Effect of Dienogest and the GnRH-a in Endometriosis: A Meta-Analysis

Objective
The aim of this study is to systematically evaluate the efficacy and safety between dienogest and some GnRH-a while treating endometriosis.

Methods
The search was applied to Cochrane Library, EMBASE, PubMed, Web of Science, CNKI, WANFANG DATA, VIP and CBM database. All types of clinical study about dienogest and GnRH-a in endometriosis were included. All authors extracted data and assessed literature quality independently. Meta-analysis was conducted using RevMan software.

Results
Six studies included show that the efficiency of prevent uteruspain MD = 1.40 (95% CI = 2.14–4.94, P = 4.94), the incidence of headache (OR = 0.75, 95% CI = 0.75–1.10, P = 0.14), and dienogest treatment of endometriosis in the possibility of hot flashes (OR = 0.18, 95% CI = 0.18–0.27, P < 0.00001) and the possibility of weight gain (OR = 0.74, 95% CI = 0.74–1.29, P = 0.29) than GnRH-a group of small, in contrast, use dienogest in the treatment of endometriosis with irregular bleeding possibility is larger than GnRH-a group (OR = 15.83, 95% CI = 15.83–30.82, P < 0.00001).

Conclusion
Compared the prevent uteruspain in treating endometriosis, dienogest and GnRH-a perform an analogous effect in prevent pain. But both could cause different degree of adverse reactions. Clinical medication should be depending upon the patients’ and clinical condition.

KEYWORDS
dienogest, endometriosis, GnRH-a, meta-analysis

INTRODUCTION
Endometriosis is a chronic disease commonly occurring in women of childbearing age. It also has the possibility of onset for adolescent girls and postmenopausal women. The prevalence rate is about 3–10% of the female population. The main clinical manifestations were chronic pelvic pain, dysmenorrhea (secondary or progressive aggravation), abnormal menstruation, infertility, pelvic nodules and mass.

On the current level of medical care, endometriosis could hardly be cured. The major treatment is to relieve its pain, reduce the recurrence of the disease, improve the quality of life of patients. Because endometriosis is a hormone dependent disease, its major treatment is using hormone drugs. Although these drugs have certain curative effect in the treatment of pain, there are some side effects that exists. On one hand, the treatment effect of GnRH-a is significant, but its long-term use would reduce systemic estrogen level in patients with excessive.

Dienogest as the fourth generation of hybrid progesterone, which maxed the common progesterone and C-19 derivatives-progester one to present a dual nature, was used to relieve the pain and other irregular bleeding symptoms caused by endometriosis. There is still a lack of certainly clinical trial research for the comparison of efficacy and safety in GnRH-a and dienogest. This research adopts the system evaluation method and meta-analysis, based on their efficacy and safety difference in endometriosis, to provide a few reliable evidence for clinical treatment.
METHODS

Search strategy and inclusion criteria

According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), statement guidelines for the meta-analysis of Random Control Trials (RCTs), we searched Cochrane Library, EMBASE, PubMed, Web of Science, CNKI, WANFANG DATA, VIP and CBM database to identify the clinical research of GnRH-a versus dienogest alone in the treatment of endometriosis in English and Chinese languages from database creation to December 2018, using the following Medical Subject Headings (MeSH) and keywords as search strategy: (dienogest, triptorelin, buserelin, leuprorelin, goserelin) AND (endometriosis) AND (GnRH-a) AND (clin* OR study* OR trial*). The reference list of articles were scanned to identify potential additional relevant studies. For articles published in Chinese, we translated the titles into English and added the DOI address in reference part. Two reviewers (Jinyu Qiu and Haihua Guo) screened the articles independently based on the inclusion and exclusion criteria. Procedure of search and select process is shown in Fig. 1.

Inclusion criteria

(1) Participants of older than 18 years with a clear pathology, clinical diagnosis of endometriosis.
(2) Intervention measures: use of dienogest or GnRH-a therapy.
(3) Type of literature: clinical trials, dienogest and GnRH-a treatment groups have higher comparability, and the feasibility of the experimental scheme is strong.
(4) Outcome indicators: the prevention of pain efficiency, the incidence of adverse reactions, including headache, irregular bleeding, loss of sexual desire, hot flashes or else.

