The Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Combined Hormonal Contraceptives

This statement has been developed and reviewed by the Women's Health Committee and approved by the RANZCOG Board and Council.

A list of Women's Health Committee Members can be found in Appendix A.

Disclosure statements have been received from all members of this committee.

Disclaimer This information is intended to provide general advice to practitioners. This information should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient. This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The document has been prepared having regard to general circumstances.

First endorsed by RANZCOG: November 2012
Current: March 2016
Review due: March 2019

Objectives: To provide advice on combined oral contraceptives.

Target audience: Health professionals providing gynaecological care, and patients.

Values: The evidence was reviewed by the Women's Health Committee (RANZCOG), and applied to local factors relating to Australia and New Zealand.

Background: This statement was first developed by Women's Health Committee in November 2012 and reviewed in March 2016.

Funding: The development and review of this statement was funded by RANZCOG.

Table of contents

1. Patient summary

With appropriate use, combined hormonal contraceptive (CHC) methods are safe and effective. Women planning to use CHCs should discuss this choice with their doctor to make sure that this is a safe and suitable choice for them. This choice will not only depend on a woman's medical and family history, but also on the findings from physical examination (blood pressure and weight, for example) and sometimes the results of tests. The choice will also take into account factors such as the desire for non-contraceptive benefits (acne, hirsutism, heavy menstrual bleeding), cost, and personal preference.

2. Introduction

2.1 Definition

Combined hormonal contraceptives (CHCs), available as combined oral contraceptives (known as 'the pill') and the vaginal ring, are preparations of an oestrogen and a progestagen. CHCs contain ethinyloestradiol (EE), oestradiol valerate, or oestradiol and one of a range of progestogens.

There are a number of different combined oral contraceptives (COC) formulations and brands. Packaging regimens for pills consist of a minimum of 21 days of hormone pills followed by up to 7 days of placebo.

COC formulations are either:

- Monophasic: All active tablets have an identical formulation.
- Multiphasic: There are two or more formulations within the active pills.

The combined vaginal ring is a 54mm ethylene vinyl acetate copolymer ring and releases a combination of 15mcg EE and 120mcg etonogestrel daily. It is available in Australia as NuvaRing®. It is placed in the vagina for 3 weeks. It is then removed, disposed of and the woman then has a 7 day hormone free week before a new ring is inserted.

The COC and vaginal ring work in the same way and are treated similarly in terms of contraindications, complications, side effects and drug interactions. It is assumed that the vaginal ring will offer similar benefits to the COC but because it is relatively new, extensive supporting evidence is lacking. The majority of this statement, unless otherwise stated, refers to both the COC and the vaginal ring.

2.2 Mechanism of action

The primary mechanism of action is prevention of ovulation. In addition, CHCs thicken cervical mucus, preventing sperm penetration.

2.3 Efficacy

One year failure rate estimates for perfect use are 99.7%, and for typical use 91%.[1] Low typical use rates emphasise the need for users to have a clear understanding of how to start, adherence and missed pill information.

3. Discussion and recommendations

3.1 Advantages as a method of contraception, CHCs

- Are very effective with correct use;
- Are readily accessible to most women;
- Are easily reversible;
- Provide predictable withdrawal bleeds and the ability to manipulate cycles;
- Can be used to manage menstrual problems, e.g. heavy menstrual bleeding (HMB),[2, 3] dysmenorrhea[4] and symptoms of endometriosis;[5]
- Can improve acne;[6]
- Can reduce the risk of endometrial[7] and ovarian cancer;[8]
- Can reduce the risk of bowel cancer;[9]
- Can be used to manage pre-menstrual syndrome (PMS), and its more severe form pre-menstrual dysphoric disorder (PMDD), in some women;[10-14]
- Can reduce the incidence of functional ovarian cysts[15] and benign ovarian tumours[16]
- Can be useful in managing symptoms of polycystic ovarian syndrome;[17, 18]
- Can assist with management of perimenopausal symptoms.[19]

3.2 Disadvantages as a method of contraception, CHCs

- Typical use failure rates are high;
- Some formulations are relatively expensive;
- As an oestrogen containing contraceptive method, there are rare but serious risks including venous thromboembolism (VTE) and arterial disease, so personal and family history are particularly important;
- Some common conditions limit use, e.g. migraine with aura (absolute contraindication; UK MEC 4 of the UK medical eligibility criteria; see link: http://www.fsrh.org/pdfs/UKMEC2009.pdf) and BMI of ≥ 35kg/m^2 (strong relative contraindication; UK MEC 3).

