



## The Role of Low Dosage Combined Oral Contraceptive Pill in Perimenopausal Women

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### ABSTRACT

The perimenopausal period refers to the time period of the menstrual cycle and endocrine changes. Usually, it starts with a variation in the menstrual cycle length and ending with FMP. The rates of unwanted pregnancies for these women are reported to be around 40–45%. Thus, contraceptive counselling and contraceptive use among perimenopausal women are important aspects of their overall health care if they are sexually active and do not wish to become pregnant. One of them is by using low dose combined oral contraceptive pill containing ethynylestradiol (EE) containing less than 50 µg EE/day. It acts by suppressing gonadotropin. There are several positive effects of COC, namely pregnancy prevention; regulation of menstrual cycle; relieving menopausal symptoms; bone protection; protection against ovarian, endometrial and colorectal cancer; lipid metabolism; and blood pressure lowering effect. In contrast, the negative effects of COC are increases the risk of breast cancer, venous thromboembolism, and myocardial infarction. We presented a literature review to describe the usage of low dosage combined oral contraceptive pill as one of contraception method in perimenopausal women, including its positive and negative effects.

### 1. Introduction

Women in midlife are a dynamic and empowered group. Many still desire pregnancy while others have moved on to another stage of their lives.<sup>1</sup> Menopause is a normal physiological event, defined as the final menstrual period (FMP) and reflects the loss of ovarian follicle function and ovulation.<sup>2,3</sup> The menopausal transition, also known as 'perimenopause', refers to the time period of the menstrual cycle and endocrine changes. Usually, it starts with a variation in the menstrual cycle length and ending with FMP, but also refers to the time from the onset of menopause-related symptoms until 1 year after FMP.<sup>2,4</sup> The onset of menopause varies in each individual, influenced by environmental, ethnic, and genetic factors, but usually ranges from 45 to 55 years of age. In the US, the average age at the onset

of menopause is 51 years.<sup>2,5</sup>

The Massachusetts women's health study used the onset of episodes of irregular bleeding after the age of 45 to describe the onset of perimenopause.<sup>5</sup> Another systematic review discussing the accuracy of diagnosis in women over 40 years of age and with irregular bleeding suggested that no symptoms or laboratory studies were found can support or rule out a diagnosis of perimenopause. The symptoms experienced include various gynecological conditions such as irregular menstruation, unpredictable menstruation, prolonged or shortened menstrual cycles, vaginal dryness and non-gynecological problems such as hot flashes, night sweats, decreased libido, mood swings, headache, and bladder symptoms.<sup>2,5</sup>

Although the menopausal transition may be

associated with decreased libido for some women, women at this age continue to be sexually active and therefore require contraception if they choose not to become pregnant. Fertility rates decline for women with advancing age, with a rapid decline during the fifth decade of life.<sup>2</sup> This results not only from the decreased fertility (likelihood of pregnancy per ovulation) but also from the increased rate of subclinical abortion that is observed with advanced age. The National Survey of Sexual Attitudes and Lifestyles (NATSAL) in 2013 showed that 1 in 5 pregnancies, when the mother was 40 years or older, was unplanned and 28% of these pregnancies ended in termination.<sup>6</sup> This phenomenon reflects changes in oocyte quality rather than receptive endometrial conditions. In addition, negative conditions that affect fertility, such as endometriosis and leiomyoma, are not uncommon in women in the fifth decade.<sup>5</sup>

Nonetheless, the rates of unwanted pregnancies for these women are similar to those observed in other age groups, reported to be around 40–45%.<sup>2,5</sup> Therefore, women who are sexually active at all ages and are not menopausal at risk for getting pregnant. Thus, contraceptive counselling and contraceptive use among perimenopausal women are important aspects of their overall health care if they are sexually active and do not wish to become pregnant.<sup>2</sup> Meanwhile, combined hormonal contraception must be stopped from women aged over 50 years.<sup>7</sup>

We presented a literature review to describe the usage of low dosage combined oral contraceptive pill as one of contraception method in perimenopausal women, including its various positive and negative effects.

