A Primer on Combined Oral Contraceptives Across the Reproductive Lifespan

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Introduction

Canadian women may use combined oral contraceptives for many indications: contraception, dysmenorrhea, management of heavy menstrual bleeding, management of polycystic ovarian syndrome... the list goes on. A recent study showed that of Canadian women age 19-49 who used hormonal contraception, over half were using an oral contraceptive.[1] Most of those oral contraceptives were combined hormonal pills. Combined oral contraceptives are an appropriate choice for many women throughout their reproductive lives. This primer will address the use of combined oral contraceptives (COCs) across the reproductive years with comments on common clinical challenges during adolescence, peak reproductive years, and perimenopause.

Combined Oral Contraceptive Formulations

Combined oral contraceptives consist of a progestin (synthetic hormone related to progesterone or testosterone) and an estrogen. The progestin provides the bulk of the contraceptive efficacy through a variety of mechanisms including ovulation inhibition, thickening of cervical mucous, induction of endometrial atrophy, and slowing gamete transfer in the fallopian tube. The estrogen component provides a small contribution to ovulation inhibition, but its primary role is cycle control and predictable bleeding pattern.

Multiple progestins are available in COCs. They are often categorized by generation, with the newer generations (desogestrel, drospirenone) having fewer androgenic effects and increased overall tolerability compared to older generations (norethindrone, levonorgestrel).[2]

In Canada, only two estrogens are available in COCs. They are ethinyl estradiol (EE), a synthetic version of estradiol, and estetrol (E4), a plant-based derivative of a natural human estrogen. While these two estrogens both have a long half-life and contribute to cycle control, these two estrogen forms differ primarily in their interaction with cell receptors. EE binds and interacts with both nucleus and cell membrane receptors. Estetrol is an agonist on nuclear estrogen receptors and has antagonistic or neutral activity on membrane estrogen receptors in the liver and breast.[3]

Non-contraceptive Benefits and Contraindications

In the absence of contraindications, COCs can be used by women seeking a reliable, reversible, coitally independent method of contraception. It may be especially suited to women who require the non-contraceptive benefits. Non-contraceptive benefits may include:

Cycle regulation with predictable withdrawal bleeds
Decreased menstrual flow
Decreased anemia associated with menstrual bleeding
Increased bone mineral density, especially during the later reproductive years
Decreased dysmenorrhea
Decreased perimenopausal symptoms
Decreased acne and hirsuitism
Decreased endometrial and ovarian cancer
Decreased risk of fibroids
Fewer functional ovarian cysts
Lower risk of benign breast disease
Decreased risk of colorectal cancer
Decreased incidence of salpingitis
Decreased incidence of severe PMS and PMDD
Reduced pelvic pain and less recurrence of dysmenorrhea and endometriomas associated with endometriosis

Adapted from Black et al. 2017[20]

Contraindications to COCs

The absolute contraindications for COCs are the following:

Postpartum for less than 21 days with other risk factors for venous thromboembolism (VTE)	Severe (decompensated) cirrhosis
Breastfeeding from less than 6 weeks postpartum	Malignant liver tumours
Age 35 or older and smokes ≥15 cigarettes/day	Hepatocellular adenoma
Vascular disease	Known thrombogenic mutation
Hypertension systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg	Current and history of ischemic heart disease
History of acute deep vein thrombosis/pulmonary embolism (DVT/PE)	Stroke
DVT/PE and established on anticoagulant therapy	Complicated valvular heart disease (pulmonary hypertension
Major surgery with prolonged immobilisation	Risk of atrial fibrillation
Migraine headaches with aura (at any age)	History of subacute bacterial endocarditis
Current breast cancer	Systemic lupus erythematosus (SLE) with positive (or unknown) antiphospholipid antibodies