3.3 CHC components

Until recently the only oestrogen used in Australian CHCs was ethinyloestradiol (EE). The active oestrogen in the recent oestradiol and oestradiol valerate pills is structurally identical to the oestradiol produced by the ovaries.

Newer progestogens, cyproterone acetate, etonogestrel, drospirenone, dienogest and nomogestrel acetate, have been developed over recent decades to avoid androgenic side effects and to have a minimal negative impact on EE induced changes to lipids.[20] Some have been designed with additional potential benefits, e.g. drospirenone is a spironolactone analogue and has a mild diuretic effect.[21] However there is insufficient clinical evidence to preferentially initially prescribe newer progestogens over the older levonorgestrel and norethisterone products. Selecting a progestogen type other than levonorgestrel or norethisterone for women with a pre-existing condition such as acne, pre-menstrual dysphoric disorder or heavy menstrual bleeding may be considered.

3.4 Contraindications

There are a number of conditions which represents an unacceptable health risk if the contraceptive method is used as defined by the UK Medical eligibility criteria for contraceptive use.For CHCs these include:

- Breastfeeding and ≤6 weeks postpartum
- Smoker ≥35 year and ≥ 15 cigarettes/day
- Presence of multiple risk factors for CVD including older age, smoking, diabetes, hypertension
- Hypertension with systolic ≥160mmHg or diastolic ≥95mmHg
- Vascular disease
- Major surgery with prolonged immobilisation

- Current or past history of venous thromboembolism (VTE);
- Known thrombogenic mutations * (Factor V Leiden, Prothrombin mutation, Protein S, Protein C and Antithrombin deficiencies)
- Migraine with aura
- Current or past history of Ischemic Heart Disease (IHD);
- Complicated valvular heart disease
- Diabetes complicated by nephropathy, retinopathy or vascular disease
- Breast cancer;
- Severe Liver disease including cirrhosis hepatocellular adenoma and hepatoma
- Raynaud's with lupus anticoagulant
- SLE with antiphospolipid antibodies

* 'Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening' (http://www.fsrh.org/pdfs/UKMEC2009.pdf).

Other important considerations are:
- Breastfeeding;
- Drug interactions.

Detailed information on contraindications to CHC use using the medical eligibility criteria (MEC) framework for contraception developed by WHO and modified by the UK Faculty of Sexual and Reproductive Health Care are available on the Faculty of Sexual Reproductive Health Care (FSRH) website (http://www.fsrh.org/pages/clinical_guidance.asp) or in Contraception: An Australian Clinical Practice Handbook (available from all Australian state Family Planning Organisations).

3.5 Serious risks

3.5.1 VTE

CHCs increase the risk of VTE 2-3 fold compared to non users, but the absolute risk of VTE remains low, particularly for those without additional risk factors. The incidence is greatest in the first 4 months after initiation[22] and then deceases over time, but always remains above that of non CHC users and below that in late pregnancy and the postpartum period.[23] The risk returns to background level within 3 months of cessation of the method.[22] Pills containing ≤35 mcg EE and either levonorgestrel or norethisterone are associated with, the lowest risk. The absolute risk of VTE in users is very low with any formulation and is much lower than the risk associated with pregnancy and the postpartum period.

3.5.2 Cancer

The results of a recent large UK cohort study indicate that COC use is not associated with an overall increased risk of cancer. In fact women are relatively protected and there was a statistically significant reduction in the overall risk of cancer in older women who had ever used oral contraceptives compared to those who had not.[24]

3.5.3 Breast cancer

Evidence is divided on whether use of CHCs increases the risk of breast cancer.[25-28] Any increased risk for current users is small and there is no significant difference in risk between ever-users and never-users of CHCs.[29, 30] Use of CHCs has not been shown to be associated with increased mortality from breast cancer.[24, 28, 31]

3.5.4 Cervical cancer

Although multiple confounders have made studies difficult to interpret, the balance of evidence supports a small increase in the risk of cervical cancer in users of CHCs. This risk increases with duration of use and gradually decreases after cessation.[32] The rate of cervical cancer in Australia is 4.9/10,000 women per year and is one of the lowest in the world.[33] Regular cervical screening minimises the risk of cervical cancer.[34]

3.5.5 Liver cancer

Early studies indicated there was an increased risk of hepatocellular carcinoma in CHC users[35] but this was not confirmed in a more recent large cohort study.[29] Regardless, there is no evidence that CHCs further increase the risk of hepatocellular carcinoma in women with chronic viral hepatitis.[36]

3.6 Choice of CHC

Consider a monophasic COC as a good first choice (a pill with levonorgestrel or norethisterone). Other pills or the vaginal ring are safe to use where there is a specific potential benefit to the woman or there are side effects to first line pills.

