

# Goserelin vs. Other Treatments in Pain Symptoms Related to Endometriosis after Surgery: An Evidence-Based Case Report

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## Abstract

**Background:** The aim of this case study is to know the efficacy of goserelin for pain treatment in endometriosis.

**Methods:** In this case report, the clinical question is about the treatment of endometriosis, which pain reliever give better outcome to decrease the pain; goserelin or other treatments. To answer this question, we did a searching in PubMed site by using three keywords using MESH, namely ("Goserelin"[Mesh]) and "Pain"[Mesh] AND "Endometriosis"[Mesh]. Apart from that, we also searched in the Cochrane database by using MeSH descriptor: [Pain] explode all trees AND MeSH descriptor: [Endometriosis] explode all trees AND MeSH descriptor: [Goserelin].

**Results:** From the searching literature, we found 22 articles which were relevant to the topic. After screening the abstract and language, we got 4 articles to be appraised.

**Conclusion:** Based on evidences, goserelin was comparable with other treatments. The most common side effect of GnRH was vasomotor symptoms and amenorrhea but that did not reduce patient satisfaction. No serious side effect was observed in goserelin treatment group.

**Keywords:** Goserelin; Pain; Endometriosis; Adenomyosis; Surgery; GnRH analog; Progesterone

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## Introduction

Endometriosis is characterized by the presence of endometrial tissue in sites other than the uterine cavity and an estrogen-dependent disorder [1]. Among women in the reproductive age group, estimates of prevalence in the general population are up to 10%. For women with subfertility the prevalence rate ranges from 25% to 40% [1,2]. Pain is universally recognized as the primary complaint of women with endometriosis. This symptom significantly impairs the patient's quality of life. The management of pain in women with endometriosis has for many years posed a challenge for healthcare professionals [3]. As the pathophysiology of endometriosis is not well understood, its treatment is often unsatisfactory and limited to symptom relief. Treatment options, ranging from / medical therapy (non-surgical intervention) to surgical intervention vary accordingly, as do treatment outcomes. NSAID, GnRH analogues, androgen derivatives, combined oral contraceptives, and progestins are the most commonly used medications in the treatment of endometriosis [4].

There have been 4 studies conducted to know the efficacy of goserelin versus other modalities for treatment of pain associated with endometriosis. However, there is still no formal publication

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about evidence-based case report (EBCR) discussing about this topic. Furthermore, there is no consensus opinion has been reached in terms of which medication should be used and how long it should be administered. Therefore, we do this analysis to solve the question which often arises during our practice.

The question formulation in this case report study is which one is better to reduce the symptom of pain after surgery in patient with endometriosis. To answer this problem, we do the searching of literature study in this case. Although this report is uncommon on scientific publications in Indonesia, we hope that it can be useful for obstetric and gynecologist specialists to do in their daily practice.

## Case History

Mrs. A is 33 years old, working as an employee, with an 8-year-old daughter, and happily married to her husband. Mrs. S has regular menstrual cycle intervals every 28 days, several year history of moderate to severe intensity lower pelvic cramps with heavy flow for about a day (effectively treated with non-steroidal anti-inflammatory agents), recent progressively increasing pelvic and lower back pain that now last for 1-3 days with each cycle (keeping Mrs. S out of work for 2 days a month), and recent diarrhea along with a sharp stabbing pain during urination at the time of her menstrual flow. Seldom, she has post coital pain. Her gynecologist told Mrs. S that she had endometriosis. She underwent laparoscopy procedure 2 weeks ago to treat endometriosis. Her gynecologist planned pain reliever that is suitable for her especially for her menstrual cycle post procedure.

## Methods

### Formulate the question

For the treatment of endometriosis, which pain reliever give better outcome to decrease the pain; goserelin or other treatments?