Exclusion criteria

Studies met any of the following criteria were excluded:
(1) Non-clinical research;
(2) non-dienogest or GnRH-a treatment;
(3) combined surgery, radiotherapy or other treatment;
(4) repeated published literature;
(5) cannot get the full text or cannot extract the data of literature;
(6) no outcome studies.

Quality assessment

Two reviewers (Ying Liufu and Jinyu Qiu) conducted a risk-of-bias assessment independently according to the standardized manner recommended in the Cochrane Handbook for Systematic Reviews of Intervention and then crosschecked. Jadad Scale1,2 was used, which consist of the following items: Random sequence generation, allocation concealment, blindness, the completeness of the outcome data, selective reporting of results, and other possible bias, scored 1–2 were regarded as low-quality research, while 3–5 were high. There were no disagreements between reviewers.

Data extraction and outcome measures

On the basis of pre-designed data extraction sheet, two reviewers (Jinyu Qiu and Haihua Guo) extracted the data from each included studies independently. The extracted information include: (1) Name of first author; (2) year of publication; (3) type of trial design; (4) characteristics of trial participants (including age, number); (5) type of intervention; (6) type of outcome measure (including the total number of effective cases).

Statistical analysis

This meta-analysis was performed using RevMan5.3 software. All the relative outcome was used as the statistical data, and the effect was expressed as 95% confidence intervals (95% CI). The heterogeneity test between the included studies was based on the I² test. If there was no statistical heterogeneity (I² ≤ 50%), the fixed effect model was used, whereas the random effect model was used. Using the hypothesis test as a statistical significance analysis of the final outcome. According to the statistical P-value of Z(u), final outcome can be analyzed whether there was statistical significance, P ≤ 0.05 for the difference was statistically significant, otherwise, the difference was not statistical significance. At the same time, the study also used the 95% CI method for analysis. In the forest plots, the 95% CI did not contain the middle line indicating the combined statistics were statistically significant.

RESULTS

Characteristics of studies in the meta-analysis

The search of Chinese and English databases provided total 123 literatures. After removing 111 non-clinical research, 12 studies were excluded after reading the title and abstract, it indicated that these articles did not meet the criteria (experimental studies, summarizes or not full-text-free article). Then examining the full-text, six trials were excluded, and finally a total of 1,333 patients were included in the meta-analysis. Details of the literature screening process were shown in Fig. 1 and Table 1.
These six included studies were randomized controlled trials comparing the matrine injection dienogest and GnRH-a. All of the trials conducted since the database exist to 2018. The main characteristics of six included trials and the quality of them assessed by Jadad score were shown in Table 1 as well. All the included studies mention the “random”, one of which was grouped by random number table method, and none of the other studies referred to the specific randomized method. And all of the included studies did not mention the allocation of concealment and blindness method.

**Efficacy of pain control in endometriosis**

Three of the six included studies reported a short-term clinical efficacy, including 730 patients, out of which 357 patients were in the eating dienogest group (EDG) and 373 patients in the GnRH-a group. For their existing statistical heterogeneity ($I^2 = 0\%$, $P = 0.91$), we used fixed effect (Mantel–Haenszel model) as the model. The result mention the efficacy of pain control in endometriosis, showed that the GnRH-a group was higher than that of the DEG group [MD = 1.40, 95% CI (−2.14, 4.94), $P = 0.44$]. None of the record infer to get pain control advantage while using dienogest or GnRH-a in endometriosis in Fig. 2.

**Headache happening**

While statistics the adverse reaction in two drugs, there were five articles, 416 patients in the EDG and 423 in the GnRH-a group. As shown in Fig. 3, statistical heterogeneity is with statistical significance ($I^2 = 6\%$, $P = 0.37$), the fixed effect model (Mantel–Haenszel model) was used as a meta-analysis method. The results tended to indicate dienogest group might get a headache happening rate, but do not perform a certainly confirm result [OR = 0.75, 95% CI (0.51, 1.10)].

$Z$-curve test ($Z(u) = 1.49, P > 0.05$) showed that the results were not statistically significant.

**Hectic fever**

Of the studies included, there were four trials reporting the hectic fever happening, a total of 665 patients, were split into two groups. There was no significant heterogeneity between the groups [$I^2 = 93\%, P < 0.01$]. As shown in Fig. 4, the results indicated that dienogest could make patients hectic fever than GnRH-a [OR = 0.18, 95% CI (0.12, 0.27)], and $Z(u)$ test showed that the results were statistically significant [$Z = 8.41, P < 0.0001$].

