A Systematic Review for the Contraceptive Efficacy and Safety of Compound Left Acetylene Progesterone Tablets

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ABSTRACT
Background and Objectives There is limited information on the efficacy and safety of compound left acetylene progesterone tablets (LNG/EE 100/20 μg) in contraception. To evaluate the efficacy and safety of LNG/EE 100/20 μg for contraception.

Method We searched the medical databases including Pubmed, Web of science, EMBase and Cochrane library through computer; extracted and evaluated the data then performed the meta-analysis by using Review Manager 5.3 software.

Result A total of seven randomised controlled trials including 1786 subjects were recruited for meta-analysis. Compared with other compound oral contraceptives, LNG/EE 100/20 μg showed no significant differences in contraception efficacy [OR = 1.08, 95% CI (0.29, 4.04), P = 0.91] and safety [OR = 0.99, 95% CI (0.81, 1.21), P = 0.92], however, it is better than the other compound oral contraceptives on cycle control efficacy of short cycle [OR = 1.75, 95% CI (1.28, 2.38), P = 0.0004].

Conclusion LNG/EE 100/20 μg were better than the other compound oral contraceptives on cycle control of short cycle, and showed no significant differences in the efficacy and safety.

KEYWORDS compound left acetylene progesterone tablets; contraception; efficacy; safety; meta-analysis

INTRODUCTION
The compound oral contraceptives (COCs) are one of the synthetic steroid hormone preparations, which are composed of progestosterone and estrogen in different proportions. In the United States and some developed countries, nearly half of the fertile women use COCs for contraception. Nowadays, the trend for the COCs all over the world is to develop the compound preparation with a high-contraceptive efficacy and low dose of progestosterone and estrogen, simulating the body’s natural secretion of the hormone level changes. In the early 1980s, according to a study of Brazil, taking COCs including levonorgestrel 100 μg and ethinylestradiol 20 μg (LNG/EE 100/20 μg) has a good effect of contraception. To prove the efficacy and safety of this compound levonorgestrel tablets, we collected randomised clinical research studies of LNG/EE 100/20 μg for contraception and did meta-analysis to make a reference in developing new drugs and making clinical decisions for the manufacturers.

METHODS
Search strategy
By adopting the combination of computer retrieval and manual retrieval, we searched the medical databases including Pubmed, Web of science, EMBase and Cochrane library for contemporary studies published from database founded through August 2015 using the search terms including ‘oral contraceptive’ and ‘‘ethinyl estradiol’ and ‘levonorgestrel’’. At the same time, also retrieved the latest published related review, system evaluation and references which included in the study.
Literature inclusion criteria and exclusion criteria

The inclusion criteria were as follows: (1) Research types: published randomised controlled trial (RCT) studies which provide the original data of LNG/EE 100/20 μg, whether blind and allocation concealment or not; (2) Subjects included healthy women ≥18 years of age. They were to have regular (21–35 days) menstrual cycles for the 3-month period before enrollment; (3) Interventions: the intervention measures for the treatment group were oral LNG/EE 100/20 μg, the control group was using other COCs; (4) Outcome indicators: assessed at least one of the following outcomes: contraceptive efficacy, cycle control and safety assessment; (5) Quality: the Jadad score ≥3; (6) Languages: restricted to English.

The exclusion criteria were as follows: (1) not provide original data studies; (2) not RCT studies; (3) literature or data that were repeatedly reported or with poor quality and cannot use. (4) Without outcome indicators that our research needed. (5) The baseline between two groups was imbalance obviously or subjects between the observation groups have too many differences.

Study selection and data extraction

The two investigators independently extracted data from each study using a standardised data collection form. This information was extracted included that (1) General information: title, author, publication date and sources of literature; (2) Study features: general situation about subjects, baseline, interventions, incidence and symptoms of adverse reactions between two groups. (3) Study quality: whether RCTs and blinded or not, randomised method and the description of withdrawals and dropouts cases; (4) Outcome indicators.

Quality assessment

We used the Jadad method to assess and score the quality of each independent study, scored 0–3, were divided into low-quality study and 4–7 were divided into high-quality study. This assessment was completed by the two investigators independently, if they hold different opinions, then it is resolved through discussion or moved to a third party to judge when necessary.

Statistical analysis

The data analysis was performed using Review Manager 5.3 software from the Cochrane Collaboration. The count data were shown by the relative risk (RR) or odds ratio (OR), the measurement data were shown by weighted mean differences (MD), both of them used the 95% confidence interval (CI). We assessed the heterogeneity of effects using the I² index, where high values suggest heterogeneity and low values suggest homogeneity across studies, for the magnitude of the heterogeneity. A value of I² of 0–25% indicates insignificant heterogeneity, 26–50% indicates low heterogeneity, 51–75% indicates moderate heterogeneity and 76–100% indicates high heterogeneity. If the heterogeneity is too big to make a meta-analysis, then it just does descriptive analysis, if it is necessary to do sensitivity analysis.