### Searching the evidences

In order to answer the question above, we did a searching in PubMed site by using three keywords using MESH, namely ("Goserelin"[Mesh]) AND "Pain"[Mesh]) AND "Endometriosis"[Mesh]. Apart from that, we also searched in the Cochrane database by using MeSH descriptor: [Pain] explode all trees AND MeSH descriptor: [Endometriosis] explode all trees AND MeSH descriptor: [Goserelin]. The search strategy identified 22 studies met the inclusion criteria between 1993-2016. From that result, we excluded studies with mandarin language and there were 4 studies could be evaluated (**Figure 1**).

## Results

### Appraise the studies

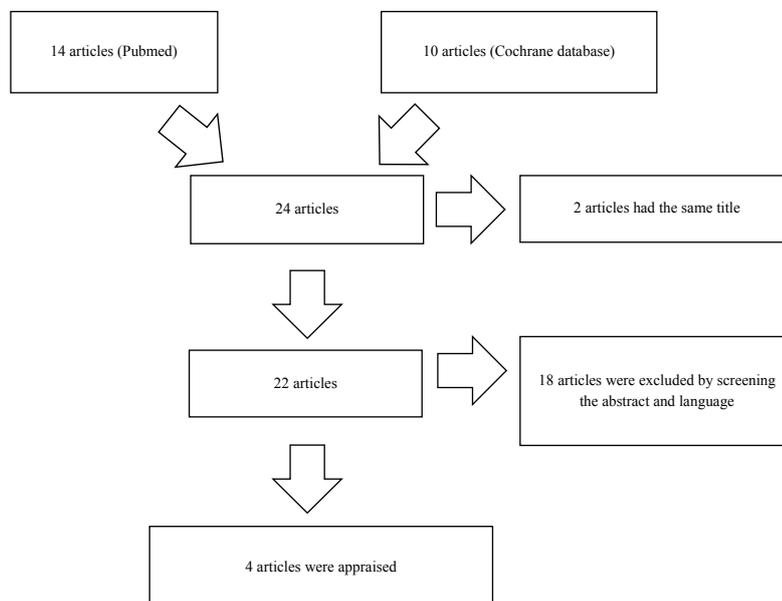
To appraise the scientific evidence of 4 articles, we use the guideline from CONSORT (Consolidated Standard of Reporting Trials) for prospective studies. The tables below describe the appraisal form from the study based on VIA (validity, importance, and applicability) methods (**Tables 1 and 2**).

## Discussion

### Apply the answers

In this EBCR, we appraised 4 studied which fulfilling the inclusion criteria after excluding 22 articles. Critical appraisal was done to randomized control trial study based on VIA (validity, importance, and applicability). A prospective cohort randomized study by Takaesu, administration of dienogest or goserelin was started at the first menstruation after surgery. Dienogest was given 2 mg orally and continued every day for 24 weeks. For goserelin 1.8 mg of subcutaneous injection was given once every 4 weeks a total of six times. Consent for a follow-up study was obtained from patients who desired no postoperative therapy that were assigned into non-treatment group [5].

Menstrual pain was significantly improved during drug administration in both the dienogest and goserelin groups ( $p < 0.05$ ) and also chronic pelvic pain ( $p < 0.05$ ). Menstruation returned at about 3 months after the end of drug administration and then menstrual pain and chronic pelvic pain gradually became worse. In the non-treatment group, menstrual pain and chronic pelvic pain also improved from immediately after the surgery for 6 months, but it was gradually exacerbated after that and showed notable exacerbation as compared with the treatment ( $p < 0.05$ ) [5]. In the non treatment group, menstrual pain and chronic pelvic pain also improved from immediately after the surgery for



**Figure 1** Flowchart of selecting articles using in EBCR.

**Table 1** Validity of the studies included in the analysis.

Study	Type of study	Focused		Primary outcome
		Research question	Selection criteria	
Takaesu et al. [5]	Research article	Yes	Yes	Degrees of menstrual pain and chronic pelvic pain measured by VAS
Tekin et al. [6]	Research article	Yes	Yes	Chronic pelvic pain measured by VAS and TESP (total endometriosis severity profile)
Vercellini et al. [9]	Research article	Yes	Yes	Pelvic pain measured by verbal rating scale
Vercellini et al. [10]	Research article	Yes	Yes	Pelvic pain measured by linear analog and verbal rating scale

