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Evaluation of Levonorgestrel-Releasing Intrauterine System (LNG) in The Management of Uterine Adenomyosis: An Update Systematic Review and Meta- Analysis

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ABSTRACT

Background & Objective: Adenomyosis is a common benign endometrial disease which causes abnormal uterine bleeding in premenopausal women and affects the quality of life. The definitive treatment is hysterectomy; however, medical treatment is an option for those who wish to preserve fertility. This systematic review aims to assess the efficacy of levonorgestrel-releasing intrauterine device as medical management in women who have adenomyosis.

Materials & Methods: We searched PubMed, Cochrane and Scopus databases from January 2000 to November 2019 for relevant studies containing the use of levonorgestrel-releasing intrauterine device (LNG-IUD) in managing patients with ultrasonographic diagnosis of adenomyosis. Main outcome measures in the study are menstrual blood loss (milliliters), pain score measured in 10 cm-visual analogue scale, and uterine volume.

Results: Pooled results from meta-analysis showed that after LNG-IUD treatment for adenomyosis, there is significant reduction in dysmenorrhoea, measured using Visual Analogue Scale after 6 months (Standardized Mean Difference (SMD): 3.68; CI: 2.11-5.25) , 12 months (SMD: 4.23; CI: 2.99-5.48), 24 months (SMD: 4.69; CI: 3.40-5.97) and 36 months (SMD: 4.01; CI: 3.57-4.45); significant reduction in menstrual bleeding after 6 months (SMD: 2.52; CI: 1.15-3.89), 12 months (SMD: 3.43; CI: 1.64-5.22) and 24 months (SMD: 3.57; CI: 1.88-5.26); significant reduction in uterine volume after 6 months (SMD: 0.49; CI: 0.04-0.93), 12 months (SMD: 0.80; CI: 0.11-1.48) and 24 months (SMD: 0.86; CI: 0.15-1.58).

Conclusion: LNG-IUS is an effective method in alleviating the symptoms of adenomyosis. It is a valuable long-term alternative for the treatment of adenomyosis for young and perimenopausal women in terms of dysmenorrhoea and heavy menstrual bleeding.

Keywords: Lenonorgestrel Intrauterine Fevice (LNG-IUD), Adenomyosis, Dysmenorrhea

Introduction

Adenomyosis is characterized by the invasion of endometrial tissue into myometrium. Most of the affected women presented with abnormal uterine bleeding, dyspareunia, dysmenorrhea and infertility, whereas a proportion are asymptomatic **(1)**. These symptoms can severely impact the quality of life due to the pain, and complications may arise from heavy menstrual bleeding **(2)**.

The main objective of the management in adenomyosis is to improve the quality of life of affected women, as the symptoms are distressing **(3)**. Even though the definitive treatment of adenomyosis is hysterectomy, the treatment can be different based on the types of disease. For instance, management of focal adenomyosis is straightforward and simple, giving medical treatment and if it fails, a focal adenomyosis resection, even so, surgery is only at an efficacy as low as 50% due to the difficulty in determining the extent of the disease **(4)**. On the other hand, the management of diffuse adenomyosis is challenging as we can only depend solely on medical therapy to preserve the uterus as focal excision becomes impossible particularly in women of child-bearing age **(5)**.

As of recently, the surgical approach to adenomyosis remains controversial as many kinds of surgical management whichwere attempted as an alternative to laparotomy, seems to have a higher risk of uterine rupture **(6)**. Although there are minimally invasive

surgical management options, robust evidence to support is lacking **(7)**.

The use of pharmacological treatment such as gonadotropin-releasing hormone analogue (GnRHa) suppresses the anterior pituitary gland and downregulates the production of follicle stimulating hormone and luteinising hormone. Subsequently, GnRHa will prevent ovulation and reduce the estrogen production, as a result it will reduce the complication caused by adenomyosis **(8)**. At the same time GnRHa improves pregnancy outcomes, however it is not a long-term treatment as it causes multiple complications due to its hypoestrogenic status. In addition, the use of levonorgestrel releasing intrauterine device (LNG-IUD) shows successful long-term treatment for reduction of bleeding, pain and uterine volume with an overall satisfaction of 72% **(9)**. This is achieved by inducing decidualization which suppresses the glandular tissues leading to atrophy of the uterus and ultimately induce amenorrhea in some **(10)**.

