

## Peer Review File

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### Reviewers' comments:

#### Major Concerns:

**Comment 1:** Grammar-The English grammar throughout the manuscript is poor. There are many fragmented sentences making the article difficult to read and understand. Additionally, the majority of the article is written in passive voice and there are a few parts with active voice. This should be consistent.

**Reply 1:** Thank you for your advice. To further improve the quality of this manuscript, we not only proofread it very carefully but also invited the expert of AME Editing Services to polish it (Certificate Verification ID: AESE2020171-v845G7sN). The article is consistently written in passive voice now. We have uploaded the editorial certificate in the Supplementary section. We hope the revised version of the manuscript will meet the standards of Annals of Translational Medicine. We have modified the whole manuscript according to the reviewer's comments and marked all changes clearly in the revised manuscript. Thank you so much again.

**Comment 2:** Clinical relevance-While it is interesting that the authors assessed different types of adenomyosis using MRI, obtaining an MRI to evaluate adenomyosis is not standard or feasible in many countries. Many clinicians would just place the LNG-IUD to treat adenomyosis without getting an MRI. Therefore, the methods may not be clinically relevant to all populations.

**Reply 2:** Thank you for the question. In this article, we used MRI as a diagnostic

method for adenomyosis for the following reasons: 1. In China, with the progress of society, the increase of income and the promotion of medical insurance, MRI is basically popularized, especially in relatively developed cities. 2. For patients with adenomyosis who are difficult to diagnose by ultrasound, MRI has more advantages in sensitivity and specificity. It can diagnose earlier adenomyosis, enable early detection of the disease, early control, and better management. Although the price is more expensive than ultrasound, it still has incomparable advantages. 3. In clinical practice, we usually perform MRI examinations for patients with severe dysmenorrhea and menorrhagia, which can better predict the effect of LNG-IUD. Appropriate intervention before the LNG-IUD placement can increase the effectiveness and reduce the loss of the device so as to avoid wasting a LNG-IUD. However, for patients who will show little effectivity to LNG-IUD placement based on the MRI classification, preoperative MRI is a clinical requirement and does not increase the patient's cost. 4. In all populations, as the popularity of MRI examinations for patients, the cost of MRI examination will be reduced, so the patients' expense on MRI examination will also be reduced. In the end, the vast majority of women can afford this examination just like the ultrasound examination.

**Comment 3:** Manuscript organization-The content of certain sections of the manuscript are incorrect. For example, the methods section, contains results -Line 124-128. The authors should elaborate on the limitations section.

**Reply 3:** We entirely agreed with the reviewer and have elaborated the corresponding sections.

**Changes in the text:** We deleted the line 124-128 in methods section and added this data in the results section. (see Page 6, Line 285-286).

**Comment 4:** Table Headings- The table headings should be improved to clearly explain the tables. The reader should be able to understand the table based on the title.

**Reply 4:** Thank you for the question. Our new table headings as follows:

Table 1 heading: The demographics and clinical characteristics of included patients.

Table 2 heading: Efficacy of LNG-IUD treatment on dysmenorrhea and menorrhagia.

Table 3 heading: Univariate analysis of risk factors for LNG-IUD expulsion in the treatment of adenomyosis.

Table 4 heading: Multifactor Cox regression analyses of risk factors for LNG-IUD expulsion in the treatment of adenomyosis.

#### **Minor Concerns:**

#### **Abstract**

**Comment 5:** The meaning of the sentence in Line 29-30 is unclear.

**Reply 5:** Thank you for the question. Adenomyosis patients treated with LNG-IUD from Jun 2013 to Jun 2016 were conducted. We have modified our text as The study comprised a cohort of 207 patients who received the LNG-IUD at the Women's Hospital, Zhejiang University School of Medicine, China, from June 2013 to June 2016.

Changes in the text: We modified this text in the abstract section. (see Page 2, Line 32-34).

## **Introduction**

**Comment 6:** Classification of adenomyosis is described in lines 83-88 and in the methods section of Line 133-139. This is repetitive.