### **Combined Oral Contraceptives (COC) Pill**

Since the introduction of COCs (COCs) in the early 1960s, there has been a trend to decrease estrogen and progestin doses and introduce progestins with fewer side effects.<sup>5</sup> Progestins have been modified to increase tolerability and reduce side effects, often using lower doses or less androgenic progestins. With regard to the estrogen component, ethinylestradiol (EE) is most commonly used, with an initial dose as

high as 100 µg but now reduced to 10 µg daily. Historically, COC containing less than 50 µg EE/day was considered 'low dose', with nearly all current pills containing 35 µg EE/day or less. Interestingly, any clinical benefit regarding the safety or tolerability of using the lowest dose formulation (10-20 µg EE) compared to regimens containing up to 35 µg EE remains unfounded. However, regimens containing low doses of EE in a shorter hormone-free regimen (24 days active hormone/4 days hormone free) have been shown to be more effective than conventional regimens (21 days active hormone/7 days hormone free).<sup>2</sup>

Estradiol (E2) has recently been included in the COC regimen as a substitute for EE, although there is no clinical evidence showing E2 pills to differ from pills containing EE in terms of safety or effectiveness. In general, any regimen containing estrogen, regardless of the type of estrogen, dose, or progestin combined with it, should be considered to have the same benefits and safety concerns, without any particular method being considered 'safer' than others. Combined oral contraceptives provide very effective contraception when used consistently and correctly. The use of perfect contraception is associated with one of the lowest failure rates among all contraceptive options, approximately 0.3% in the first year of use. Typical use failure rates may be as high as 8%, often due to non-adherence to the dosage regimen.<sup>2,5</sup>

In 2016, the Centers for Disease Control and Prevention (CDC) presented guidelines, based on currently published evidence, regarding which contraceptive methods can be used safely when various medical conditions are present. In these guidelines, contraceptive methods are categorized as follows: category 1, when a suitable contraceptive method can be used without restriction; category 2, when the benefits generally outweigh the risks if the appropriate contraceptive method is used; category 3, when the risks outweigh the benefits when an appropriate contraceptive method is used; and category 4, when an appropriate contraceptive method should not be used. In these guidelines, the

only age limit for COC use is for women 35 years of age or older who smoke 15 or more cigarettes per day. Thus, age in itself is not a contraindication to combined oral contraceptives and the guidelines state that COC can be used until menopause. However, women under 40 were included in category 1 (unlimited use), while age 40 or over was included in category 2. Age 40 was used as the limit value because of the risk of several diseases, including cardiovascular disease, increases with age and the risk can increase even more when taking COC. Therefore, when considering the use of COC, as with women in other age groups, those aged 40 years or over should be checked for any disease that is contraindicated for COC and the risk factors associated with it, including obesity, hypertension, and cardiovascular disease or other risk factors such as smoking.<sup>8</sup>

### **The Mechanism of Action of Combined Oral Contraceptives**

Combined oral contraceptives suppress gonadotropins. The estrogen component prevents the increase in Follicle Stimulating Hormone (FSH), while the progestin component inhibits Luteinizing Hormone (LH). This dual-action causes inhibition of follicular development and ovulation. The lowest amount of progestin required to suppress LH is known as the ovulation inhibition dose. Changes in the cervical mucus (which prevents the transport of sperm into the uterus), the fallopian tubes (which interfere with the transport of gametes), and the endometrium (which reduce the likelihood of implantation) are other important contraceptive effects of the progestin component. Because the progestin dose is below the ovulation inhibition dose in the mini pill, this other mechanism becomes the main mechanism. With both types of formulations, neither gonadotropin production nor ovarian steroidogenesis can be completely eliminated. Endogenous E2 levels in peripheral blood during high-dose COC consumption are similar to those found in the early follicular phase of the normal cycle.<sup>9</sup>