**Table 2** Importance of the studies included in the analysis.

Study	Design of the Studies	Number of subjects	Validity appraisal	Intervention	Duration follow up	Dosage	Outcome
Takaesu et al. [5]	Prospective	111	Yes	Dienogest vs. goserelin vs. non treatment group	24 months	Dienogest 2 mg PO for 24 weeks. Goserelin 1.8 mg sub cutaneous once/4 weeks, 6 times.	Improvement in symptom $p < 0.05$ in Dienogest and goserelin group.
Tekin et al. [6]	Prospective	40	Yes	LNG-IUS vs. GnRH-a	24 months	GnRH was given every month for 6 months. LNG-IUS: 19-C progestogen (levonorgestrel) 20 µg/day	LNG-IUS: 19-C progestogen (levonorgestrel) 20 µg/day. GnRH: VAS was significantly reduced ( $p < .001$ ). TESP score showed a significant decrease ( $P < .001$ ).
Vercellini et al. [9]	Prospective	269	Yes	Goserelin vs. post-operative expectant management	6 months	Subcutaneous goserelin depot injections 3.6 mg on six occasions, 28 days apart vs. expectant management	Dysmenorrhoea, alone or associated with other symptoms, was the most frequent moderate or severe event recorded. The cumulative 24-month probabilities of pain recurrence by disease severity in the post-operative medical treatment and surgery only arms were, respectively: 100% and 80% at Stage I; 20% and 48% at Stage II; 13% and 18% at Stage III; and 20% and 23% at Stage IV.
Vercellini et al. [10]	Prospective	57	Yes	Goserelin vs. EE2 +Desogestrel Pill	6 months	Goserelin 3.6 mg in a 28 day-subcutaneous depot formulation vs. EE2 0.02 mg+Desogestrel 0.15 mg per pill	Dysmenorrhea (No between group evaluation was performed because of the obvious absence of dysmenorrhea in amenorrhea patients). Dyspareunia (A significant reduction in deep dyspareunia was observed in both groups, with goserelin superior to OC according to linear analog scale (mean difference, 1.8; 95% confidence interval, 0.1 to 3.5). Non Menstrual pain (Non menstrual pain was diminished on both scales without differences between treatments)

6 months, but it was gradually exacerbated after that and showed notable exacerbation as compared with the treatment groups [5]. For coital pain no great improvement was observed in the either of treatment groups or the non-treatment group. The number of subject who had sexual intercourse after surgery was 16 (30%) in dienogest group and 14 (27%) [5].

Other randomized controlled trial compared the effectiveness of levonorgestrel-releasing intrauterine system (LNG-IUS) with GnRH-a treatment on endometriosis related chronic pelvic pain (PCC) [2]. The LNG-IUS delivers levonorgestrel locally, with the result of causing lower systemic progeteron levels, and does not require repeated administration [6,7]. On the other hand

the TESP score showed a significant decrease at the first, third, and sixth months of the treatment ( $P < 0.001$ ) in both groups. However, at the final follow-up visit the score was elevated up to the pretreatment levels ( $P > 0.05$ ) in the LNG-IUS group. The lowest levels were detected at the month visit. In the GnRH-a group the TESP score was significantly reduced at the 1-year follow-up ( $P < 0.001$ ) [6].

In the LNG-IUS group, the most common side effects were irregular menstrual bleeding and abdominal pain. Two patients complained of weight gain and in 11 patients simple ovarian cysts were detected, 8 of whom presented with one-sided abdominal pain. None of the patients with ovarian cysts had

surgical intervention and the cysts regressed spontaneously. The most common side effects in the GnRH-a group were vasomotor symptoms and amenorrhea, but it did not reduce patient satisfaction [6].

