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Review Article

Shifting paradigms in uterine fibroids treatment: insights from current therapeutic approaches

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ABSTRACT

This review examined the effectiveness of ulipristal acetate (UPA) compared to leuprolide acetate (LEU) in the treatment of symptomatic uterine fibroids. The primary objective was to analyze relevant studies that investigated the improvement of symptoms, complications, alternative treatment options, and surgical outcomes for fibroids. Using the PICO format as a research approach, various aspects were compared for each treatment, including diagnostic accuracy, side effects, quality of life, and patient satisfaction measured through the Uterine fibroid symptoms and quality of life scale. UPA proved to be a safe, well-tolerated, and effective treatment option for symptomatic uterine fibroids, leading to amenorrhea and reduced heavy menstrual bleeding. On the other hand, LEU also effectively reduced fibroid size but had a higher incidence of adverse events such as hot flashes, vaginal dryness, and decreased bone density. It is crucial to consider all the aforementioned factors when selecting the most suitable treatment option for individual patients, as each treatment has its own advantages and disadvantages, including dosing requirements, side effects, endometrial changes, and their impact on treatment adherence and outcomes. Currently, there is limited evidence supporting the superiority of UPA over other drugs like LEU in short-term therapy for symptomatic uterine fibroids. Further research is necessary to establish UPA as a reliable and promising alternative. Treatment decisions should be individualized, taking into account patient comorbidities and considering both surgical and conservative approaches.

Keywords: Ulipristal acetate, Leuprolide acetate, Uterine fibroids, Diagnosis, Side effects, Quality of life, Patient satisfaction, Efficacy

INTRODUCTION

Symptomatic uterine fibroids have a significant impact on patients' well-being, causing symptoms such as heavy menstrual bleeding, pelvic pain, and pressure on adjacent organs. These fibroids can have adverse effects on patients' social life, leading to decreased energy levels and sexual desire. The primary objectives of treating uterine fibroids are to alleviate symptoms, particularly excessive uterine bleeding and pelvic pain, and to reduce fibroid size before considering surgery. Ulipristal (UPA) and leuprolide (LEU) are two commonly used medications for short-term therapy of symptomatic fibroids.

UPA acts by regulating progesterone receptors and inhibiting fibroid growth, while LEU suppresses ovarian

function, resulting in decreased estrogen levels and fibroid shrinkage. Comparing the effectiveness of UPA and LEU is crucial for healthcare providers and patients, as it provides additional treatment options for managing uterine bleeding and improving quality of life. Studies have demonstrated that both treatments effectively control uterine bleeding and reduce fibroid size, with UPA being associated with fewer side effects. Consequently, UPA and LEU are considered first-line treatments before considering surgery, as they can minimize bleeding during surgical procedures and alleviate most of the associated symptoms. In some cases, these treatments can even obviate the need for surgery, as they lead to significant improvements in symptomatology and reduce the surgical risks without substantial benefits to the patient's quality of life.[1,2]

METHODS

This study focused on reviewing the efficacy of ulipristal acetate (UPA) versus leuprolide acetate (LA) in treating symptomatic uterine fibroids, with attention to diagnostic accuracy, side effects, quality of life, and patient satisfaction. Our review was structured using the PICO format, defining patients (P: individuals with symptomatic uterine fibroids), intervention (I: treatment with ulipristal acetate), comparison (C: therapy with leuprolide acetate), and outcomes (O: diagnostic accuracy, side effects, quality of life, patient satisfaction).

We conducted a thorough search in the renowned medical and scientific database PubMed, encompassing scientific literature published from January 1, 2010, to April 30, 2023. This search was guided using specific search terms derived from our PICO structure, assisting us in identifying relevant studies. The selection of studies was based on their relevance to our research question and the contribution they made to our understanding of the topic. To keep our focus on the research question, we employed predefined questions and keywords aligned with the components of the PICO format. These elements will be presented in a table, Table 1 in the results section, where each question will be addressed individually.

The results will be organized according to these predefined questions, and graphs and tables will be used to present the information clearly and concisely. In the discussion, we will analyze trends, similarities, and differences emerging from the selected studies, always focusing on their relation to our research question. This discussion will allow a detailed interpretation of the results and will provide more flexibility than traditional systematic reviews, enabling us to contemplate both the practical and theoretical implications of our findings.