Steroid contraceptives prevent ovulation primarily by interfering with the release of Gonadotropin Releasing Hormone (GnRH) from the hypothalamus. Most research also supports that steroid contraception directly affects the pituitary. Immediate pituitary inhibition occurs in about 80% of women taking high doses of COC. Pituitary suppression was not related to the woman's age or duration of steroid use but to formulation potency. The effect was more pronounced with formulations containing the stronger progestin and with those containing 50 µg or more of estrogen compared with 30 to 35 µg of estrogen. It has not been shown that the amount of pituitary suppression is associated with the development of amenorrhea after discontinuing oral contraceptive use, but if there is a relationship, low-dose formulations should be associated with a lower frequency of these events. Some data suggest that the meantime of conception after discontinuation of oral contraceptives is shorter in women taking preparations with less than 50 µg of estrogen than in those taking formulations with 50 µg of estrogen or more.<sup>9</sup>

Progestin-only daily preparations do not consistently inhibit ovulation. They used contraceptive measures via the other mechanisms mentioned earlier, but because of the inconsistent inhibition of ovulation, their effectiveness was lower than the combination pill. Physicians should advise their patients who are taking the mini pill that the preparations must be made consistently at the same time to ensure that blood levels do not fall below the level of effective contraception.<sup>9</sup>

Although the reported Pearl Index of the various formulations differed slightly, no significant difference in clinical effectiveness has been demonstrated among the various combination formulations currently available in the United States. As long as no tablets are missed (complete use), the pregnancy rate is approximately 0.3% at the end of the first year with all marketed combination formulations. In typical use, the failure can range as high as 8% .<sup>2,5,9</sup>

The balance between estrogen and progestin

affects the bleeding profile of COC. Estrogen induces endometrial proliferation. Progestins counter the mitotic action of estrogens, leading to a stable decidual endometrium. Although women who use COC are exposed to both hormones at the same time rather than consecutively, they will usually undergo some endometrial proliferation. Bleeding that COC users experience during the hormone-free interval is called withdrawal bleeding. Therefore, it occurs after discontinuation of the progestin component of the pill. Bleeding that occurs while the pill is being actively used is called unscheduled, intracyclic, or breakthrough bleeding. The dose of progestin used in the mini pill is below the dose for inhibiting ovulation. Therefore, the estradiol and progesterone produced by the ovaries will affect endometrial bleeding. Withdrawal bleeding will be inhibited and the bleeding pattern may be very irregular depending on the effect of synthetic progestins on the endometrium.<sup>9</sup>

#### **Positive effects of combined oral contraceptives.**

##### **Pregnancy prevention**

The most basic goal of using COC is pregnancy prevention. Perimenopausal women often believe that they cannot get pregnant or that they no longer need to use contraception. However, perimenopausal women still experience fecundity, even though their pregnancy rates tend to be low. According to a 2014 report by the Korea Women's Development Institute, the percentage of unwanted pregnancies among women aged 40 years or over was 26.9%, higher than 3.3% and 17.88%, found in those aged 20-s and 30-s respectively. In other words, contraception is necessary if pregnancy was not intended, even during perimenopause. The CDC guidelines also state that women over 44 years of age should continue to use contraception if they do not wish to become pregnant, as well as recommendations from the American Society for Reproductive Medicine (ASRM) and the North American Menopause Society (NAMS) showed that contraception should be used up to 12 months after the last menstrual period.<sup>10</sup>

#### **Regulation of the menstrual cycle**

About 90% of women experience a change in menstrual patterns during the 4-8 years before final menopause. These changes can include shorter or longer menstrual cycles, as well as premenstrual spotting, excessive menstrual bleeding, and/or unexpected bleeding. In such cases, as long as other causes are eliminated, the menstrual cycle can be controlled effectively using COCs in 80% of cases. 30-35 µg of ethinylestradiol is recommended, because use of COCs containing 20 µg of ethinylestradiol results in a significantly higher incidence of irregular bleeding and discontinuation of drugs due to irregular bleeding compared to use of COCs containing 30-35 µg of ethinylestradiol.<sup>10</sup>

