The efficacy of non-contraceptive uses for hormonal contraceptives

Ian S Fraser and Gabor T Kovacs

ABSTRACT

- In addition to providing safe and effective contraception, both the combined oral contraceptive pill (COCP) and selected long-acting progestogen-only contraceptives have significant health benefits. The COCP
  - ➤ may reduce menstrual blood loss, dysmenorrhoea and premenstrual syndrome;
  - ➤ unequivocally reduces the later incidence of endometrial and ovarian cancer;
  - ➤ appears to help protect future fertility, probably by reducing the risk of acute pelvic inflammatory disease, endometriosis and uterine fibroids.
- The quality of evidence for individual non-contraceptive health benefits of the COCP is very variable.

MJA 2003; 178: 621–623

THE COMBINED OESTROGEN–PROGESTOGEN oral contraceptive pill (COCP) was first marketed for the treatment of menstrual disturbances in 1957 in the United States.[1] With the steadily increasing popularity of "the pill" for contraception, anecdotal evidence began to accumulate for a range of beneficial health effects, and it became widely used (without rigorous supporting evidence) for treating various gynaecological symptoms.[2] Over time, it became clear that the COCP could provide health benefits for women in three ways: by providing highly effective contraception, treating some gynaecological symptoms, and preventing some gynaecological and medical conditions.[3] In recent years, good quality evidence has begun to accumulate for the non-contraceptive health benefits of some long-acting progestogen-only methods, such as depot medroxyprogesterone acetate[4] and the levonorgestrel intrauterine system (LNG-IUS; Mirena, Schering).[5]

Health benefits associated with use of hormonal contraceptives have not received the same degree of research or publicity as potential adverse effects, and the quality of evidence for such benefits is highly variable. It is probable that different COCPs and long-acting delivery systems (with different steroid combinations, dosages and routes of delivery) will provide varying degrees of benefit.

Treatment of gynaecological disease

Conditions that may respond to COCP treatment are listed in Box 1. The condition that responds best is primary dysmenorrhoea. While most of the evidence for this comes from studies with medium-dose (50 μg oestrogen) COCPs,[9] low-dose (20 μg oestrogen) COCPs are likely to have a similar effect.[10] The benefit is probably associated primarily with suppression of ovulation. Secondary dysmenorrhoea due to endometriosis or chronic pelvic inflammatory disease may also respond, to a lesser degree, to COCP treatment. One randomised, open-label study reported that the COCP was as effective as a gonadotrophin-releasing-hormone agonist in reducing dysmenorrhoea due to endometriosis, but less effective in reducing deep dyspareunia.[11]

Menorrhagia due to ovulatory dysfunctional uterine bleeding usually responds well to COCP treatment, whereas the response of menorrhagia caused by other conditions is quite variable.[11] The best evidence comes from studies with COCPs containing 50 μg oestrogen.[7] It is not clear whether the same level of benefit occurs with the lowest-dose pills currently available,[14] although a randomised placebo-controlled double-blind trial of COCPs delivering either 20 μg or 35 μg of oestrogen has shown that these dosages significantly reduce dysfunctional uterine bleeding.[8] Low-dose COCPs may have a particularly important role as contraceptives in perimenopausal women.[15] The use of COCPs tends to raise haemoglobin levels, especially in women with a convincing clinical history of menorrhagia, and reduce the severity of iron deficiency anaemia.[16]

The connection between hormonal secretions of the ovary and premenstrual syndrome was suggested as early as 1931,[17] and it has been common practice to treat premenstrual syndrome with the COCP to inhibit ovulation. However, no satisfactory controlled studies supporting the effectiveness of this treatment have been published.[12]

Acne responds well to treatment with most COCPs.[13] The mechanism of suppression of acne appears to involve partly a decrease in ovarian secretion of testosterone, partly an increase in the production of sex-hormone-binding globulin, and partly antiandrogenic effects (eg, with cyproterone acetate). Hirsutism is less likely to respond to COCPs, and usually requires substantially higher doses of an antiandrogen.[18]

The evidence that the COCP alleviates other cyclical symptoms, such as mid-cycle pain, perimenstrual migraine, menses-related epilepsy and rarer symptoms, is limited. Many of these conditions are so uncommon that randomised treatment trials are not feasible. The most effective approach to treating these conditions may be the continuous use of the COCP (ie, with no monthly break) or use of a