3.7 Commencing CHCs

Women who are not using another method of contraception may choose a Traditional or Quick Start initiation regimen. The Quick Start method means starting the pill on the day it is prescribed if the user is unlikely to be pregnant already. A back-up form of birth control (eg, condoms) is needed for the first seven days after the Quick Start.

3.8 Return for review

CHC use may be reviewed after four months initially, and then yearly, provided the woman is at low risk for cardiovascular disease.

3.9 Extended use/ tricycling or continuous COC pack use

This method is a useful way to minimise bleeding. Extended use can also be useful to:

- Decrease the risk of break-through ovulation associated with missed pills in women who forget pills regularly.[37] Another method not relying on daily intake is preferred for these women.
- Avoid withdrawal headaches, in the hormone free week.[38-40]
- Avoid PMS.[39, 40]
- Avoid unacceptably heavy or painful withdrawal bleeds.
- Decrease the risk of breakthrough ovulation in women taking liver enzyme inducers.

Traditionally women wanting to minimise menstruation have been advised to tricycle, meaning to run 3 cycles of the active hormonal pills or vaginal ring together, omitting the placebo break for 2 packs out of 3. A Cochrane review did not demonstrate any additional safety issues for women taking CHCs continuously without placebo breaks for up to 12 months.[41]

Disadvantages are the increased cost, and for some women unpredictable bleeding.[42-44]

Adapted from Contraception: An Australian Clinical Practice Handbook, 2012, 3rd edition.
Family Planning NSW, Family Planning Qld, Family Planning Victoria (member organisations of Sexual Health and Family Planning Australia).

4. Conclusion

Provided they are used correctly, all combined hormonal contraceptive methods in Australia and New Zealand have high efficacy. Choice of CHC type for medically eligible women will be determined by a variety of factors including desire for non-contraceptive benefits (acne, hirsutism, heavy menstrual bleeding), cost and personal preference.

5. References

1. Trussell J. Contraceptive failure in the United States. Contraception. 2011;83(5):397-404.
2. Farquhar C, Brown J. Oral contraceptive pill for heavy menstrual bleeding. The Cochrane database of systematic reviews. 2009(4):CD000154.
3. 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. Obstetrics and gynecology. 2011;117(4):777-87.
4. Larsson G, Milsom I, Lindstedt G, Rybo G. The influence of a low-dose combined oral contraceptive on menstrual blood loss and iron status. Contraception. 1992;46(4):327-34.
5. Harada T, Momoeda M, Taketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2008;90(5):1583-8.
6. Arowojolu AO, Gallo MF, Lopez LM, Grimes DA, Garner SE. Combined oral contraceptive pills for treatment of acne. The Cochrane database of systematic reviews. 2009(3):CD004425.
7. Mueck AO, Seeger H, Rabe T. Hormonal contraception and risk of endometrial cancer: a systematic review. Endocr Relat Cancer. 2010;17(4):R263-71.
8. Collaborative Group on Epidemiological Studies of Ovarian C, Beral V, Doll R, Hermon C, Peto R, Reeves G. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008;371(9609):303-14.
9. Bosetti C, Bravi F, Negri E, La Vecchia C. Oral contraceptives and colorectal cancer risk: a systematic review and meta-analysis. Human reproduction update. 2009;15(5):489-98.
10. Joffe H, Cohen LS, Harlow BL. Impact of oral contraceptive pill use on premenstrual mood: predictors of improvement and deterioration. American journal of obstetrics and gynecology. 2003;189(6):1523-30.
11. Seidman DS, Yeshaya A, Ber A, Amodai I, Feinstein I, Finkel I, et al. A prospective follow-up of two 21/7 cycles followed by two extended regimen 84/7 cycles with contraceptive pills containing ethinyl estradiol and drospirenone. Isr Med Assoc J. 2010;12(7):400-5.
12. Lopez LM, Kaptein AA, Helmerhorst FM. Oral contraceptives containing drospirenone for premenstrual syndrome. The Cochrane database of systematic reviews. 2012;2:CD006586.
13. Pearlstein TB, Bachmann GA, Zacur HA, Yonkers KA. Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. Contraception. 2005;72(6):414-21.
14. Yonkers KA, Brown C, Pearlstein TB, Foegh M, Sampson-Landers C, Rapkin A. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. Obstetrics and gynecology. 2005;106(3):492-501.
15. Holt VL, Cushing-Haugen KL, Daling JR. Oral contraceptives, tubal sterilization, and functional ovarian cyst risk. Obstetrics and gynecology. 2003;102(2):252-8.
16. Westhoff C, Britton JA, Gammon MD, Wright T, Kelsey JL. Oral contraceptive and benign ovarian tumors. Am J Epidemiol. 2000;152(3):242-6.
17. Costello M, Shrestha B, Eden J, Sjoblom P, Johnson N. Insulin-sensitising drugs versus the combined oral contraceptive pill for hirsutism, acne and risk of diabetes, cardiovascular disease, and endometrial cancer in polycystic ovary syndrome. The Cochrane database of systematic reviews. 2007(1):CD005552.
18. Consensus on women's health aspects of polycystic ovary syndrome (PCOS). . Human reproduction. 2012;27(1):14-24.
19. Casper RF DS, Reid RL. The Effect of 20 [mu]g Ethinyl Estradiol/1 mg Norethindrone Acetate (MinestrinTM), a Low-Dose Oral Contraceptive, on Vaginal Bleeding Patterns, Hot Flashes, and Quality of Life in Symptomatic Perimenopausal Women. Menopause. 1997;4(3):139-47.
20. Kuhl H. Comparative pharmacology of newer progestogens. Drugs. 1996;51(2):188-215.
21. Krattenmacher R. Drospirenone: pharmacology and pharmacokinetics of a unique progestogen. Contraception. 2000;62(1):29-38.
22. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet. 1995;346(8990):1575-82.

23. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism: a five-year national case-control study. Contraception. 2002;65(3):187-96.
24. Hannaford PC, Iversen L, Macfarlane TV, Elliott AM, Angus V, Lee AJ. Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. Bmj. 2010;340:c927.
25. Imkampe AK, Bates T. Correlation of age at oral contraceptive pill start with age at breast cancer diagnosis. Breast J. 2012;18(1):35-40.
26. Kahlenborn C, Modugno F, Potter DM, Severs WB. Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. Mayo Clin Proc. 2006;81(10):1290-302.
27. Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, et al. Oral contraceptives and the risk of breast cancer. The New England journal of medicine. 2002;346(26):2025-32.
28. Collaborative Group on Hormonal Factors in Breast C. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet. 1996;347(9017):1713-27.
29. Hannaford PC, Selvaraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. Bmj. 2007;335(7621):651.
30. Vessey M. Oral contraceptives and cancer. J Fam Plann Reprod Health Care. 2007;33(2):133.
31. Lu Y, Ma H, Malone KE, Norman SA, Sullivan-Halley J, Strom BL, et al. Oral contraceptive use and survival in women with invasive breast cancer. Cancer Epidemiol Biomarkers Prev. 2011;20(7):1391-7.
32. International Collaboration of Epidemiological Studies of Cervical C, Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, et al. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. Lancet. 2007;370(9599):1609-21.
33. International Cancer Screening Network NCI. Age-Adjusted Cervical Cancer Incidence and Mortality Rates for 2008 for 32 countries, . Available from: http://appliedresearch.cancer.gov/icsn/cervical/mortality.html.
34. Mitchell HS. How much cervical cancer is being prevented? The Medical journal of Australia. 2003;178(6):298.
35. Neuberger J, Forman D, Doll R, Williams R. Oral contraceptives and hepatocellular carcinoma. Br Med J (Clin Res Ed). 1986;292(6532):1355-7.
36. Combined oral contraceptives and liver cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer. 1989;43(2):254-9.
37. Vandever MA, Kuehl TJ, Sulak PJ, Witt I, Coffee A, Wincek TJ, et al. Evaluation of pituitary-ovarian axis suppression with three oral contraceptive regimens. Contraception. 2008;77(3):162-70.
38. Sulak PJ, Scow RD, Preece C, Riggs MW, Kuehl TJ. Hormone withdrawal symptoms in oral contraceptive users. Obstetrics and gynecology. 2000;95(2):261-6.
39. Halbreich U, Freeman EW, Rapkin AJ, Cohen LS, Grubb GS, Bergeron R, et al. Continuous oral levonorgestrel/ethinyl estradiol for treating premenstrual dysphoric disorder. Contraception. 2012;85(1):19-27.
40. Coffee AL, Kuehl TJ, Willis S, Sulak PJ. Oral contraceptives and premenstrual symptoms: comparison of a 21/7 and extended regimen. American journal of obstetrics and gynecology. 2006;195(5):1311-9.
41. Edelman AB, Gallo MF, Jensen JT, Nichols MD, Schulz KF, Grimes DA. Continuous or extended cycle vs. cyclic use of combined oral contraceptives for contraception. The Cochrane database of systematic reviews. 2005(3):CD004695.
42. Teichmann A, Apter D, Emerich J, Greven K, Klasa-Mazurkiewicz D, Melis GB, 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):504-11.
43. Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. Obstetrics and gynecology. 2003;101(4):653-61.
44. Miller L, Verhoeven CH, Hout J. Extended regimens of the contraceptive vaginal ring: a randomized trial. Obstetrics and gynecology. 2005;106(3):473-82.

