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The Effect of Continuous Combination Oral Contraceptive use on Subsequent Fertility

Won Bahng Hwee
Pacific University

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The Effect of Continuous Combination Oral Contraceptive use on Subsequent Fertility

Abstract

Background: Combination oral contraceptive (COC) is the most common method of contraception utilized in the United States. Currently, the traditional 28-day cyclic COC is the most popular. The newly developed continuous COC shows multiple advantages over the traditional cyclic COC, both in reducing the frequency of menses and the severity of associated symptoms, as well as providing the lifestyle benefits and convenience for women. This systematic review evaluates the effect of continuous COC use on subsequent fertility in healthy women of child-bearing age.

Method: An extensive search of MEDLINE, CINAHL, and Evidence Based Medicine Review Multifile was conducted using fertility and oral contraceptives as key words. Articles written in the English language between 1990 and the present with human subjects were included. The GRADE system was utilized to assess the quality of each study.

Results: Two studies were included in this systematic review. For women who had discontinued continuous COC for pregnancy intent, the pregnancy rate at 12 months was 81%, comparable to the pregnancy rate of women with previous traditional cyclic COC use. The median time to return of spontaneous menses after cessation of continuous COC use was 1 month. These studies seem to indicate that continuous COC use does not delay the time to fertility. However, the studies utilized were both of very low quality.

Conclusion: Based on current research, continuous COC has a good safety and efficacy profile. Recent studies point towards lack of delay in return to fertility; however, more high quality research is necessary to ascertain the effect of continuous COC use on subsequent fertility. At this time, women should be educated about the limitations of current research to make their own decisions in choosing continuous COC as a contraceptive method.

Keywords: continuous oral contraceptives, time to pregnancy, return to fertility

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Master of Science in Physician Assistant Studies

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Keywords
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The Effect of Continuous Combination Oral Contraceptive use on Subsequent Fertility

Won Bahng Hwee, PA-S

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 11, 2012

Faculty Advisor: James Ferguson, PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Won Bahng Hwee was born and raised in Seoul, Korea and emigrated to the U.S.A. when she was 12 years old. Won and her family settled in Lake Oswego, Oregon where she attended Lake Oswego Junior High and High school. Afterwards, she went on to pursue a double degree in biology and chemistry at Santa Clara University in California, while her parents started a restaurant called Mashita Teriyaki in Tualatin, Oregon. Won met Mark, a financial advisor and an awesome fisherman, in 2005 and they got married in July 2006. Their daughter Elinor loves singing and dancing and wants to be a princess when she grows up. Won is a foodie, an avid swimmer, a Korean soap opera addict, and a proud owner an energetic beagle named Bailey. She aspires to work in a primary care setting and build long-term relationships with her patients and serve her Portland community.
Abstract

**Background:** Combination oral contraceptive (COC) is the most common method of contraception utilized in the United States. Currently, the traditional 28-day cyclic COC is the most popular. The newly developed continuous COC shows multiple advantages over the traditional cyclic COC, both in reducing the frequency of menses and the severity of associated symptoms, as well as providing the lifestyle benefits and convenience for women. This systematic review evaluates the effect of continuous COC use on subsequent fertility in healthy women of child-bearing age.

**Method:** An extensive search of MEDLINE, CINAHL, and Evidence Based Medicine Review Multifile was conducted using *fertility* and *oral contraceptives* as key words. Articles written in the English language between 1990 and the present with human subjects were included. The GRADE system was utilized to assess the quality of each study.

**Results:** Two studies were included in this systematic review. For women who had discontinued continuous COC for pregnancy intent, the pregnancy rate at 12 months was 81%, comparable to the pregnancy rate of women with previous traditional cyclic COC use. The median time to return of spontaneous menses after cessation of continuous COC use was 1 month. These studies seem to indicate that continuous COC use does not delay the time to fertility. However, the studies utilized were both of very low quality.

**Conclusion:** Based on current research, continuous COC has a good safety and efficacy profile. Recent studies point towards lack of delay in return to fertility; however, more high quality research is necessary to ascertain the effect of continuous COC use on subsequent fertility. At this time, women should be educated about the limitations of current research to make their own decisions in choosing continuous COC as a contraceptive method.