Department of Obstetrics and Gynaecology, University of Sydney, Sydney, NSW.
Ian S Fraser, MD FRANZCOG CREI, Professor in Reproductive Medicine.
Department of Obstetrics and Gynaecology, Monash University at Box Hill Hospital, Box Hill, VIC.
Gabor T Kovacs, MD FRANZCOG FRCOG, Professor of Obstetrics and Gynaecology.
Reprints will not be available from the authors. Correspondence: Professor Ian S Fraser, Department of Obstetrics and Gynaecology, University of Sydney, Sydney, NSW 2006. helena@med.usyd.edu.au

progestogen-only method that inhibits ovulation, provided that breakthrough bleeding is not a problem.[19]

Of the newer hormonal methods of contraception, the one that probably has the greatest health benefits is the levonorgestrel intrauterine system. After one year of use, this system, which involves local release of high concentrations of progestogen, produces a dramatic 95% reduction in measured menstrual blood loss in menorrhagia caused by ovulatory dysfunctional uterine bleeding.[20] It probably has similar effects in most women with menorrhagia due to *an*ovulatory dysfunctional uterine bleeding (including endometrial hyperplasia), small intramural fibroids and coagulopathies. Recent small-scale studies also indicate substantial symptomatic benefits with adenomyosis and endometriosis.[21,22] The menstrual effects of this therapy are discussed in more detail in an article by Hickey and Farquhar in this issue of the Journal (*page 625*).[23]

1: Evidence for treating symptoms with COCPs*

Symptom	Approximate proportion of sufferers whose symptoms are reduced by COCPs	NHMRC level of evidence[6]
Menorrhagia		
Ovulatory dysfunctional uterine bleeding[7,8]	60% (with 50 µg oestrogen COCPs)	II
Anovulatory dysfunctional uterine bleeding[7,8]	Uncertain	IV
Coagulopathy	Uncertain	IV
Uterine fibroids	Uncertain	IV
Iron deficiency anaemia	Uncertain	II
Primary dysmenorrhoea[9,10]	70% (with 50 µg oestrogen COCPs)	II
Secondary dysmenorrhoea[11]	40%	II
Premenstrual syndrome[12]	< 30%	III
Acne[13]	30%–80% (depending on formulation)	II
Hirsutism	< 10%	IV
Other cyclical symptoms	Variable	IV

COCP = combined oestrogen–progestogen oral contraceptive pill.
* There have been few randomised controlled trials of the effect of COCPs on these disorders. Much of the evidence comes from case–control and cohort studies, often with older and higher-dose preparations (similar studies using modern very low-dose [20 µg] COCPs are rare). References have not been included for uncommon conditions or weak associations.

2: Evidence for preventing gynaecological and other conditions with COCPs

Condition	Relative risk of developing condition after 5 years of COCP use*	Evidence for greater degree of protection with longer COCP use	NHMRC level of evidence[6]
Endometrial cancer[25]	0.4	Strong	III-2
Ovarian cancer[25]	0.6	Strong	III-2
Colon cancer	Evidence conflicting	Weak	IV
Acute pelvic inflammatory disease[27]	0.5	None	II
Endometriosis	0.7	Weak	III-2
Uterine fibroids[27]	0.8	Strong	III-2
Infertility[27]	0.5	Weak	III-2
Recurrent ovarian cysts[27]	0.5	Weak	III-2
Benign breast disease[27]	0.5	Strong	III-2

COCP = combined oestrogen–progestogen oral contraceptive pill.
* Changes in absolute risk cannot be reliably calculated.

Prevention of gynaecological and other disease

Possible small associations between the COCP and breast or cervical cancer have been given extensive publicity.[24] By contrast, the very large degrees of protection afforded COCP users against endometrial and ovarian cancer are much less well known. The long-term risk of ovarian cancer is reduced by 40% after 4 years of COCP use, 54% after 8 years and 60% after 12 years.[25] The risk of endometrial adenocarcinoma is reduced by 56% after 4 years of COCP use, 67% after 8 years and 72% after 12 years. Protection against these two forms of cancer continues for many years after discontinuation of COCP use,[25] and appears to be related to the progestogenic component of the pill.[26] There is also reasonably sound evidence from case–control studies that long-term use of the COCP provides some protection against the later development of uterine fibroids, endometriosis, recurrent ovarian cysts, acute pelvic inflammatory disease, infertility, iron-deficiency anaemia, benign breast lumps, toxic shock syndrome, premenstrual syndrome, acne and hirsutism.[27] There is less substantial evidence for beneficial effects in reducing the later incidence of thyroid disease, rheumatoid arthritis, duodenal ulcer and *Trichomonas vaginalis* infection, and in assisting long-term maintenance of bone mineral density.