RESULTS

Retrieved results

Our search strategy yielded 8538 potentially relevant studies. After the exclusion of 76 duplications, 8462 articles underwent title and abstract review. 8441 articles were excluded as they were clearly not observational studies, leaving 21 articles for full-length article review. After screening step by step, 7 RCT studies met inclusion criteria, which contain a total of 1786 subjects (LNG/EE 100/20 μg group 813, control group 973). Figure 1 outlines the search methodology and review process.

Baseline data and quality evaluation of included studies

The baseline data included in the studies are shown in Table 1. According to the Jadad score, the quality evaluation is scored as follows: random sequence produced, concealment of allocation, withdrawals and dropouts, respectively and blinded. This is shown in Table 2. The study data are complete and the results were reported without selectivity.

Meta-analysis

Contraception efficacy

There are 511–14,16 studies reported about the contraception efficacy, including 1197 subjects totally, the treatment group has 574 subjects and the other 623 subjects were in the control group. A total of nine subjects were reported to be pregnant in two studies11,14 and the rest...
## Table 1 Baseline data of included studies.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Study design</th>
<th>Age (T/C, y)</th>
<th>Case number</th>
<th>Randomisation methods</th>
<th>Interventions</th>
<th>Homogeneity between groups</th>
<th>Blinded</th>
<th>Outcome indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reisman et al. (1999)</td>
<td>RCT</td>
<td>26.8 ± 6.07/26.0 ± 6.09</td>
<td>155/167</td>
<td>Simple random</td>
<td>LNG/EE 100/20 μg</td>
<td>NET/EE 500/1000/1500 μg</td>
<td>Preferably</td>
<td>No</td>
</tr>
<tr>
<td>Endrikat et al. (2001)</td>
<td>RCT</td>
<td>25.3 (18–36)/25.4 (17–36)/26.1 (18–35)</td>
<td>380/380</td>
<td>Not specified</td>
<td>LNG/EE 100/20 μg</td>
<td>LNG/EE 150/30 μg; NET/EE 500/20 μg</td>
<td>Preferably</td>
<td>No</td>
</tr>
<tr>
<td>Jespersen et al. (2004)</td>
<td>RCT</td>
<td>23.5 (19–28)/24.1 (20–30)</td>
<td>22/27</td>
<td>Not specified</td>
<td>LNG/EE 100/20 μg</td>
<td>LNG/EE 100/30 μg</td>
<td>Preferably</td>
<td>No</td>
</tr>
<tr>
<td>Sabatini et al. (2006)</td>
<td>RCT</td>
<td>31.0 ± 6.1/29.4 ± 5.7/30.2 ± 5.9</td>
<td>94/186</td>
<td>Simple random</td>
<td>LNG/EE 100/20 μg</td>
<td>GSD/EE 60/15 μg; ENG/EE 120/15 μg</td>
<td>Preferably</td>
<td>No</td>
</tr>
<tr>
<td>Seidman et al. (2015)</td>
<td>RCT</td>
<td>25.0 ± 3.85/26.8 ± 3.92/26.4 ± 4.43</td>
<td>48/94</td>
<td>Simple random</td>
<td>LNG/EE 100/20 μg</td>
<td>DSG/EE 150/20 μg; DRSP/EE 300/20 μg</td>
<td>Preferably</td>
<td>No</td>
</tr>
<tr>
<td>DelConte et al. (1999)</td>
<td>RCT</td>
<td>26.7 ± 6.62/28.0 ± 6.68</td>
<td>84/89</td>
<td>Not specified</td>
<td>LNG/EE 100/20 μg</td>
<td>NETA/EE 1000/20 μg</td>
<td>Preferably</td>
<td>No</td>
</tr>
<tr>
<td>Endrikat et al. (2002)</td>
<td>RCT</td>
<td>22.7 (18–27)/24.2 (18–32)</td>
<td>30/30</td>
<td>Not specified</td>
<td>LNG/EE 100/20 μg</td>
<td>LNG/EE 150/30 μg</td>
<td>Preferably</td>
<td>No</td>
</tr>
</tbody>
</table>

T: treatment group; C: control group; 2) some literatures set two groups of the control group. NET: norethindrone, GSD: gestodene, ENG: etonogestrel, DSG: desogestrel, DRSP: drospirenone, NETA: norethindrone acetate.
Table 2  Quality evaluation of literature results.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Random sequence produced</th>
<th>Concealment of allocation</th>
<th>Withdrawals and dropouts</th>
<th>Blinded</th>
<th>Jadad score (score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reisman et al. (1999)</td>
<td>Appropriate</td>
<td>Appropriate</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Endrikat et al. (2001)</td>
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<td>Unclear</td>
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<td>No</td>
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<tr>
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<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>3</td>
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<tr>
<td>Sabatini et al. (2006)</td>
<td>Appropriate</td>
<td>Appropriate</td>
<td>Yes</td>
<td>No</td>
<td>5</td>
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<tr>
<td>Seidman et al. (2015)</td>
<td>Appropriate</td>
<td>Appropriate</td>
<td>Yes</td>
<td>No</td>
<td>5</td>
</tr>
<tr>
<td>DelConte et al. (1999)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>3</td>
</tr>
<tr>
<td>Endrikat et al. (2002)</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
<td>3</td>
</tr>
</tbody>
</table>

