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Systematic Review

Levonorgestrel intrauterine system versus oral progestin for preventing the recurrence of endometrial polyps after hysteroscopic resection: A meta-analysis of 19 randomized controlled trials

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Summary

Background: The aim of this meta-analysis was to compare levonorgestrel intrauterine system (LNG-IUS) with oral progestin for preventing the recurrence of endometrial polyps after hysteroscopic resection. *Materials and Methods:* Computerized literature search was performed in PubMed and several Chinese databases to screen for relevant trials. Quality assessment and meta-analysis were performed for the included trials. *Results:* A total of 19 randomized controlled trials were identified. Meta-analysis indicated that the LNG-IUS group was associated with lower recurrence rate of endometrial polyps than the oral progestin group ($p < 0.0001$), while there was no significant difference in the incidence of abnormal uterine bleeding between groups ($p > 0.05$). In terms of adverse effects related to progestin, the LNG-IUS group had significantly fewer adverse effects than the oral progestin group ($p < 0.0001$). Additionally, the LNG-IUS group had thinner endometrium and higher hemoglobin levels than the oral progestin group ($p < 0.00001$). *Conclusion:* The LNG-IUS was more effective and safer in preventing the recurrence of endometrial polyps after hysteroscopic resection than oral progestin.

Key words: Endometrial polyps; Levonorgestrel intrauterine system; LNG-IUS; Oral progestin; Meta-analysis.

Introduction

Endometrial polyps (EMP), which are associated with endometrial hyperplasia, are common in gynecology with a high incidence of recurrence [1-3]. Clinical manifestations of EMP include abnormal uterine bleeding, pelvic pain and even infertility or abortion [1-3]. The risk of EMP progression to atypical hyperplasia and endometrial cancer could be up to 23.8% and 12.9% respectively [4, 5]. The exact pathogenesis of EMP has not been fully elucidated. Local hormone levels and inflammatory factors may be involved in the development and progression of EMP [1-3]. With the development of the minimally invasive technique, hysteroscopic endometrial polyps resection (transcervical resection of polyps, TCRP) is regarded as the "gold standard" for the diagnosis and treatment of EMP [4]. However, TCRP cannot improve the local microenvironment of endometrium, which is prone to relapse of EMP. The therapeutic goal for EMP is not only to remove the polyps or relieve symptoms, but also to reduce the recurrence rate. Anti-estrogen therapy is the common method for recurrent EMP prevention [5]. Oral progestin is also the traditional way, but systemic adverse effects such as liver dysfunction, venous thrombosis and risk of breast cancer limit its application [6, 7].

Levonorgestrel intrauterine system (LNG-IUS) with sustained release intrauteine progestin can induce endometrial gland atrophy and interstitial decidualization, which makes the endometrium thin and prevents EMP recurrence [8-11]. To date there have been several randomized controlled trials suggesting that LNG-IUS can prevent the recurrence of tamoxifen induced EMP in women with breast cancer [12, 13]. However, women of childbearing age without breast cancer and tamoxifen exposure are the main population of patients with EMP, but no large sample study or meta-analysis has focused on the recurrence of EMP after TCRP in this population.

A total of 19 randomized controlled trials (RCT) from China (In Chinese) reported the efficacy and safety of LNG-IUS compared with oral progestin in preventing the recurrence of EMP after TCRP with different conclusions, listed in Table 1 and provided as a supplement [14-32]. The aim of this study was to perform a meta-analysis to compare LNG-IUS with oral progestin for preventing the recurrence of EMP after TCRP.