This systematic review aims to compile evidence that measures the efficacy of levonorgestrel-releasing intrauterine device as a management for uterine adenomyosis, so we are able to provide a comprehensive assessment of the efficacy of LNG-IUS to give healthcare professionals a clearer idea of its efficacy to make better treatment choices. Specific objectives include to compare menstrual blood loss (milliliters) difference in reported pain score measured in 10 cm-visual analogue scale in the included studies, and to compare the measured uterine volume changes among the included studies.

Methods

Search Strategy

The electronic database of PubMed, Cochrane and Scopus were searched from January 2000 until November 2019 for studies which described the role of levonorgestrelintrauterine device in management of adenomyosis. The Mesh terms and text word were combined using Boolean operators 'AND' and 'OR', adapting the search to the rules of each database. The following keywords were used: ('levonorgestrelintrauterine device' or 'levonorgestrel IUD') AND ('treatment' or 'management') AND ('adenomyosis') AND ('trial'). The reference lists of all known review articles were examined for additional relevant citations.

Inclusion and Exclusion Criteria

All prospective studies investigating the effect of levonorgestrel-intrauterine system in management of adenomyosis were considered eligible for inclusion. The articles had to be written in English and published from 2000 to 2019.

The following criteria were used to determine the study eligibility:

a. Populations: Women who were diagnosed by transvaginal ultrasound examination (TVS) or transabdominal ultrasound (TAS) for adenomyosis with symptoms of dysmenorrhea, and menorrhagia.

b. Intervention: Treatment with levonorgestrel intrauterine system

c. Outcomes: menstrual blood loss (milliliters), pain score measured in 10 cm-visual analogue scale, and uterine volume

Data extraction

Titles and abstracts of all identified studies were screened, and the full paper of the preselected articles was read by two researchers (CN and AIS). Data from the articles was extracted independently by both researchers. Any disagreements were resolved by consultation with a third reviewer (JK).

Assessment of study quality

Quality Evaluation

The 22-item Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist **(11)** was used to evaluate the standard reporting of the studies. The methodological quality of observational studies was assessed using the Newcastle-Ottawa Scale by Wells et al. **(12)**. This systematic review was written in accordance with the proper order. We utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Statistical analysis

Results from the articles were described using mean, standard deviation, absolute and relative frequencies. The mean and standard deviation were abstracted from the studies. A meta-analysis was performed on pooled data from homogeneous studies, which are defined as studies that assessed outcomes using the same validated questionnaire(s), with a similar study design (i.e.: assessment done pre- and post-treatment) and for the same follow-up period. Treatment outcomes evaluated for the meta-analysis included VAS score for dysmenorrhea, menstrual blood loss (using PBAC) and uterine volume. Meta-analysis was performed using the generic inverse variance method with random effects using Review Manager (RevMan) version 5.3, Pooled results comparing before and after treatment outcomes were described as Standardized Mean Difference (SMD). SMD of zero means that there is no difference before and after treatment. SMD value of 0.2 indicates a small effect of the treatment, a value of 0.5 indicates a medium effect and a value of 0.8 or larger indicates a large effect. A p-value <0.05 was considered significant.

Results

Selected studies characteristics

The present study identified 222 articles. Of the 221 articles, nine full-text studies were evaluated for inclusion, of which 5 were excluded for not reporting clinical outcomes, and not evaluating patients both before and after treatment. A total of four articles were included in the final systematic review for qualitative analysis synthesis and all studies were allowed for meta-analysis. Included studies are prospective studies. Figure 1.

