Comparison of the Effects of Leuprolide Acetate and Dienogest on Endometrioma Size at Ulin Hospital Banjarmasin for the Period of January-December 2022

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ABSTRACT

Endometrioma is a type of cyst formed when endometrial tissue grows on the ovarian epithelium. Leuprolide acetate and dienogest are the most frequently used endometrioma therapies and are included in the drugs covered by health insurance in Indonesia. This study aims to compare changes in endometrioma size after the administration of leuprolide acetate and dienogest for 6 months. This study used an analytical observational method with a pre and post design approach in endometrioma sufferers aged 18-45 years who sought treatment at the Obstetrics and Gynecology Polyclinic at Ulin Banjarmasin Regional Hospital for the period of January-December 2022. Women with endometrioma were evaluated for its endometrioma size before and after the administration of leuprolide acetate or dienogest therapy for 6 months using ultrasound examination. The number of samples obtained is 30 women each who received leuprolide acetate or dienogest therapy. The average change in endometrioma size in the dienogest group was 2.0247 cm, while in the leuprolide acetate group was 1.5083 cm. However, the results of statistical analysis showed no significant difference in endometrioma size between the two treatment groups (P > 0.05). Based on the research results, it can be concluded that the administration of leuprolide or dienogest does not make a difference in the size of the endometrioma.

Keywords: Dienogest, Endometrioma, Leuprolide Acetate

INTRODUCTION

Endometrioma, often referred to as a "chocolate cyst," is a cystic formation that arises from the same underlying disease mechanism. Typically located on the ovaries, it signifies a more advanced stage of endometriosis, potentially impacting fertility by diminishing ovarian reserve. Endometrioma occurs when cysts develop as endometrial tissue attaches and grows onto the ovarian surface (1).

Although there is little information available regarding the frequency of endometrioma, it is thought that between 17 and 44 percent of endometriosis patients also have this condition (2). The estimation of its prevalence in the general population range from 10% to 50%, with the highest rates seen in women who present with infertility or pelvic pain. While not all women have symptoms, those who do, frequently include infertility, dysmenorrhea, dyspareunia, and chronic pelvic pain.

In regards to endometrioma formation, Rizzello and Coccia have updated a number of theories. Among these is the suggestion that endometrioma may arise from pseudocyst invaginations caused by the build-up of menstrual remnants, including active implantation at the site of invagination. Ovarian follicles may be the source of endometrioma, according to certain researchers, but there is no conclusive evidence to support this theory. Coelomic metaplasia is derived from invaginated ovarian coelomic epithelium, which undergoes changes in the type of glandular epithelium and stroma.

Given the absence of a definitive cure for endometrioma, present guidelines prioritize
strategies aimed at managing symptoms effectively and safely. The primary goals include alleviating pain, enhancing overall quality of life, and facilitating conception. This can lead to decreased quality of life as well as psychological stress and depression. Treatment options include surgery, assisted reproductive technology, pharmaceuticals (such as hormone therapy and analgesics), or a combination of these (3).

Research at Dr Soetomo Surabaya Hospital in 2014 showed that there were around 5120 endometriosis sufferers or 20% of all gynecology patients who visited the Gynecology Polyclinic (4). According to research carried out by Nurhayati (2017), 23 (28%) of the 82 respondents who had their fertility checked had endometriosis. This information was derived from research conducted at the Fertility and Gynecology Polyclinic at Ulin Hospital, Banjarmasin. The Fertility and Gynecology Polyclinic at Ulin Hospital, Banjarmasin saw 194 endometriosis patient visits out of a total of 580 patients (33%), according to data from the 2019 and 2020 Annual Report of SMF Obsgyn, Ulin Hospital, Banjarmasin (5)

The two main types of endometrioma treatment modalities are surgical and medicinal. Recurrence and reoperation rates are high after undergoing operative therapy. The first line of treatment for endometriosis patients is medical therapy, which is symptomatic and aims to suppress symptoms without stopping the medication. This is especially true for women who have endometrioma (6,7). Endometrioma can cause pain due to space-intensive lesions brought on by their size or because they have sensory transduction pathways connecting the spinal cord to the brain, which allows stimuli from the outside world to be perceived as pain. There is no intrinsic sensory nerve supply associated with endometrial fragments in this pathway. Nonetheless, endometrial lesions can cause pain due to the development of new sensory nerves (neurogenesis), and the more nerve cells that are sensitized, the larger the endometrioma (8).

