The Effect of Dose-Reduced Combination Oral Contraceptives Containing 20 µg of Ethinyl Estradiol and 100 µg of Levonorgestrel on Lipid Metabolism: A Meta-Analysis

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Abstract: Lipid metabolic disturbance induced by the synthetic steroids used in combination oral contraceptives (COCs) has been considered as one of the potential risk factors of cardiovascular diseases. A lower-dose preparation that contains 20 µg of ethinyl estradiol and 100 µg of levonorgestrel (20EE/LNG) has proven effective in most clinical studies, whereas its effect on lipid metabolism is still unclear. The purpose of this study was to estimate the effect of a lower dose of a COC (containing 20 µg of ethinyl estradiol and 100 µg of levonorgestrel) on lipid metabolism by conducting a systematic review and a meta-analysis. A literature search was performed using MEDLINE (PubMed), Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL database). The studies that are randomized controlled trials to compare a lower-dose COC (20EE/LNG) with a placebo or another COC that differed in terms of the drug, dosage, regimen, and study length were included. Meanwhile, studies should have evaluated the index of lipid metabolism changes. However, the studies with the interventions fewer than three consecutive cycles or the patients were primarily used the treatment of non-contraceptive were excluded. We pooled the low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG) results, and compared 20EE/LNG with conventional-dose COCs using fixed-effects meta-analysis with inverse-variance weighting. Five randomized controlled trials, with a total of 423 participants (age range: 18–35 years), were included in this study. The results derived from all the included studies were pooled. LDL-C of 20EE/LNG group showed significant lower than control group after three (SMD, 0.16; 95% CI, 0.03–0.30; $P=0.02$) and six (SMD, 0.16; 95% CI, 0.01–0.31; $P=0.04$) cycles of treatment. However, there was no difference between the two groups after 12 cycles of administration (SMD, -0.06; 95% CI, -0.31 to 0.18; $P=0.61$). The pooled results showed there was a significant increase in HDL-C in the 20EE/LNG group after three cycles of treatment (SMD, 0.43; 95% CI, 0.13–0.73; $P=0.005$). No significant difference was observed between TC and TG groups. For LDL-C, the low-dose group shows a higher risk of suffering from cardiovascular diseases after three and six cycles of treatment, while no difference is observed after 12 cycles of treatment. For HDL-C, the 20EE/LNG group exhibits favorable effects after three cycles of treatment compared with the control groups. Similar effects are found between TC and TG profiles groups.

Keywords: Combination Oral Contraceptives, Ethinyl Estradiol, Levonorgestrel, Lipid Metabolism, Systematic Review and Meta-Analysis

1. Introduction

Combination oral contraceptives (COCs) are hormonal preparations that contain the hormones estrogen and progestin. Since their introduction in the late 1950s, millions of women worldwide have reaped the benefits of using oral contraceptives as a reliable method of birth control.

COCs play a major role in the management of women's reproductive health; however, their serious side effects also raise controversy. The first oral hormonal contraceptive Enovid™, which contains a large amount of estrogen (0.15 mg of mestranol) and progestin (9.85 mg of norethynodrel), was approved by the FDA (Food and Drug Administration) in the U.S. in 1959. However, severe cardiovascular diseases such as venous thromboembolism, stroke, and myocardial infarction were observed shortly after the introduction of Enovid™. It was recently proposed that the side effects are largely associated with these high-dose preparations.

Epidemiologic literature suggests that reducing the dose of estrogen in COC formulations can reduce the risk of cardiovascular diseases. The first such reduction focused on estrogen, and the risk of venous thromboembolism dramatically declined [1]. It appears that the risk of acceleration of arterial disease is no longer present in healthy users of low-dose COCs [2]. Reduction of the progestin content followed, as evidence mounted that lowering progestin intake might lower the risk of cardiovascular complications such as stroke and ischemic heart disease. However, the mechanism by which lower-dose COCs reduce the risk of cardiovascular diseases is unclear.

The non-contraceptive effects of oral contraceptives, especially changes in lipid metabolism, have been considered as one of the indications of cardiovascular risk. Elevated low-density lipoprotein cholesterol (LDL-C), low levels of high-density lipoprotein cholesterol (HDL-C), and elevations in triglyceride (TG), total cholesterol (TC), and lipoprotein (a) all contribute to cardiovascular risk [3, 4]. In general, estrogen tends to have an effect on the lipid profile that theoretically would offer protection from the development of cardiovascular diseases by producing an increase in high-density lipoproteins and a decrease in low-density lipoproteins [5]. Progestogen, conversely, exhibits an opposite and adverse effect by decreasing HDL-C and increasing LDL-C. These effects of COCs on lipid metabolism depend on both the absolute doses of the estrogen and progestogen components and on their relative ratios. Initial investigations demonstrated that users of high-dose pills experience increases in serum TGs and TC [5, 6]. Therefore, a lower dose of ethinyl estradiol (EE) and levonorgestrel (LNG) might be favorable to reduce the side effects if its contraceptive effect was assured.

