestins with longer half-lives. Norgestrel and levonorgestrel and the third generation desogestrel are the most potent progestins. Second generation progestins have more androgenic activity compared to the first generation drugs and may be associated with more androgenic side effects, such as hirsutism, acne, or dyslipidemia. The androgenic effect may also translate to improvements in libido. Norgestrel is the most androgenic of the progestins. The third generation drugs are similar to the second generation drugs in their progestational activity but have less androgenic activity; adverse effects, such as acne, may occur less frequently. Norgestimate and desogestrel have the least androgenic activity of the progestins; however, they have been associated with a slightly higher risk of thrombosis than earlier agents. Dienogest, the most recently introduced progestin, is antiandrogenic.^{12,13}

The progestin-only OCs all contain 35 mcg of norethindrone. They contain active drug in all tablets taken throughout the monthly cycle; there is no hormone free period. They are primarily used during lactation and in women who need to avoid estrogen due to tolerance issues or contraindications. Progestin only OCs are associated with more breakthrough bleeding and possibly higher failure rates than combination OCs.^{14,15} For maximum effectiveness, it is essential that progestin-only tablets be taken at the same time each day.¹⁶

Combination Oral Contraceptives

Combination OCs (estrogen/progestin) are generally grouped based on the dosage regimen strategy used by a specific product. Most are based on a 28-day monthly cycle and are available as monophasic, biphasic, triphasic, and 4-phasic products. There are also extended cycle products and a continuous cycle product available.

Monophasic products contain the same amount of estrogen and progestin in each tablet taken throughout the cycle and are most frequently dosed as a daily active combined pill for 21 days followed by 7 days of no pills or a placebo pill. Several monophasic pills vary the duration of active versus inactive pills (e.g., Minastrin® 24 FE has 24 days of active combination pills followed by a 4-day placebo period in each cycle).

Multiphasic pills (biphasic, triphasic, and 4-phasic) contain differing doses of 1 or both hormones in the active pills in an attempt to emulate the body's natural menstrual cycle and decrease dose-related adverse effects. For example, triphasic products with an increased progestin dose at the end of the cycle may prevent premenstrual breakthrough bleeding, while a triphasic pill with a higher estrogen to

progestin ratio at the beginning of the cycle may prevent breakthrough bleeding early in the cycle, and a mid-cycle increase in both estrogen and progestin may improve mid-cycle breakthrough bleeding. Many multiphasic products contain a lower total dose of hormones over the course of a cycle.^{17,18}

There is a paucity of good quality controlled clinical trials comparing monophasic OCs to any of the multiphasic OCs. A Cochrane systematic review published in 2006 identified 1 randomized, controlled trial of limited quality comparing a monocyclic and a biphasic OC. The outcome measures of interest were efficacy, cycle control, and discontinuation due to side effects. Their study found no significant differences in intermenstrual bleeding, amenorrhea, or study discontinuation due to intermenstrual bleeding between the 2 products.¹⁹ A similar study was conducted in 2011 to compare monophasic OCs to triphasic OCs using the same outcome measures. The investigators identified 23 studies, 19 of which reported contraceptive effectiveness. No significant difference in efficacy was observed. Several trials reported less spotting, breakthrough bleeding, or amenorrhea in the triphasic OC groups compared to the monophasic groups. They were not able to conduct a meta-analysis due to variability in progestin used, dosages, and inconsistency in measuring and reporting cycle disturbance data. There was no significant difference in discontinuation due to medical reasons, cycle disturbances, intermenstrual bleeding, or other adverse events.²⁰

Extended-cycle OCs provide active combination tablets for a longer period of time than the traditional 28-day cycle. These products provide an active tablet daily for 3 months followed by a 7-day period of placebo tablets (e.g., Seasonique®) during which menstrual bleeding occurs. A continuous-cycle product, Amethyst®, contains active hormones in each tablet and is meant to be taken every day for a year, suppressing all menstrual bleeding. Avoidance of menstruation may be desirable to some women and, in using an extended cycle product, they may benefit from improved compliance, fewer menstrual symptoms, and less menstruation-related work or school absenteeism.²¹