The 2022 Asian Consensus states that progestin is the first line of initial medical treatment for patients with clinically diagnosed endometriosis, and that hormonal therapy is more effective in treating pelvic pain in these patients. Hormonal therapy is recommended for patients not intending to conceive in the near future. Dienogest, an oral progestin, has gained approval in 157 countries, including 15 in Asia, for endometriosis treatment. It's increasingly preferred over GnRH agonists due to its moderate estrogen suppression and minimal androgenic, mineralocorticoid, or glucocorticoid effects, making it suitable for long-term use. Dienogest boasts good tolerability and has been demonstrated in numerous studies to reduce both the size of recurrent endometriomas and the associated painful symptoms of endometriotic lesions (9).

The latest progestin on the market, Dienogest (DNG), derived from 19-nortestosterone, is recommended for treating endometriosis. DNG has shown significant efficacy in reducing both the diameter and volume of endometriomas across various endometriosis phenotypes. Long-term treatment (up to 60 months) effectively reduces endometriosis-associated pain and prevents post-operative pain recurrence without notable adverse effects, particularly on bone mineral density (BMD). Consequently, it is considered an attractive first-line therapy for managing chronic and bothersome endometriosis-related pain over the long term. According to a large-scale Korean study, patient satisfaction rates regarding efficacy and tolerability were generally high. The most commonly reported side effects included headache (1.2%), weight gain (2.5%), and abnormal uterine bleeding (4.1%). Furthermore, the proportion of patients experiencing favorable bleeding patterns, including amenorrhea, increased with prolonged treatment duration (10).

Since the 1990s, one of the primary treatment options for endometriosis has been Gonadotropin-Releasing Hormone agonists (GnRH-a), including medications such as goserelin, leuprolide, nafarelin, buserelin, and triptorelin. They attach to the GnRH receptor and cause the
pituitary gland to release LH and FSH during the first ten days of therapy. Moreover, long-term, continuous exposure to the agents results in a reduction in GnRH receptors, which lowers LH and FSH levels and inhibits the production of ovarian estrogen. Endometriotic lesions recede when hypotrogenism is induced and amenorrhea follows. Numerous studies have shown that GnRHa is useful in shrinking endometriomas (6,10).

A meta-analysis of 41 trials comparing various doses, regimens, and routes of administration of Gonadotropin-Releasing Hormone agonists (GnRH-a) indicated their effectiveness compared to placebo and their equivalence to other progestins in relieving pain associated with endometriosis. Several studies have shown that GnRH-a can significantly alleviate pain in women with endometriosis. Specifically, administering GnRH-a three to six months before starting Assisted Reproductive Technology (ART) can increase the likelihood of a clinical pregnancy by fourfold in women affected by endometriosis. However, GnRH-a therapy is associated with serious hypogonadal side effects such as amenorrhea, vasomotor symptoms, irregular sleep patterns, urogenital atrophy, and accelerated bone loss. Given that adolescents may not have reached their optimal bone density, caution is advised when considering GnRH-a therapy for this population. The addition of "add-back" therapy, including low-dose Combined Oral Contraceptives (COCs), estrogen or progestin-only therapy, bisphosphonates, tibolone, or raloxifene, alongside GnRH-a treatment, may mitigate these side effects without compromising pain relief efficacy.