Fig. 2  Compared contraception efficacy of LNG/EE 100/20 μg vs. other compound oral contraceptives.

Fig. 3  Compared cycle control efficacy of LNG/EE 100/20 μg vs. other compound oral contraceptives.

...of the three studies were no subjects reported with pregnancy. There is no statistical heterogeneity among these 5 studies ($P = 0.55$, $I^2 = 0$%), so use the fixed-effects model to do the meta-analysis. The results showed that when compared with other COCs, LNG/EE 100/20 μg showed no statistically significant difference in contraception efficacy [OR = 1.08, 95% CI (0.29, 4.04), $P = 0.91$], as shown in Fig. 2.

Cycle control efficacy

The cycle control mainly includes five aspects: (1) menstrual cycle; (2) intermenstrual bleed; (3) duration of intermenstrual bleeding; (4) days of irregular bleeding (not intermenstrual bleeding); (5) degree of irregular bleeding (not menstrual bleeding). Among these five aspects, based on the bleeding volume, the degree of irregular bleeding can be divided into breakthrough bleeding and spotting. Because, the observation of cycle length in each study is different, so we extract the cycle 3 data to analyse. There are 4 studies reported the cycle control efficacy in cycle 3, including 1351 subjects totally; the treatment group has 667 subjects and the other 684 subjects are in the control group. There is no statistical heterogeneity among these 4 studies ($P = 0.22$, $I^2 = 33$%), so used the fixed-effects model to do meta-analysis. The results showed that when compared with other COCs, LNG/EE 100/20 μg had statistically significant difference in the cycle control efficacy in cycle 3 [OR = 1.75, 95% CI (1.28, 2.38), $P = 0.0004$], as shown in Fig. 3.

Incidence of adverse events

The seven included studies reported all adverse events, including 1692 subjects totally, the treatment group has 813 subjects and the other 879 subjects were in the...
control group. The reported adverse events are mainly concentrated with headache, breast pain, nausea, depression, dizziness, vomiting, acne and so on. There is no statistical heterogeneity among these 7 studies ($P = 0.21$, $I^2 = 29\%$), so used the fixed-effects model to do meta-analysis. The results showed that when compared with other COCs, LNG/EE 100/20 μg showed no statistically significant difference in safety [OR = 0.99, 95% CI (0.81, 1.21), $P = 0.92$], as shown in Fig. 4.

**CONCLUSION**

**Quality analysis for including literatures**

According to the study standard, there are a small number of the literatures which confirm the inclusion criteria, especially the lack of a multicenter clinical trial of large sample and long follow-up results. In doing the methodological quality evaluation of the including studies, the results show that 4 of the studies are in inferior quality and the other 3 are in high quality. Although all the studies mentioned random methods, only 3 of them specifically describes the method. All the included studies are open and no blinded experiment was performed. Therefore, a positive conclusion for the contraceptive efficacy and safety of LNG/EE 100/20 μg is still a lack of better evidence.

**Meta-analysis conclusion**

The estrogen and progesterone contain in COCs has synergy. Estrogen through negative feedback effect on the hypothalamus–pituitary–ovarian axis, through inhibiting the secretion of gonadotrophic hormone (GnRH–Gn), then further inhibiting the secretion of follicle stimulating hormone (FSH) and luteinising hormone (LH), which have the effect on inhibiting the ovulation. The progesterone is working by making the cervix mucus thicken and change the lining of endometria, prevent the implanting of sperm. The progesterone and estrogen ratio of 5:1 is the same as the traditional formula with high-dose contraceptives, however, the content of estrogen descend from 30 to 20 μg can greatly reduce the incidence of adverse events, such as vascular embolisation, abdominal distension, breast pain, nausea and so on. In addition, the estrogen is one of the important factors in determining cycle control, so descend of the estrogen levels can make the efficacy of cycle control to be better.

In conclusion, as the meta-analysis show, LNG/EE 100/20 μg was better than other COCs on cycle control efficacy in short cycles, no significant differences in the contraception efficacy and safety. So, if women have the need of contraception in short time, they can choose the LNG/EE 100/20 μg. But due to the limited quantity and quality of the included studies, these results need to be further confirmed by a larger sample and well-designed clinical trials.

**REFERENCES**