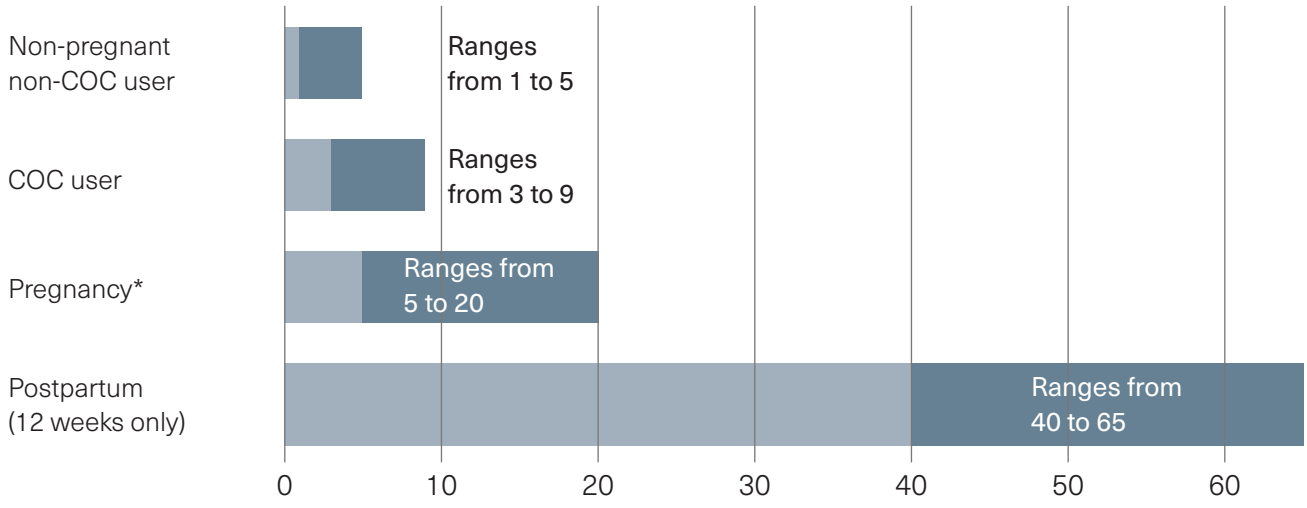
Adapted from WHO 2015[21]

Important Considerations: Risk of VTE and Tolerability

Safety: VTE risk

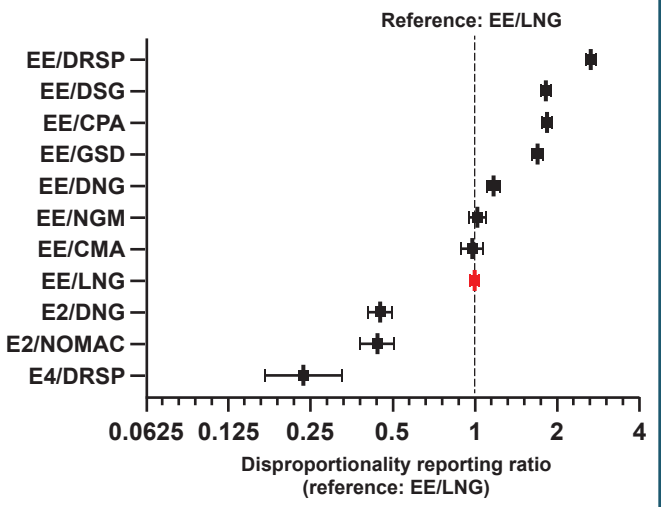
It did not take long after the introduction of COCs in the 1960's for clinicians to realize that there was an increased VTE risk associated with use. Although VTE is rare in healthy young individuals, the risks associated with pregnancy and post-partum are well recognized. The background risk of VTE for individuals of reproductive age is 1-5 per 10,000 women years. Increasing age increases the risk. During pregnancy, this risk rises to 5-20 per 10,000 women years, and post partum the risk is 40-65 per 10,000 women years. Against this backdrop of very increased risks related to pregnancy, most clinicians will accept a VTE risk of 3-9 per 10,000 women years for users of ethinyl estradiol COCs.[4] (See Figure 1)

A European study examined the reporting rates of VTE from the EudraVigilance database up to July 2024 including COCs with natural estrogens (estradiol [E2] and estetrol [E4]) and synthetic estrogen-based COCs (ethinylestradiol [EE]). Researchers calculated how often VTEs were reported relative to all reported side effects for each type of COC. COCs containing natural estrogens had lower reporting rates of VTEs compared to COCs with EE. The E4-drospirenone combination had a reporting rate of 0.07.[5] The lowest reporting rate was the progestin only (DRSP) method. (Figure 2)



* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy is 9 months, the rate is 7 to 27 per 10,000 WY.

Figure 1. Risk of VTE Across Reproductive Years (per 10,000 women years) Chen et al., Contraception, 2022



CMA = chlormadinone acetate; CPA = cyproterone acetate; DNG = dienogest; DRSP = drospirenone; DSG = desogestrel; GSD = gestodene; LNG = levonorgestrel; NGM = norgestimate; NOMAC = nomegestrol acetate.

Figure 2. Disproportionality reporting ratios and their 95% CIs for each estroprogestative combination.