SAFETY AND ADVERSE EFFECTS

The use of OCs is associated with increased risks of serious conditions, including myocardial infarction (MI), thromboembolism, stroke, hepatic tumors, and gallbladder disease; while the risk of serious morbidity or mortality is very small in healthy women, underlying risk factors, such as obesity, diabetes, hypertension, and hyperlipidemia, can increase morbidity and mortality. OCs are contraindicated in women with a prior thromboembolic event or stroke, hepatic disease, cerebral vascular or coronary artery disease, undiagnosed abnormal uterine bleeding, uncontrolled hypertension, migraine headaches, particularly with focal neurologic symptoms, diabetes, a history of estrogen-dependant tumor, such as breast cancer or endometrium cancer, or major surgery with prolonged immobilization.^{22,23,24}

Studies have not found an increased risk of birth defects among women who have inadvertently continued to take OCs after they unknowingly became pregnant; however, OCs are contraindicated during pregnancy since there is no reason for their use. In addition, both pregnancy and OC use are associated with an increased risk of thromboembolic events.

Because the risk of post-operative thromboembolic complications may be increased with the use of OCs, when possible, OCs should be discontinued at least 4 weeks prior to and for 2 weeks after elective surgery that may also increase the risk of thromboembolism or require prolonged immobilization. In

addition, risk of thromboembolism is increased during the immediate postpartum period; OCs should be started no earlier than 4 weeks after delivery in women who do not breastfeed.

The incidence of thrombotic stroke in OC users increases with age.²⁵ OCs are contraindicated in women 35 years of age and older who smoke. Older OC formulations contained higher concentrations of ethinyl estradiol (≥ 50 mcg) and are associated with an increased risk of MI and ischemic stroke.²⁶ This risk was especially higher in smokers and women with uncontrolled hypertension. Newer OCs, with lower doses of estrogen, are associated with a lower risk of venous thromboembolism (VTE).^{27,28} A Cochrane meta-analysis compared the risk of MI and ischemic stroke using 24 observational studies of users and non-users of combined oral contraceptives (ages 18 to 50 years).²⁹ They found the risk of arterial thrombosis (stroke or MI) to be 1.6 times higher in patients using combined oral contraceptives compared to non-users, but the risk did not vary clearly by progesterone type. Similar to earlier studies, they also found that the risk increased (approximately twice as high) with higher doses of estrogen. However, a meta-analysis of studies published between 1980 and 2002 was limited to low-dose combinations of second and third generation OCs and reported an increased risk of stroke with these products (odds ratio [OR], 2.12). A large Danish 15-year cohort study (14,251,063 person-years) reported the risk of thrombotic stroke and myocardial infarction was increased by a factor of 0.9 to 1.7 with OCs containing 20 mcg of ethinyl estradiol and by a factor of 1.3 to 2.3 with OCs containing ethinyl estradiol in dosages from 30 to 40 mcg.³⁰ It should be noted that this risk is lower than the risk of VTE or stroke associated with pregnancy itself. There is no convincing evidence that the progestin component affects the risk of VTE.³¹ A systematic review and meta-analysis of progestogen-only OCs showed no significant increased risk of stroke.³² Progestin-only or nonhormonal contraception can be considered for women at increased risk of cardiovascular or thromboembolic events.

There are conflicting findings that drospirenone-containing OCs increase the risk of VTE, particularly compared to levonorgestrel-containing contraceptives.^{33,34,35,36,37,38,39} However, poor study methodologies limit interpretation of the results.⁴⁰ Unlike other progestins, drospirenone is a third generation progestin and is a spironolactone analogue. In April 2012, the FDA announced that drospirenone-containing OCs may be associated with a higher risk for VTE than other progestin-containing tablets and required labels of OCs containing drospirenone to include more information on the risk. The label notes that some studies reported as high as a 3-fold increase in the risk of blood clots for drospirenone-containing products when compared to products containing levonorgestrel or other progestins, while other studies found no additional risk of blood clots with drospirenone-containing products.⁴¹ A 2013 Cochrane review of 25 publications concluded the risk of VTE for OCs with 30 to 35 mcg ethinyl estradiol and gestodene, desogestrel, cyproterone acetate, and drospirenone was similar and about 50% to 80% higher than with levonorgestrel. Based on these findings, it is recommended that if prescribing a combination OC, to prescribe one with the lowest possible dose of ethinyl estradiol combined with levonorgestrel.⁴² Results from the more recent Cochrane review of arterial thrombosis (MI and stroke) also suggest this finding; however, the moderate quality and limited number of included studies with each progesterone type must also be considered.⁴³

The estrogen component of OCs can cause nausea and breast tenderness and/or enlargement.