Materials and Methods

Eligibility and search strategy

A computerized search of the PubMed, CNKI, WanFang, WeiPu and Chinese Medical Journal Network litera-

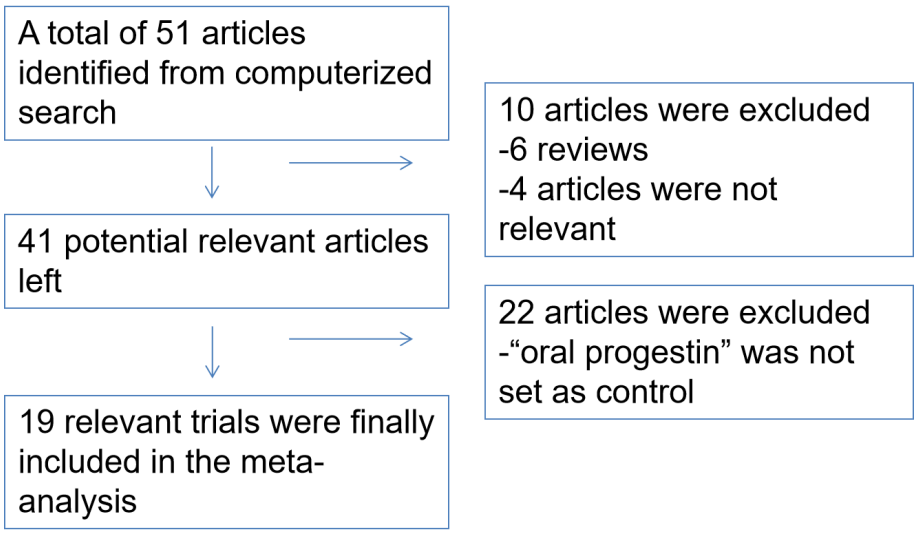

Figure 1. — Trial selection flow chart. The flow chart shows the process for selecting relevant randomized clinical trials enrolled in this meta-analysis.

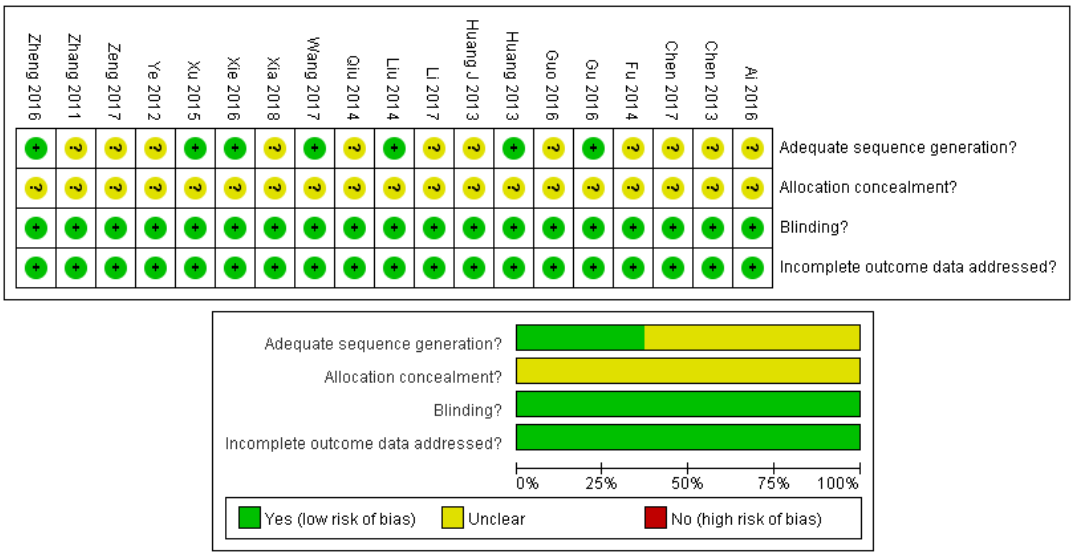

Figure 2. — Risk of bias in the methodological quality assessment. Red means high risk, green means low risk, and yellow means insufficient information from one article about the process to permit judgment of high or low risk of bias.

ture databases was performed to identify all published trials that compared LNG-IUS with oral progestin for preventing the recurrence of EMP after transcervical resection through May 2018. The Medical Subject Headings (MeSH) terms used were: ((LNG-IUS) OR (levonorgestrel-releasing intrauterine system) OR (levonorgestrel intrauterine system)) AND ((endometrial polyps) OR (endometrial polyp) OR (EMP)) AND ((randomized controlled trial) OR (randomized) OR (random)). Manual searches were done to identify any potentially relevant studies in reference lists. Only randomized control trials were included, while reviews, letters, case reports, case control studies and cohort studies were excluded.