Initially limited to six months, GnRH-a administration has been permitted for longer durations with the introduction of "add-back" therapy. Clinical trials and cohort studies have demonstrated the efficacy of combining GnRH-a with steroid "add-back" therapy over durations ranging from 30 months to 10 years (10). Endometrioma is the issue; it is a chronic gynecological disease that will either not go away or grow larger over time, causing symptoms to worsen. Medical therapy is becoming the preferred method of treating endometriosis rather than surgery. Leuprolide acetate and dienogest are the two medical therapies available to Ulin Hospital patients with endometriosis; both are covered by the National Health Insurance (JKN) therapy formulary. Up until now, no studies have been conducted in Banjarmasin, particularly in Indonesia, to determine how endometrioma tumor size responds to leuprolide acetate and dienogest therapy.

This study aims to fill this gap by presenting direct comparative data regarding the effects of leuprolide acetate and dienogest on endometrioma size in a local population, with the hope of providing more concrete insights into the therapeutic management of endometriosis in Indonesia. This will be one of the first studies in Banjarmasin, which not only looks at the therapeutic effects of the drug but also contributes to the existing literature regarding its effect on endometrioma, particularly in terms of changes in tumor size.

**METHOD**

The pre-post design approach was used in this observational study, which was approved by the Ulin Banjarmasin Hospital's research ethics commission under the number No.99/V-Reg Research/RSUDU/23. The study was conducted at the Gynecology Polyclinic of the hospital. Patients' medical records from January 2022 to December 2022 were examined in order to gather data. The purpose of this study is to compare the size of endometrioma before and after Leuprolide Acetate or Dienogest treatment. Under the supervision of a subspecialist in Obstetrics and Gynecology (F.E.R.), the size of the endometrioma was measured using ultrasound results and documented in the patient's medical file before and after therapy.

The study sample was women aged 18-45 years who were diagnosed with endometrioma.
and received leuprolide acetate or dienogest therapy. In this case, the inclusion criteria were patients who had undergone an ultrasound examination to measure endometrioma size before starting therapy and after therapy for a 6 month period. Meanwhile, the exclusion criteria included patients who received therapy other than dienogest or leuprolide acetate, incomplete medical record data, patients with loss of follow-up, and patients who underwent surgical procedures during the treatment period. In the period of January-December 2023, there were 154 patients with endometriosis and 90 patients met the inclusion and exclusion criteria, consisting of 53 samples in the Leuprolide Acetate group and 37 samples in the Dienogest group. After the data were randomized, 30 samples from the leuprolide acetate therapy group and 30 samples from the dienogest therapy group were analyzed.

Statistical analysis in this research was carried out using descriptive analysis and bivariate analysis. Descriptive analysis was used to present demographic data and basic characteristics of research subjects such as age, marital status, domicile (Banjarmasin or outside Banjarmasin), parity, and main symptoms. Before proceeding with hypothesis testing, the data will undergo evaluation for normal distribution using the Kolmogorov-Smirnov test. If the data exhibit a normal distribution, a paired t-test will be employed to compare the size of endometriomas before and after treatment within each therapy group. However, if the data distribution are not normal, the Mann-Whitney test would be used with a confidence level of 95% and a significance threshold set at 0.05.

**Figure 1. Research Sample Selection Scheme**

- Women diagnosed with endometrioma (n=154)
  - Surgery (n=13)
  - Received therapy other than LA and dienogest (n=14)
  - Incomplete data (n=30)
  - Missing follow-up (n=9)

- Grouped (n=90)
  - Leuprolide Acetate Group (n=53)
    - Analyze (n=30)
  - Dienogest Group (n=37)
    - Analyze (n=30)
RESULT

The initial research population obtained from report data from outpatient clinic patients diagnosed with endometrioma is 154 respondents. The study excluded 54 endometrioma respondents in total because 30 had incomplete data, 13 had surgery, 9 had vanished during follow-up, and the remaining respondents had received medical therapy other than leuprolide or dienogest. Table 1 displays the demographic information used in this investigation.