**Keywords:** continuous oral contraceptives, time to pregnancy, return to fertility
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To Mark Hwee: Thank you for your encouragement and support financially and emotionally through my journey. You have made so many sacrifices to take care of Elinor while I was away, to come travel with me to different rotations, and to provide for our family. You have endured greatly and I am so grateful and proud of you.

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To my parents: Thank you for instilling honesty and perseverance in me. You are the hardest working parents I know and you never complain. I truly appreciate all the sacrifices you have made to provide for us as we settled in America so that Gun and I could have a better future.

To Mark’s parents: Thank you for helping us take care of Elinor, cooking dinner for us daily, praying for our family, and loving us in innumerable ways. I am forever indebted to you.

To my classmates: Thank you for making PA school so much fun and so rewarding. I do not think anyone could quite understand what we have endured except each other. Thank you always for your encouragements, humor, willingness to lend a hand, and super nerdiness that always kept me going.

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List of Abbreviations

COC……………………………………………………...Combination Oral Contraceptive
LNG………………………………………………………………………...Levonorgestrel
EE………………………………………………………………………...Ethinyl Estradiol
GRADE………..Grading of Recommendations Assessment, Development and Evaluation
The Effect of Continuous Combination Oral Contraceptive use on Subsequent Fertility

BACKGROUND

In the United States, more than 99% of women of child-bearing age who have been sexually active have used at least one contraceptive method.\(^1\) The combination oral contraceptive (COC), also known as the Pill, was developed in 1960.\(^2\) This reversible form of contraceptive is the leading method in the United States.\(^1\) Since its development, the 28-day cycle COC has been the mainstay. The traditional cyclic 28-day COC, containing 21 active pills and 7 placebo pills, was designed to simulate the monthly menstrual cycle; however, this menstruation is not natural.\(^2\) The bleeding that occurs during the hormone-free interval is not due to the endometrial build-up, but rather due to the hormone withdrawal.\(^3\) The decision for this 28-day design was based on social pressure for naturalness and acceptance by women rather than on any biological evidence.\(^2\)

In the twenty-first century, continuous COC became available. Continuous COC use is defined as when a pill is taken daily without a pill-free or a placebo period. The traditional 28-day cyclic COC produces significant withdrawal symptoms during the placebo period similar to the symptoms related to menstruation including headaches, bloating, pelvic pain, and breast-tenderness.\(^4\) In comparison, continuous COC will induce cycle suppression and amenorrhea in most women.\(^5\) Therefore, continuous COC may be preferred over the traditional cyclic COC for the reduction in the frequency of menses and the severity of associated symptoms. Women may also favor continuous COC for lifestyle benefits and convenience.\(^5\) Potential advantages include “less interference of
daily activities or special events, decreased expense for feminine hygiene products, and less menstruation-related absenteeism from work or school.”

Recently, a large phase 3 contraceptive trial has demonstrated that continuous COC containing Levonorgestrel (LNG) and Ethinyl estradiol (EE) has a good safety profile and efficacy comparable to the cyclic COC. The efficacy was demonstrated by the inhibition of menses through the induction of amenorrhea and the absence of bleeding and spotting. However, this trial did not examine the effect of continuous COC use on subsequent fertility. For some women, the fear of adverse effect on subsequent fertility following continuous COC use is an important concern. This systematic review evaluates the literature that addresses the effect of previous continuous COC use on the return to fertility in healthy women of child-bearing age.

METHODS

Search Strategy

A comprehensive electronic search of MEDLINE, CINAHL, and Evidence-Based Medicine Review Multifile was conducted to identify all relevant studies published between January 1, 1990 and present. The combined search terms used were: fertility, and oral contraceptives. Articles were included if they evaluated the effect of continuous COC use on subsequent fertility in healthy women of child-bearing age. The return to fertility after the cessation of continuous COC was measured utilizing either the return to spontaneous menses or time to pregnancy. The exclusion criteria entailed articles assessing the traditional cyclic COC or the use of COC for therapeutic purposes. The search was restricted to English language reports and human subjects. In addition to the
electronic database search, the reference lists of all identified publications were examined for previously unidentified articles.

