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Review Article

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MEDICAL TREATMENT IN MYOMA UTERINE: A LITERATURE REVIEW

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ABSTRACT

Myoma uterine was regarded as a serious public health issue that has a substantial financial, social, and medical impact on both patients and the healthcare system. It affects many women of reproductive ages. Approriate management is needed to treat the myoma uterine. In this review, we will describe about medical treatment in myoma uterine. This study was literature review which carried out from August to September 2024 through literature sources in the form of textbooks, clinical guidelines, and online scientific journals from the last 5 years. Based on the literature study, it was found that there are several therapies for uterine myoma including oral contraceptives (OCs), gonadotrophin-releasing hormone (GnRH) agonist and antagonist, levonorgestrel-releasing intrauterine system (LNG-IUS), progestin-releasing intrauterine device (IUD), selective progesterone receptor modulators (SPRMs), aromatase inhibitors (AIs), tranexamic acid, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Keywords: Myoma uterine, Medical treatment, Management, Reproductive health.

INTRODUCTION

Women's reproductive health is one of the parameters of the country's ability to provide health services to the community. However, there are many health problems experienced by women of reproductive age that can affect a woman's fertility. One of these reproductive problems is uterine myoma. Because uterine myoma affects women of reproductive age at a rate of about 70% overall and about 25% of these patients have clinical symptoms that need to be treated, it is regarded as a serious public health issue that has a substantial financial, social, and medical impact on both patients and the healthcare system.[1] Uterine myomas are found in 2.39%-11.7% of all gynecological patients treated in Indonesia and are most often found in women aged 35-45 years, approximately 25% and rarely occur in women aged 20 years and post-menopausal.[2]

Uterine myoma, also known as uterine fibroids or leiomyoma, is a benign tumor originating from the smooth muscle of the uterus.[3] Tumor cells are formed due to genetic mutations that develop due to stimulation from the hormones estrogen and progesterone. Uterine myoma can occur in women at any age, and rarely affects prepubertal age because the nature of its growth is influenced by hormones.[4] Uterine myoma can be caused by a number of risk factors such as genetics, race, age over 30 years, sedentary lifestyle, foods with a high glycemic index and omega-3 fatty acids, obesity, premature menarche and late menopause, nulliparous parity status, use of hormonal contraception, uterine infections, stress and several comorbid diseases such as hypertension, diabetes mellitus and Polycyclic Ovary Syndrome (PCOS).[5,6]

Most cases of uterine myoma are asymptomatic. Therefore, doctors often find them accidentally due to other complaints. Vaginal bleeding is the most common symptom, apart from that, abdominal enlargement and signs of anemia can be found in patients. This tumor often causes female sub fertility and can cause abortion and prematurity during pregnancy.[4,7] The recommended supporting examination for the diagnosis of uterine myoma is ultrasonography. Transvaginal ultrasound is more sensitive than abdominal ultrasound, but is less recommended in unmarried patients who have submucous myoma. On that condition, it is recommended to use a hyteroscope. Another examination is a complete blood laboratory examination to determine anemia status. Endometrial biopsy and MRI are recommended to rule out malignancy.[7,8]

Management of uterine myoma includes observation, medication or surgery. Observation is carried out if there are no complaints of any symptoms because it is hoped that the tumor will shrink when the patient menopause. Medication is given to reduce bleeding, reduce tumor volume and as a pre-operative procedure. Surgery is carried out by hysterectomy and myomectomy, the choice of which depends on the patient's condition and wishes.[9] In this review, we will describe about medical treatment in myoma uterine.

METHODS

This study was literature review which carried out by the four authors from August to September 2024 through literature sources in the form of textbooks, clinical guidelines, and online scientific journals from the last 5 years. The keywords used in the search were “myoma uterine”, “myoma fibroid”, “leiomyoma”, “treatment” and “medicine”. After conducting a literature study, the study is then screened to be used as the main reference.

RESULTS AND DISCUSSION

Oral Contraceptives

In order to lessen the symptoms brought on by the fibroids' heavy bleeding, contraception is also often employed. Hormonal contraceptives primarily work by inhibiting ovulation through an

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antigonadotropic action.[10] The most widely used method of reversible contraception is the oral contraceptives (OCs). OCs can provide control of the menstrual cycle by thinning the endometrium, thereby reducing menstrual blood loss.[11] Estrogens or compounds with estrogenic properties are also present in the majority of hormones used in contraception. The gestagenic ingredient alters cervical mucus density and inhibits the luteal phase of the ovulatory cycle, both of which prevent sperm from moving freely. Follicle stimulation hormone (FSH) suppression, which is stimulated by the estrogen component, limits the development of the follicle and increases the influence of progesterone, which together prevents the implantation of an embryo by altering the endometrium in the secretory phase.[12] For cyclic intakes, combined estrogen/progestogen formulations are the preferred monophasic medication of choice. Furthermore, longer schedules or ongoing supervision are gradually implemented. This enhances the appealing convenience or efficacy of such regimens.[13]