Table 1. Data on Research Subject Characteristics

<table>
<thead>
<tr>
<th>Demographic Data</th>
<th>Leuprolide Acetate</th>
<th>Dienogest</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amount</td>
<td>%</td>
</tr>
<tr>
<td>Average Age</td>
<td>35.9</td>
<td>34.4</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>Married</td>
<td>27</td>
<td>90%</td>
</tr>
<tr>
<td>Domicile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banjarmasin</td>
<td>19</td>
<td>63%</td>
</tr>
<tr>
<td>Outside</td>
<td>11</td>
<td>37%</td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>43%</td>
</tr>
<tr>
<td>no</td>
<td>14</td>
<td>47%</td>
</tr>
<tr>
<td>Paritas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17</td>
<td>57%</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
<td>20%</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>7</td>
<td>23%</td>
</tr>
<tr>
<td>Main symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menstrual pain</td>
<td>24</td>
<td>80%</td>
</tr>
<tr>
<td>Infertility</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td>Lumps in the stomach</td>
<td>4</td>
<td>13%</td>
</tr>
</tbody>
</table>

Source: Demographic distribution for polygynecology research sample distribution in 2022

The mean age of the two cohorts was found to be relatively similar: 35.9 years old for the leuprolide acetate group and 34.4 years old for the dienogest group. Married women also experience a higher rate of endometrioma than any other group; among them, 27 respondents (90%) reported having one in the leuprolide acetate group and 25 respondents (83%) in the dienogest group. The number of respondents who are not married is 3 (10%) in the leuprolide acetate group and 5 (17%) in the dienogest group.

Within the leuprolide acetate group, 13 respondents (43%) reported being infertile, while 14 respondents (47%), did not experience infertility. Out of the respondents in the dienogest group, 8 (27%) reported experiencing infertility, while 17 (57%) reported not experiencing it. Parity of 0 in the leuprolide acetate group included 17 respondents (57%), parity of 1 included 6 respondents (20%), and parity of more than 2 included 7 respondents (23%). The number of parities was also demonstrated in the study. Thirteen respondents (43%) had parity of 0, eight respondents (27%) had parity of 1, and nine respondents (30%) had parity of more than 2. These numbers represent the dienogest group results.

Menstrual pain was the most common symptom that sent patients to the hospital, as reported by 24 respondents (80%), stomach lumps by 4 respondents (13%), and infertility in the leuprolide acetate group is 2 respondents (7%). Menstrual pain was the most common complaint among patients in the dienogest group, accounting for 84% of the responses from 25, 13% from lumps in the stomach, and 3% from infertility.

Before therapy, the average endometrioma size of the 30 respondents in the dienogest group was 6,031 cm, with the smallest size being 1.23 cm and the largest being 13.9 cm. Furthermore, 2.8 cm was the smallest and 28 cm was the largest size of the endometrioma in
the leuprolide acetate group, compared to an average of 7,186 cm before administration. The average size of the dienogest group changed to 5,084 cm after each group received therapy. Following therapy, the biggest change measured 12.3 cm, while the smallest was only 1.7 cm. The size of the leuprolide acetate group also changed significantly; the average change was 5,082 cm, the smallest change was 1.9 cm, and the largest change was still 24 cm.

The dienogest group experienced changes in size reduction of 0.1 cm per therapy cycle until the change reached 5 cm. Leuprolide acetate administration resulted in size changes ranging from 0.16 cm to 4.8 cm, which was the largest. In the dienogest group, the average change in endometrioma size was 2.0247 cm, whereas in the leuprolide acetate group, it was 1.5083 cm.

The research findings were then subjected to tests for homogeneity and normality, which are prerequisites for performing parametric statistical analysis. The study data are regularly distributed, according to the normality test results. A p value of above 0.05 in the Kolmogorov normality test indicates that the data distribution is normal. It satisfies the requirements for the t test Table 2-3 because the homogeneity test (Levenes) obtained p value of 0.418, so p is above 0.05, indicating homogeneity (both sample characteristics are the same).

