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Efficacy of levonorgestrel releasing intrauterine system as a postoperative maintenance therapy of endometriosis: A meta-analysis

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Abstract

Objective

To compare the efficacy of levonorgestrel releasing intrauterine system (LNG-IUS) with other treatments as a postoperative maintenance therapy for endometriosis in terms of pain reduction, recurrence prevention, side effects and patients' satisfaction.

Study Design

We searched MEDLINE, EMBASE, and the Cochrane Library from January 1986 until February 2018. Two evaluators independently extracted and reviewed prospective and retrospective articles based on pre-determined selection criteria. Outcomes were expressed as mean difference (MD), risk ratios (RR) or odds ratios (OR) in a meta-analysis model, using Revman software.

Results

Among the 962 studies, 7 studies were selected: 7 studies included 4 randomized controlled trials with 212 patients, 1 prospective cohort study with 88 patients, and 2 retrospective studies with 191 patients. A meta-analysis showed that LNG-IUS was significantly effective in reducing pain after surgery (MD=12.97, 95% confidence interval (CI): 5.55~20.39), with a comparable effect to gonadotropin-releasing hormone analogues (MD=-0.16, 95% CI: -2.02~1.70). LNG-IUS was also effective in decreasing the recurrence rate (RR=0.40, 95% CI: 0.26~0.64), with an effect comparable to OC (OR=1.00, 95% CI: 0.25~4.02) and danazol (RR=0.30, 95% CI: 0.03~2.81). Furthermore, patients' satisfaction with LNG-IUS was significantly higher than that with OC (OR=8.60, 95% CI: 1.03~71.86). However, vaginal bleeding was significantly higher in the LNG-IUS group than in the gonadotropin-releasing hormone analogue group (RR=27.0, 95% CI: 1.71~425.36).

Conclusion

Our meta-analysis found a positive effect of LNG-IUS as a postoperative maintenance therapy for endometriosis on pain relief, prevention of dysmenorrhea recurrence, and patients' satisfaction.

Key words: endometriosis; levonorgestrel-releasing intrauterine system; maintenance therapy; meta-analysis

Introduction

Endometriosis is a gynecological condition defined as the presence and growth of endometrial tissue outside the uterus [1]. Pathogenesis of endometriosis is still unclear, yet many hypotheses have been suggested such as deregulation of genes and signaling pathway which leads to deregulation of mesoderm and aberrant placement of stem cells, altered inflammatory process caused by oxidative stress and reactive oxygen species in peritoneal cavity [2-4], It affects 10%~20% of women of reproductive age and women with endometriosis often suffer from dysmenorrhea and infertility [5]. Moreover, painful symptoms caused by endometriosis can lead to decreased quality of life and significant psychopathological comorbidities, such as somatization depression and anxiety [6, 7]. The current treatment for endometriosis includes surgery to remove the endometriotic lesion, and medical treatments such as gonadotropin releasing hormone analogue, danazol, and oral contraceptives [8]. However, the recurrence rate following surgical treatment is approximately 21.5% at 2 years and 40%~50% at 5 years after surgery [9]. Therefore, effective long-term maintenance therapy after surgery is critical to prevent recurrence of endometriosis.

Among several maintenance therapies after surgery for endometriosis, oral contraceptives (OC) should be taken every day and adverse reactions have been reported, including headache, acne, and nausea [10]. Also, post-operative gonadotropin-releasing hormone (GnRH) analogues treatment can cause menopausal symptoms and the effect on relief of pain have been reported to disappear quickly after the cessation of treatment [11]. Levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena, Bayer Ag, Turku, Finland) is a intrauterine device used as a contraception by releasing 50 ug/d of levonorgestrel for over 5 years [12]. Several previous studies showed LNG-IUS is effective for the relief of endometriotic pain and has a high patient satisfaction [13-15]. However, some studies report

disadvantages of LNG-IUS treatment such as short duration of pain relieving effect and treatment failure due to side effects such as unpredictable and prolonged vaginal bleeding [16, 17].

The aim of this meta-analysis is to compare the efficacy of LNG-IUS with other options such as other types of hormonal treatments or expectant management as a postoperative maintenance therapy of endometriosis in terms of the relief of symptoms, prevention of recurrence and side effects, and patients' satisfaction.