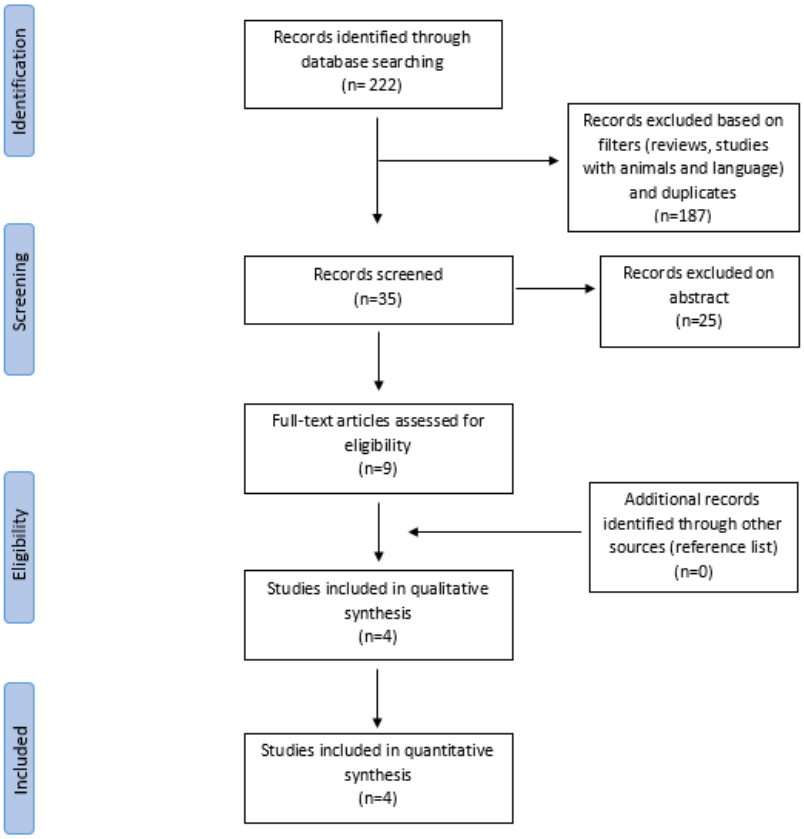

Figure 1. Flowchart for selection of studies

The main diagnostic imaging method for adenomyosis was transvaginal ultrasound (TVS) examination. Degree of dysmenorrhea was assessed by a 10-cm linear visual analogue scale (VAS), in which 0 represented no pain and 10 represented the most severe pain. For the severity of menstrual blood loss, it was measured by the Pictorial Blood Assessment Chart (PBAC). Uterine volume was calculated by using the formula of ovoid: volume = D1 x D2 x D3 x 0.52. Recruited subject underwent insertion of levonorgestrel-intrauterine system (LNG-IUS). The LNG-IUS is composed of a T-shaped polyethylene core surrounded by a reservoir of 52 mg of LNG, which is delivered to the endometrium at a release rate of 20 mcg/day in a sustained fashion for five years.

Baseline characteristics of patients included for treatment with LNG-IUD are shown in Table 1. A total of 1287 patients with adenomyosis were included.

Table 1. Summary of study characteristics and interventions for adenomyosis from individual studies

Author, year	Study design	Intervention	Age	Total (n)	Treatment in months	STROBEScore
Sheng et al., 2009 (5)	Prospective longitudinal	LNG-IUD	36.80 ± 4.30	94	36	19
Cho et al., 2008 (13)	Prospective longitudinal	LNG-IUD	39.89 ± 3.91	47	36	21
Alizzi et al., 2018 (14)	Prospective longitudinal	LNG-IUD	44.50 ± 2.50	46	24	21

Author, year	Study design	Intervention	Age	Total (n)	Treatment in months	STROBEScore
Li et al., 2019 (15)	Prospective longitudinal	LNG-IUD	36.00	1100	60	22

Effect on dysmenorrhea (Figure 2)

Three out of four of the included studies with a total of 1241 patients evaluated the effect of levonorgestrel-releasing intrauterine system on dysmenorrhoea using VAS measured at 6, 12, 24 and 36 months after treatment. Pooled results from meta-analysis showed a significant reduction in VAS after 6 months (SMD: 3.68; CI: 2.11-5.25), 12 months (SMD: 4.23; CI: 2.99-5.48), 24 months (SMD: 4.69; CI: 3.40-5.97) and 36 months (SMD: 4.01; CI: 3.57-4.45).