The unpaired T-test was used to conduct statistical tests after meeting the requirements of the normality and homogeneity tests for parametric tests. The difference in size between leuprolide acetate and Visanne therapy is 1.04962 cm, but the t value is 0.381, p 0.704, p > 0.05, indicating that there is no significant difference in size. Table 4 shows this difference.

Table 2. Normality test using Kolmogorov-Smirnov

| Kolmogorov-Smirnov |  
|-------------------|---|
| Size              | 0.2a |

If the value is > 0.05 then the data is normally distributed

Table 3. Homogeneity Test

| Uji Homogenitas Lavene’s Test |  
|-------------------------------|---|
| Size                          | 0.418a |

If the value is > 0.05 then the data is homogeneous

Table 4. Differences in size of endometrioma tumors treated with leuprolide acetate and dienogest

<table>
<thead>
<tr>
<th>Leuprolide acetate</th>
<th>Dienogest</th>
<th>Unpaired T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>5.23</td>
<td>15.12</td>
<td>4.19</td>
</tr>
</tbody>
</table>

If the Sig value (2-tailed) > 0.05 then H0 is accepted and H1 is rejected

a If the value is > 0.05 then the data is normally distributed
DISCUSSION

Compared to the dienogest group, which had a mean age of 34.4 years old, the Leuprolide acetate group had a mean age of 35.9 years old. According to research done by Techatraisak in six Asian countries, the average age of people who have endometriosis is 34.4 +/- 7.6 years. Age may play a role in the therapy that is chosen. Leuprolide Acetate is a GnRH agonist that inhibits the ovaries’ ability to produce estrogen. While the symptoms of endometriosis can be effectively reduced by this estrogen suppression, menopause-like side effects, including hot flashes, night sweats, and osteoporosis, may also result. For older women or those with more severe symptoms who need stronger estrogen suppression, leuprolide acetate may be the more popular choice. However, unlike leuprolide acetate, dienogest is a progestin that inhibits the growth of endometriosis tissue without as strongly suppressing the production of estrogen. Because dienogest has fewer negative effects, younger women are more likely to accept it. On the other hand, younger women might favor treatments with milder estrogen-suppressive effects because they are more worried about the possible long-term side effects of strong estrogen suppression, such as the risk of osteoporosis (12).

In the group receiving leuprolide acetate, 24 respondents (80%) and in the group receiving dienogest, 25 respondents (84%) reported menstrual pain as the most prevalent complaint among patients with endometrioma. Endometriosis is identified as the primary cause of secondary dysmenorrhea. Research indicates its presence in 70% of adolescents experiencing pelvic discomfort unresponsive to NSAIDs and/or combined oral contraceptives, and in 62–75% of adolescents undergoing laparoscopy for chronic pelvic pain and/or dysmenorrhea. Moreover, individuals with endometriosis are 13 times more likely than healthy women to suffer from abdominal pain, with over 60% of diagnosed women reporting pelvic pain, particularly during menstruation (13).

Another common complaint from patients with endometriosis is infertility. There were 13 respondents (43%) in the leuprolide acetate group and 8 respondents (27%), respectively, in the dienogest group who reported experiencing infertility. A pro-inflammatory state brought on by endometriosis influences oocyte implantation and pelvic anatomy, and 30–50% of affected women may become infertile (9). From an endocrine standpoint, the majority of theories take abnormal serum hormonal levels, like hyperprolactinemia, into account along with defects in ovulation and folliculogenesis. The mechanisms underlying immunological alterations center on molecularly driven events like sperm phagocytosis, embryotoxicity, and implantation defects. From a biochemical standpoint, one of the most researched elements linked to infertility caused by the endometrium is oxidative stress. Unnatural rises in Reactive Oxygen Species (ROS) brought on by oxygen metabolism damage DNA structure, proteins, and lipids in endometrial cells, changing cellular cycles and function (14).