Materials and methods

Study selection

This systematic review was conducted by searching the Cochrane central register of controlled trials, MEDLINE, and EMBASE with the key words 'levonorgestrel' and 'endometriosis' for any prospective and retrospective data published from January 1986 until February 2018. Restrictions by language, publication type or date were not applied. Two review authors independently selected studies, crosschecked selected studies and discussed with third reviewer for any disagreements. We included trials that met all of the following criteria: patients with pathologically confirmed endometriosis who had undergone surgical treatment; intention to treat with LNG-IUS, either right after surgery or after GnRH analogue treatment following surgery; and a parallel design study with a control group to compare with the LNG-IUS group. The control group included expectant management (no treatment after surgical treatment) and other types of hormonal therapy such as GnRH analogue, oral contraceptives, or danazol. The primary outcome was the efficacy of treatment modalities such as the reduction of pain and recurrence of endometriosis. Secondary outcomes included side effects and patients' satisfaction. Irregular vaginal bleeding and hypermenorrhea were assessed as side effects. Treatment failures were also assessed, such as dislocation of the device, lack of compliance with the treatment, and early cessation of treatment due to side effects.

Assessment of study quality

Quality assessment was performed using different tools for each of the studies according to the type of study design [18]. Randomized controlled trials were assessed using the Cochrane risk of bias assessment tool. Each type of risk was graded as low, high or unclear. Assessment categories include: (i) sequence generation; (ii) allocation concealment; (iii) blinding of participants, providers, and outcome assessors; (iv) completeness of outcome data; (v) selective outcome reporting; and (vi) other potential sources of bias. Studies without a high risk of bias for any domain were considered of good quality. Studies with high risk for one criterion or two unclear risks for two criteria were considered of

fair quality. Prospective or retrospective cohort studies were assessed using the Newcastle Ottawa scale. Stars awarded for each quality item were added to assess the quality of each study. Quality items include: (i) representativeness of the cohort; (ii) ascertainment of exposure; (iii) absence of outcome of interest at the start of the study; (iv) comparability of cohorts; (v) assessment of outcome; (vi) adequacy of follow-up periods; and (vii) follow-up of cohorts. Studies with 3 or more stars in the selection domain, 1 or more stars in the comparability domain, and 2 or more stars in the outcome/exposure domain were considered of good quality. Fair quality was defined as 2 stars in the selection domain, 1 or 2 stars in the comparability domain, and 2 or 3 stars in the outcome/exposure domain.

Statistical analysis

Statistical analysis was carried out using RevMan software (version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For binary outcome, data were collected to calculate the overall risk ratios (RRs) or odds ratios (ORs) with 95% confidence interval (CI). For continuous data, data were collected to calculate the mean difference (MD). When substantial heterogeneity was not observed, MD calculated based on the fixed-effects model was reported. Otherwise, MD based on the random-effects model was reported. If the study only provided data of median and range, then mean and standard deviation were calculated [19]. All studies were grouped together depending on the control groups, and then analyzed. Heterogeneity of the data was assessed using the chi square test with a 10% level of statistical significance, and I^2 statistics for quantification of variability due to heterogeneity rather than sampling error. A *P* value of less than 0.1 with an I^2 value with a lower confidence boundary of 50% or greater was considered as having substantial heterogeneity. However, we did not use Begg's funnel plot or Egger's test to assess the publication bias due to the small number of included studies.

Results

Figure 1 shows a flow diagram indicating our process for identifying the relevant studies. Ultimately, 7 studies with a total of 491 patients were selected, including 4 randomized controlled trials [5, 8, 20, 21], 1 prospective cohort study [22] and 2 retrospective cohort studies [23, 24]. Of the 7 studies, 3 compared LNG-IUS with expectant management [5, 20, 21], 2 compared LNG-IUS with OC [23, 24], 1 compared LNG-IUS with GnRH analogue [8], and 1 compared LNG-IUS with danazol [22]. The characteristics of the included studies are described in Table 1. Of the 4 randomized controlled trials, the follow-up period was 12 months in 3 studies [5, 8, 21] and 30 months in one study [20]. In one prospective cohort study, the follow-up period was 6 months [22]. Of the 2 retrospective studies, Morelli et al. evaluated the outcomes at 24 months [24], while Cho et al. evaluated the recurrence rate at the end of the treatment, which differed among the patients, with a median follow-up duration of 17 months [23]. Quality assessment of all studies is described in table 2 and table 3. Among the 4 randomized controlled studies, 2 were of fair quality and 2 were of poor quality. Among the 3 cohort studies, 1 was of fair quality and 2 were of poor quality.

