

Therapeutic benefits of the estrogen component in combined hormonal contraceptives (beyond contraception)

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Introduction

While the negative effects of combined oral contraceptives (COCs) often receive considerable attention, their numerous positive effects are frequently underestimated and underreported. Estrogens play a crucial role in the non-contraceptive benefits of COCs, and selecting the appropriate oestrogen-progestin combination can help alleviate symptoms in various clinical scenarios [1].

The broader health benefits of COCs, beyond contraception, have been highlighted in reviews on their non-contraceptive effects [2,3]. For example, COCs can relieve a range of menstruation-related symptoms, including premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), heavy menstrual bleeding, dysmenorrhea, and irregular bleeding [1-3]. In cases with bleeding problems or dysmenorrhea, continuous use to avoid bleeding episodes is recommended [4,5]. Additionally, COCs may help reduce the frequency of migraines, particularly menstruation-related migraines [1,3].

COCs are effective in reducing pain associated with endometriosis, benefiting from post-operative continuous use of these regimens over cyclical [6-8], and can decrease menstrual bleeding in cases of fibroids, although there is no evidence that they affect fibroid size, either positively or negatively [9]. COCs mitigate symptoms of polycystic ovary syndrome (PCOS) by reducing ovarian androgen activity through pituitary suppression and by increasing hepatic production of sex hormone binding globulin (SHBG) and thereby lowering circulating free androgens [10]. Due to these antiandrogenic properties, COCs are also used to treat dermatological conditions such as hirsutism and acne [1].

Findings from systematic reviews and meta-analyses suggest that while the use of COCs may be associated with an increased risk of breast cancer and cervical cancer, it is associated with a reduced risk of endometrial cancer, ovarian cancer, and colorectal cancer [11,12]. The increases in breast and cervical cancer risk appear to be transient, returning to baseline within 5–10 years after discontinuation, with no late-emerging risks reported [13,14]. The protective effects against endometrial, ovarian, and colorectal cancer are substantial and long-lasting. Some of the apparent increases in breast and cervical cancer risk may also reflect detection bias from more frequent screening among users. Further details, including effect sizes, duration of protection, and differences across populations, are provided in Section 9.

Certain health benefits of COCs, including heavy menstrual bleeding and PMDD, have been recognised by regulatory authorities, with specific formulations receiving approval for therapeutic use. In the section below, an overview is provided of the effects of COCs on various diseases, with a focus on dermatological conditions, endometriosis, and PMDD.

Dermatological conditions

COCs are frequently prescribed for dermatological conditions such as acne and hirsutism, particularly in women with hyperandrogenic features such as PCOS [1]. The antiandrogenic properties of certain progestins, including drospirenone (DRSP) and dienogest (DNG), enhance the ability of these formulations to reduce sebaceous gland activity and control acne. A Cochrane review by Arowojolu et al. provides strong evidence that COCs containing estrogens are effective in improving facial acne in women [15]. Estrogens exert

this benefit by lowering circulating androgens through suppression of pituitary luteinising hormone and increasing SHBG, thereby reducing sebum production, a key factor in acne development. Most COCs studied contained ethinylestradiol (EE) paired with various progestins, including levonorgestrel, norgestimate, DRSP, DNG, and cyproterone acetate, all of which showed significant reductions in lesion counts compared to placebo.

It is worth noting that COCs containing progestogens with androgenic activity can exacerbate acne and other signs of androgenisation [16]. In contrast, COCs containing progestogens with antiandrogenic effects, such as DRSP, cyproterone acetate, chlormadinone acetate, DNG, and norgestimate, are more effective in improving acne and reducing seborrhoea and hirsutism [17-19]. The combination of DRSP with EE demonstrated particularly favourable outcomes, including a 29% greater improvement in total lesion count. In contrast, a formulation combining the natural estrogen estradiol (E2) with norgestimate showed less benefit, suggesting that synthetic EE may be more effective in acne treatment when paired with specific progestins. Although specific clinical trials evaluating the effect of estetrol (E4) on skin health are still underway, its combination with DRSP may confer benefits comparable to those of EE-containing regimens in acne management [1].

Furthermore, antiandrogenic formulations are also used for managing androgenetic alopecia, especially in premenopausal women. When oral contraceptives alone are insufficient, additional antiandrogens such as cyproterone acetate, spironolactone, or finasteride may be added [16]. Current evidence regarding the efficacy of COCs containing natural estrogens in reducing hirsutism is limited. Therapy targeting hirsutism should be administered for at least six months before re-evaluation, given the duration of the hair follicle growth cycle [20,21]. Overall, the estrogen component in COCs plays a crucial role in managing acne and hirsutism, although the choice of progestin and type of estrogen can significantly influence treatment efficacy.

