

Use of Combined Oral Contraceptives in Perimenopausal Women

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While perimenopausal women have low fecundity, they are still capable of becoming pregnant and the majority of pregnancies occurring during perimenopause are unintended pregnancies. Therefore, even during perimenopause, contraception must be used if unintended pregnancies are to be avoided. However, many perimenopausal women and healthcare providers believe that older people should not take combined oral contraceptives (COC) because doing so may be dangerous. However, to date, there is no evidence that taking COC presents an increased risk of cardiovascular events or breast cancer for middle-aged women as compared to other age groups, and in their recommendations, the Centers for Disease Control and Prevention (CDC) also do not list age itself as a contraindication for COC. Perimenopausal women often experience menstrual irregularity, heavy menstrual bleeding, and vasomotor symptoms. Taking COCs can help control these symptoms and significantly reduce the risk of ovarian cancer, endometrial cancer, and colorectal cancer. The objective of the present review is to examine the usage methods of COC among perimenopausal women and the health issues that may arise from taking COC in perimenopausal women.

Key Words: *Female; Contraceptives, Oral, Combined; Perimenopause; Risk Factors*

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INTRODUCTION

Perimenopause is defined as the time around menopause and begins in the years prior to menopause and ends 12 months after the final menstrual period.¹ The average age of a perimenopausal woman is between 40-50 years of age. Perimenopausal women can experience irregular menstrual cycles, bleeding problems, menopausal symptoms, and so on. Combined oral contraceptives (COC) offer various health benefits, in addition to their contraceptive effect (Table 1).²⁻⁸ As there are symptoms that commonly appear during perimenopause, perimenopausal women taking COC may experience additional benefits compared to women in their 20s and 30s. These additional benefits may promote an improved quality of life in perimenopausal women. However, a majority of middle-aged women believe that they should not take COCs because taking COCs at an older age may be dangerous,⁹ and in some cases, even healthcare providers are hesitant to prescribe COCs to middle-aged women because of potential negative health effects. The objective of the present review is to examine

the recommendations of the Centers for Disease Control and Prevention (CDC) on the use of COCs in perimenopausal women while exploring the benefits and risks of COC use in perimenopausal women.

TABLE 1. Contraceptive and non-contraceptive benefits using combined oral contraceptives

Benefit	Reduction %
Contraceptive	
Pregnancy	>90
Deaths at delivery	>90
Abortion	>90
Ectopic pregnancy	>90
Non-contraceptive	
Irregular menstruation	25-50
Dysmenorrhea	25-50
Heavy menstrual bleeding	25
Ovarian cancer	50
Endometrial cancer	50
Colorectal cancer	30

CAN PERIMENOPAUSAL WOMEN USE COCs?

In 2016, the CDC presented guidelines, based on the current published evidence, regarding which contraceptive methods can be used safely when various medical conditions are present.¹⁰ In these guidelines, contraceptive methods were categorized as follows: category 1, when the corresponding contraceptive methods can be used without any restrictions; category 2, when the benefits generally outweigh the risks when the corresponding contraceptive methods are used; category 3, when the risks outweigh the benefits when the corresponding contraceptive methods are used; and category 4, when the corresponding contraceptive methods should not be used. In these guidelines, the only age restriction on the use of COCs mentioned is for women aged 35 years or older who smoke 15 or more cigarettes per day. Thus, age itself is not a contraindication for COCs, and the guideline mentions that COCs can be used until menopause.¹⁰ However, women under 40 years old fall into category 1 (unrestricted use), whereas ages 40 years or older fall into category 2. Forty years of age is used as the cut-off value not because the age itself is a problem, but because the risks for some diseases, including cardiovascular disease, increase with age and those risks may increase even more when taking COC. Therefore, when considering the use of COCs, just as with women in other age groups, those aged 40 years or older should be checked for the presence of diseases that are contraindications for COCs and for risk factors associated with such diseases. The quick reference chart provided by the CDC, which summarizes the conditions that correspond to contraceptive method categories 3 and 4, can be helpful when checking for contraindications or risk factors and can prevent overlooking them. For instance, the amount of insulin in injections does not increase for women with insulin-dependent or non-insulin-dependent diabetes who present without vascular complications, even though they are taking COCs. COCs can be administered in these cases because they do not have a negative effect on long-term diabetes control (e.g., glycosylated hemoglobin levels) or progression to retinopathy.¹⁰ They are, therefore, classified under category 2.¹⁰ However, they should be classified as category 3 or 4 in cases where the patient exhibits nephropathy, retinopathy, neuropathy, or more than 20 years of diabetes history.¹⁰