LNG-IUS versus expectant management

The studies comparing LNG-IUS and expectant management after surgical treatment of endometriosis were 3 randomized controlled trials [8, 13, 20]. The analysis of these 3 studies is given in Figure 2.

a. Primary outcome

Dysmenorrhea and non-cyclic pelvic pain were assessed in all three studies, but the assessment of dyspareunia was absent in the study by Chen et al. [20]. Dysmenorrhea (MD=21.32, 95% CI: 13.39~29.24, I^2=0%) and non-cyclic pelvic pain (MD=7.78, 95% CI: 0.30~15.26, I^2=31%) were significantly reduced by LNG-IUS compared to expectant management; however, the reduction of

dyspareunia was not statistically significant (MD=-1.08, 95% CI: -27.63~25.47, I^2=40%). Overall, LNG-IUS significantly reduced pain associated with endometriosis (MD=12.97, 95% CI: 5.55~20.39, I^2=51%).

In terms of recurrence, all 3 studies demonstrated the recurrence of dysmenorrheal; however, recurrence of endometrioma was not compared in the study by Vercellini et al. [13]. Recurrence of dysmenorrhea was significantly decreased (RR=0.30, 95% CI: 0.16~0.57, I^2=0%); however, the reduction on the recurrence of endometrioma was not statistically significant (RR=0.60, 95% CI: 0.31~1.14, I^2=0%). In defining the recurrence of endometriosis as either recurrence of endometrioma or dysmenorrhea, the recurrence rate was significantly reduced by LNG-IUS (RR=0.40, 95% CI: 0.26~0.64, I^2=0%).

b. Secondary outcome

Vaginal bleeding caused by LNG-IUS was assessed by Chen et al. and Tanmahasut et al. [5, 20]. Compared to expectant management, LNG-IUS caused increased incidence of unpredictable vaginal bleeding (RR=6.09, 95% CI: 1.68~22.13, I^2=0%).

Satisfaction of the patients was assessed in the study by Vercellini et al. [13], in which the satisfaction of the patients was not decreased by the use of LNG-IUS (RR=1.58, 95% CI: 0.99~2.54).

Treatment failure was reported by Vercellini et al.,[21] and Tanmahasut et al. [5]. The rate of treatment failure was not significantly different between the LNG-IUS and expectant management groups (RR=5.74, 95% CI: 0.71~46.40, I^2=0%).

LNG-IUS versus OC

Two retrospective studies compared LNG-IUS and OC after surgical treatment of endometriosis [23, 24]. The analysis of these studies is shown in figure 3.

a. Primary outcome

Only the study by Morelli et al. described the improvement of dysmenorrhea [24], in which the pain reduction was more effective with OC compared to LNG-IUS (MD=-8.60, 95% CI: -17.06~-0.14).

Assessment of recurrence differed between the two studies by Cho et al. and Morelli et al. Cho et al. assessed the recurrence of ovarian endometrioma using ultrasonography [23], whereas Morelli et al. assessed the recurrence of endometriosis using the VAS score, physical examination of cul-de sac, and sonographic examination of ovarian endometrioma [24]. Therefore, the recurrence of endometrioma and dysmenorrhea could not be assessed separately. Nevertheless, no significant differences were found between the two treatment modalities in terms of disease recurrence (OR=1.00, 95% CI: 0.25~4.02, I^2=50%).

b. Secondary outcome

Neither change in vaginal bleeding nor treatment failure was assessed in either study. Satisfaction of the patients was assessed by Morelli et al., and the patients treated with LNG-IUS were significantly more satisfied than patients treated with OC (OR=8.60, 95% CI: 1.03~71.86) [24].

LNG-IUS versus GnRH analogue

One randomized controlled trial compared LNG-IUS and GnRH analogue (Figure 4) [8].

a. Primary outcome

The pain reduction did not significantly differ between the two groups (MD=-0.16, 95% CI: -2.02~1.70). Recurrence was not assessed in this study.

b. Secondary outcome

The rate of irregular vaginal bleeding was significantly more frequent in patients treated with LNG-IUS (RR=27.00, 95% CI: 1.71~425.36). Satisfaction of patients or treatment failure was not described

in this study.