Table 1: Results.

Subtitles	Questions	Keywords
Comparison between ulipristal acetate and leuprolide acetate to other treatment options for uterine fibroids	How do ulipristal acetate and leuprolide acetate compare to other treatment options for symptomatic uterine fibroids regarding efficacy, side effects, quality of life, and patient satisfaction?	'Ulipristal acetate,' 'leuprolide acetate,' 'efficacy,' 'side effects,' 'quality of life,' 'patient satisfaction,' 'symptomatic uterine fibroids'
Factors influencing the efficacy of ulipristal acetate and leuprolide acetate in uterine fibroid treatment	What factors can influence the efficacy of ulipristal acetate and leuprolide acetate in patients with uterine fibroids?	'Efficacy,' 'ulipristal acetate,' 'leuprolide acetate,' 'uterine fibroids,' 'factors,' 'predictors,' 'therapeutic response,' 'treatment outcome'
Impact of ulipristal acetate and leuprolide acetate on life quality in uterine fibroid patients	How do ulipristal acetate and leuprolide acetate affect the quality of life for patients with symptomatic uterine fibroids?	'Ulipristal acetate,' 'leuprolide acetate,' 'symptomatic uterine fibroids,' 'quality of life,' 'patient satisfaction,' 'symptom relief'
Side effects of ulipristal acetate and leuprolide acetate in uterine fibroid treatment	What are the side effects of ulipristal acetate and leuprolide acetate in treating uterine fibroids?	'Ulipristal acetate,' 'leuprolide acetate,' 'uterine fibroids,' 'side effects,' 'complications'
Efficacy of ulipristal acetate versus leuprolide acetate in treating uterine fibroids	How does the efficacy of ulipristal acetate compare to leuprolide acetate in treating symptomatic uterine fibroids?	'Ulipristal acetate,' 'leuprolide acetate,' 'efficacy comparison,' 'symptomatic uterine fibroids'
Diagnosis and assessment of uterine fibroids	How are uterine fibroids diagnosed and assessed?	'Uterine fibroids,' 'diagnosis,' 'assessment,' 'fibroid imaging techniques,' 'diagnostic methods'
Pathophysiology of uterine fibroids	What are the underlying pathophysiological mechanisms of uterine fibroids?	'Uterine fibroids,' 'pathophysiology,' 'leiomyoma,' 'etiology,' 'molecular mechanism,' 'abnormal growth'

RESULTS

Pathophysiology of uterine fibroids

Uterine fibroids, or leiomyomas, are benign tumors arising from the uterine wall's smooth muscle cells. Their pathogenesis, influenced by genetic, hormonal, and environmental factors, still needs to be completed. They are marked by genomic instability in fibroid cells and influenced by hormonal factors like estrogen and progesterone.

Obesity is a significant risk factor, with obese patients showing increased fibroblast activation, autophagy dysregulation, and oxidative stress. Insulin resistance and chronic inflammation are also contributing factors in the development of these tumors.

The role of hormones, including estrogen and androgen, in fibroid development is currently a subject of study. Studies have associated high bioavailable testosterone levels and high estradiol levels with an increased risk of fibroids. The relationship between hormonal imbalance and fibroid development, however, remains complex and necessitates further research.

The extracellular matrix (ECM) components, elevated in uterine leiomyoma, induce the mechano-transduction process, resulting in altered signaling between leiomyoma cells and the ECM. Treatment with UPA decreases gene expression and protein production of ECM proteins, suggesting that ECM accumulation is a crucial target for future therapeutics.[2-7]

Immune function plays a role in fibroid development and progression. High-intensity focused ultrasound (HIFU) treatment for fibroids preserves short-term postoperative immune function better than conventional myomectomy.

Angiogenic growth factors contribute to abnormal vasculature, growth, and survival of the tumor, demonstrating the significant role of angiogenesis in fibroid pathogenesis.[8-11]

Several risk factors are associated with fibroid development, such as age, obesity, high blood pressure, family history, and black race, are associated with fibroid development. They are hormone-dependent, with their growth pattern influenced by endocrine and paracrine factors during pregnancy.

Fibroids increase the risk of adverse pregnancy outcomes and are linked to certain medical conditions. Notably, their development seems inversely associated with severe overweight.