**Weight gain**

Three studies evaluated the adverse reactions in put on weighting, a total of 479 patients (233 in EDG and 246 in GnRH-a group) were included. There was statistically significant heterogeneity between studies [$I^2 = 66\%, P = 0.05$]. Meta-analysis result makes no sense in forest gram [OR = 0.74, 95% CI (0.43, 1.29)]. $Z(u)$ test demonstrated the similar results [$Z = 3.76, P = 0.29$] (Fig. 5).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of parents (control/treatment)</th>
<th>Intervention</th>
<th>Duration (weeks)</th>
<th>Random</th>
<th>Jadad Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strowitzki</td>
<td>2010</td>
<td>109/120</td>
<td>Dienogest</td>
<td>24</td>
<td>Mention</td>
<td>3</td>
</tr>
<tr>
<td>Gerlinger</td>
<td>2012</td>
<td>120/128</td>
<td>Dienogest</td>
<td>24</td>
<td>Mention</td>
<td>1</td>
</tr>
<tr>
<td>Takaesu</td>
<td>2016</td>
<td>56/55</td>
<td>Dienogest</td>
<td>24</td>
<td>Mention</td>
<td>2</td>
</tr>
<tr>
<td>Vercellini</td>
<td>1993</td>
<td>28/29</td>
<td>Dienogest</td>
<td>24</td>
<td>Mention</td>
<td>2</td>
</tr>
<tr>
<td>Vercellini</td>
<td>2016</td>
<td>90/90</td>
<td>Dienogest</td>
<td>96</td>
<td>Mention</td>
<td>1</td>
</tr>
<tr>
<td>Harada</td>
<td>2010</td>
<td>129/126</td>
<td>Dienogest</td>
<td>24</td>
<td>Mention</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 1 Characteristics of included trials.
DISCUSSION AND CONCLUSION

Treatment of endometriosis after surgery for stage endometriosis through surgery is still not completely cured, follow-up treatment mainly play an inhibitory effect rather than therapeutic effect, combined with the characteristics of endometriosis recurrence, so in the long period of treatment, not only to consider the effectiveness of drug therapy also want to consider the safety of drug treatment. GnRH-a drugs and dienogest is recognized as a safe and effective drug, but they take effect in different mechanisms. Aims to study the safety and efficacy, this research measure GnRH-a drug and dienogest in endometriosis using meta-analysis. The results showed that the efficacy in GnRH-a drug and dienogest for pain control are similar, adverse reactions in patient perform different, such as in headache, hectic fever.

Dienogest is a selective progesterone, which combines the pharmacological properties of 19-progesterone and progesterone derivatives, have significant effect on endometrium and ovarian androgen, no moderate inhibitory activity, due to modification of dienogest in structure, compared with the other progesterone, side effects are fewer. GnRH-a is a hypothalamic preparation, as an inhibition of ovarian release. Compared with dienogest, GnRH-a take IOTA advantage in increase of weight gain and decrease of hot flashes.

But this study has some limitations: According to the analysis of the above statistics, while measuring the pain control efficacy, we do not include the analysis of the remaining four studies which also showed the dienogest and GnRH-a in advantage in endometriosis but higher and miscellaneous pain happen. From forest grams, we saw that most of the result contain invalid line (the middle line), with a small number of suggesting statistical significance. In the compare in adverse reaction, mainly from dienogest and GnRH-a in endometriosis patients, due to the outcome measure difference in articles, the numbers of samples and studies asymmetry. There is no statistical
significance in weight gain, and not enough evidence that the different cause by gender or dose. It may need further research.

With regard to the incidence of hectic fever, in RevMan software make a hiatus funnel map, which mention the data deficient in our study. In this study, the quality of the most included studies is not high. Dienogest and GnRH-a was used in Japan and Europe, but there is a few data in China or other Asian countries, that may make a bias in race. Because the dienogest is novelty relatively, its efficacy and safety for endometriosis requires a scientific clinical study yet.

DISCLAIMER:
Any views expressed in this paper are those of the authors and do not reflect the official policy or position of the Department of Defense.

ACKNOWLEDGMENT
Special thanks are due to Guohua Cheng of CTMRC, as the major mentor of this research, and Haihua Guo of JNU-ZH health Institute, for assistance with write and revising to this article, Rong Wang of Pharmacy School-JNU, for technical assistance.

REFERENCES