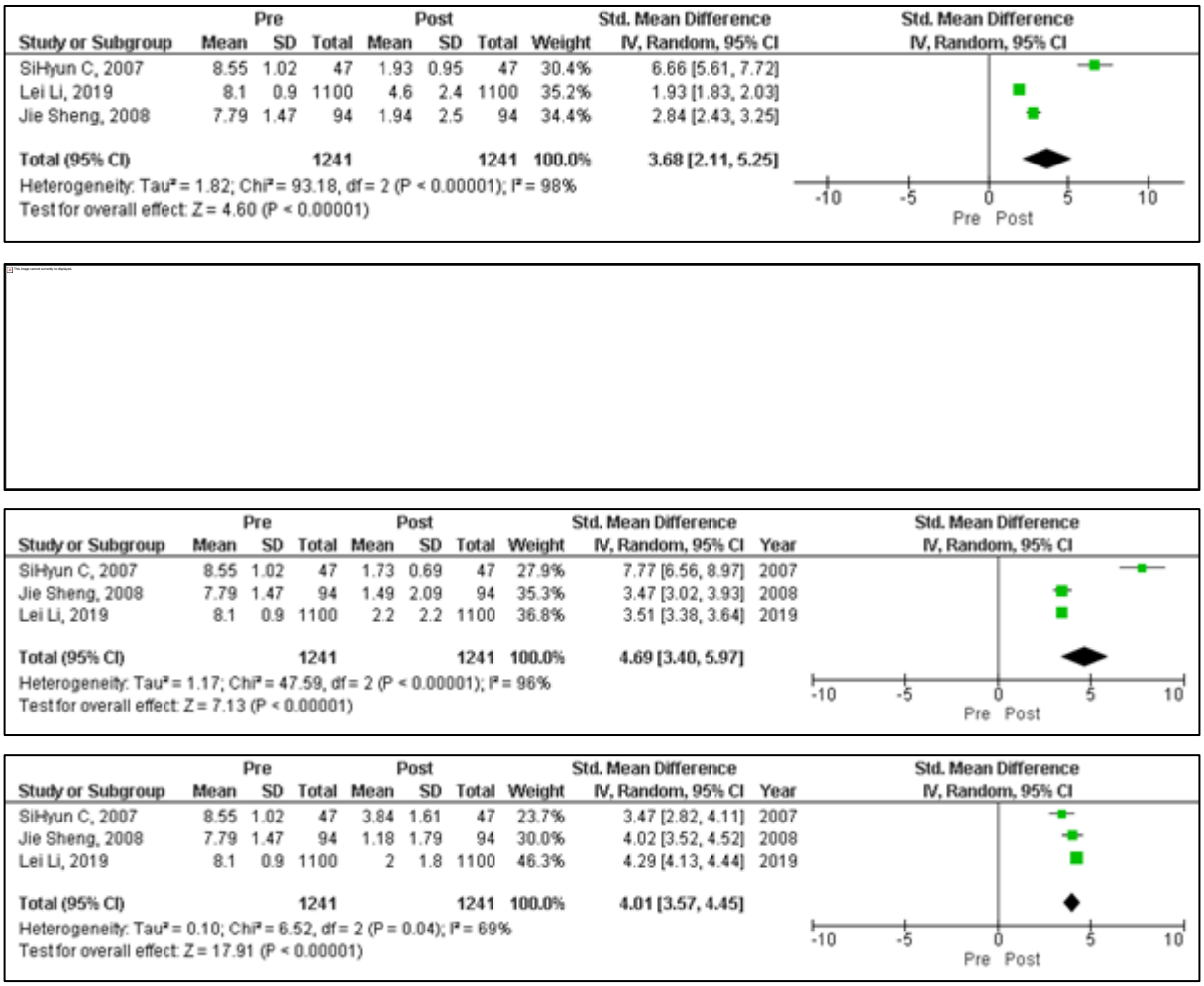

Figure 2. Meta-analysis of the effect of LNG-IUD on dysmenorrhea (VAS score) at baseline, 6 months, 12 months, 24 months and at 36 months.