LNG-IUS versus danazol

One prospective cohort study compared LNG-IUS with danazol (Figure 5) [22].

a. Primary outcome

The number of patients with decreased pain was significantly higher in the LNG-IUS group compared to that in the danazol group (RR=1.71, 95% CI: 1.10~2.66). The rate of recurrence for endometrioma was not significantly different between the two treatments (RR=0.20, 95% CI: 0.03~2.81).

b. Secondary outcome

Vaginal bleeding was not assessed in this study. The percentage of satisfied patients in the LNG-IUS group was 68%, but the satisfaction of patients in the danazol group was not assessed. The rate of treatment failure was not significantly different between the two groups (RR=0.92, 95% CI: 0.24~3.47).

Comments

This meta-analysis analyzed 5 prospective and 2 retrospective studies to examine the efficacy of LNG-IUS as a postoperative maintenance therapy on patients with endometriosis. In the present study, LNG-IUS was significantly effective on the relief of pain and preventing the recurrence of endometriosis. This effect was superior to danazol, and comparable to the GnRH analogues. Although LNG-IUS caused irregular vaginal bleeding, it did not lead to a decreased satisfaction of patients compared to patients treated with expectant management [5, 13, 20]. Furthermore, the satisfaction of patients treated with LNG-IUS was significantly higher than in those treated with OC [24]. The current study therefore recommends LNG-IUS as a long term maintenance therapy after surgical treatment for endometriosis.

The efficacy of LNG-IUS in preventing the recurrence of dysmenorrhea has been demonstrated in many studies [17, 21, 25]. Moreover, several studies have reported that LNG-IUS is effective not only in the relief of pain, but also in the prevention of endometrioma recurrence [23, 24, 26]. On the contrary, recent randomized controlled trial by Chen et al. reported that LNG-IUS as a postoperative maintenance therapy was not significantly effective in preventing the recurrence of endometrioma compared to the expectant management group after surgical treatment [20]. In the present study, LNG-IUS was as effective as other medical managements after surgical treatment in reducing the recurrence of endometrioma. This finding needs to be confirmed in a larger population in the future.

Irregular vaginal bleeding was the most common and well-known side effect of hormonal treatment [27]. In this current study, a significantly higher incidence of irregular vaginal bleeding was shown among patients with LNG-IUS treatment compared to expectant management or GnRH analogue treatment. Lockhat et al. reported irregular and unpredictable bleeding were reasons for dissatisfaction [16]. Nevertheless, in this current study, increased rate of irregular vaginal bleeding did not lead to patient dissatisfaction. Most patients found LNG-IUS to be tolerable, and did not ask for early removal

of the device. Rather, quality of life was increased significantly after LNG-IUS treatment. In fact, LNG-IUS treatment in conditions other than endometriosis has been shown to be effective in improving sexual functions and quality of life. For example, patients with sexual dysfunction experienced positive effect on their sexual life [28] and patients who underwent abortion for unintended pregnancies experienced significant decrease in dyspareunia and improved quality of life [29]. Effect of LNG-IUS on improving sexual function and quality of life in patients with endometriosis needs to be confirmed in clinical studies.

In all seven studies except one by Bayoglu Tekin, more than half of patients were in either stage III or IV disease. In study by Bayoglu Tekin, the number of patients in each stage was not mentioned, but the mean rASRM score exceeded 46, which is categorized as stage IV disease. Variation in degree of endometriosis, body mass index, age, laterality of lesions, size of endometrioma coexistence of uterine myoma, completeness of the surgery can all be risk factors for recurrence of endometriosis [30], and can be confounding factors for assessing the effect of LNG-IUS on endometriosis in terms of pain relief and prevention of recurrence. Although these variations among included studies can be an important consideration for the analysis, it was not possible to adjust all possible confounding factors for analysis.

Dienogest, a fourth generation selective progestin, has recently been promoted as a targeted progestin for treatment of endometriosis [31]. As a postoperative maintenance therapy, dienogest has been effective in the reduction of pain and recurrence prevention compared to expectant management [32, 33]. The effect on the reduction of recurrence rate was comparable to GnRH analogue, with less side effects associated with hypoestrogenism such as hot flushes and bone loss [34]. Recent retrospective study showed long term (60 months) dienogest treatment in women with endometriosis was effective in pain reduction and prevention of pain recurrence [35]. For this reason, experts are considering dienogest as one of the first line drug of choice for endometriosis [36]. However, no data has been presented on the comparison of dienogest with LNG-IUS as a postoperative management. Morellli compared the dienogest with LNG-IUS as a postoperative treatment, but dienogest was co-

administered with estradiol valerate as estrogen-progestin combination oral contraceptive [24]. Further studies are needed that compare the effect of two modalities in terms of postoperative maintenance therapy for endometriosis.