The degree of symptoms is one consideration when selecting an endometriosis treatment plan. In order to reduce pain and suppress the hormonal activity of active endometriosis tissue, medical therapy for endometriosis will cause atrophy of the hormone-dependent ectopic endometrial tissue. This will result in a reduction in the number and size of lesions. It has been demonstrated that giving endometriosis patients hormone therapy can lessen their discomfort and improve their fertility ratio. According to Cochrane research (2018), progesterone administration can lessen dysmenorrhea or dyspareunia. Androgens are additional hormones that can be administered; however, they come with negative effects such as hirsutism, acne, and voice worsening. Hormone therapy typically only reduces symptoms by 11–19%, and up to 5–15% of patients discontinue treatment due to side effects (15).

The dienogest group exhibited a reduction in size of 0.1 cm per therapy cycle until reaching a total reduction of 5 cm. On average, the dienogest group experienced a change in
endometrioma size of 2.0247 cm. Similar findings were reported in a 2019 study by Angioni et al. involving 81 patients with endometriomas. Among them, 40 received daily treatment with 2 mg of dienogest (DNG), while 41 received cyclic oral estro-progestin (ethinyl estradiol 30 mcg plus 2 mg of dienogest) (DNG+EE). Significantly smaller endometrioma cyst sizes were observed in the DNG group. After six months of treatment, the DNG group experienced a 75% reduction in volume, with the mean cyst diameter decreasing from 52 ± 22 mm at baseline to 32 ± 12 mm (p < 0.001). Notably, the reduction in endometrioma cyst size observed in women treated with progestin alone may help mitigate ovarian-related adverse effects and potentially avoid the need for surgery (16).

Takenaka et al. (2013) conducted research in two hospitals in Japan that demonstrated a reduction in endometrioma cyst size prior to surgery. Dienogest was used to reduce the size of endometrioma cysts by 10.2% and 18.2% in the leuprolide group, respectively, although the difference was not statistically significant. This is due to the small sample size used in Takenaka's research—15 participants per treatment group—in his study (17).

The average size of endometrioma cysts observed prospectively in the third and sixth months decreased in 64 patients treated with dienogest alone, according to research done in Turkey by Gokmen et al in 2023. The patients were followed for three and six months. At three months, endometrioma cyst size decreased by 10%, and at six months, it decreased by 21.4% (p <0.01). In the third and sixth months of the study, there was also a decrease in the rates of dysparunia and dysmenorrhea (18).

The difference in the maximum visual analogue scale score between leuprolide and relugolix in phase three clinical trials was 52.6 for relugolix with a standard deviation of 1.3 and 57.5 for leuprolide with a standard deviation of 1.4. For relugolix and leuprolide, the volume of ovarian endometrioma decreased by 12.26 and 14.10 cm³, respectively, with a standard deviation of 17.52 and 18.81 cm³, respectively. The following drug-related side effects were more common in both groups than 10%: headaches, vaginal bleeding, hot flashes, and metrorrhagia. For relugelix and leuprolide, the percentage of treatment discontinuations due to side effects was 2.9% and 4.3%, respectively (19).

After six months of dienogest treatment, the average volume of endometrioma was found to have decreased by 66.71%, according to a different study conducted in 2020 by Vignali et al. Following a year of treatment, the endometrioma's average volume reduction was 76.19%. Endometrioma volume and pain symptoms are statistically significantly reduced with dienogest (20).

After six months of dienogest treatment, the average volume of endometrioma was found to have decreased by 66.71%, according to a different study conducted in 2020 by Vignali et al. Following a year of treatment, the endometrioma's average volume reduction was 76.19%. Endometrioma volume and pain symptoms are statistically significantly reduced with dienogest (7). The study's findings also demonstrated that the endometrioma's size changed from 0.16 cm to 4.8 cm, the largest size, following the administration of leuprolide acetate. In the leuprolide acetate group, the average change in endometrioma size was 1.5083 cm. A 2018 study by Cantor et al. compared leuprolide acetate + letrozole (add-back combination therapy) with leuprolide 3.75 mg for 60 days in 126 women. The results showed that the average maximum endometrioma diameter was 1.8 ± 0.4 cm (P = 0.0001) following treatment. In a research by Tsujioka et al, 34 patients showed a decrease in endometrioma diameter from 66.0 ± 2.0 mm to 51.0 ± 2.4 mm following three to six months of GnRHa treatment (22).