Study selection and data extraction

Potentially relevant trials were selected for inclusion in the meta-analysis if they met the following criteria: 1) based on the patients after TCRP; 2) randomized control trials to compare LNG-IUS with oral progestin; 3) clinical outcomes comprised the recurrence of EMP, as well as complications within 6 to 24 months after TCRP. Trials with incomplete or unclear data were excluded. Two authors (Y.S. and X.Y.) independently reviewed the full texts of the potentially relevant trials according to the inclusion criteria. Any disagreements were resolved by discussion and consensus.

The following information such as first author, published year, total and recurrent cases of groups, and the inci-

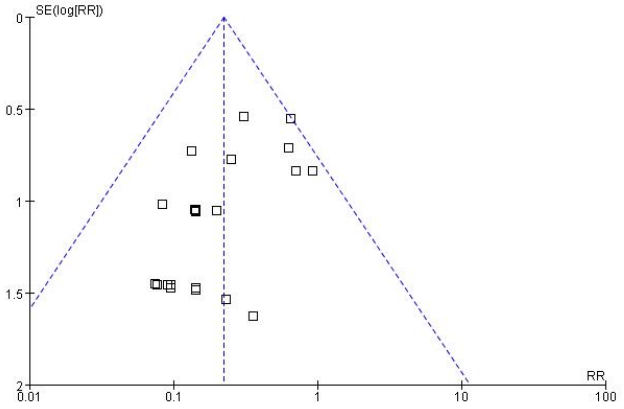

Figure 3. — Funnel plot (publication bias). The funnel plot of primary outcome is almost symmetrical suggesting no significant publication bias existed in this meta-analysis.

dence of adverse effects as well as the endometrial thickness and the hemoglobin level were extracted from selected studies. Clinical characteristics such as age and the presence of multiple polyps were also recorded.

Methodological quality was assessed using the Review Manager (RevMan 5.3) program, which classifies items related to an individual study's randomization, allocation concealment, blinding, and dropouts according to three potential responses: yes, no, and unclear.

Statistical analysis

Statistical analyses were carried out with the RevMan 5.3 and STATA 10.0 program. For categorical variables, the risk ratio (RR) and 95% confidence interval (CI) were calculated by using a fixed-effects model with the Mantel-Haenszel test. In cases where significant heterogeneity was found to exist across studies, the calculated RR was further assessed by the DerSimonian-Laird random-effects model to account for the inter-study differences. For continuous variables, the mean difference (MD) and 95% CI were calculated by the inverse variance weighting method to minimize the variance of the sum. Statistical heterogeneity was evaluated using the Q statistic with a p-value less than 0.1. Statistical significance was considered to have been reached if the p-value was less than 0.05.

Results

Eligible studies

A total of 51 potentially relevant articles were identified by the initial computerized literature search. After screening the summary and abstract, 32 articles were excluded based on: meta-analysis design or reviews (n = 6); not related with the subject (n = 4); not having oral progestin as the control group (n = 22). Finally, nineteen articles met the inclusion criteria for this meta-analysis. The selection process for the included trials is presented in Figure 1.

The characteristics of the included trials are summarized in Table 1. The methodological quality assessment of the included trials is summarized in Figure 2. A total of 2,135 patients were included in the 19 trials, among which 968 (45.3%) were randomly assigned to the LNG-IUS group and 1,167 (54.7%) to the oral progestin group. There was no significant difference in the mean age and the multiple polyps ratio between two groups. The funnel plot of primary outcome was symmetrical suggesting no publication bias existed in the meta-analysis (Figure 3), which was identified by a negative Egger's test ($p > 0.05$).