This study has several limitations. First, the use of a control group differed between the studies causing significant heterogeneity in study designs. For example, in 2 studies, patients were treated not only with LNG-IUS, but also with GnRH analogue treatment whereas in other studies, LNG-IUS was inserted without other medical treatment. Also, the time at which the outcome was evaluated differed among the studies. This can lead to over or underestimate the efficacy of LNG-IUS. Second, the number of included studies was small. The available data was derived from seven trials including only 491 patients. Subgroup analysis was performed depending on the control group, and not all outcomes of interest were reported in each study, rendering the number of included studies even smaller. Third, the follow-up period of included studies were not long enough to evaluate the postoperative recurrence of disease, which occurs mostly within 5 years after surgery, The longest follow-up period among prospective studies were 30 months, in study by Chen et al.. Further studies with longer study period are needed to confirm the efficacy of LNG- IUS on prevention of disease recurrence on long term basis. Fourth, the quality of studies was poor: 2 of the 4 RCTs and 2 of the 3 cohort studies were of poor quality. The strength of evidence for the outcomes was low due not only to the small number of included studies, but also to the poor quality of studies. Nevertheless, all studies relevant to the subject were included in this study, and the selection was not restricted by language, publication type or study design. Thus, this meta-analysis is expected to help physicians for counselling patients on treatment options after surgical treatment of endometriosis in clinical practice,

In conclusion, the present analysis demonstrates that LNG-IUS has a significant effect on preventing the recurrence of dysmenorrhea. Also, LNG-IUS showed a higher satisfaction rate of patients without systemic adverse drug reaction than other treatments. Therefore, LNG-IUS might be a treatment option as a maintenance therapy after surgical management for endometriosis.

Essential points of the present study

LNG-IUS as a postoperative maintenance therapy for endometriosis is effective in pain relief, prevention of dysmenorrhea recurrence, and patients' satisfaction.

Conflict of interest

The authors have no conflicts of interest to report.

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Table 1. Characteristics of included studies

author	year	Study type	Participants (n)	Follow-up (Months)	Intervention	Outcomes
Vercellini et al. [21]	2003	RCT	40	12	LNG-IUS or expectant management after surgical treatment	- Significant pain reduction with LNG-IUS treatment - Significant reduction in dysmenorrhea recurrence with LNG-IUS treatment
Bayoglu Tekin et al.[8]	2011	RCT	40	12	LNG-IUS or GnRH agonist treatment after surgical treatment	- Comparable pain reduction with both treatments
Tanmahasamut et al.[5]	2012	RCT	55	12	LNG-IUS or expectant management after surgical treatment	- Significant pain reduction with LNG-IUS treatment
Chen et al.[20]	2017	RCT	80	30	LNG-IUS or expectant management after surgical treatment and 6 cycles of GnRH agonist treatment	- Significant pain reduction with LNG-IUS treatment - Significant reduction in dysmenorrhea recurrence with LNG-IUS treatment - No significant reduction in endometrioma recurrence
Morelli et al.[24]	2013	Retrospective	92	24	Treated with LNG-IUS or EP within 1 month after surgical treatment	- Significant pain, CA-125 reduction with both treatments ; Greater effects with EP treatment - No significant difference in recurrence rate
Cho et al.[23]	2014	Retrospective	99	17	Treated with LNG-IUS or OC after surgical treatment and 3 cycles of GnRH agonist treatment	- Comparable reduction in endometrioma recurrence with both treatments

Taneja et al.[22]	2017	Prospective non-randomized	88	6	Treated with LNG-IUS or danazol after surgical treatment	- Significant pain, endometrioma recurrence reduction with both treatments ; Greater effects with LNG-IUS treatment

RCT: randomized controlled trial; LNG-IUS: levonorgestrel-releasing intrauterine system; GnRH: gonodogropin-releasing hormone; EP: estradiol valerate+dienogest;

Table 2. Risk of bias of included randomized controlled study using the Cochrane risk of bias assessment tool