Concurrent use of OCs with certain anticonvulsants, antibiotics, antifungals, anti-HIV medications, and medications that can alter renal function and serum potassium levels should be monitored.⁴⁴

The effects of OCs are reversible and do not negatively impact long-term fertility. In healthy nonsmoking women, hormonal contraception can be continued until menopause.

Noncontraceptive benefits of OCs include reduced risk of epithelial ovarian and endometrial cancer, which is evident after 1 year of use and extends after discontinuation.⁴⁵ It also appears that OCs do not increase risk of breast cancer.⁴⁶ Other benefits include a lower incidence of ectopic pregnancy, increased hemoglobin levels, more regular menstrual cycles, and reduced dysmenorrhea and menorrhagia, as well as improved hirsutism and acne. Progestin components, such as desogestrel and norgestimate, with lower androgenic activity have claimed greater acne improvement than older progestins; however, evidence from controlled trials is lacking.⁴⁷

SUMMARY

Oral contraceptives are a reasonable contraceptive method for many women of childbearing age.

A current product listing appears in Appendix A (in a separate document).

REFERENCES

- 1 Edelman A, Micks E, Gallo MF, et al. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. *Cochrane Database of Systematic Reviews* 2014;7:CD004695.
- 2 de Bastos M, Stegeman BH, Rosendaal FR, et al. Combined oral contraceptives: venous thrombosis. *Cochrane Database of Systematic Reviews* 2014; 3: CD010813. DOI: 10.1002/14651858.CD010813.pub2.
- 3 Facts and Comparisons eAnswers. Available at: <http://online.factsandcomparisons.com>. Accessed March 15, 2016.
- 4 Clinical Pharmacology. Available at: <http://www.clinicalpharmacology.com>. Accessed March 15, 2016.
- 5 Facts and Comparisons eAnswers. Available at: <http://online.factsandcomparisons.com>. Accessed March 15, 2016.
- 6 Oral Contraception. Kronenberg: Williams Textbook of Endocrinology, 11th ed. 2008.
- 7 Facts and Comparisons eAnswers. Available at: <http://online.factsandcomparisons.com>. Accessed March 15, 2016.
- 8 Clinical Pharmacology. Available at: <http://www.clinicalpharmacology.com>. Accessed March 15, 2016.
- 9 Kiley J, Shulman L. Estradiol valerate and dienogest: a new approach to oral contraception. *Int J Women's Health*. 2011; 3:281-286.
- 10 Anon. PL Detail-Document Hormonal Contraception. Pharmacist's Letter/Prescriber's Letter. March 2013.
- 11 Facts and Comparisons eAnswers. Available at: <http://online.factsandcomparisons.com>. Accessed March 15, 2016.
- 12 Anon. PL Detail-Document Hormonal Contraception. Pharmacist's Letter/Prescriber's Letter. March 2013
- 13 Facts and Comparisons eAnswers. Available at: <http://online.factsandcomparisons.com>. Accessed March 15, 2016.
- 14 Taylor AL, LaValleur J. Women's health topics. Hormone therapy. *Cecil Essentials of Medicine*. 6th ed. 2004. 655-656.
- 15 Grimes DA, Lopez LM, O'Brien PA, et al. Progestin-only pills for contraception. *Cochrane Database Syst Rev*. 2010; 20(1):CD007541.
- 16 Facts and Comparisons eAnswers. Available at: <http://online.factsandcomparisons.com>. Accessed March 15, 2016.
- 17 Anon. Choice of contraceptives. Treatment guidelines from The Medical Letter. 2010; 8(100:89-95).
- 18 Anon. PL Detail-Document Hormonal Contraception. Pharmacist's Letter/Prescriber's Letter. March 2013.
- 19 Van Vliet HA, Grimes DA, Helmerhorst FM, Schulz KF. Biphasic versus monophasic oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2006; 19;(3):CD002032.
- 20 Van Vliet HA, Grimes DA, Lopez LM, et al. Triphasic versus monophasic oral contraceptives for contraception. *Cochrane Database Syst Rev*. 2011; 9;(11):CD003553
- 21 Edelman A, Micks E, Gallo MF, et al. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. *Cochrane Database of Systematic Reviews* 2014;7:CD004695. DOI: 10.1002/14651858.CD004695.pub3.
- 22 Clinical Pharmacology. Available at: <http://www.clinicalpharmacology.com>. Accessed March 15, 2016.
- 23 Holt VL, Scholes D, Wicklund KG, et al. Body mass index, weight, and oral contraceptive failure risk. *Obstet Gynecol*. 2005; 105(1):46-52.
- 24 Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. *Obstet Gynecol*. 2002; 99(5 Pt 1):820-827.
- 25 Bushnell C, McCullough LD, Issam A, et al on behalf of the American Heart Association Stroke Council. Guidelines for the prevention of stroke in women: A statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45(5): 1545-1588. DOI: 10.1161/01.str.0000442009.06663.48.. Available at: <http://stroke.ahajournals.org/content/early/2014/02/06/01.str.0000442009.06663.48.long>. Accessed March 15, 2016.
- 26 Combination oral contraceptives and the risk of venous thromboembolism. *Med Lett Drugs*. 2010; 52:23.
- 27 Van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, et al. The venous thrombotic risk of oral contraceptives, effects of estrogen dose and progestogen type: results of the MEGA case-control study. *BMJ*. 2009; 339:b2921.
- 28 Lidegaard Ø, Løkkegaard E, Svendsen AL, et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ*. 2009; 339:b2890.