Study by Kwas *et al.,* (2021) showed the likelihood of uterine fibroids is reduced by the use of OCs, particularly in people between the ages of 30 and 40. After using OCs, the risk of myomas resulting from a favorable family history can also be reduced.[10] A systematic review by Jahanfar *et al.,* (2024) found hormonal contraceptives are known to greatly lessen the discomfort, intensity of symptoms, and atypical bleeding patterns experienced by women with endometriosis, uterine fibroids, and excessive monthly flow.[11] Meanwhile, cohort study by Hoffman *et al.,* (2024) stated estimates for the OCs-usage parameters that could have been anticipated to be linked with decreased fibroid risk were less accurate and directionally inconsistent, despite the fact that the use of combined OCs was shown to have an inverse connection with the development of uterine fibroid.[14] Therefore, its use is still being debated at this time due to its inconsistent benefits.

For the most majority of women, low-dose OCs (formulations containing <50 mcg ethinyl estradiol) are a safe and effective method of contraception. However, it is appropriate to begin with a dosage of 20 mcg; if unplanned bleeding becomes an issue, that can then be increased. OCs with 50 mcg of ethinyl estradiol are available to relieve uterine bleeding immediately, but they shouldn't be used as a method of contraception. The majority of OCs adverse effects are modest and go away if you use the medication consistently or switch to a different formulation. Bleeding breakthrough is the most frequent side effect of combined OCs therapy. In addition, women may report experiencing headaches, nausea, cramps in the abdomen, breast tenderness, increased vaginal discharge, or diminished libido. By taking the medicine right before bed, nausea can be prevented. The majority of other effects will go away with time or when OCs is switched to an alternative preparation. The contraindication for OCs includes hypertension, smokers, history of VTE, stroke, breast or endometrial cancer, and valvular heart disease, thrombogenic mutation.[13]

Gonadotropin Releasing Hormone (GnRH) Agonist

The working mechanism of GnRH is through down regulation of its receptors which results in a decrease in FSH and LH production which will decrease estrogen production.[4] This drug is recommended for submucous myoma, but is contraindicated in several conditions such as pregnancy, breastfeeding, undiagnosed bleeding and a history of hypersensitivity to other gonadotropin-releasing hormone agonists. This drug should be given with caution in patients with heart disease and decreased bone density.[15]

The recommended duration of administration is 3-6 months; long-term administration >6 months should be combined with progesterone with or without estrogen.[4] During initial administration, complaints may worsen due to side effects of the drug.[16] GnRH analogs can also be used preoperatively for 3-4 months before surgery. Examples of types of GnRH drugs and their doses are leuprorelin, which is used in combination with iron therapy for the management of anemia caused by uterine fibroids at a dose of 3.75 mg every month by intramuscular or subcutaneous injection. Goserelin (Zoladex) at a dose of 3.6 mg every month for 3 months is known to be able to treat iron deficiency due to uterine fibroids.[17]

This class of drugs has some of the most common side effects, namely headaches, hot flashes and migraines.[16] Other side effects may include alopecia, nausea, vomiting, diarrhea, GI disturbances, fatigue, edema, insomnia, upper respiratory tract infections, fever, nasal congestion, mood changes, weight gain, vaginitis, testicular atrophy, weakness, dizziness, hyperlipidemia, hyperglycemia, impotence, decreased libido, dermatological changes, and arthropathy.[18] A 2020 study looking at NAV 3 as a tumor suppressor found that Leuprolide can increase NAV 3 in leiomyoma cells.[19] Another study in Iraq in 2020 stated that administration of goserelin can reduce serum levels of inflammatory cytokines, tumor necrosis factor-α and monocyte chemotactic protein-1, improve leiomyoma-related symptoms with good tolerability in patients with uterine leiomyoma.[20]

Gonadotropin Releasing Hormone (GnRH) Antagonist

GnRH antagonists work by competitively binding to and blocking GnRH receptors in the anterior pituitary gland. This action prevents the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in decreased serum estradiol and progesterone concentrations to postmenopausal levels. Low ovarian hormone levels prevent hormone-dependent proliferative effects on the endometrium, resulting in reduced HMB associated with uterine fibroids. Estradiol is an estrogen that may reduce the risk of bone loss and hot flashes.[21] Contraindications to the use of GnRH antagonists include: venous thromboembolic disorders, arterial thromboembolic disorders, pregnancy, lactation, osteoporosis, hormone-sensitive or sex steroid-induced malignancies, severe liver disease or disorders, undiagnosed abnormal uterine or genital bleeding and hypersensitivity to any component of the drug or any of the excipients.[22]