Evidence of efficacy of the COCP in preventing other conditions is summarised in Box 2. Limited evidence is emerging to indicate that long-acting progestogen-only contraceptive methods will also offer some degree of protection against many of these conditions. We are confident that longer-term experience with the levonorgestrel intrauterine system will show that it provides substantial protection against endometrial hyperplasia[28] and cancer, but has little or no influence on ovarian cancer. The levonorgestrel intrauterine system may thus be an ideal contraceptive method for women who are perimenopausal or have risk factors for conditions such as polycystic ovary syndrome. These situations are commonly associated with anovulation and an increased risk of endometrial hyperplasia.

Data from individual studies as to whether depot medroxyprogesterone acetate and the levonorgestrel intrauterine system protect against acute episodes of pelvic inflammatory disease are conflicting.[29-31] Depot medroxyprogesterone acetate appears to help prevent recurrent vaginal candidiasis,[32] but it is too early to say what other conditions may be alleviated by long-term use of progestogen-only methods.

Conclusion

Over the past 40 years, information has gradually accumulated to show that a number of non-contraceptive health benefits should be an important part of the decision-making process about COCP use. The same will almost certainly apply to the newer long-acting progestogen-only methods. Awareness of these potential advantages of hormonal contraception may assist women in the increasingly complex matter of choosing a contraceptive method.[33]

Competing interests

The authors are both members of the independent Implanon Advisory Board. Ian Fraser has been a member of the Leiras International Reproductive Health Advisory Board and is currently a member of the International Committee for Contraception Research of The Population Council (New York). Gabor Kovacs is an occasional adviser to Schering and Wyeth Pharmaceuticals.