Effect on menstrual blood loss (Figure 3)

Three studies with a total of 1193 patients evaluated the effect of levonorgestrel-releasing intrauterine system on menstrual blood loss using Pictorial Blood Assessment Chart (PBAC) at six, twelve and twenty-four months after treatment. Pooled results from meta-analysis showed a significant reduction in menstrual bleeding after 6 months (SMD: 2.52; CI: 1.15-3.89), 12 months (SMD: 3.43; CI: 1.64-5.22) and 24 months (SMD: 3.57; CI: 1.88-5.26).

Effect on uterine volume (Figure 4)

Four studies with a total of 1287 patients evaluated the effect of levonorgestrel-releasing intrauterine system on uterine volume at 6, 12 and 24 months after treatment. Pooled results from the meta-analysis showed a significant reduction in uterine volume after 6 months (SMD: 0.49; CI: 0.04-0.93), 12 months (SMD: 0.80; CI: 0.11-1.48) and 24 months (SMD: 0.86; CI: 0.15-1.58).

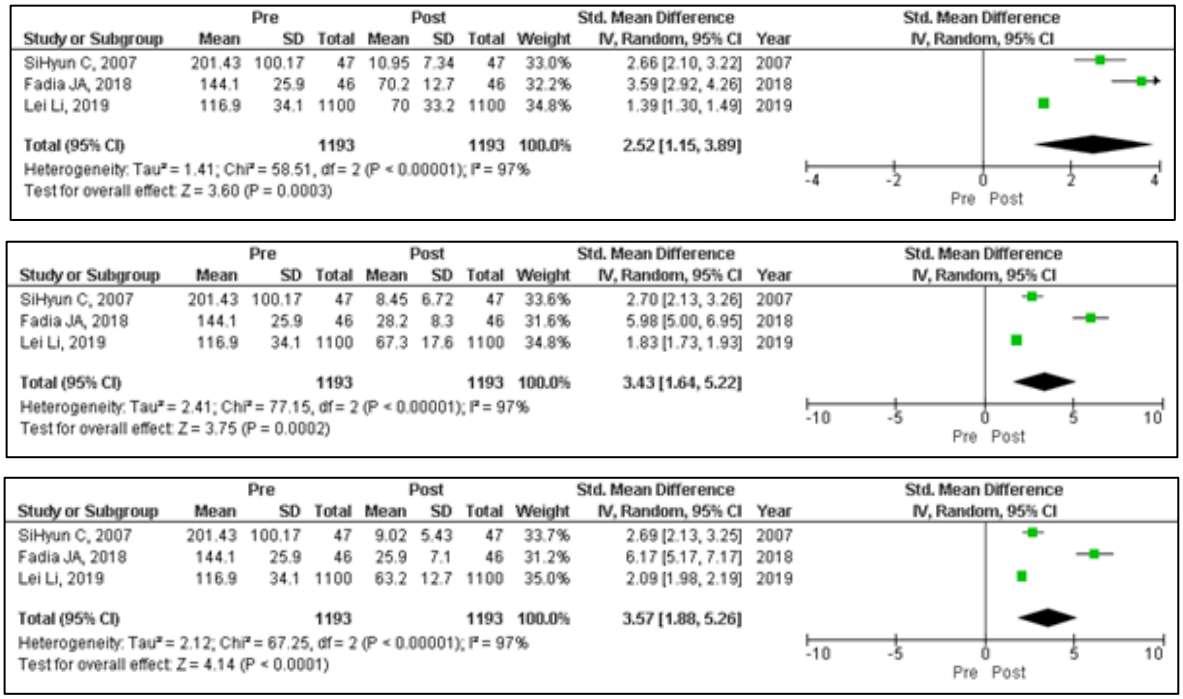

Figure 3. Meta-analysis of effect of LNG-IUD on menstrual blood loss (PBAC) at baseline, 6 months, 12 months and at 24 months.