In summary, even women aged 40 years or older can safely use COCs if they are not obese, are non-smokers, have normal blood pressure, and do not have any cardiovascular disease or risk factors.¹¹

UNDER WHAT CIRCUMSTANCES CAN PERIMENOPAUSAL WOMEN USE COC?

The most basic purpose of COCs use is contraception. Perimenopausal women often believe that they cannot get pregnant or no longer need to use contraception.¹² However, perimenopausal women still possess fecundity, although

their pregnancy rate tends to be low.¹³ According to a 2014 report by the Korean Women's Development Institute, the percentage of unintended pregnancies among women aged 40 years or older was 26.9%, which was higher than 3.3% and 17.88%, found for those in their 20s and 30s, respectively. In other words, contraception is needed if pregnancy is not intended, even during perimenopause. The CDC guidelines also mention that even women who are older than 44 years should continue to use contraception if they do not want to become pregnant,¹⁴ and the recommendations from the American Society for Reproductive Medicine (ASRM) and North American Menopause Society (NAMS) also indicate that contraception should be used up to 12 months after the last menstruation.^{15,16}

COCs are a highly effective contraceptive method, with a failure rate of <1%.² Even so, people who have completed their family planning often choose permanent birth control methods, and thus, the actual use of COCs among perimenopause women is relatively lower than among women in their 20s and 30s.¹⁷ Nonetheless, even women who have undergone permanent birth control surgery may use COCs for other purposes, if the additional effects of COCs are needed, such as for the control of some perimenopause symptoms. One purpose is regulation of the menstrual cycle during perimenopause. Approximately 90% of women experience changes in their menstrual patterns for the 4-8 years before complete menopause is reached.¹⁸ Such changes may take the form of shorter or longer menstrual cycles, as well as premenstrual spotting, excessive menstrual bleeding, and/or unpredictable bleeding. In such cases, as long as other underlying causes are eliminated, menstrual cycles can be effectively controlled by using COCs in 80% of cases.³ If the purpose of taking COCs is to control the menstrual cycle, then using COCs containing 30-35 µg of ethinyl estradiol is recommended, as the use of COCs containing 20 µg of ethinyl estradiol results in a significantly higher incidence of irregular bleeding and drug discontinuation due to such irregular bleeding than does the use of COCs containing 30-35 µg of ethinyl estradiol.¹⁹ The peak incidence for heavy menstrual bleeding (HMB) occurs in the late 40s. COCs can reduce the amount of menstrual bleeding by approximately 40%.⁴ Suitable COCs include an estradiol valerate/dienogest combination drug approved by the U.S. Food and Drug Administration (FDA) for the treatment of HMB.²⁰ In 70% of those who take the drug, an estradiol/dienogest combination can reduce the amount of menstrual bleeding by more than 50%.²¹ Certainly, monophasic pills containing ethinyl estradiol can also be used. In such cases, instead of a standard regimen with 21-24 days of drug administration followed by 4-7 days of a pill-free interval, increasing the pill-free interval to every 3 months or continuing drug administration for 6 or 12 months can be more effective in reducing the amount of menstrual bleeding.²² However, when the pill is taken continuously, unexpected breakthrough bleeding may occur as the administration period increases. In this situation, the amount of menstrual bleeding can be effectively reduced by using a tailored regimen, where