Currently, a lower-dose preparation that contains 20 µg of EE and 100 µg of LNG (Alesse®) has been approved by the FDA and has proven effective in clinical applications [10-15], whereas its effect on lipid metabolism is unclear. The purpose of this study was to estimate the effect of this lower dose of a COC on lipid metabolism including LDL-C, HDL-C, TC, and

TG, and thus to evaluate its cardiovascular benefits indirectly, by conducting a systematic review and meta-analysis.

2. Methods

2.1. Search Strategy and Selection Criteria

We conducted a literature search using MEDLINE (PubMed), Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL database) (updated on January 15, 2015). Search terms were as follows:

- #1 ethinyl estradiol
- #2 ethinylestradiol
- #3 levonorgestrel
- #4 LDL-C
- #5 HDL-C
- #6 TC
- #7 TG
- #8 (#1 or #2) and #3 and (#4, #5, #6, or #7).

We included all randomized controlled trials (RCTs) that compared the lipid metabolism changes of a lower-dose COC, containing 20 µg of EE and 100 µg of LNG (20EE/LNG), with a placebo or other COCs that differed in terms of the drug, dosage, regimen, and study length. Meanwhile, these studies should have evaluated the index of lipid metabolism changes. However, the studies were excluded if the interventions in these studies were less than three consecutive cycles or the patients were primarily used the treatment of non-contraceptive. We pooled the LDL-C, HDL-C, TC, and TG results to compare 20EE/LNG with conventional-dose COCs.

Two authors independently screened all evidence identified by the search strategy according to selection criteria, and disagreements were resolved by discussion between the two authors.

2.2. Data Extraction

Two investigators (Lin Chen and Jun Xu) independently read the full texts and extracted data from the included studies. The primary outcome indicators for this study were serum lipid profiles including LDL-C, HDL-C, TC, and TG. For each study, we extracted the following data: authors; year of publication; country of study; study design; patient characteristics; sample size; outcome indicators, and duration of treatment.

2.3. Quality Assessment

The methodological quality of the included trials was assessed by the risk tool of bias recommended by the Cochrane Collaboration. This tool consists of seven items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete data outcome (attrition bias), selective reporting (reporting bias), and other sources of bias. Each item was graded as a low or high risk of bias if there was sufficient information to be assessed, otherwise it was graded

as unclear. Two authors (Lin Chen and Jun Xu) independently assessed the quality of each included RCT, and disagreements were resolved by discussion between the two authors.

2.4. Statistical Analysis

RevMan 5.2 software was applied in the statistical analysis process. For continuous data, measures of effect were expressed as standardized mean difference SMD with 95% CIs. The I^2 statistic was used to evaluate heterogeneity among studies. When $I^2 < 50\%$, heterogeneity was not statistically significant, and then the data of studies were pooled and analyzed by a fixed-effects model. When $I^2 > 50\%$, the data of studies were pooled and analyzed by a random-effects model for significant heterogeneity.

3. Result

3.1. Search Results and Study Selection

In total, 217 articles were initially identified by electronic and manual searches. Through screening titles and abstracts, 200 were excluded because they were duplicated (86), review articles (32), nonclinical trials (9), or case reports (1) or because the interventions did not meet the inclusion criteria (72). We then proceeded to full-text evaluation for the remaining 17 articles, and 12 articles were excluded because they did not meet our inclusion criteria. Among these, two articles lacked original data, two articles did not meet the inclusion criteria, the interventions in seven articles did not meet the inclusion criteria, and one study lacked a control group. Finally, a total of five RCTs, which involved 423 patients, were selected for data extraction and analysis. The detailed steps of our literature search are shown in Figure 1.

Figure 1. Diagram of the study selection procedure.

3.2. Characteristics of the Included Studies

The characteristics of the five studies are summarized in Table 1. All eligible studies were published between 1997 and 2000. These studies were conducted in Germany (2), the

Netherlands (1), Denmark (1), and America (1). In total, 423 patients, aged from 18 to 35 years, were involved. All the studies used lipid values as the primary outcome. The study duration varied from 6 to 13 28-day cycles.

Table 1. Characteristics of the included studies.