-
- 29 Roach RE, Helmerhorst FM, Lijfering WM, et al. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev.* 2015; 8 : CD011054. DOI: 10.1002/14651858.CD011054.pub2.
- 30 Lidegaard O, Lokkegaard E, Jensen A, Skovlund CW, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. *N Eng J Med* 2012; 366:2257-66. DOI: 10.1056.
- 31 Reid RL, Westhoff C, Mansour D, et al. Oral contraceptives and venous thromboembolism consensus opinion from an international workshop held in Berlin, Germany in December 2009. *J Fam Plann Reprod Health Care.* 2010; 36(3):117-122.
- 32 Chakhtoura Z, Canonico M, Gompel A, et al. Progestogen-only contraceptives and the risk of stroke: a meta-analysis. *Stroke* 2009;40:1059-1062 DOI: 10.1161.
- 33 Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ.* 2011; 342:d2151.
- 34 Parkin LL, Sharples K, Hernandez RK, et al. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *BMJ.* 2011; 342:d2139.
- 35 Van Hylckama V, Helmerhorst FM, Vandembroucke JP, et al. The venous thrombotic risk of oral contraceptives, effects of estrogen dose and progestogen type: results of the MEGA case-control study. *BMJ.* 2009; 339:b2921.
- 36 Lidegaard Ø, Løkkegaard E, Svendsen AL, et al. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ.* 2009; 339:b2890.
- 37 Dinger JC, Heinemann LA, Kühl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception.* 2007; 75:344-354.
- 38 Seeger JD, Loughlin J, Eng PM, et al. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol.* 2007; 110(3):587-593.
- 39 Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm277346.htm>. Accessed March 15, 2016.
- 40 Brown DA, Vartan CM. Risk of venous thromboembolism with drospirenone-containing oral contraceptives. *AJHP.* 2011; 68(11):1003-1010.
- 41 Birth control pills containing drospirenone: Label change-products may be associated with a higher risk for blood clots. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm299605.htm?source=govdelivery>. Accessed March 15, 2016.
- 42 de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, Dekkers OM. Combined oral contraceptives: venous thrombosis. *Cochrane Database of Systematic Reviews* 2014; 3: CD010813.
- 43 Roach RE, Helmerhorst FM, Lijfering WM, et al. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev.* 2015; 8 : CD011054. DOI: 10.1002/14651858.CD011054.pub2.
- 44 Clinical Pharmacology. Available at: <http://www.clinicalpharmacology.com>. Accessed March 15, 2016.
- 45 Contraception and adolescents. Committee on adolescence. *Pediatrics.* 2007; 120:1135-1148. Available at: <http://www.pediatrics.org/cgi/content/full/120/5/1135>. Accessed March 15, 2016.
- 46 Contraception and adolescents. Committee on adolescence. *Pediatrics.* 2007; 120:1135-1148. Available at: <http://www.pediatrics.org/cgi/content/full/120/5/1135>. Accessed March 15, 2016.
- 47 Choice of contraceptives. *Treat Guidel Med Lett.* 2010; 8(100):89-95.