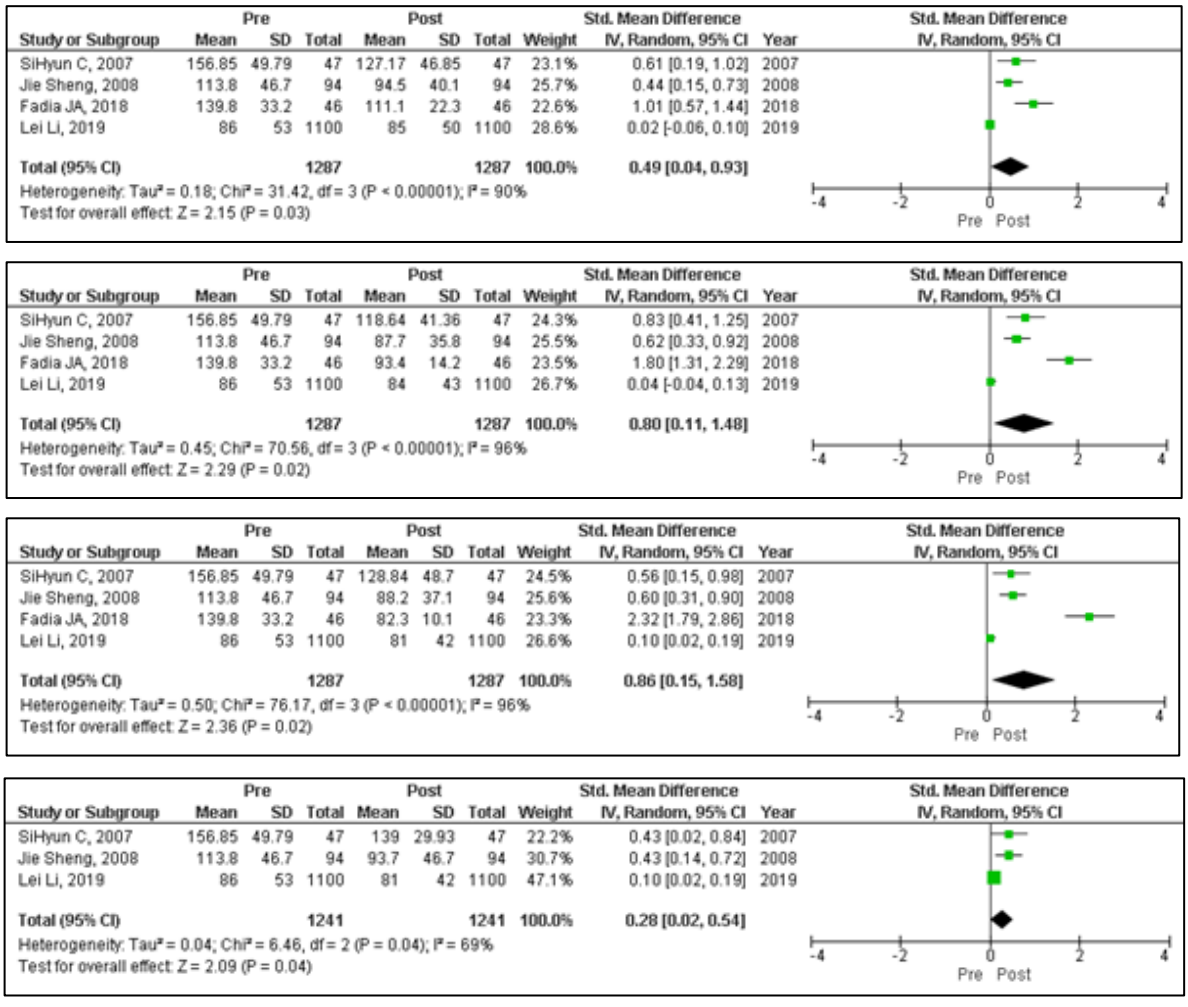

Figure 4. Meta-analysis of effect of LNG-IUD on uterine volume at baseline, 6 months, 12 months, 24 months and at 36 months

Discussion

Based on the studies included in this analysis, levonorgestrel-releasing intrauterine system are effective in reducing the symptoms in adenomyosis. This can be seen in its significant effect on dysmenorrhoea, menstrual blood loss and uterine volume. These results are similar to a recent meta-analysis done by Abbas et al. in agreement with our findings **(16)**. In the present meta-analysis, LNG-IUS exhibited significant improvement in VAS score and menstrual blood loss starting from 6 months until 36 months after insertion. LNG-IUS has medium effect on the uterine volume on 6 months, improves significantly on 12 and 24 months, but has minimal effect 36 months onward after insertion.