References

1. Diczfalusy E. Gregory Pincus and steroidal contraception: a new departure in the history of mankind. *J Steroid Biochem* 1979; 11(1A): 3-11.
2. Mishell DR. Non-contraceptive health benefits of oral steroidal contraceptives. *Am J Obstet Gynecol* 1982; 142: 809-818.
3. Fraser IS. Benefits and risks of steroidal contraception. In: Salamonsen L, editor. Hormones and women's health: the reproductive years. Amsterdam: Harwood Academic Publishers, 2000: 161-172.
4. Hickey M, Fraser IS. The contraceptive use of depot medroxyprogesterone acetate. In: Peterson CM, editor. Clinical use of progestins and androgens. *Clin Obstet Gynecol* 1995; 38: 849-858.
5. Sturridge F, Guillebaud J. Gynaecological aspects of the levonorgestrel-releasing intrauterine system. *Br J Obstet Gynaecol* 1997; 104: 285-289.
6. National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC, 2002. Available at: http://www.health.gov.au/nhmrc/publications/pdf/cp69.pdf (accessed May 2003).
7. Nilsson L, Rybo G. Treatment of menorrhagia. *Am J Obstet Gynecol* 1971; 110: 713-720.
8. Davis A, Godwin A, Lippman J, et al. Triphasic norgestimate-ethinyl estradiol for treating dysfunctional uterine bleeding. *Obstet Gynecol* 2000; 96: 913-920.
9. Kremser E, Mitchell GM. Treatment of primary dysmenorrhea with a combined type oral contraceptive: a double-blind study. *J Am Coll Health Assoc* 1971; 19: 195-199.
10. Proctor ML, Roberts H, Farquhar C. Combined oral contraceptive pill (OCP) as treatment for primary dysmenorrhoea (Cochrane Review). In: The Cochrane Library, 2003; Issue 2. Oxford: Update Software.
11. Vercellini P, Trespidi L, Colombo A, et al. A gonadotrophin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. *Fertil Steril* 1993; 60: 75-79.
12. Keye WR. Premenstrual syndrome. In: Fraser IS, Jansen RPS, Lobo RA, Whitehead MI, editors. Estrogens and progestogens and clinical practice. London: Churchill Livingstone, 1998: 387-403.
13. van der Vange N, Blankenstein MA, Kloosterboer HJ, et al. Effects of seven low-dose combined oral contraceptives on sex hormone binding globulin, corticosteroid binding globulin, total and free testosterone. *Contraception* 1990; 41: 345-352.
14. Iyer V, Farquhar C, Jepson R. Oral contraceptive pills for heavy menstrual bleeding (Cochrane Review). In: The Cochrane Library, 2003; Issue 2. Oxford: Update Software.
15. Kaunitz AM. Oral contraceptive use in perimenopause. *Am J Obstet Gynecol* 2001; 185 (2 Suppl): S32-S37.
16. Peterson HB, Lee NC. The health effects of oral contraceptives: misperceptions, controversies and continuing good news. *Clin Obstet Gynecol* 1989; 32: 339-355.
17. Frank RT. The hormonal causes of premenstrual syndrome. *Arch Neurol Psychiat* 1931; 36: 1053-1057.
18. Barth J, Cherry C, Wojnarowska F. Cyproterone acetate for severe hirsutism: results of a double-blind dose-ranging study. *J Clin Endocrinol Metab* 1991; 35: 5-10.
19. Kwiecien M, Edelman A, Nichols MD, Jensen JT. Bleeding patterns and patient acceptability of standard or continuous dosing regimens of a low-dose oral contraceptive: a randomised trial. *Contraception* 2003; 67: 9-13.
20. Andersson JK, Rybo G. The levonorgestrel-releasing intrauterine contraceptive device in the treatment of menorrhagia. *Br J Obstet Gynaecol* 1990; 97: 690-694.
21. Vercellini P, Ami G, Panazza S, et al. A levonorgestrel-releasing intrauterine system for the treatment of dysmenorrhoea associated with endometriosis: a pilot study. *Fertil Steril* 1999; 72: 505-508.
22. Fedele L, Bianchi S, Raffaelli R, et al. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device. *Fertil Steril* 1997; 68: 426-429.
23. Hickey M, Farquhar CM. Update on treatment of menstrual disorders. *Med J Aust* 2003; 178: 625-629.
24. Grimes DA. Breast cancer, the pill and the press. In: Mann RD, editor. Oral contraceptives and breast cancer. Carnforth, UK: Parthenon Publishing, 1995: 309-322.
25. Schlesselman JJ, Collins JA. The influence of steroids on gynecologic cancers. In: Fraser IS, Jansen RPS, Lobo RA, Whitehead MI, editors. Estrogens and progestogens in clinical practice. London: Churchill Livingstone, 1998: 831-864.
26. Rosenblatt KA, Thomas DB. Hormonal content of combined oral contraceptives in relation to the reduced risk of endometrial carcinoma. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer* 1991; 49: 870-874.
27. Drife JO. The benefits and risks of oral contraceptives today. 2nd ed. London: Parthenon Press, 1996.
28. Perino A, Quartararo P, Catinella E, et al. Treatment of endometrial hyperplasias with levonorgestrel-releasing intrauterine devices. *Acta Eur Fertil* 1987; 18: 132-140.
29. Ryden G, Fahreus L, Molin L, Ahman K. Do contraceptives influence the incidence of acute pelvic inflammatory disease in women with gonococcus? *Contraception* 1979; 20: 149-158.
30. Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova-T) IUDs during five years of use: a randomized comparative study. *Contraception* 1994; 49: 56-72.
31. Sivin I, Stern J. Health during prolonged use of levonorgestrel 20 microgram per day and the Copper T 380Ag intrauterine contraceptive devices: a multi-center randomized study. *Fertil Steril* 1994; 61: 70-77.
32. Dennerstein G. Depo-provera in the treatment of recurrent vulvo-vaginal candidiasis. *J Reprod Med* 1986; 31: 801-803.
33. Hannaford P, Webb A. Evidence-guided prescribing of combined oral contraceptives: a consensus statement. *Contraception* 1996; 54: 125-129.

(Received 29 Apr 2003, accepted 27 May 2003) ❑