Author (year)	Region	Design	Period of study	Outcome measures	Age range (years)	No. of participants	Interventions		Follow-up (28-day cycles)
							Control	Test	
Endrikat 2002 [7]	The Netherlands	RCT	1998.05–1999.12	LDL-C, HDL-C, TC, and TG	18–35	23/25	20 µg of EE/100 µg of LNG	30 µg of EE/150 LNG	13
Wiegratz 2002 [8]	Germany	RCT	Unknown	LDL-C, HDL-C, TC, and TG	18–35	25/25/25	20 µg of EE/100 µg of LNG	30 µg of EE/2 mg of DNG 20 µg of EE/2 mg of DNG 10 µg of EE/2 mg of DNG/2 mg of EV	6
Scharnagl 2004 [9]	Germany	RCT	Unknown	LDL-C, HDL-C, TC, and TG	18–35	22/27	20 µg of EE/100 µg of LNG	30 µg of EE/150 LNG	12
Skouby 2005 [10]	Denmark	RCT	1997.12–2000.04	LDL-C, HDL-C, TC, and TG	18–35	34/33	20 µg of EE/100 µg of LNG	30 µg of EE/150 LNG	13
Beasley 2012 [20]	America	RCT	2006.07–2008.12	LDL-C, HDL-C, TC, and TG	18–35	58/51	20 µg of EE/100 µg of LNG	30 µg of EE/150 LNG	3

Abbreviations: EE = ethinyl estradiol; LNG = levonorgestrel; DNG = dienogest; EV = estradiol valerate;

A

B

Figure 2. Assessment of risk of bias in this meta-analysis.

3.3. Quality of the Included Studies

We evaluated the risk of bias in the five published RCTs using the Cochrane Risk of Bias Tool. The result is demonstrated in Figure 2. For the five observational studies, only one study described the methods used to generate the allocation sequence and described its blinding method. No study reported incomplete results. There was little heterogeneity among these studies.

A: Risk of bias graph. Graph showing each risk of bias item presented as percentages across all included studies. B: Risk of bias summary. Summary of the risk of bias for each trial assessed by the Cochrane Collaboration tool.

3.4. Pooled Lipid Profile Analysis

The data from the five included RCTs were pooled for analysis. The outcomes were evaluated at the third, sixth, and twelfth cycles of treatment. For long-term effects, although some studies reported their results at the thirteenth month, we regarded them as the same period as the twelfth cycle of treatment. We compared lipid values between groups in different cycles of treatment and compared lipid values with that at the baseline.

3.5. LDL-C

Five studies (423 participants) reported LDL-C changes in blood lipids after the third, sixth, and twelfth treatment cycles. Figure 3 shows the results of meta-analysis of LDL-C changes between groups in different cycles of treatment. No significant heterogeneity existed and the fixed-effects model was used. Both the test and control groups had a significantly increased concentration of LDL-C ($P \leq 0.05$) after medications compared with the baseline values, except for the control groups after the third and sixth treatment cycles. The pooled estimates of differences in the mean LDL-C between the test and control groups showed a significant difference after three (SMD, 0.16; 95% CI, 0.03–0.30; $P=0.02$) and six (SMD, 0.16; 95% CI, 0.01–0.31; $P=0.04$) cycles of treatment. There was no difference between the two groups after 12 cycles of administration (SMD, -0.06; 95% CI, -0.31 to 0.18 to 0.31;

$P=0.61$). Figure 4 shows the results of meta-analysis of LDL-C changes between groups in different cycles of treatment.

3.6. HDL-C

HDL-C changes in blood lipids after the third treatment cycle were reported by two RCTs (176 participants). The fixed-effects model was used to evaluate the changes in HDL-C, and the results are shown in Figures 5 and 6. There was a significant difference after three cycles of treatment (SMD, 0.43; 95% CI, 0.13–0.73; $P=0.005$) (Figure 5). Data of HDL-C changes after long-term use were not reported or could not be obtained. Both the test and control groups had decreased concentrations of HDL-C compared with the baseline values (Figure 6).

3.7. TC

Five studies including 423 patients reported TC changes after the third treatment cycle. Four studies including 314

patients reported TC changes after three and six cycles of treatment. Three studies including 164 patients reported TC changes after 3, 6, and 12 cycles of treatment. Figures 7 and 8 show the results of meta-analysis of TC changes. The pooled estimates of differences in mean TC showed no difference between groups (Figure 7). Both the test and control groups had increased concentrations of TC compared with the baseline values (Figure 8).

3.8. TG

Figures 10 and 11 show the results for TG. Four studies including 273 patients reported TG changes after the third treatment cycle. Three studies including 164 patients reported TG changes after 6 and 12 cycles of treatment. The fixed-effects model was used. No difference between the groups was found ($P>0.05$, Figure 9). Both the test and control groups had increased TG significantly ($P\leq 0.05$) compared with the baseline values, except for the lower dose group after the third treatment cycle (Figure 10).

Figure 3. Forest plot and meta-analysis of LDL-C changes.

Figure 4. Forest plot and meta-analysis of LDL-C changes (compared with baseline values). A: Test group; B: Control groups.

Figure 5. Forest plot and meta-analysis of HDL-C changes.

A

B

Figure 6. Forest plot and meta-analysis of HDL-C changes (compared with baseline values). A: Test group; B: Control groups.