Vercellini et al. [8] compared after surgery the women were assigned to treatment with subcutaneous goserelin depot injections (goserelin) for six months or to expectant management. Post-operative treatment with goserelin significantly prolonged the pain-free interval after conservative surgery for symptomatic endometriosis and did not influence reproductive prognosis. Among the 210 women evaluable for pain recurrence at one-year follow up, 14/107 (13.01%) had moderate or severe symptoms in the goserelin group, compared with 22/103 (21.4%) in the expectant management group ( $P=0.143$ , Fisher's exact test), with an observed difference of 8.3% in symptoms recurrence rate (95%CI -2.9% to +19.4%; OR 0-55, 95%CI 0-25 to 1.22) [4].

A open-label randomized trial conducted by Vercellini et al. [9] showed the efficacy of goserelin with a low-dose cyclic oral contraceptive (OC) at the end of treatment and end of follow up with linear analog and verbal rating. For dyspareunia and non-menstrual pain in both goserelin and OC group showed the symptoms improved significantly ( $p<0.01$ ), with goserelin superior to OC according to the linear analog scale (mean difference, 1.8; 95% confidence interval (CI) 0.1 to 3.5). Women taking OCs experienced a significant reduction in dysmenorrhea on both pain scales ( $p<0.01$ ) [9].

### Assess the outcomes

Our patient with endometriosis experienced with non-steroidal anti-inflammatory agents as pain reliever before surgery. The patient planned to get better drugs to decrease pain caused by endometriosis post-surgery. There are a number of studies about postoperative treatment for endometriosis. However, there is no consensus opinion about which drugs is the best.

Takaesu et al. [5] revealed that significant improvement of symptoms, such as various pains post-surgery, was observed by drug administration in this report. Recurrence of endometriosis could not be prevented by administration of goserelin as compared with endometriosis without drug administration after the endometriosis was successfully prevented by administration of dienogest. The guideline from the European Society of Human Reproduction and Embryology shows that secondary prevention is defined as interventions to prevent the recurrence of pain

symptoms or the recurrence of disease in the long term, which is defined as more than 6 months post-surgery. Hence, dienogest administration could be a first choice to prevent recurrence of endometriosis post-surgery in the future.

Tekin et al. [6] reported that the VAS score had no significant alteration during the follow-up period in the LNG-IUS group, the GnRH-a group showed a significant decrease in the VAS score and endometriosis score at the end of one year. Vercellini et al. [6] revealed that at 6 months of treatment, a significant reduction in deep dyspareunia was observed in both groups, with goserelin superior to the OC at linear analog scale assessment. In 1999, they also reported that post-operative treatment with goserelin significantly prolonged the pain-free interval after conservative surgery for symptomatic endometriosis and did not influence reproductive prognosis [8].

In this evidence-based case report (EBCR), we reported a woman with endometriosis post surgery would like to get pain reliever. She effectively treated with nonsteroidal anti-inflammatory drugs before surgery. From the critical appraisal focused on 4 articles collected from PubMed and Cochrane database with specific criteria, we could summarize that goserelin was comparable with other treatments. The other treatments were dienogest, levonogestrel intra uterine system, oral contraception, and expectant management.

Long-acting GnRH agonists had effect inducing a hypogonadotropic hypogonadal state that had been dubbed pseudomenopause [10]. The most common side effect of GnRH was vasomotor symptoms and amenorrhea but that did not reduce patient satisfaction [6]. No serious side effects were observed in goserelin treatment group in those study [5]. Some concern remains about long term effect of GnRH analogues on bone loss [11]. The decrease in bone mineral associated with standard GnRH agonist treatment regimens (6 months) is significant. Bone loss occurs in both the lumbar spine (trabecular bone) and femoral neck (cortical bone) and can approach or even exceed 1% per month [10].

### Conclusion

Based on evidences, goserelin was comparable with other treatments. The most common side effect of GnRH was vasomotor symptoms and amenorrhea but that did not reduce patient satisfaction. No serious side effects were observed in goserelin treatment group.

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