6. Links to other College statements

Evidence-based Medicine, Obstetrics and Gynaecology (C-Gen 15)
http://www.ranzcog.edu.au/component/docman/doc_download/894-c-gen-15-evidence-based-medicine-obstetrics-and-gynaecology.html?Itemid=341

Appendices

Appendix A Women's Health Committee Membership

Name	Position on Committee
Associate Professor Stephen Robson	Chair and Board Member
Dr James Harvey	Deputy Chair and Councillor
Associate Professor Anusch Yazdani	Member and Councillor
Associate Professor Ian Pettigrew	Member and Councillor
Dr Ian Page	Member and Councillor
Professor Yee Leung	Member of EAC Committee
Professor Sue Walker	General Member
Dr Lisa Hui	General Member
Dr Joseph Sgroi	General Member
Dr Marilyn Clarke	General Member
Dr Donald Clark	General Member
Associate Professor Janet Vaughan	General Member
Dr Benjamin Bopp	General Member
Associate Professor Kirsten Black	General Member
Dr Bernadette White	General Member
Dr Jacqueline Boyle	Chair of the ATSIWHC
Dr Martin Byrne	GPOAC representative
Ms Catherine Whitby	Community representative
Ms Sherryn Elworthy	Midwifery representative
Dr Michelle Proud	Trainee representative

Appendix B Overview of the development and review process for this statement

i. Steps in developing and updating this statement

This statement was originally developed in November 2012 and was most recently reviewed in November 2015. The Women's Health Committee carried out the following steps in reviewing this statement:

- Declarations of interest were sought from all members prior to reviewing this statement.
- Structured clinical questions were developed and agreed upon.
- An updated literature search to answer the clinical questions was undertaken.
- At the November 2015 face-to-face committee meeting, the existing consensus-based recommendations were reviewed and updated (where appropriate) based on the available body of evidence and clinical expertise. Recommendations were graded as set out below in Appendix B part iii)

ii. Declaration of interest process and management

Declaring interests is essential in order to prevent any potential conflict between the private interests of members, and their duties as part of the Women's Health Committee.

A declaration of interest form specific to guidelines and statements was developed by RANZCOG and approved by the RANZCOG Board in September 2012. The Women's Health Committee members were required to declare their relevant interests in writing on this form prior to participating in the review of this statement.

Members were required to update their information as soon as they become aware of any changes to their interests and there was also a standing agenda item at each meeting where declarations of interest were called for and recorded as part of the meeting minutes.

There were no significant real or perceived conflicts of interest that required management during the process of updating this statement.

iii. Grading of recommendations

Each recommendation in this College statement is given an overall grade as per the table below, based on the National Health and Medical Research Council (NHMRC) Levels of Evidence and Grades of Recommendations for Developers of Guidelines. Where no robust evidence was available but there was sufficient consensus within the Women's Health Committee, consensus-based recommendations were developed or existing ones updated and are identifiable as such. Consensus-based recommendations were agreed to by the entire committee. Good Practice Notes are highlighted throughout and provide practical guidance to facilitate implementation. These were also developed through consensus of the entire committee.

Recommendation category		Description
Evidence-based	A	Body of evidence can be trusted to guide practice
	B	Body of evidence can be trusted to guide practice in most situations
	C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
	D	The body of evidence is weak and the recommendation must be applied with caution
Consensus-based		Recommendation based on clinical opinion and expertise as insufficient evidence available
Good Practice Note		Practical advice and information based on clinical opinion and expertise

Appendix C Full Disclaimer

This information is intended to provide general advice to practitioners, and should not be relied on as a substitute for proper assessment with respect to the particular circumstances of each case and the needs of any patient.

This information has been prepared having regard to general circumstances. It is the responsibility of each practitioner to have regard to the particular circumstances of each case. Clinical management should be responsive to the needs of the individual patient and the particular circumstances of each case.

This information has been prepared having regard to the information available at the time of its preparation, and each practitioner should have regard to relevant information, research or material which may have been published or become available subsequently.

Whilst the College endeavours to ensure that information is accurate and current at the time of preparation, it takes no responsibility for matters arising from changed circumstances or information or material that may have become subsequently available.