Primary outcomes (Recurrence of endometrial polyps)

All the nineteen articles reported data on EMP recurrence. Heterogeneity testing showed no statistical evidence of heterogeneity among these studies ($p = 0.89$). Pooled analysis showed that the LNG-IUS group was associated with a lower recurrence rate of EMP compared to the oral progestin group during the follow-up from 6 months to 24 months (Figure 4: RR = 0.12, $p = 0.0001$; RR = 0.17, $p < 0.0001$; RR = 0.34, $p < 0.0001$).

Secondary outcomes (Adverse effects)

(1) Abnormal uterine bleeding

Ten articles reported the data on abnormal uterine bleeding. Pooled analysis showed no difference in the incidence of abnormal uterine bleeding between the LNG-IUS group and the oral progestin group during the follow-up from 6 to 24 months (Figure 5A: $p = 0.30$).

(2) Other adverse effects

Eight articles reported the data on other adverse effects, such as liver dysfunction, acne, nausea and vomiting. Pooled analysis showed that the LNG-IUS group had significantly fewer adverse effects than the oral progestin group during the follow-ups (Figure 5B: RR = 0.17, $p < 0.0001$).

(3) Endometrium thickness

Eleven articles reported data on endometrial thickness. Pooled analysis showed that the mean endometrial thickness of the LNG-IUS group was significantly lower than that of the oral progestin group during the follow-up from 6 to 24 months (Figure 6: MD = -2.26, $p < 0.0001$).

(4) Hemoglobin level

Four articles reported the data on hemoglobin levels. Pooled analysis showed that the mean hemoglobin level of the LNG-IUS group was significantly higher than that of the oral progestin group during the follow-up from 6 to 24 months (Figure 7: MD = 15.57, $p < 0.0001$).

Discussion

Endometrial polyps are a common gynecologic disease, prevalence of 7.8% [33], characterized by local endometrial hyperplasia, which can cause abnormal uterine bleeding, infertility and may undergo malignant transformation. Endometrial polyps are more common in women over 35 years old but rare after 70 years of age [2, 33]. However, the prevalence of malignant EMP is statistically significantly higher in postmenopausal women at 4.93% compared to

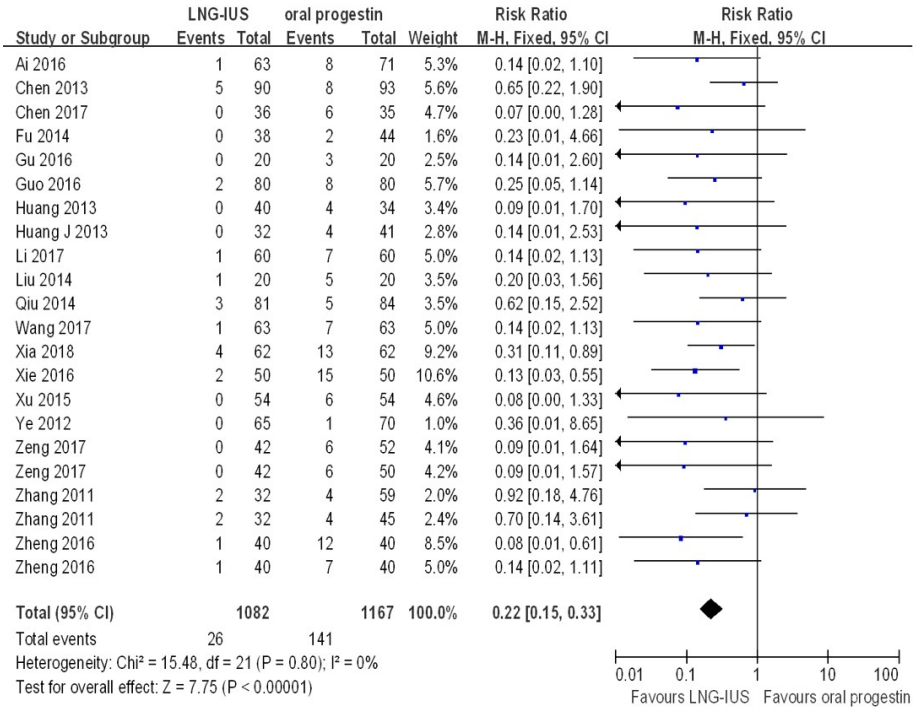

Figure 4. — LNG-IUS versus oral progestin in the incidence of endometrial polyps recurrence with risk ratios and 95% confidence intervals. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. CI, confidence interval; M-H, Mantel-Haenszel.