Genetics also plays a significant role in fibroid development, as supported by studies on the familial predisposition of uterine myomas.[12-15]

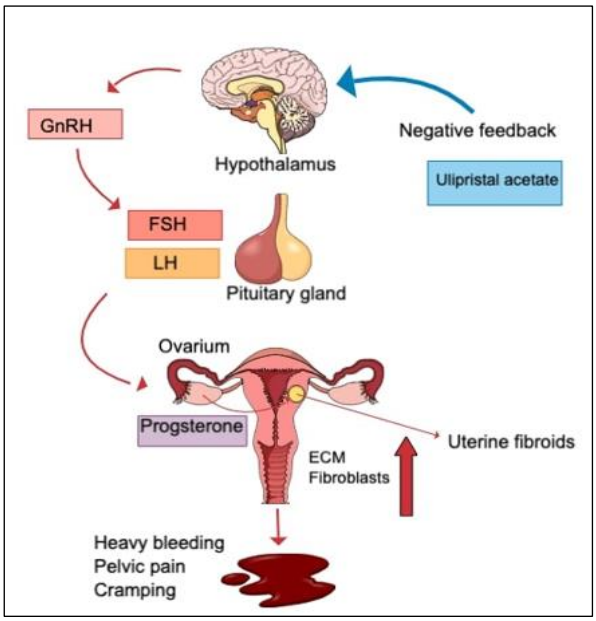

Figure 1: Hypothalamus-pituitary gland-ovarium signaling axis. The GnRH secretion from the hypothalmus realeses FSH and LH from the pituitary gland, inducing progesterone production from the ovarium, estimulating ECM and fibroblast, therefore fibroid growing. UPA inhibits the parth by negative feedback, producing fibroid shrinking.

Diagnosis and assessment of uterine fibroids

The presence of uterine fibroids in patients often results in severe symptoms, including heavy menstrual bleeding, constipation, bloating, diarrhea, the passage of clots, spotting or bleeding between periods, and pelvic pressure. Women with these fibroids are more likely to report moderate or severe dyspareunia and noncyclic pelvic pain than those without fibroids. These symptoms are reported as highly bothersome by some patients with uterine fibroids.[16-18]

Magnetic resonance imaging (MRI) is considered a more effective diagnostic modality than transabdominal ultrasonography for detecting uterine fibroids and evaluation, as it is more sensitive, specific, and accurate. In addition to imaging and medical history, comprehensive assessment of uterine fibroids in patients involves endometrial biopsies. Endometrial biopsy and pelvic MRI help detect non-enhancing fibroids, intracavitary fibroids, and ovarian and endometrial malignancies, which can alter patient management strategies. This comprehensive assessment also includes evaluating health-related quality of life (HRQOL) in patients using instruments such as EQ-5D, SF-36, and UFS-QOL, providing scores on symptom severity and various HRQOL dimensions. Treatment efficacy is evaluated at different intervals using ultrasound measurements, symptom scores, and laboratory parameters.[19,20]

The size and location of uterine fibroids can influence the diagnosis process. For example, fibroids on the posterior uterine wall are associated with more severe pelvic pain than fibroids anteriorly. There can be variability in fibroid size measurements, which must be considered when assessing fibroid growth. However, this variability is not affected by the type of fibroid (submucosal, intramural, or subserosal).[21-23] Treatment options are discussed after diagnosing uterine fibroids primarily through MRI and an evaluation of the patient's history and physical examination. These options can range from conservative management to uterine-preserving options and, ultimately, hysterectomy. The size and location of the fibroids can impact the management approach. Pelvic imaging helps assess uterine and fibroid size and evaluates the association with pelvic floor symptoms. However, uterine and fibroid size does not correlate with the bother caused by pelvic floor symptoms. To consider management options, a comprehensive evaluation by a multidisciplinary fibroid treatment center can help facilitate a shift towards less invasive options over hysterectomy for symptomatic fibroid treatment. [24-26]

Diagnostic tests used to confirm the presence of these fibroids include ultrasound, commonly used in clinical settings, and laparoscopic ultrasound. This latter method can detect additional fibroids during laparoscopic myomectomy. Further advancements in diagnostics have been seen in artificial intelligence-assisted methods, which have shown promise in enhancing the diagnostic performance of uterine fibroids in ultrasound images.[27-29]