	Bayoglu et al.[8]	Tanmahasamut et al.[5]	Vercellini et al.[21]	Chen et al.[20]
Random sequence generation (selection bias)	Low risk	Low risk	Low risk	Low risk
Allocation concealment (selection bias)	Unclear risk	Low risk	Low risk	Low risk
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear risk	High risk	Unclear risk
Blinding of outcome assessment (detection bias)	Unclear risk	Low risk	High risk	Low risk
Incomplete outcome data (attrition bias)	Low risk	Low risk	Low risk	Low risk
Selective reporting (reporting bias)	Low risk	Low risk	Low risk	Low risk
Other bias	Low risk	Low risk	Unclear risk	Low risk

Table 3. Quality assessment of included cohort studies using the New castle – Ottawa scale

		Cho et al.[23]	Morelli et al.[24]	Taneja et al.[22]
Selection	Representativeness of exposed cohort	*	*	*
	Selection of nonexposed cohort	*	*	*
	Ascertainment of exposure	*	*	*
	Outcome not present at the start of the study	*	*	
Comparability		**		
Outcome	Assessment of outcomes	*	*	*
	Length of follow up			*
	Adequacy of follow up	*	*	
Total		********	******	*****

Figure Captions

Figure 1. Flow diagram of study selection

Figure 2. Comparison of levonorgestrel-releasing intrauterine system and expectant management (A) pain reduction (B) disease recurrence (C) vaginal bleeding (D) patients' satisfaction (E) treatment failure

Figure 3. Comparison of levonorgestrel-releasing intrauterine system and oral contraceptive (A) pain reduction (B) disease recurrence (C) patients' satisfaction

Figure 4. Comparison of levonorgestrel-releasing intrauterine system and gonadotropin releasing hormone analogue (A) pain reduction (B) vaginal bleeding

Figure 5. Comparison of levonorgestrel-releasing intrauterine system and danazol (A) pain reduction (B) disease recurrence (C) treatment failure