1.12% in premenopausal women, $p < 0.0001$ [34]. The potential mechanism of EMP includes estrogen and inflammatory stimulation [1-3]. Polycystic ovary syndrome, endometriosis, postmenopausal hormone replacement and tamoxifen medication are the risk factors for EMP [2]. On the other hand, local inflammatory environment, such as inflammatory cell infiltration and inflammatory factors secretion, promotes the occurrence and development of EMP [3].

Presently, hysteroscopy is regarded as the "gold standard" for the diagnosis and treatment of EMP [4], but endometrial curettage under hysteroscopy can neither remove all the basal layer intima of lesions nor change the estrogen level or the local inflammatory environment. Therefore, EMP commonly recurs with an average recurrence time of 6 to 12 months after TCRP [5]. It has been reported that the recurrence rate of EMP is as high as 50% [5]. As estrogen stimulation is a potential mechanism of EMP, anti-estrogen therapy could be one of the useful methods to prevent EMP from recurrening [5]. However, oral progestin is associated with systemic adverse effects, such as liver dysfunction, venous thrombosis and other issues. These potential side effects may limit the application of oral progestin [6, 7].

The main component of levonorgestrel intrauterine system (LNG-IUS) is a small and soft T shaped stent, which is convenient to place into the uterine cavity as a contraceptive device [8]. The longitudinal arm of the T stent is a unique store of hormone, containing 52 mg levonorgestrel, releasing at the speed of 20 μg/24h, and maintained for up to 7 years [8]. After LNG-IUS insertion, the concentration of levonorgestrel in the local endometrium is high, while the amount absorbed into the systemic circulation is very low [9]. Therefore, LNG-IUS has a major effect on the endometrium, such as endometrial gland atrophy and interstitial decidualization, but minimal effect systemically, such as on liver function, coagulation profile and other adverse effects related to progestin [10, 11].

This meta-analysis enrolled 19 RCTs that had reported the efficacy and safety of LNG-IUS compared with oral progestin in preventing EMP after hysteroscopic resection. The results showed that the LNG-IUS group had a lower recurrence rate of EMP after hysteroscopy than that of the oral progestin group without increasing the risk of abnormal uterine bleeding. In terms of systemic adverse effects related to progestin, such as liver dysfunction, acne, nausea and vomiting, the LNG-IUS group has obvious advantages over the oral progestin group. In addition, the average endometrial thickness in the LNG-IUS group was significantly lower than that of the oral progestin group during follow-up, while the average hemoglobin level was significantly higher than that in the oral progestin group.

The molecular mechanism of EMP relapse is unclear. Taylor's study suggested that the local increase of Bcl-2 expression and the consequent decrease of apoptosis were the potential mechanism of EMP [35]. The increase of Bcl-2 expression made EMP' tissues unable to apoptose pe-