**Quality Assessment**

The included articles were critically appraised for validity and quality using the GRADE system. The following factors were examined: study design, limitation of the methodology, consistency of the results, directness of the evidence, precision of the results, and possible publication bias. Each study was categorized into high, medium, low, or very low quality of evidence. The characteristics and the quality assessment of these studies are shown in Table 1.

**RESULTS**

The literature search identified 21 studies, but only two remained after duplicates and irrelevant studies were excluded. The two studies in this systematic review, Barnhart et al. and Davis et al., are both follow-up studies of a phase 3 contraceptive trial. The phase 3 trial evaluated the safety and efficacy of a continuous daily regimen of a low dose combination oral contraceptive. This open-label study was conducted at 92 medical centers in North America between February 2003 and September 2004. The COC utilized in this trial was 90 mcg of levonorgesterel (LNG) and 20 mcg of ethinyl estradiol (EE). The trial included healthy women between 18 and 49 years of age who were sexually active and likely to become pregnant. Moreover, these women had regular menstrual cycles lasting 21-35 days for the three months preceding the trial. The exclusion criteria in the phase 3 trial involved the standard contraindications for oral contraceptive use and the use of medications that could interfere with the efficacy of the oral contraceptive.
The phase 3 contraceptive trial’s follow-up studies by Barnhart et al and Davis et al evaluated the return to fertility after the cessation of continuous COC use. Table 2 illustrates the summary of findings from these two studies.

**Barnhart et al**

From the phase 3 contraceptive trial, 34 women who had stopped continuous COC treatment due to the intention of becoming pregnant were qualified for this follow-up study. Out of these 34 women, 21 subjects actually underwent the study. In this prospective, observational study, there was no control group for comparison. For the 21 participants, the mean duration of continuous COC treatment was 197 days, approximately 6.6 months.

The primary endpoint examined was the return to fertility measured by the pregnancy rate within 12 months after the cessation of continuous COC. The participants were contacted by phone at 3 months and then at 12 months for the pregnancy status. For the 21 participants, the pregnancy rate at 3 months was 57% and at 12 months was 81%. Figure 1 shows the survival function estimating the time to return to fertility. A total of 18 participants became pregnant which resulted in 17 live births and 1 spontaneous abortion. This study concluded that the pregnancy rate after the cessation of continuous COC is comparable to the pregnancy rate after the cessation of traditional cyclic COC. Of the 3 participants who did not become pregnant within 12 months, 1 had stopped trying to become pregnant and 2 were lost to follow-up.
In this prospective, observational follow-up study of the phase 3 contraceptive trial, the participants who had taken COC continuously for at least 6 months were included. After the cessation of continuous COC, women who were using non-hormonal contraceptives (primarily condoms) or those seeking to become pregnant were eligible. The exclusion criteria involved intra-uterine or hormonal contraceptive use and women older than 35 years of age who smoked more than 15 cigarettes per day. There was no control group for comparison. Of the 198 subjects enrolled in the study, 187 completed the study, 7 were lost to follow-up, and 4 were excluded for protocol violation. For the 187 participants, the mean duration of continuous COC treatment was 349 days, approximately 11.6 months.

The primary endpoint measured by the authors was the time to return to spontaneous menses or pregnancy after the cessation of continuous COC. “Spontaneous menses” was defined as at least 2 consecutive days of bleeding requiring sanitary protection. The authors inferred that the spontaneous menses were post-ovulatory and utilized the occurrence of menses as an indication for return to fertility. The subjects recorded in daily diary cards the occurrences of spontaneous menses or pregnancy and returned the card with these occurrences. For those who did not have either of these occurrences by day 90, a post-study visit was conducted where the diaries were collected and a serum pregnancy test was performed.