There is evidence to support the relationship between ovarian function and endometrioma size. One major consequence of endometriosis is infertility, which can be caused by the presence of an adnexal mass and can impact ovarian function. In 2020, Somigliana and
colleagues studied eighteen women with unilateral endometriomas who underwent cystectomy and continued IVF. This study discovered that tumors larger than 4 cm in diameter affected infertility and had a poor ovarian response (23).

Endometriosis is known to cause an aberrant inflammatory response (24). Endometriosis-related to pain is caused by a variety of factors, including inflammation (25). Serum levels of IFN-Ɣ have been identified as a potential non-invasive biomarker for endometriosis (26). IFN-Ɣ levels were significantly increased in the peritoneal fluid of endometriosis patients compared with healthy individuals. Mali et al conducted a purely experimental research study using mice (Mus musculus) as experimental subjects (in vivo research). Blood samples were collected to measure IFN-Ɣ levels in mouse serum. In a mouse model of endometriosis (Mus musculus), Leuprolide Acetate effectively reduced IFN-Ɣ (pro-inflammatory) levels. In contrast, Dienogest increased IFN-Ɣ (anti-inflammatory) levels in a mouse model of endometriosis. In this in vivo study, 3 times administration of Leuprolide Acetate was effective in reducing IFN-Ɣ levels in endometriotic mice (Mus musculus). In patients with endometriosis, the use of Leuprolide Acetate is limited to a maximum of 6 months. Apart from its ability as an excellent anti-inflammatory, Leuprolide Acetate is known to have side effects, causing a hypoestrogenic state which causes menopausal symptoms (27).

Although there are numerous studies that have investigated the effectiveness of leuprolide acetate and dienogest in the management of endometriosis, there is still a lack of data regarding a direct comparison between these two therapies, especially in the context of changes in endometrioma size. Previous research has tended to focus on reducing symptoms or improving quality of life, with little information about how these drugs affect endometrioma size specifically. In addition, most of the existing data comes from populations outside Indonesia, which may have different demographic and genetic characteristics, as well as different access to health services. There was also a decrease in the VAS score in both treatment groups.

There are a number of research weaknesses that should be taken into account. Firstly, the results may not be statistically reliable due to the sample limitation of 60 patients, which may also not accurately represent the diversity of the endometriosis community as a whole. Second, it is challenging to determine a direct cause-and-effect link between therapy and symptom improvement or endometrioma size reduction due to the observational design employed. In addition, the relatively brief observation period following therapy makes it impossible to assess long-term effects, like relapse. The lack of consideration for the potential influence of concomitant conditions or genetic factors on patient response to therapy can also limit the generalizability of the findings due to variability in patient response. Lastly, these studies neglected other crucial factors like quality of life, sexual function, and reproductive outcomes in favor of narrowly defined outcome measures, chiefly the reduction of endometrioma size and pain intensity. Acknowledging these shortcomings is crucial for accurate interpretation of study findings and provides a solid foundation for designing more thorough and representative follow-up investigations.

CONCLUSION

One of the things that causes endometriosis patients to experience chronic pain is the size of the endometrioma. This study demonstrates that while dienogest and leuprolide acetate do not differ statistically and significantly in their effects on tumor size, leuprolide acetate produces a greater macroscopic size reduction than dienogest. It is intended that the findings of this study will help physicians choose a course of treatment for patients with chronic endometriosis while taking potential side effects into account. It is hoped that this study will serve as a foundation for future investigations into the other factors that contribute to
endometriosis pain as well as the efficacy of the two medications that are the first line of treatment for people with endometriosis: leuprolide acetate and dienogest.

REFERENCES