**Reply 6:** Thank you for pointing this out. Actually these two parts are repetitive. We deleted the part of Line 83-88. The Classification of adenomyosis is described just in the methods section.

**Changes in the text:** We deleted this text in the introduction section. (see Page 4, Line 130).

**Comment 7:** Is there a reference associated with the statement in Line 88-90?

**Reply 7:** Thank you for the question. We provided a reference associated with the statement in Line 88-90.

(5) Kobayashi H, Matsubara S. A Classification Proposal for Adenomyosis Based on Magnetic Resonance Imaging. Gynecol Obstet Inves. 2020;85(2):118-26.

**Changes in the text:** We added this reference in the introduction section. (see Page 4, Line 131).

## **Methods**

**Comment 8:** Categorization of adenomyosis by MRI- How many different radiologists read the MRIs to determine the subtype of adenomyosis?

**Reply 8:** The diagnosis and categorization of adenomyosis by MRI was established when the agreement of the common diagnosis and subtype by the three radiologists

was reached.

**Changes in the text:** We added this text in the Categorization of adenomyosis by MRI section. (see Page 6, Line 291-293).

**Comment 9:** Inclusion criteria- How did you define if a patient has dysmenorrhea and menorrhagia?

**Reply 9:** Thank you for the question. In this study, we defined dysmenorrhea as the numeric rating scale (NRS) score from 1 to 10, and menorrhagia as the pictorial blood loss assessment chart (PBAC) score >100.

**Changes in the text:** We added this text in the Inclusion and exclusion criteria section. (see Page 7, Line 357-359).

**Comment 10:** How did you determine if the patients had endometriosis? Symptoms vs. laparoscopic diagnosis?

**Reply 10:** Thank you for the question. We suspected the diagnosis of endometriosis by patients' symptom, ultrasound, MRI and determined the diagnosis by laparoscopic findings.

**Changes in the text:** We added this text in the Inclusion and exclusion criteria section. (see Page 7, Line 362).

**Comment 11:** How many different providers inserted the LNG-IUDs.

**Reply 11:** Thank you for the question. There were 2 providers who inserted the LNG-IUDs, and both of them are well seasoned professionals.

**Comment 12:** Evaluation of clinical characteristics- When was the phone interview conducted in relation to the LNG-IUD insertion?

**Reply 12:** Thank you for the question. We did the first phone interview 3 months after the LNG-IUD insertion.

**Changes in the text:** We added this text in the Evaluation of clinical characteristics section. (see Page 7, Line 374).

**Comment 13:** After the LNG-IUD was inserted, how often were the patients interviewed to obtain data for the numeric rating scale and the pictorial blood loss assessment chart?

**Reply 13:** Thank you for the question. The patients were interviewed at 1-, 2- and 3-year intervals after insertion of the LNG-IUD to obtain data for the numeric rating scale and the pictorial blood loss assessment chart.

**Changes in the text:** We added this text in the Evaluation of clinical characteristics section. (see Page 8, Line 446-447).

**Comment 14:** Why are the definitions for menstrual bleeding pattern evaluation (Line 169-174) included? They are not discussed elsewhere in the paper.

**Reply 14:** Thank you for the question. The main side effect of LNG-IUD women often worry about is the change of menstrual pattern, such as amenorrhea and irregular bleeding. We mentioned the change of menstrual pattern in the Menstrual bleeding pattern changes and evaluation of side effects area. There is no obvious menstrual pattern change difference among the three subtypes. So we did not discuss

so much.

**Comment 15:** The sample size calculation is unclear. What is the difference in the outcome that you are trying to calculate?