The peak incidence for heavy menstrual bleeding occurs in the late 40s. Combined oral contraceptives can reduce the amount of menstrual bleeding by about 40%. Suitable combined oral contraceptive pills includes the combination drug estradiol valerate/dienogest that is approved by the United States Food and Drug Administration (FDA) for the treatment of heavy menstrual bleeding. In 70% of those using this drug, the combination estradiol/dienogest can reduce the amount of menstrual bleeding by more than 50%. Monophasic pills containing ethinylestradiol can also be used. In such cases, the standard regimen with 21-24 days of drug administration followed by a 4-7 day pill-free interval is replaced by increasing the pill-free interval to every 3 months or continuing drug administration for 6 or 12 months to reduce the amount of menstrual bleeding. However, if the pills are taken continuously, unexpected bleeding can occur as the administration period increases. In this situation, the amount of menstrual bleeding can be reduced effectively by using an adapted regimen, in which COC is used until bleeding occurs, and if bleeding continues for more than 3 days, the drug is stopped for 3-4 days.<sup>6,10</sup>

#### **Relieving menopause symptoms**

Combined oral contraceptives can reduce menstrual pain, so prolonged or prolonged treatment may be more effective. An extended or sustained

regimen can also be useful for controlling headaches associated with menstruation or premenstrual syndrome.<sup>10</sup> All COC is useful for relieving symptoms of estrogen deficiency such as vasomotor instability and vaginal dryness associated with hormonal fluctuations that are characteristic of the menopausal transition.<sup>2,5,10</sup> Vasomotor symptoms appear during the pill-free interval, estrogen can be added during the pill-free interval or an adjusted extended or continuous regimen can be used.<sup>9</sup> COC pills can also reduce the incidence of hot flashes.<sup>6,8</sup> Studies in Chinese women have shown improvement in menopausal symptoms based on the Kupperman score after treatment with drospirenone-estradiol at 1, 3, and 6 months.<sup>11</sup>

### **Bone protection**

The imbalance between bone formation and bone resorption starting in the mid-twenties, bone loss accelerates in the early years of menopause, although at varying rates.<sup>5</sup> After 40 years of age, bone mineral density (BMD) is known to decrease by 1% every year, and if women in their 40s use COC, they will be able to maintain their BMD. Women who used COC at least 6 years before menopause had significantly increased postmenopausal BMD in the femur and lumbar vertebrae, compared with those who did not use COC. Although there are not many studies discussing whether the use of premenopausal COC reduces the risk of postmenopausal bone fracture, it has been reported that taking COC, especially after the age of 40 years, reduces the risk of postmenopausal hip fracture by 30%.<sup>9</sup> Retrospective case control study at Sweden showed the same result, a 25% reduction in hip fracture risk for women aged 50-81 years using COC.<sup>4</sup> A prospective trial of 64 postmenopausal women in China who took one tablet containing 1.0 mg of estradiol and 2.0 mg of drospirenone once daily for 6 months showed improvement in BMD of the lumbar vertebrae and hip at 6 months post-treatment. After 3 and 6 months of treatment, the post-treatment bone turnover index also increased.<sup>11</sup>

### **Protection against ovarian, endometrial and colorectal cancer**

Combined oral contraceptives have been associated with a reduced risk of epithelial ovarian, endometrial, and colorectal cancers, although these benefits are best realized when COC is started earlier in the reproductive years.<sup>2,5</sup> This effect occurs immediately after administration and increases proportionally with the duration of use. Even after the drug is stopped, the effects can last for 30 years. The preventive effect against ovarian epithelial cancer also appears within the first year of drug administration, increases proportionally to the duration of use, and persists for 20-30 years after discontinuation. Even though the duration of drug administration was less than 1 year, the risk reduction effect was maintained for 20 years after discontinuation. Using COC can also reduce the risk of colorectal cancer by about 20%. Because the incidence of cancer increases with age, the preventive effect of COC on cancer can be considered very important especially for middle-aged women.<sup>10</sup>