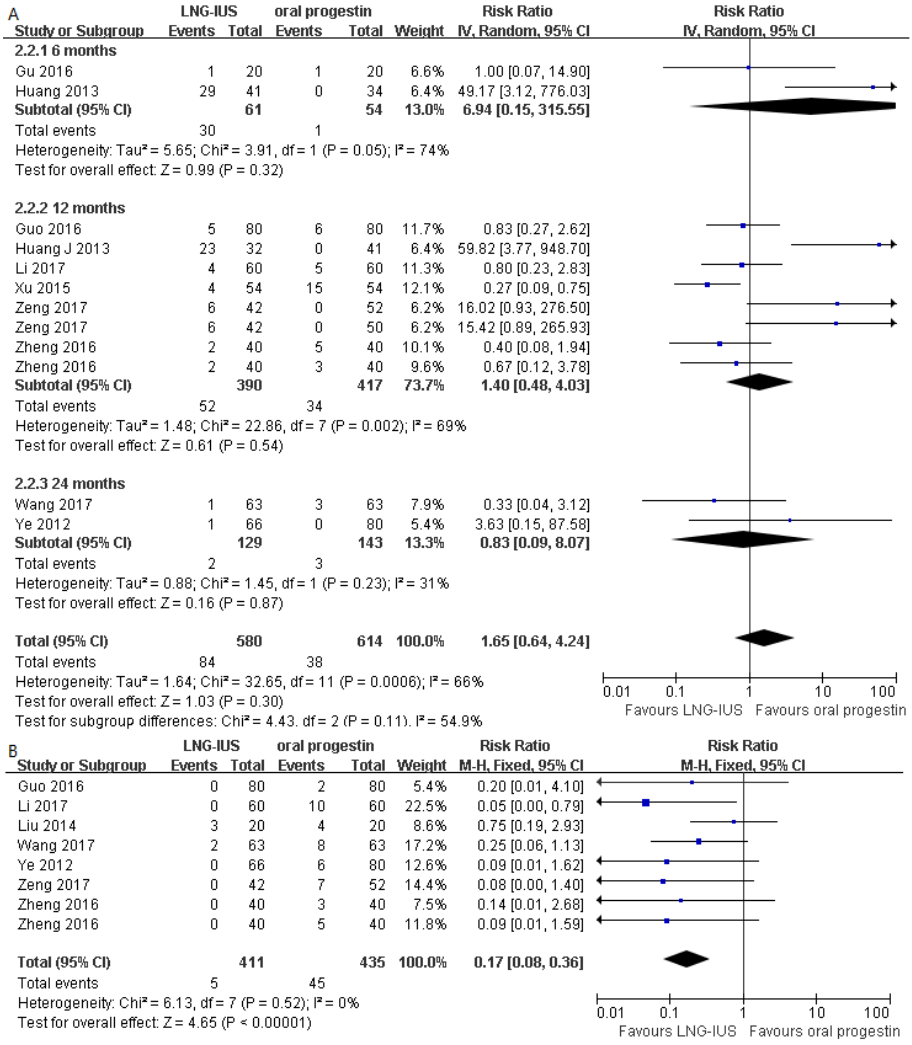

Figure 5. — LNG-IUS versus oral progestin in the incidence of adverse effects (A: abnormal uterine bleeding and B: other adverse effects) with risk ratios and 95% confidence intervals. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. CI, confidence interval; IV, Inverse Variance; M-H, Mantel-Haenszel.

riodically during the secretory period and EMP failed to fall off does the normal endometrium, so EMP was considered as a kind of maladjusted tumor that cannot proliferate and differentiate with normal endometrium [35]. Alternatively, the high expression of epidermal growth factor receptor (EGFR) and the low expression of Mig-6 gene in the endometrium were also suspected to be related to the recurrence of EMP [36-39]. The molecular mechanism of EMP recurrence still need to be further explored through clinical and experimental researches.

There were some limitations in this meta-analysis. First, all the 19 included trials were from China [14-32]. Second, the sample size of some included studies was small and the randomization concealment of trials was not very rigorous.

In conclusion, LNG-IUS was more effective and safer in preventing the recurrence of EMP after hysteroscopy than oral progestin, which could be applicable to clinical practice.

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Conflict of Interest

The authors declare no conflict of interest.