**Reply 15:** Thank you for pointing this out. According to our clinical experience, we assumed that the efficacy rate of LNG-IUD would be approximately 70% in the subtype I group, 85% in the subtype II group, and 50% in the subtype IV group. To achieve a two-sided  $\alpha$ -level of 0.05 and 90% power, approximately 134 patients would be needed. Considering that there would be patients lost to follow-up, 147.2 patients (50 patients per group) were needed if the loss rate was 10%. This was a retrospective research which was performed in the Department of Gynecology at Women's Hospital, Zhejiang University School of Medicine in China from June 2013 to June 2016. Patients were enrolled according to various Inclusive and exclusive criteria. So we can not change the actual sample size. We did the sample size calculation before the study to evaluate whether the sample size was sufficient or not. The results showed the sample size was sufficient. But it added complexity in manuscript to understand the sample size, we deleted the sample size calculation part.

**Changes in the text:** We deleted this text in the Evaluation of clinical characteristics section. (see Page 9, Line 572).

**Comment 16:** Line 190- What "operation" are the authors referring to?

**Reply 16:** Thank you for pointing this out. The adenomyosis patients who co-existed with endometriosis diagnosed by ultrasound and MRI were performed laparoscopic

endometriotic lesion removal surgery. The “operation” is referring to laparoscopic surgery.

**Changes in the text:** We have modified our text in the Evaluation of clinical characteristics section. (see Page 9, Line 574).

**Comment 17:** Line 193-194- How was IUD expulsion confirmed?

**Reply 17:** Thank you for the question. We confirmed IUD expulsion as either the patient reporting expulsion from the vagina or ultrasound, showing no device in the uterine cavity.

**Changes in the text:** We added this text in the Evaluation of clinical characteristics section. (see Page 9, Line 577-579).

**Comment 18:** The results section should not include data that is obvious in the table.

**Reply 18:** Thank you for the question. We deleted the obvious data in the results section.

**Changes in the text:** We have modified our text in the Comparison of clinical characteristics of the three participant subtypes. (see Page 10, Line 663-664).

**Comment 19:** Line 229 – What is “VAS score”?

**Reply 19:** We apologize for this careless mistake. Actually, it should be numeric rating scale score (NRS).

**Changes in the text:** We have modified our text in the Comparison of clinical

characteristics of three subtypes of participant's section. (see Page 11, Line 721).

**Comment 20:** How do you differentiate if the decrease in blood loss is due to the LNG-IUD or the GnRHa?

**Reply 20:** Thank you for the question. In the study, patients injected GnRHa for 6 months at most and ovulatory cycles usually return to normal within 1 to 3 cycles after cessation of GnRHa treatment. When the patients stopped the GnRHa treatment for 3 months and recovered ovulation, the effect of GnRHa on blood loss gradually disappeared. In particular, we assessed the patient's average blood loss during the device stable period from 3-6 months after the last injection of GnRHa to the time when the IUD removal or expulsion to get rid of the effect of GnRHa.

**Changes in the text:** We have modified our text in the Efficacy of the three subtypes after LNG-IUD treatment section. (see Page 11, Line 733-736).

**Comment 21:** Line 247- What does "dropped" mean?

**Reply 21:** Thank you for the question. "dropped" means IUD expulsion unintentional.

**Changes in the text:** We have modified our text with "expelled" in Efficacy of the three subtypes after LNG-IUD treatment section. (see Page 12, Line 789).

**Comment 22:** Line 271-274- This sentence describes the tables and is unnecessary.

**Reply 22:** Thank you for the question. We agree with the Reviewers and have now deleted the unnecessary sentence.

***Changes in the text:*** We have modified our text in the Analysis of device expulsion in the three subtypes section. (see Page 13, Line 896)

***Comment 23:*** Line 285- What does “carrying” mean?

***Reply 23:*** Thank you for pointing this out. “carrying” means the status with LNG-IUD in uterus cavity.

***Changes in the text:*** We have modified our text in the Menstrual bleeding pattern changes and evaluation of side effects section. (see Page 13-14, Line 907-908)

#### **Table 3 & 4**

***Comment 24:*** What is “uterine size”?

***Reply 24:*** Thank you for pointing this out. “uterine size” means “uterine volume”, we have corrected in the Table 3 & 4

***Comment 25:*** What does “Placing device time” mean?

***Reply 25:*** Thank you for pointing this out. “Placing device time” means “IUD insertion time”, we have corrected in the Table 3 & 4