### **Lipid Metabolism**

When metabolic effects were evaluated in COC users over 40 years of age, no clinically significant changes were observed. Although many studies confirm the safety of using COC among women with controlled diabetes or dyslipidemia, the American College of Obstetricians and Gynecologists (ACOG) recommends avoiding the use of COC in women over 35 years of age. During perimenopause, women may be more concerned about possible weight changes. Although studies discussing the effects of using COC on body weight are still controversial, a recent Cochrane review found no evidence of a significant effect of COC on the weight gain. However, there are no relevant data for the perimenopausal age group.<sup>5</sup>

Studies in Chinese women taking drospirenone-estradiol one tablet a day showed the concentrations of total cholesterol, triglycerides, and LDL cholesterol were significantly reduced compared to pre-treatment levels at 1, 3 and 6 months after treatment. After 1, 3 and 6 months of treatment, the mean HDL

cholesterol concentration increased significantly from the pre-treatment level of  $2.0736 \pm 0.3935$  mmol/l, to  $2.2670 \pm 0.4172$  mmol/l,  $2.5845 \pm 0.5447$  mmol/l, and  $2.7302 \pm 0.488786$  mmol/l, respectively. There are many studies that have shown that estrogen replacement therapy in postmenopausal women can lower total cholesterol and LDL cholesterol concentrations, but has no effect on triglycerides or HDL cholesterol concentrations, and can even lead to elevated triglycerides. Although progesterone is usually considered to have a weakness in lipid metabolism, research showed that after 6 months of drospirenone-estradiol treatment, levels of total cholesterol, triglycerides, and LDL cholesterol are significantly lower than pre-treatment values, and HDL cholesterol concentrations are significantly higher than the value before treatment. This change in lipid parameters was also statistically significant after 1 month of treatment, which is consistent with findings from previous studies. The addition of the progestin drospirenone to estradiol not only does not have a harmful effect on lipid metabolism, it can also counteract the elevated triglyceride levels associated with estradiol alone.<sup>11</sup>

Another observational study in Modena and Naples demonstrated weight loss, fat mass and waist-to-hip ratio in 36 women taking estradiol valerate/dienogest, leading to speculation that estradiol/dienogest exerts beneficial effects on the health of perimenopausal women. The study was conducted over a period of 12 months, so further research is needed to evaluate the long-term effects of estradiol valerate/dienogest on women's body composition during the menstrual transition period.<sup>12</sup>

### **Blood pressure-lowering effect**

The mechanisms responsible for the increased blood pressure (BP) in postmenopausal women are not completely clear, Experimental and clinical evidence suggests a role for female hormones, androgens, salt sensitivity, oxidative stress, the renin-angiotensin-aldosterone system (RAAS) and endothelin. The reduction in BP is a major clinical

benefit in postmenopausal women, which provides a significant reduction in stroke and coronary events. Conventional hormonal therapy causes sodium and water retention and hypertension in susceptible women.<sup>13</sup>

The drospirenone-estradiol combination as a hormone therapy has a clinically significant BP-lowering effect in postmenopausal women with hypertension, consistent with the antiminerocorticoid properties of drospirenone. These clinically relevant BP decreases are within the range of reductions seen with several classes of antihypertensive agents. The combination of drospirenone 2 mg and estradiol 1 mg appears to be the lowest effective dose providing clinically relevant BP reduction. The combination has an attractive tolerability profile compared to conventional progestogens because of its positive effect on body weight and sodium excretion.<sup>13,14,15</sup>