COCs are used until bleeding occurs, and if bleeding persists for more than 3 days, the drug is discontinued for 3-4 days.^{23,24} COCs may also reduce menstrual pain, for which an extended or continuous regimen may be more effective.²⁵ An extended or continuous regimen can be useful for controlling menstruation-related headaches or premenstrual syndrome.²⁶⁻²⁸ Approximately 70-80% of perimenopausal women experience vasomotor symptoms,²⁹ and COCs may be used to control such vasomotor symptoms.^{30,31} If vasomotor symptoms appear during the pill-free interval, estrogen may be supplemented during the pill-free interval or an extended or continuous tailored regimen may be used.^{32,33}

COCs also have a preventive effect for some diseases. COCs reduce the risk of endometrial cancer, and this effect appears immediately after administration and increases proportionately with the duration of use. Even after the drug is discontinued, the effect can be sustained for 30 years.⁵ A preventive effect against epithelial ovarian cancer also appears within the first year of drug administration, increases proportionately with duration of use, and is sustained for 20-30 years after discontinuation. Even if the duration of drug administration is less than 1 year, the risk reduction effect can be sustained for 20 years after discontinuation.^{6,7} Use of COCs can also reduce colorectal cancer by approximately 20%.⁸ As the incidence of cancer increases with age, the preventive effect of COCs on cancer can be considered especially important for middle-aged women. COCs also have bone protection effects. After the age of 40 years, bone mineral density (BMD) is known to decrease by 1% each year, and if women in their 40s take COCs, they will be able to maintain their BMD.^{34,35} Women taking COCs for at least 6 years prior to menopause can significantly increase postmenopausal BMD in the femur neck and lumbar spine, as compared to those not taking COCs.³⁶ Although there are not many studies addressing whether premenopausal COCs use can reduce postmenopausal fracture risk, it has been reported that taking COCs, especially after the age of 40, can reduce postmenopausal hip fracture risk by 30%.³⁷

HOW DO YOU EXPLAIN THE POTENTIAL NEGATIVE HEALTH IMPACT OF COC?

While COCs offer many benefits, there still are negative views about COCs. Therefore, when recommending COCs to patients, it is important to describe the risks that may occur while using COCs as absolute risks, so that the patient can accurately understand the potential, negative health impact of COCs and maintain compliance.³⁸

1. Breast cancer

In studies that analyzed data collected mostly before 2000, most of the results suggested that COCs cause a statistically significant increase in the risk of breast cancer.^{39,40} However, recent studies on COCs with lower estrogen doses have reported that the risk of breast cancer asso-

ciated with COCs is lower than previously reported (RR=1.08).⁴¹⁻⁴³ When a 1.08-fold risk is applied to the prevalence of breast cancer in women in their 40s in Korea, the additional incidence of breast cancer due to taking COCs is 3.4 per 10,000 persons each year, which is considered a rare event with respect to the frequency of adverse drug reactions, as defined by the Council for International Organizations of Medical Sciences (Table 2). Moreover, there is no evidence that taking COCs after the age of 45 years results in a greater risk of breast cancer, as compared to those under the age of 45 years.

2. Venous thromboembolism (VTE)

Decreasing the estrogen dose in COCs resulted in a slight decrease in the risk of VTE due to COCs.⁴⁴ However, the risk was still approximately 3-6 times higher than that for non-users.⁴⁵⁻⁴⁷ VTEs may cause serious outcomes, and thus, this must be explained prior to drug administration. The patients should be instructed to consult with their physician immediately when symptoms characteristic of VTE, such as upper abdominal pain, chest pain, severe headache, visual impairment, and pain and swelling in the lower legs, appear.¹² However, the increase in the risk of VTE due to taking COCs amounts to only 1/10 to 1/2 of the increased risk during pregnancy or the puerperal period.⁴⁸ In particular, the prevalence of VTE in Korea is much lower than that of western countries; for example, it is only 1/7-1/8 of the prevalence in Denmark.⁴⁹ When a 3-6-fold relative risk was applied to the prevalence of VTE among Korean women in their 40s in 2008 (0.97 per 10,000 persons), the additional incidence of VTE due to women in their 40s taking COCs can be viewed as a rare event since VTEs occur in approximately 2 per 10,000 persons each year when using COCs containing levonorgestrel and 3-5 per 10,000 persons each year when using COCs containing gestodene or desogestrel.