Out of the 187 participants, 185 (98.9%) had return of spontaneous menses or were pregnant within 90 days, or 3 months, following the cessation of continuous COC.
use. In Figure 2, the survival function estimating the time to return to spontaneous menses or pregnancy is shown. Of these 185 subjects, 181 had spontaneous menses and 4 were pregnant. The median time to spontaneous menses was 32 days, or 1 month. Out of 4 women who were pregnant, 3 had full-term babies and 1 was lost to follow-up. Two participants did not have menses by day 90.10

The authors also examined the length of amenorrhea induced by continuous COC use and the time to return of menses and found no association between the two. The amenorrhea produced by continuous COC use appears to be readily reversible regardless of the duration of amenorrhea.10

DISCUSSION

This systematic review appraised the current research on the effect of continuous COC use on subsequent fertility in healthy women of child-bearing age. The two included studies9,10 suggest that continuous COC use does not delay the return to fertility. The congruity of the results adds one positive characteristic to the overall quality of the studies. However, these two studies possessed major flaws in numerous areas as discussed below, that whether continuous COC use does not have any negative impact on subsequent fertility cannot be established with certainty.

The most significant flaw is the lack of control group for comparison in both studies, thus causing serious limitation in the methodology and serious inconsistency of the results. The participants in Barnhart et al9 were 21 women who had ceased continuous COC from the phase 3 trial to attempt to achieve pregnancy and for these women, the pregnancy rate was 81% at 12 months post treatment. Barnhart et al9 compared this
pregnancy rate to the 84% pregnancy rate at 12 months post treatment with the traditional cyclic COC found in another study. In Davis et al, the subjects were 187 women from the phase 3 trial who had at least 6 months of continuous COC treatment and 98.9% of these women had spontaneous return of menses or pregnancy within 3 months of treatment discontinuation. There was no comparison group to contrast the time of spontaneous return of menses or pregnancy after cessation of the traditional cyclic COC. The lack of control groups limited their methodologies making it likely to result in biased assessment of the treatment effect. Furthermore, it also made it impossible to determine if the results were consistent.

Additionally, in Davis et al, the time to fertility was evaluated for women who may not have necessarily wanted to become pregnant, further degrading their methodology. The inclusion criteria allowed women with at least 6 months of previous continuous COC treatment, who then were using non-hormonal contraceptives or were seeking to become pregnant. The article does not explicitly identify how many of the 187 participants were using non-hormonal contraceptives vs. seeking to become pregnant. Therefore, it is difficult to decipher if the 4 out of 187 women who became pregnant in this study were the only women who desired pregnancy and if the 181 women who had spontaneous menses were the ones using non-hormonal contraceptives.

Another major flaw is the indirectness of evidence in Davis et al. The authors of this study utilized the occurrence of spontaneous menses along with the time to pregnancy as a measure of return to fertility. They assumed that the occurrence of first menses was an indication for ovulation; yet, the bleeding could have resulted from the withdrawal of COC hormones and not necessarily from the post-ovulatory endometrial
shedding. In fact, this very mechanism is how COC works: ovulation is inhibited by the hormone use, and the bleeding during a traditional cyclic COC placebo period is due to the withdrawal of hormones. So when a woman has been using combination oral contraceptives, whether continuously or in the typical cyclic 28-day fashion, then stops taking them, it is the withdrawal of hormones that typically causes the bleeding. Right now, return to fertility is truly best estimated by the time to pregnancy, not by the time to return to spontaneous menses. Davis et al\textsuperscript{10} used the time to the occurrence of spontaneous menses as a surrogate outcome, and thereby minimized the directness of their evidence.

Fourthly, it must also be noted that the mean duration of continuous COC treatment was very short in both studies, making it difficult to postulate the effect of long-term continuous COC use on return to fertility. Women were treated for the mean duration of 6.6 months in Barnhart et al\textsuperscript{9} and 11.6 months in Davis et al\textsuperscript{10}. Davis et al\textsuperscript{10} concluded that the duration of amenorrhea induced by continuous COC use is unrelated to the time to return of menses, yet the maximum duration of continuous COC treatment in this study was merely 13 months.