### **Negative effects of combined oral contraceptives.**

#### **Increases the risk of breast cancer**

COC users had a slightly increased risk of developing breast cancer (OR 1.5) compared to nonusers, but decreased risk after treatment discontinuation.<sup>5</sup> Recent studies of COCs with lower doses of estrogen have reported that breast cancer risk is associated with lower COC than previously reported (RR = 1.08).<sup>9</sup> The use of COC did not increase the overall cancer risk and did not increase the risk of death from cancer.<sup>6</sup> The possible link between COC and breast cancer becomes particularly important during perimenopause, when the incidence of breast cancer is increasing. Epidemiological data show that the use of COC, as in pregnancy, can accelerate the growth of existing breast cancer nidus.<sup>4</sup> The use of COC is not contraindicated in women with benign breast disease or those with first-degree relatives with breast cancer.<sup>5,6</sup>

#### **Venous thromboembolism (VTE)**

While the pill contains estrogen, there is a

potential for increased risk of thromboembolic events which perimenopausal women should be informed of before starting treatment.<sup>2</sup> The risk of venous thromboembolism (VTE) increases in proportion to the dose of estrogen in combination pills.<sup>5</sup> In nonhormonal contraceptive users, 2 per 10,000 women per year.<sup>6</sup> Decreasing the dose of estrogen in COCs results in a slightly reduced risk of VTE due to COC. However, the risk is still around 3-6 times higher than that of non-users. Venous thromboembolism can cause serious outcomes, and therefore, this should be clarified before drug administration.<sup>10</sup>

The risk of VTE increases with age, increasing exponentially over the course of 50 years of age. The risk is highest in the first few months after starting COC; the incidence then decreased during the first year of use. The risk of VTE increases again when restarting COC after a short break of 1 month and therefore continuing COC is safer than stopping and resuming treatment.<sup>6</sup> Other risks associated with VTE among users of COC include obesity, smoking, general poor health and asthma.<sup>5</sup>

Two of the third-generation progestins used in some COC preparations, desogestrel, and gestodene, were involved in a higher (two to threefold) risk of VTE, whereas pills containing levonorgestrel, norethisterone, and norgestimate had the lowest risk.<sup>5,6</sup> This can be influenced by other variables such as age and prescribing bias. There are not enough comparative data among the progestins currently on the market that are sufficient to make recommendations regarding the specific progestin COC component recommended during perimenopause.<sup>6</sup>

### **Myocardial infarction**

The COC pill increased the relative risk of myocardial infarction by 1.6-fold.<sup>9</sup> When the risk factors for myocardial infarction were adjusted, use of COC alone was thought to contribute to one case of myocardial infarction/100,000 women/year. Among all the factors, smoking has the highest synergistic effect with COC. In addition, all data agree

that prior use of COC does not increase the likelihood of myocardial infarction. It is now safe to state that when currently marketed COC formulations are used, age does not appear to play a role in the development of myocardial infarction, provided users are nonsmokers, non-diabetic and normotensive.<sup>5</sup>

### **Other adverse effects**

A prospective study conducted in 2015 showed no serious side effects occurred during the 6-month drospirenone-estradiol treatment period. Ten patients (15.63%) experienced mild breast pain but with continued treatment, breast pain gradually decreased. There were no significant abnormal findings on breast ultrasound scanning in any patient. Six patients (9.38%) experienced slight irregular vaginal bleeding at the start of treatment, but the bleeding stopped with continued treatment.<sup>10</sup>

## **2. Conclusion**

If women are sexually active and do not wish to become pregnant during perimenopausal period, contraceptive counselling and contraceptive use are important aspects of their overall health care. One of the methods is by using low dose combined oral contraceptive pill containing ethynylestradiol (EE) containing less than 50 µg EE/day which acts by suppressing gonadotropin. There are several positive impacts of COC, namely pregnancy prevention; regulation of menstrual cycle; relieving menopausal symptoms; bone protection; protection against ovarian, endometrial and colorectal cancer; lipid metabolism; and blood pressure lowering effect. However, its negative effects are increasing the risk of breast cancer, venous thromboembolism, and myocardial infarction.

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