The reduction of pain is explained by Sheng et al. as the effect of high concentration of levonorgestrel on the ectopic endometrium, which results in glandular atrophy and stromaldecidualization **(5)**. They also explained that it could be due to effect on the ectopic endometrium, resulting in endometrial inactivity which reduces prostaglandin activity. Besides that, another explanation proposed is that the direct effect of progestin leads to a reduction in the invasion and progression of myometrial hypertrophy. In Cho et al. the explanation of reduction of pain were related to the effects of LNG-IUD on endometrium or on the vascular supply to the pelvis with relief from pelvic congestion **(13)**. LNG-IUS also showed to reduce the prostaglandin release within the endometrium and therefore minimize the dysmenorrhea event as reported in Farquhar et al. **(17)**.

The uterine volume in most studies decreased after the insertion of LNG-IUS. However, Cho et al. study revealed that its efficacy began to decrease two years after the insertion, it might be due to the tachyphylaxis effect of LNG-IUS, which the concentration of the levonorgestrel diminished after a certain period **(13)**. There was a high expulsion rate of the device in the study by Sheng et al. which could be the reason for premature removal **(5)**. Irregular bleeding followed by low abdominal pain is also the reason for premature removal. The other side effect noted in the study is weight gain. But we cannot conclude that the device causes weight gain **(18)**.

PBAC scores and hemoglobin levels improved significantly in six months after insertion. Bleeding volume and hemoglobin had a good ability to predict failure of implantation, while uterine volume had excellent ability to predict failure. This is shown in the study by Alizzi et al. **(14)**

TVS as a diagnostic tool for adenomyosis is appropriate compared to MRI because it is of low cost and convenient for use in outpatient clinics **(2, 19)**. However, it has a few false positive or false negative cases noticed in a few studies in this analysis. Without incorporating other evaluating tools such as MRI or histopathology studies, this might have given rise to misdiagnosis **(15, 20)**.

In this meta-analysis, we concede the presence of limitation. The small number of high-quality studies with larger size of study group lead to bias in this study. In addition, our meta-analysis employees pre-post effect size in which the difference between baseline and post-test within one (treatment group) due to limitation of databases and comparative studies. As a result, the SMD will be highly influenced under the natural processes and characteristics of the patients and settings, and these cannot be discerned from the effects of the intervention. Furthermore, the search is limited to only English, thus might lead to missing out some important, related studies that can boost up the reliability of the analysis.

Conclusion

From the systematic review, LNG-IUS is promising for management of symptomatic adenomyosis in terms of relieving dysmenorrhea and heavy menstrual bleeding. For patients with the diagnosis of adenomyosis, the LNG-IUS was observed to improve dysmenorrhea and heavy menstrual bleeding over time and is effective for the reduction of uterine volume. However, the efficacy of LNG-IUS on uterine volume may begin to decrease, 36 months after insertion. This review suggests that LNG-IUS is an effective method in alleviating the symptoms of adenomyosis; hence it improves quality of life of the patient. It is a valuable long-term alternative for the treatment of adenomyosis for young and perimenopausal women, and it is a good strategy to reduce the number of hysterectomies in women with adenomyosis.

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Author's Contributions

KC and CN, AD considered the study, interpreted the results, and co-wrote the manuscript. CS and LL collected the data, assisted with information interpretation, and co-wrote the manuscript. HK, KN contributed to scientific writing. All the authors read and accepted the last manuscript.

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Conflict of Interest

The author declared no conflict of interest.

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