The fifth key limitation is the small sample size in Barnhart et al\textsuperscript{9} and Davis et al\textsuperscript{10}, thus inducing some imprecision overall. Barnhart et al\textsuperscript{9} had a total of 21 participants and Davis et al\textsuperscript{10} had 187 subjects who completed the study. These were both follow-up studies from the same large phase 3 contraceptive trial\textsuperscript{7} and the small sample size was probably not modifiable.
Lastly, in examination of other possible biases, it was discovered that Wyeth Research, the manufacturer of Lydrel, the drug utilized in both studies, sponsored Barnhart et al.\textsuperscript{9} and Davis et al.\textsuperscript{10} The results from both studies suggest that Lydrel, the continuous COC containing LNG and EE, does not negatively impact the return to fertility.\textsuperscript{9,10} Due to these positive findings for the drug, the probability for publication bias in both studies cannot be eliminated.

The quality of evidence in both Barnhart et al.\textsuperscript{9} and Davis et al.\textsuperscript{10} are very low. But the result from each study appears to suggest that continuous COC does not negatively impact the subsequent fertility. Thus, more extensive research of high quality evidence is crucial.

The next step in ascertaining whether the previous use of continuous COC delays the return to fertility is to conduct a prospective, cohort study of healthy women of child-bearing age desiring pregnancy in the future with no previous history of COC use. The control group will be on no method of contraception, while the experimental group will be placed on continuous COC for at least 6 months. For the control group, the time to pregnancy will be measured from the study initiation and for the experimental group, the time to pregnancy will be measured from the time of treatment discontinuation. It is vital to have a control group for comparison in order to eliminate the limitations of the methodology as well as to minimize the inconsistency of the results. Large sample size is also recommended to improve the precision of the study. Prolonged continuous COC treatment lasting more than several years should also be considered to provide long-term effect on return to fertility.
For healthy women who are seeking to try continuous COC as a contraceptive method, the clinicians need to inform them about the limitations of the current research. Continuous COC does induce amenorrhea in most women and this could be advantageous for some desiring to have less frequent menstruations and related symptoms, as well as lifestyle benefits and convenience. While continuous COC does have a good safety and efficacy profile comparable to the traditional cyclic COC, its effect on subsequent fertility needs further research.

**CONCLUSION**

Combination oral contraceptive is the leading method of contraception utilized in the United States. The traditional 28-day cyclic COC has been the standard COC prescribed due to its *naturalness* and acceptance by women. Yet, the newly developed continuous COC may provide superior benefits for women by reducing the frequency of menses and severity of related symptoms and offering lifestyle benefits and convenience.

Based on a large phase 3 contraceptive trial, continuous COC has a good safety and efficacy profile comparable to the traditional cyclic COC. Recent studies suggest that the pregnancy rate after continuous COC use is similar to the pregnancy rate after the traditional cyclic COC use. The amenorrhea induced by continuous COC use also seems to be readily reversible regardless of the duration of amenorrhea. However, more high quality research is necessary to determine the effect of continuous COC use on the subsequent fertility. Presently, women should be educated about the limitations of current research and encouraged to make their own decisions in choosing continuous COC as a contraceptive method.
References


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- ✳ Failure to include control group
- ✭ Surrogate outcome used to measure return to fertility (occurrence of menses used along with time to pregnancy)
- ◆ Small sample size
- ❖ Study sponsored by drug manufacturer
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<th>Participants</th>
<th># Enrolled</th>
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<td>Women after discontinuation of continuous COC for pregnancy intent</td>
<td>34</td>
<td>21</td>
<td>18-49</td>
<td>26.9</td>
<td>198 days = 6.6 months</td>
<td>90 mcg LNG / 20 mcg EE</td>
<td>Time to pregnancy</td>
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<td>Davis et al&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>Women with previous continuous COC treatment for 6-12 months</td>
<td>198</td>
<td>187</td>
<td>18-49</td>
<td>30.4</td>
<td>349 days = 11.6 months</td>
<td>90 mcg LNG / 20 mcg EE</td>
<td>Time to return to spontaneous menses or pregnancy</td>
<td>98.9% with return of spontaneous menses or pregnancy by 3 months post treatment</td>
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<td>Median time to spontaneous menses = 1 month</td>
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Figure 1. Time to return to fertility

**FIGURE 1**

Time to return to fertility. Kaplan-Meier survival function estimates.

Figure 2. Time to return to spontaneous menses or pregnancy