Fig `1

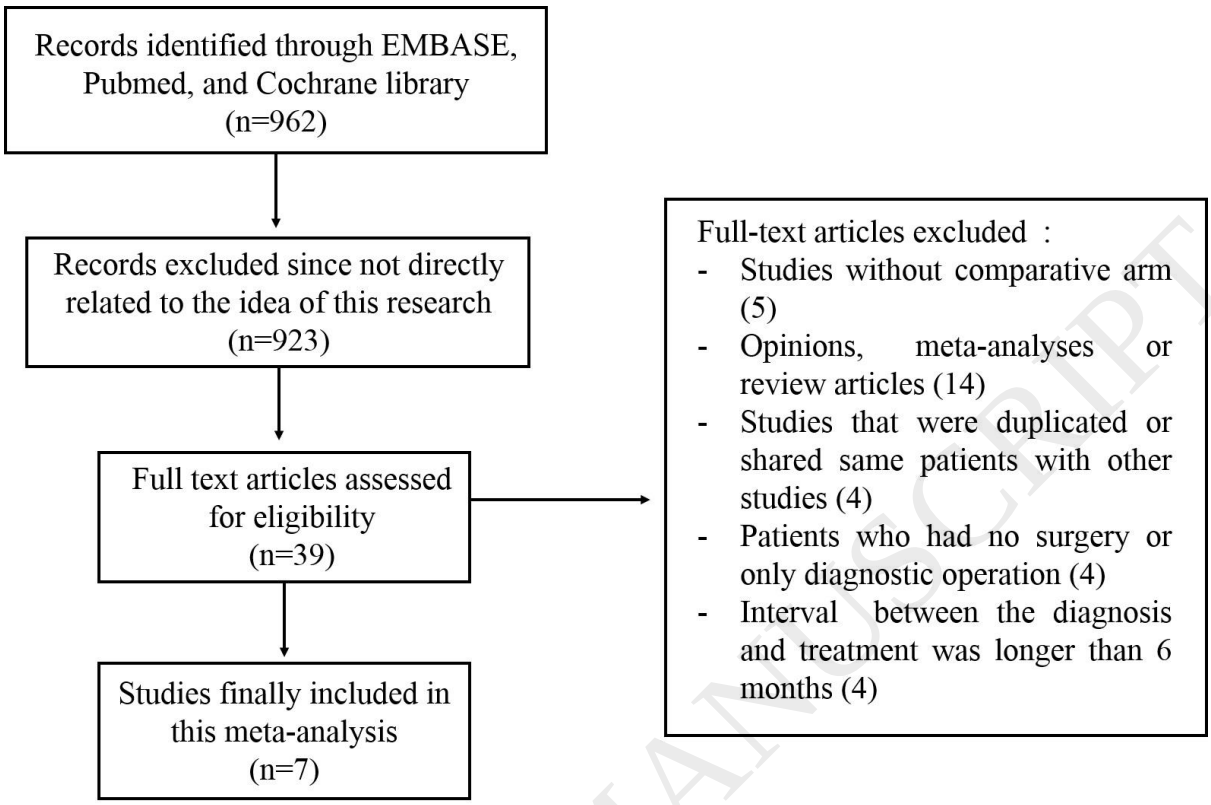

Fig 2

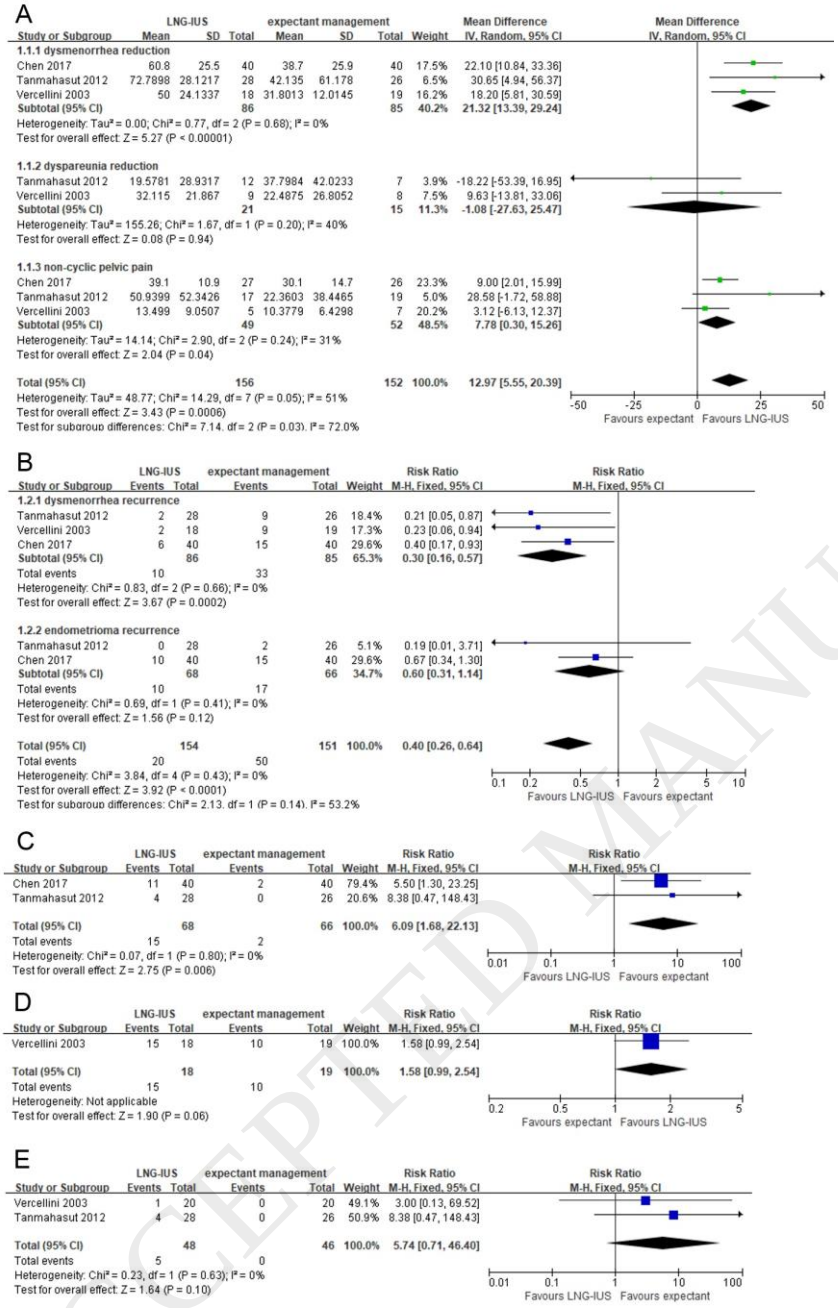