Efficacy of ulipristal acetate verses leuprolide acetate in treating uterine fibroids

Uterine fibroids are a common health concern among women, and their management often involves medical therapy. Among these, UPA and LEU have been frequently studied.[30,31]

UPA is known for its efficacy in the treatment of symptomatic uterine fibroids. A double-blind noninferiority trial shows that UPA administered daily at 5 mg and 10 mg dosages are just as effective as once-monthly LEU in controlling uterine bleeding. This study is corroborated by another research, in which a 13-week UPA treatment significantly controlled heavy bleeding and reduced fibroid size compared to a placebo.[32,33]

However, the effectiveness of UPA has been observed to vary depending on certain patient-specific factors. For example, patients under 35 years of age have been associated with a higher rate of imaging failure after three months of UPA therapy. Furthermore, a dominant fibroid of 80mm or larger is linked with clinical failure in UPA treatment. Regarding fibroid location, submucosal fibroids respond better to UPA treatment than intramural fibroids. Additionally, fibroids' initial number and volume play a significant role, with fewer fibroids predicting a more positive response to UPA treatment.[34,35]

Nevertheless, UPA has certain advantages. It is generally well-tolerated and induces fewer hot flashes than LEU. Additionally, UPA significantly improves the quality of life in women with uterine fibroids by inducing amenorrhea and reducing heavy menses, as evidenced in a systematic review and meta-analysis.[36,37]

On the other hand, LEU, particularly its once-monthly dosage, has also shown efficacy in fibroid management. A pilot study documented a significant decrease in fibroid volume and vascular index after three months of LEU treatment. Interestingly, the duration of preoperative LEU treatment impacts the level of uterine shrinkage, with longer durations leading to more considerable shrinkage.[38,39]

However, LEU therapy has particular challenges, such as the increased operative time during myomectomy, potentially due to post-treatment fibroid softness. Despite this, LEU treatment can reduce blood loss and operative time during laparoscopic myomectomy. Comparatively, pre-treatment with UPA may yield less consistent results in reducing fibroid volume and vascular index than LEU.[40]

Side effects of ulipristal acetate and leuprolide acetate in uterine fibroid treatment

Ulipristal acetate may be preferable over leuprolide acetate for minimizing side effects in patients being treated for uterine fibroids. However, ulipristal acetate may also increase the risk of adverse effects. Studies have shown that ulipristal acetate effectively controls excessive bleeding and reduces the size of fibroids. Further, repeated use of ulipristal acetate has been suggested to improve the patient's condition and quality of life.[41]

Over half of the women treated with ulipristal acetate experienced side effects, but in most cases, these were not severe enough to discontinue. The most common adverse events associated with ulipristal acetate treatment were headache and breast tenderness.[42]

LEU treatment for uterine fibroids leads to significant but temporary reductions in uterine size and fibroid-related symptoms. Nearly all women treated with leuprolide acetate experience some side effects related to hypoestrogenism, including hot flashes, and bone loss is possible. Only five patients (8%) terminated treatment prematurely due to side effects.[43] Three randomized controlled trials reported increased non-physiological endometrial-related changes following the use of UPA. These changes, however, returned to normal within six months. The phase III randomized controlled trial comparing UPA with leuprorelin reported adverse events in 78.0% of patients in the UPA group, and 88.8% of patients in the leuprorelin group, but no specific side effects were mentioned.[44]

A prospective cohort trial involving women with symptomatic fibroids found no significant complications

or adverse effects due to using UPA. No liver function abnormalities were reported during the treatment or in follow-up. No other side effects of UPA or LEU in treating uterine fibroids were mentioned in these sources.[45]

Impact of ulipristal acetate and leuprolide acetate on quality of life in uterine fibroid patients

Symptomatic women with fibroids experience a significant decrease in health-related quality of life (QOL) and productivity, with racial minorities and those in lower income brackets suffering more. While surgical management is the primary treatment for fibroids impacting fertility, other treatment options need to be considered based on their clinical outcomes.[46]

In the management of uterine leiomyomas, ulipristal acetate (UPA) has proven to be effective, improving the health-related quality of life and reducing the severity of symptoms, as demonstrated in randomized controlled trials.[45-47]