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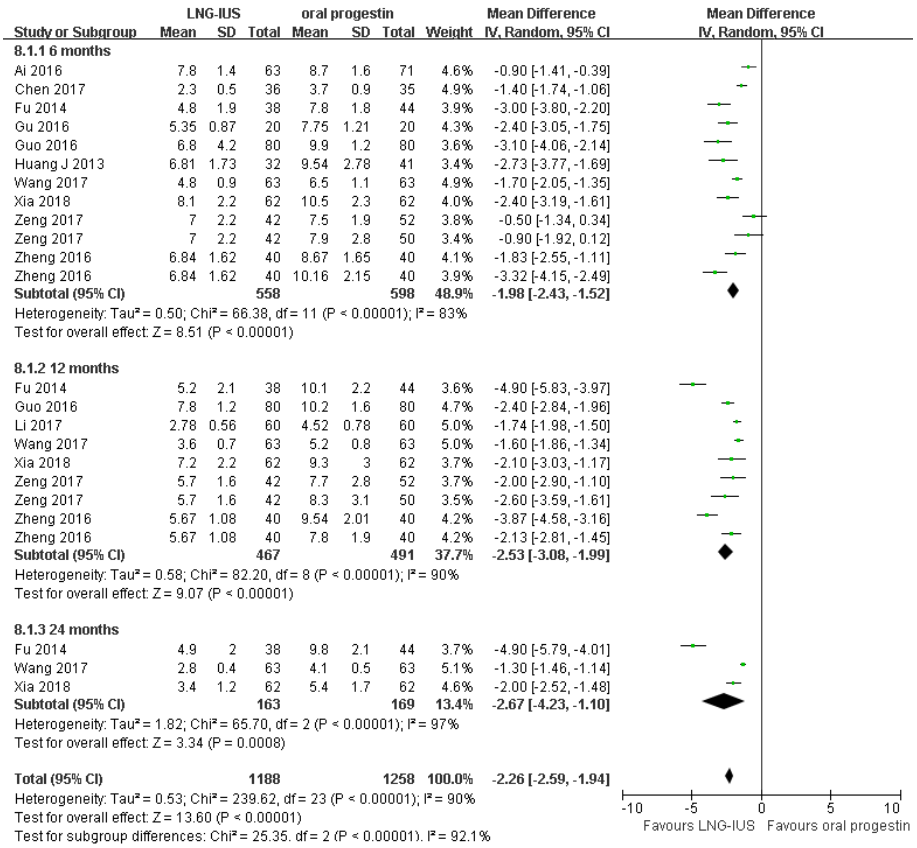

Figure 6. — LNG-IUS versus oral progestin in the mean thickness of endometrium with mean difference and 95% confidence intervals. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. CI, confidence interval; IV, inverse variance.