3. Myocardial infarction (MI)

COCs increase the relative risk of MI by 1.6 fold.⁵⁰ When this risk is applied to the MI incidence among Korean women aged 45-54 years (9.6 per 10,000 persons),⁵¹ the additional incidence of MI due to taking COCs was 5.7 per 10,000 persons each year, which is also viewed as a rare event.

TABLE 2. CIOMS III working group recommended following categories for description of adverse reaction frequency

Very common	≥ 1/10 (≥ 10%)
Common, Frequent	≥ 1/100 and <1/10 (≥ 1% and <10%)
Uncommon, Infrequent	≥ 1/1000 and <1/100 (≥ 0.1% and <1%)
Rare	≥ 1/10000 and <1/10000 (≥ 0.01% and <0.1%)
Very rare	<1/10000 (<0.01%)

CIOMS: Council for International Organizations of Medical Sciences.

4. Metabolic effect

According to a cohort study published in 2005, glucose tolerance, triglycerides, serum albumin, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase levels increased, and total cholesterol, HDL cholesterol, total bilirubin, and alkaline phosphatase levels decreased in perimenopausal women taking COCs when compared with those who were not taking COCs. However, these changes were clinically insignificant, and the values were within their normal ranges. The limitations of this study were that it was a short-term study conducted for only 6 months and its sample size was small.⁵²

WHEN SHOULD COCs BE STOPPED IN PERIMENOPAUSAL WOMEN?

Estrogen doses in COCs are 4-7 times higher than in menopause-specific regimens, and thus, continuing to use COCs during menopause may lead to unnecessarily high health-related risks in menopausal women.^{53,54} Therefore, it is important to discontinue COCs at the appropriate time, or switch to menopausal hormone therapy if necessary. In general, menopause is defined as not having menstruation for 12 consecutive months, but women who take COCs may continue to show withdrawal bleeding even during menopause or become amenorrhic even though they are not in menopause, and thus, menopause may not be determined by the status or duration of amenorrhea.⁹ One method to check for menopause while taking COCs is to discontinue use for 2-3 months at the age of 50 years and observe whether menstruation returns. However, this method is not suitable when using COCs not only for symptom control purposes but for contraceptive purpose.³⁸ While taking COCs, menopausal status can be checked by evaluating serum FSH levels and vasomotor symptoms during pill-free intervals, while considering the patient's age.³⁸ At the age of 50 years, if the s-FSH level is measured on the 7th day of the pill-free interval, twice in a 6-8-week interval, and if both measurements show a s-FSH level ≥ 30 IU/L, then the patient can be diagnosed as menopausal. If the results show an s-FSH level <30 IU/L, the patient can follow up at 1-year intervals.⁵⁵ There are studies that recommend measurement on the 14th day of the pill-free interval, as measurement on the 7th day may produce false negatives, meaning the results may indicate pre-menopause even if the patient is in menopause, due to insufficient FSH rebound. In cases where COCs are discontinued for 14 days, another backup contraception method would be needed if the drug was being used for contraception.³⁸

CONCLUSION

In perimenopausal women, COCs may be used not only for their contraceptive effect, but also for the improvement of various symptoms that commonly appear during perimenopause, including menstrual irregularity, heavy menstrual bleeding, menstrual pain, and vasomotor symptoms.

Additionally, COCs can also aid in reducing the risk of endometrial cancer, ovarian cancer, and colorectal cancer, as well as maintaining BMD. Although COCs increase the risk of breast cancer, VTE, and MI, the additional events that occur are considered rare, even for patients in their 40s. Therefore, even perimenopausal women can safely use COCs, as long as they are not obese, do not smoke, and have normal blood pressure with no cardiovascular disease.

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CONFLICT OF INTEREST STATEMENT

None declared.

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