UPA's effectiveness extends beyond symptom control; it has also been shown to enhance general health and quality of life. UPA treatment has significantly reduced discomfort, pain, anxiety, and depression while improving mobility and usual activity impairment. In addition, improvements in social and physical activities have been reported among women with symptomatic uterine leiomyomas following UPA treatment.[48-50]

Comparing UPA to LEU, another standard treatment, UPA is as effective as once-monthly LEU in controlling uterine bleeding. Importantly, it has a significantly lesser likelihood of causing hot flashes. However, the information provided must facilitate a comprehensive comparison of UPA and LEU, particularly regarding their efficacy and side-effect profiles relating to adverse events.[51-53]

The impact of LEU treatment on the quality of life in patients with uterine fibroids remains to be determined due to insufficient information in the provided context. As such, further research is needed to understand these treatments' effects fully.[54-56]

DISCUSSION

Fibroids diagnosis is not easy; it requires multiple steps, initially in the primary care unit with a complete patient's clinical history and physical examination. Afterward, USG is usually the first cabinet study to find suggestive findings, and MRI is the definitive diagnosis. The treatment choice depends on fibroid characteristics such as size and localization, from conservative management to surgical options like hysterectomy. For symptomatic fibroids, less invasive treatments are a viable option over hysterectomy if assessed by a comprehensive multidisciplinary team.[57-59] As one of the main objectives of this review, the efficacy of UPA and LEU is worthy of discussion. A study found UPA to be as effective as LEU in controlling heavy menstruating bleeding without as many adverse effects as this one, including hot flashes and vaginal dryness. Compared to placebo, UPA significantly reduced the amount of heavy menstrual bleeding as much as fibroids size.[60]

The impact of UPA and LEU has proven to be significant regarding life's quality. Remarkably UPA improved health's related quality of life in several randomized controlled trials compared to a placebo. Regarding uterine bleeding, it is as effective as once a moth LEU. Even so, more studies are needed to demonstrate its efficacy over LEU and its safety regarding side effects.[61,62]

Pre-operative administration of UPA and LEU can reduce blood loss and operative time during laparoscopic myomectomy. The duration of the preoperative treatment with UPA and LEU showed different results regarding fibroids shrinking. Long-term treatment with LEU can result in a more significant decrease in uterine volume, while UPA may be less consistent in reducing fibroid volume.[63]

UPA users tend to present non-physiological endometrial-related changes. Even so, in the next six months, these changes reverted. In LEU side effects, one study reported presented them in 88% of the group; unfortunately, the study did not mention the side effects.[64,65]

CONCLUSION

Uterine fibroids are noncancerous tumors that develop from the smooth muscle cells of the uterine wall and are influenced by hormonal factors. The diagnosis and assessment of fibroids involve techniques like MRI, patient history, and physical examination, while treatment options are determined based on the size and location of the fibroids. UPA and LEU are two medications used to treat symptomatic uterine fibroids. UPA has been found to be as effective as LEU in controlling uterine bleeding and is associated with a significantly lower incidence of hot flashes. It is considered a beneficial treatment option for symptomatic uterine fibroids due to its improved tolerability and side effect profile compared to LEU. Studies have shown that UPA can enhance health-related quality of life and reduce symptom severity compared to a placebo, although more research is needed to establish the comparative efficacy and side effect profiles of UPA and LEU for adverse events. LEU has demonstrated the ability to reduce fibroid size and vascular index after three months of treatment, with longer-term use resulting in a more significant decrease in uterine volume. However, the softening of fibroids due to pre-treatment with LEU may lead to increased operative time during myomectomy, although it has been found to reduce blood loss and operative time during laparoscopic myomectomy. UPA may need to exhibit more consistent effects in reducing fibroid size and vascular index compared to LEU. When comparing UPA and LEU to other treatment options for

uterine fibroids, UPA proves to be an effective, safe, and well-tolerated option with comparable efficacy to LEU. While UPA may induce benign histologic changes in the endometrium that resolve after therapy and has similar side effects to a placebo, such as headaches and breast tenderness, there is limited evidence supporting its superiority over other treatments like LEU. Further research is necessary to establish the true advantages of UPA compared to alternative therapies for symptomatic uterine fibroids.

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