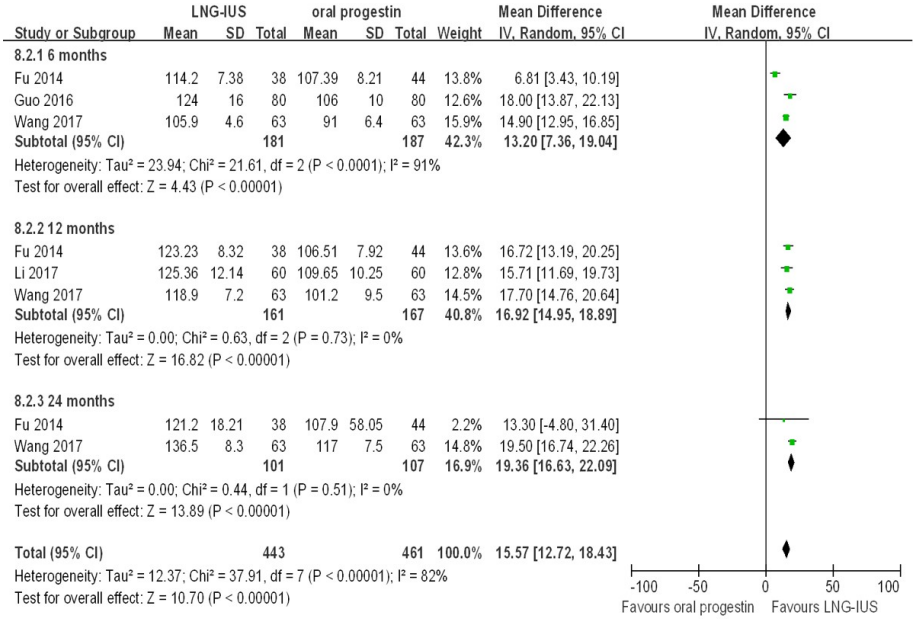

Figure 7. — LNG-IUS versus oral progestin in the mean level of hemoglobin with mean difference and 95% confidence intervals. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial. CI, confidence interval; IV, inverse variance.

Table 1. — *Characteristics of 19 trials included in the meta-analysis.*

Authors	Publication year	Country	Type of Study	Age (LNG-IUS/Oral progestin)	Multiple polyps ratio (LNG-IUS/Oral progestin)	Sample size (LNG-IUS)	Sample size (Oral progestin)	Time of follow-up (months)	Adjusted variables
Ai	2016	China	RCT	37.42/35.28	41.2%/49.3%	63	71	6	Recurrence of EMP, endometrium thickness
Chen	2013	China	RCT	41.1/37.9	63.3%/56.3%	90	93	12, 24	Recurrence of EMP
Chen	2017	China	RCT	34.18/34.26	61.1%/57.1%	36	35	6	Recurrence of EMP, endometrium thickness
Fu	2014	China	RCT	—/—	—/—	38	44	24	Recurrence of EMP, endometrium thickness, hemoglobin level
Gu	2016	China	RCT	31.9/32.2	—/—	20	20	6	Recurrence of EMP, incidence of AUB, endometrium thickness
Guo	2016	China	RCT	34.3/34.4	30%/37.5%	80	80	12	Recurrence of EMP, incidence of AUB, incidence of other adverse effects, endometrium thickness, hemoglobin level
Huang	2013	China	RCT	34.2/32.4	17.9%/11.8%	40	34	6	Recurrence of EMP, incidence of AUB
Huang J	2013	China	RCT	32/32	37.5%/34%	32	41	12	Recurrence of EMP, effects, endometrium thickness incidence of AUB, endometrium thickness
Li	2017	China	RCT	35.52/35.54	36.7%/33.3%	60	60	12	Recurrence of EMP, incidence of AUB, Incidence of other adverse effects, endometrium thickness
Liu	2014	China	RCT	—/—	—/—	20	20	12	Recurrence of EMP, incidence of other adverse effects
Qiu	2014	China	RCT	33.4/34.5	—/—	81	84	12	Recurrence of EMP
Wang	2017	China	RCT	31.7/31.8	28.6%/30.2%	63	63	24	Recurrence of EMP, incidence of AUB, incidence of other adverse effects, endometrium thickness, hemoglobin level
Xia	2018	China	RCT	36.8/36.6	—/—	62	62	24	Recurrence of EMP, endometrium thickness
Xie	2016	China	RCT	35.11/35.15	62%/60%	50	50	12, 24	Recurrence of EMP
Xu	2015	China	RCT	—/—	—/—	54	54	12	Recurrence of EMP, incidence of AUB
Ye	2012	China	RCT	35.8/36.5	—/—	65	70	24	Recurrence of EMP, incidence of AUB, incidence of other adverse effects
Zeng	2017	China	RCT	40.9/38.45	19%/23.5%	42	52/50	12	Recurrence of EMP, incidence of AUB, incidence of other adverse effects, endometrium thickness
Zhang	2011	China	RCT	38.2/38.2	—/—	32	59/45	24	Recurrence of EMP
Zheng	2016	China	RCT	33.7/34.1	60%/60%	40	40/40	6,12	Recurrence of EMP, incidence of AUB, incidence of other adverse effects, endometrium thickness

RCT, randomized controlled trial; LNG-IUS, levonorgestrel intrauterine system; EMP, endometrial polyps; AUB, abnormal uterine bleeding.

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