In the Phase 3 clinical trials for E4/DRSP contraceptive, there was one VTE event recorded during the trial, rendering an estimate of 3.66 per 10,000 women years of use.[6,7] Caution must be taken in the interpretation, as only 2735 women years of exposure was included in the study.[6,7]

Tolerability: Bleeding pattern

Changes in bleeding pattern are common in the first few months of use of a COC, and bleeding irregularities are often cited as the primary reason for discontinuation.[8] It is the role of the estrogen in a COC to support the endometrium and provide a more predictable bleeding pattern.

COCs with higher ethinyl estradiol doses tend to have more predictable bleeding patterns[9] but the trade off may be more estrogen related side effects such as mastalgia. Products containing natural estradiol (not available in Canada) may have greater amounts of unscheduled bleeding secondary to the short half-life of estradiol[10]. Estetrol-containing oral contraceptive pills (OCPs) show a high rate of scheduled bleeding and a low rate of unscheduled bleeding[11] while maintaining good tolerability[12].

Special populations:

Adolescents

Dysmenorrhea (painful menstruation) and heavy menstrual bleeding is common in adolescents, with up to 75% experiencing dysmenorrhea affecting quality of life, and over 20% experiencing heavy menstrual bleeding[13]. COCs have shown efficacy in the management of dysmenorrhea, and are recommended therapy in the SOGC dysmenorrhea guidelines.[14] There is little in the literature to support or differentiate choice of COC for this indication. In a recent publication in this field, a phase 3 open-label study of 105 adolescents age 12-17 trialed E4/DRSP for 6 months. In this group, dysmenorrhea pain reduced by 34.8%, and use of pain medication dropped from 63.9% of subjects to 31.6%.[15]

Frequently asked is the impact of COCs, and specifically estrogen dosing, on adolescent bone health. It is widely accepted that use of a COC in adolescence results in a lower peak bone mass. Whether or not this directly impacts risk of osteoporotic fracture is under study. A prospective Canadian study of adolescents and young women demonstrated that age at initiation of OCPs was not related to bone mineral density (BMD) changes. This same study also did not demonstrate a difference in BMD between those who used 30 µg pills and higher vs those who used sub-30 µg pills.[16] This data does not support the Canadian Pediatric Society Position Statement on Contraceptive Care for Canadian Youth, where the recommendation was made that adolescents should be preferentially prescribed COCs containing 30 to 35 µg of ethinyl estradiol to reduce the impact on bone health.[17] The reference for this recommendation was older data. In the face of conflicting information, until there can be alignment, it is left to the clinician to use their clinical judgement when choosing a product or dose.

Perimenopausal women

Perimenopause begins when cycles become irregular and terminates at the twelve month anniversary of the final menstrual period. During the early perimenopause (defined by cycle duration which differs by at least 7 days from the previous cycle up to 59 days of amenorrhea) and later perimenopause, which is defined by cycles that are 60-364 days apart.[18] During this time, it is estimated that 90% of women will experience at least one symptom for which they will consult a health care provider. Symptoms may include vasomotor symptoms, abnormal uterine bleeding, sleep and mood changes, and vaginal dryness and sexual concerns.

The hormonal physiology of the early perimenopause is one of loss of pituitary inhibition, resulting in widely fluctuating levels of estradiol and aberrant ovarian function. High estradiol levels are responsible for some symptoms (frequent menses, heavy menstrual bleeding, mastalgia) while low estrogen levels may be responsible for other symptoms (ie vaginal dryness). It is the rapid changes in levels which is felt to precipitate the vasomotor symptoms.

For those whose treatment goals are cycle control, contraception and symptoms relief, a combined hormonal contraceptive is recommended, if contraindications don't exist. For those in the early perimenopause who have a contraindication to estrogen, use of a drospirenone-only pill to suppress ovulation may be successful. A

levonorgestrel intrauterine system (IUS) may be helpful for heavy bleeding and contraception, but as it does not suppress ovulation is unlikely to assist with estrogen excess symptoms.

In the late perimenopause, the hormonal physiology is that of low estradiol levels. COCs or cyclical menopause hormone therapy may provide symptoms relief.[19] Cyclical menopausal hormone therapy (MHT) is not contraceptive.

Summary

Combined hormonal contraceptives may play varying roles across a woman's lifespan: dysmenorrhea and cycle control in adolescence, contraception and management of heavy menstrual bleeding in the peak reproductive years, and management of perimenopausal symptoms including vasomotor symptoms and bleeding abnormalities.

Safety, specifically venous thromboembolic risk, should be a primary consideration when using COCs for any reason, but especially when using for non-contraceptive benefits in the absence of pregnancy risk.

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