Figure 7. Forest plot and meta-analysis of TC changes.

Figure 8. Forest plot and meta-analysis of TC changes (compared with baseline values). A: Test group; B: Control groups.

Figure 9. Forest plot and meta-analysis of TG changes.

Figure 10. Forest plot and meta-analysis of TG changes (compared with baseline values). A: Test group; B: Control groups.

4. Discussion

In this study, we performed a meta-analysis based on five studies with a total of 423 participants. We observed that LDL-C, TC, and TG increased between the baseline and the third, sixth, and twelfth medication cycles for both the lower dose group and the conventional dose group. HDL-C concentration decreased between the baseline and the third medication cycle for both groups. Evidence of the long-term effect on HDL-C changes is lacking because of the insufficient number of studies.

This meta-analysis revealed that the conventional dose group appears to have a more favorable effect on the LDL-C profile than the lower dose group after three and six medication cycles. However, no statistically significant difference was found between the two groups after 12 medication cycles, and furthermore, the lower-dose COC tended to result in smaller changes. HDL-C between the test and control groups showed a significant difference in favor of the test group after three cycles of treatment. There was no difference between the lower-dose group and the conventional dose group in terms of TC and TG changes after 3, 6, and 12 medication cycles, but the test group tends to cause less change.

Our study was the first analysis to explore the effect of the lower dose of COCs versus the conventional dose of COCs on lipid metabolism. Each of the five included studies was a RCT.

There was little heterogeneity among these studies from the methodological perspective. However, for the five observational studies, only one described the methods used to generate the allocation sequence and described its blinding method. Other studies lacked details of the randomization, allocation concealment, and blinding methods, which may lead to reduced reliability of our evaluation results to some extent. Other limitations of our study are as follows: (1) publication bias in meta-analyses of published studies; (2) the data regarding long-term COC medication were incomplete; (3) this meta-analysis was based predominantly on European and American research, and no study from another part of the world was found, which may lead to a partial result; and (4) a lack of data on the obesity subgroup. Obesity independently impacts dyslipidemia [11]. We should be sure that changes in serum lipid levels are only the effect of COCs, which would make our results more reliable. Future prospective cohort studies can address many of the limitations of our meta-analysis by exploring the effect of the lower dose of a COC on lipid metabolism.

The efficacy and safety of a COC containing 20 µg of EE and 100 µg of LNG have been demonstrated [12-14]; however, few data concerning the effect of use of this COC on lipid metabolism are available. The present study is the first to conduct a meta-analysis evaluating the effect of this lower dose of a monophasic COC containing 20 µg of EE and 100 µg of LNG on plasma lipid metabolism.

Since the first COC was launched in the late 1950s, both the estrogen and progestogen doses have been progressively reduced to minimize the risk of cardiovascular diseases, while maintaining an equally good contraceptive efficacy. The most frequently used estrogen is EE, and its dosage has been steadily reduced from 150 µg to 50 µg, and even lower. The first COC containing 20 µg of EE was introduced in 1973 [15]. More recently, additional products containing 20 µg of EE have been introduced and advocated for general use. The first COC containing LNG was introduced in 1968 at a dose of 250 µg in combination with 50 µg of EE. In 1974, a lower-dose formulation, also with a LNG:EE ratio of 5:1 (150 µg of LNG and 30 µg of EE), was introduced and has been used extensively for several decades. A new lower-dose preparation containing 20 µg of EE and 100 µg of LNG that was derived from the original formulation with a progestogen: estrogen ratio of 5:1 was introduced, and the amounts of both estrogen and progesterone were reduced by one-third.

Although this new lower-dose preparation was proven to be clinically effective from the perspective of female contraceptive, its cardiovascular risk is still uncertain. Because of the rarity of cardiovascular events in young women, evaluation of the cardiovascular effects of a COC requires many thousands of women. As a consequence, metabolic risk markers for arterial diseases have become widely used as surrogates for the clinical sequelae of the disease [14, 16].

The combination of EE with higher doses of LNG may cause an increase in LDL-C and a decrease in HDL-C [16], which is supposed to increase the risk of arterial disease. This new formulation, which contained so far the lowest dose of LNG and EE utilizing the 5:1 dose ratio, was introduced and is expected to be neutral with regard to metabolic risk markers for arterial disease or to even bring arterial benefit. The most significant finding of this study was that favorable results were found for the lower-dose preparation in terms of the lipid profiles. The lower-dose COC showed significant differences for decrease of HDL-C after three cycles of treatment versus the other preparation. Furthermore, the lower-dose COC tends to result in smaller changes in LDL-C, TC, and TG after long-term usage, which may point to a potentially more favorable arterial profile. Overall, lipid metabolism change is just one of the metabolism system disturbances that COCs cause.

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