Endometriosis

The findings from two recent studies collectively highlight the therapeutic potential of COCs containing natural estrogens, specifically E2 and E4, for managing endometriosis-associated pain [22,23]. In a large comparative study conducted between 2018 and 2023, five COCs and DNG monotherapy were evaluated for their effects on chronic pelvic pain, dysmenorrhoea, and dyspareunia [23]. All treatment groups showed significant pain reduction over six months; however, COCs containing natural estrogens (E2 or E4) demonstrated significantly greater improvements in symptoms compared to those containing synthetic EE. Notably, the combination of E4 15 mg and DRSP 3 mg

produced pain relief comparable to that of DNG, with superior outcomes compared to E2-based COCs at six months. Improvements were also more pronounced in dysmenorrhoea and dyspareunia for users of E2, E4, and DNG versus EE-based formulations, indicating that natural estrogens may offer a more effective and tolerable approach for women seeking non-pregnancy contraception and pain management [23].

Complementing these results, a double-blind, placebo-controlled study in Japan assessed the efficacy and safety of E4/DRSP in 162 women with endometriosis over 24 weeks [22]. E4/DRSP significantly reduced visual analogue scale (VAS) scores for the most severe pelvic pain by 33.2 mm from baseline, outperforming the placebo with a between-group difference of 8.5 mm (95% CI: -16.1 to -0.9 mm). Moreover, response rates, defined as $\geq 30\%$ and $\geq 50\%$ VAS reduction, were markedly higher in the E4/DRSP group than in the placebo group (53.2% vs. 29.6% and 36.4% vs. 12.3%, respectively). Gynaecological findings such as induration of the cul-de-sac, pelvic tenderness, and restricted uterine mobility improved significantly, as did patient-reported quality of life and global impression scores. The treatment also led to a reduction in endometrioma size. Importantly, no safety concerns or significant differences in haemostasis parameters were observed, suggesting a favourable safety profile [22].

Overall, COCs containing natural estrogens appear effective in reducing endometriosis-associated pain while also improving gynaecological health, quality of life, and safety outcomes. The consistency of findings across studies underscores the potential of E2- and E4-based COCs as well-tolerated alternatives to EE-containing formulations and DNG monotherapy, particularly for women seeking both contraception and relief from endometriosis symptoms.

Premenstrual dysphoric disorder

Premenstrual dysphoric disorder (PMDD) is a severe and disabling form of PMS, characterised by marked mood disturbances and physical symptoms that cyclically occur during the luteal phase of the menstrual cycle and interfere significantly with daily functioning, relationships, and occupational activities [24]. Unlike typical PMS, PMDD is clinically recognised as a mental health disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), placing it within the category of depressive disorders due to the intensity and impact of its emotional symptoms. Core features include extreme mood swings, irritability or anger, depressed mood or hopelessness, marked anxiety or tension, and cognitive difficulties such as poor concentration. Somatic complaints like bloating, breast tenderness, fatigue, or musculoskeletal pain often accompany these. Epidemiological studies estimate that PMDD affects 3–8% of menstruating individuals

worldwide, though prevalence can vary depending on diagnostic criteria and population characteristics [25]. Despite its global presence, PMDD remains underdiagnosed and undertreated, especially in low-resource settings where mental health services and awareness about menstrual-related disorders are limited.

A growing body of research underscores the importance of biopsychosocial approaches in understanding and managing PMDD, including the role of hormonal sensitivity, genetic predisposition, and psychosocial stressors [26]. For example, recent findings highlight a potential overlap between PMDD and attention-deficit/hyperactivity disorder (ADHD), with women with PMDD more likely to have comorbid ADHD and to experience heightened inattention across the menstrual cycle as well as phase-specific impulsivity, underscoring the importance of assessing ADHD comorbidity when evaluating or managing these symptoms [27].

COCs containing DRSP and EE in a 24-day active pill regimen followed by a 4-day hormone-free interval have been approved for the treatment of PMDD in several countries [28]. In the United States, the Food and Drug Administration has approved this specific formulation for the treatment of PMDD. In Europe, while this combination has been approved and marketed primarily as an oral contraceptive, its approval for PMDD treatment varies by country and specific indications. Although studies in China confirm its efficacy and safety for PMDD, its approval status there remains unspecified in the literature [29].

Conclusion

The therapeutic role of the estrogen component in COCs extends well beyond pregnancy prevention, offering meaningful benefits in dermatological conditions, endometriosis, PMDD, and cancer risk modulation. Natural estrogens (E2, E4) show promise in improving tolerability and broadening treatment options, while evidence from systematic reviews supports both risk awareness and protective effects in cancer outcomes. Continued research is needed to refine patient selection, clarify long-term safety, and establish the optimal integration of natural-estrogen COCs into clinical practice.

Gaps and Future Directions

More research is essential to confirm long-term safety, define the role of natural-estrogen COCs, and optimise individualised treatment strategies.

Need for larger trials to confirm benefits in endometriosis, dermatological conditions, and PMDD.

Comparative studies with EE-based COCs and non-contraceptive therapies are lacking.

Greater focus on individualised care and regulatory recognition of more non-contraceptive indications.



Key messages

COCs provide important health benefits beyond contraception, including relief from dermatological conditions, endometriosis-associated pain, and PMDD.

Natural estrogens (E2, E4) in COCs are associated with improved tolerability and symptom control compared with traditional EE-containing formulations.

Evidence supports the protective effects of COCs against endometrial, ovarian, and colorectal cancers, with transient increases observed for breast and cervical cancer risk.

Regulatory approvals for indications such as PMDD and acne highlight the recognised therapeutic value of specific COC formulations.

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