Fig 3

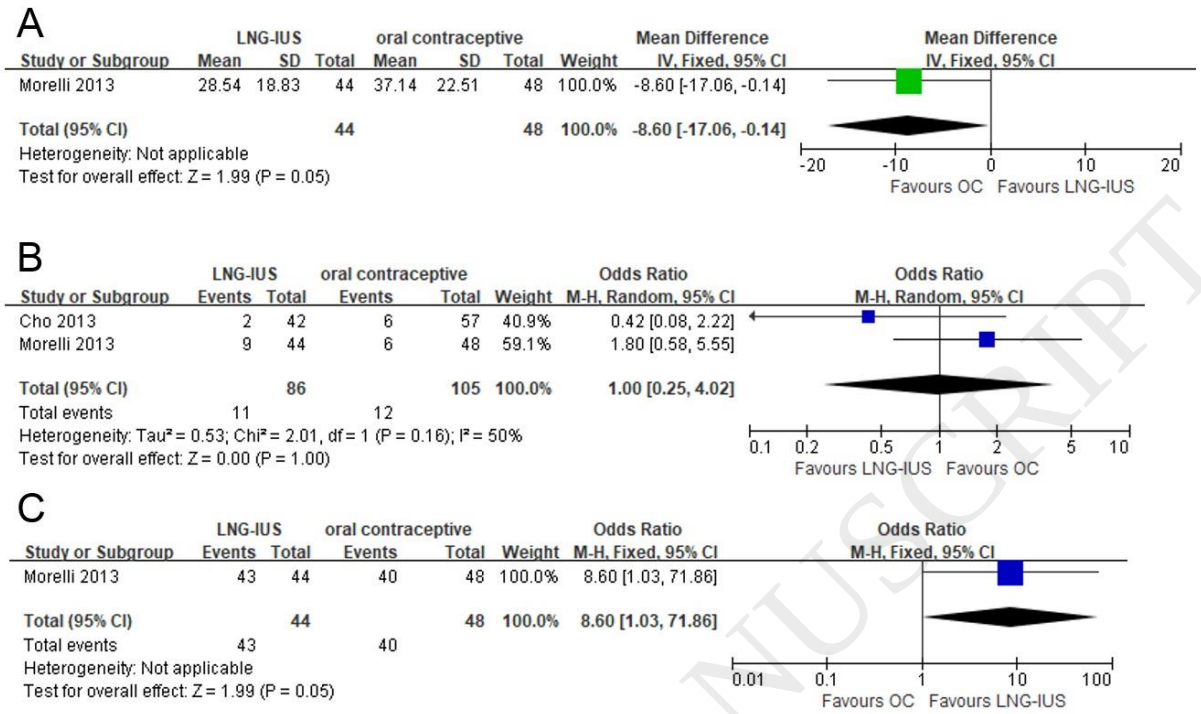

Fig 4

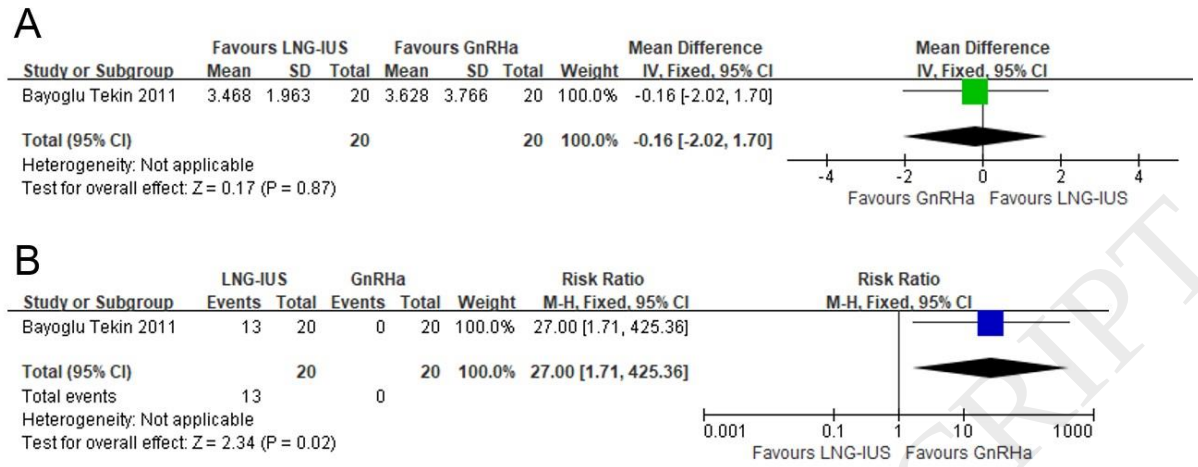

Fig 5