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The combined oral contraceptive pill- recent developments, risks and benefits

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The introduction of the birth control pill as an effective, coitally-independent method of contraception was a public health milestone of the last century. Over time, combined oral contraception (COC) formulations and pill-taking regimens have evolved with improved safety and tolerability while maintaining contraceptive efficacy. In addition to protection against pregnancy, use of combined oral contraception confers a number of significant non-contraceptive benefits to users. COC use is also associated with well-studied risks. Common side effects are generally self-limiting and improve with increasing duration of use while serious adverse events, including venous thromboembolism, are rare among healthy COC users. Contraceptive decision-making should include consideration of both the risks and benefits of a given method versus the real consequences of unintended pregnancy.

Introduction

The development of combined hormonal oral contraception has been hailed as one of the most important public health achievements of the twentieth century [1]. Since 1960, “the pill” has been used by hundreds of millions of women worldwide to prevent unintended pregnancy and its accompanying downstream consequences such as unsafe abortion and maternal morbidity and mortality. In 2013, the UNDP reported that 9% of women between the ages of 15 to 49 years who are married or in union use combined oral contraception (COC) [2]. Globally, COC is the second most commonly used form of reversible contraception and has the widest geographic distribution of all modern methods.

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Combined oral contraception confers a number of significant benefits to users. Not only do COCs offer safe, effective and reversible protection against pregnancy, but women also derive additional non-contraceptive health benefits from their use. COC use is also associated with well-studied risks. Common side effects are generally self-limiting and improve with increasing duration of use while serious adverse events, notably venous thromboembolism, are rare among healthy COC users. Contraceptive decision-making should include consideration of both the risks and benefits of a given method versus the consequences of unintended pregnancy.

Combined oral contraception: past, present and future

Correct, consistent use of COC interrupts the usual functioning of the hypothalamic-pituitary-gonadal axis by suppressing secretion of luteinizing hormone (progestogen) and follicle stimulating hormone (estrogen) to primarily prevent ovulation [3]. Additional contraceptive effects attributable to progestogen exposure include endometrial atrophy, cervical mucus thickening and decreased tubal motility. Although progestogens provide the dominant contraceptive benefit, estrogen importantly stabilizes the endometrium to minimize breakthrough bleeding and potentiates the action of progestogens, allowing lower doses for contraceptive protection [4].

While the early birth control pills provided effective protection against pregnancy, they were far from perfect. The first combined hormonal oral contraceptive pill contained high doses of both synthetic estrogen (mestranol 150 mcg) and progestogen (norethynodrel 10 mg) and use was associated with significant side effects and unacceptable cardiovascular health risks [5,6]. Subsequent modifications have maintained COC effectiveness while improving safety and tolerability. Additionally, the diverse formulations and variations in pill-taking regimens currently on offer provide expanded choices to women considering COC use.

Once the dose-dependent association between estrogens in COC and thromboembolism became apparent, COC with progressively lower doses were developed, resulting in significant decreases in venous thrombosis and cardiovascular risk [7,8]. Most available pills today are manufactured with 20 to 35 mcg of ethinyl estradiol (EE), but some containing EE doses as low as 10 mcg are available [9,10]. While there are no differences in contraceptive effectiveness among COC containing $\leq$ 20 mcg EE and higher dose (up to 50 mcg) pills, women using the former may discontinue more frequently and earlier as well as experience more bleeding disturbances [11]. Theoretically, the lower estrogen content might translate to further reductions in the rare risk of arterial and venous thromboembolism associated with modern COC use but this trend has not been consistently observed in large, population-based studies [12,13].

Contemporary COC typically contain EE paired with one of a number of progestational agents that vary in potency, affinity for steroid receptors, interaction with estrogens, and physiological effects [4]. Older progestins derived from testosterone (e.g. norethindrone, levonorgestrel) are typically associated with more androgenic side effects including acne, excess hair growth and altered carbohydrate and lipid metabolism. Newer progestins derived from progesterone and spironolactone (e.g. chlormadinone acetate, drospirenone) have been designed to bind more selectively to progesterone receptors and minimize androgenic, estrogenic and glucocorticoid side effects. In addition, some progestins, like drospirenone, have a partial antiandrogenic effect [14]. COCs containing 35 mcg EE or less in combination with any one of the existing progestins do not demonstrate obvious differences in contraceptive effectiveness, side effects, cycle control or continuation rates, but further studies are needed [15]. Whether or not there are differences in risk for venous thromboembolism (VTE) across COC formulations with various progestogens remains a point of debate [16,17].

Monophasic COC regimens provide a uniform dose of estrogen and progestin in all active pills during a cycle. In contrast, multiphasic COC vary the dose of either or both steroid hormones. The intention behind this innovation, initiated in the 1980s, was to reduce both total hormone exposure as well as side effects by producing cycles that more closely mimic normal physiology. Several systematic reviews have concluded, however, that multiphasic regimens do not offer superior contraceptive protection or clearly demonstrate any clinical advantage over monophasic formulations [18,19]. Rather, in the absence of greater benefits, use of monophasic regimens over multiphasic regimens may be preferred. Multiphasic COC require stricter adherence to a specific sequential pill-taking order given