Based on a phase 3 trial involving Japanese women with symptomatic fibroids, relugolix at a dose of 40 mg was able to provide improvements similar to those observed with leuprolide acetate with regard to heavy menstrual bleeding, anemia, and pain and significant pain reduction compared with placebo.[23] A 2021 meta-analysis stated that oral GnRH antagonists are effective for myoma-related bleeding with an acceptable safety profile for short-term use, but affect lipid metabolism.[24] To achieve efficacy, minimize hypoestrogenic side effects, and maintain bone mineral density, the recommended therapy is to use a combination of relugolix consisting of 40 mg relugolix, 1 mg estradiol, and 0.5 mg norethindrone acetate once daily to maintain estradiol levels within the physiologic range of the early follicular phase of the menstrual cycle, with the addition of a progestin to reduce uncontrolled estrogen action that may cause endometrial hyperplasia.[25]

Levonorgestrel-Releasing Intrauterine System (LNG-IUS)

Levonorgestrel-releasing intrauterine system can be one of the medical therapies for fibroids with several mechanisms, namely, thinning the endometrium by suppressing the growth of the uterine lining. This therapy can also reduce the volume and duration of menstrual bleeding which is often exacerbated by fibroids.[26]

Indications for administering LNG-IUS are to prevent heavy bleeding due to uterine fibroids and as an alternative to surgical therapy in women who wish to maintain fertility.[27] Contraindications for LNG-IUS include pregnancy or suspected pregnancy, active reproductive tract infection, active breast cancer or genital cancer, significant anatomical malformations of the uterus and uncontrolled blood clotting disorders.[28] Side effects that may occur include irregular bleeding (usually improves over time), abdominal pain or cramps, mood changes, risk of infection during insertion and abnormal vaginal discharge.[29]

The current study confirms that the LNG-IUS statistically reduces the PBAC (Pictorial Blood Loss Assessment Chart) score and hemoglobin values in women with AUB-L.[30] Several studies have found that uterine volume decreases significantly after LNG-IUS insertion.[31–33] With a natural growth rate of leiomyoma of 30% per 6 months[34], it seems plausible that the LNG-IUS inhibits its growth. Ovarian steroid hormones regulate the growth of leiomyomas and are regulated by local growth factors. IGF-1 mRNA levels in fibroid cells in vitro decreased dramatically after treatment with 25 mcg/ml LNG for 72 hours.[35] This suggests that down regulation of IGF-1 may lead to cell growth retardation and cell death in uterine leiomyomas.[36]

Progestin

Progestin is a synthetic progestogen that has a progestinic effect similar to progesterone. Depot medroxyprogesterone acetate (DMPA) is a synthetic progestin that can be injected for three months. DMPA can be chosen as a contraceptive method for women with uterine fibroids.[37] An American study showed that the use of DMPA for 2 years was associated with reduced leiomyoma development and reduced leiomyoma size.[38]

Selective Estrogen Receptor Modulators (SPRMs)

Progesterone is essential for fibroid growth. In comparation with the myometrium, fibroids over express estrogen and progesterone receptors. It also has been shown that exogenous progesterone increases mitotic activity and cellularity in fibroids. These observations of the progesterone effects on uterine fibroid, stimulated research for the development of progesterone antagonist and/or SPRM drugs. Selective Estrogen Receptor Modulators (SPRMs) are small molecules modulating the activity of the PR (progesterone) receptor through binding with high affinity to the PR receptor binding pocket. SPRMs include a wide spectrum of substances ranging from highly potent receptor antagonists such as UPA or vilaprisan, to compounds with a balanced mix of partial-agonistic and antagonistic effects such as mesoprogestins like ASO.[39]

Selective Estrogen Receptor Modulators (SPRMs) can induce collagen degradation through matrix metalloproteinase 2 and an increase of the apoptotic index rate of uterine fibroid cells. Ulipristal acetate (UPA), one of the SPRMs reducing both fibroid and uterine volume, together with a reduction of heavy menstrual bleeding (HMB), anemia and pain. Two randomized clinical trial that demonstrated the efficacy of UPA therapy continuously for 3 months compared with placebo or GnRH agonists confirmed these benefits. In patient receiving UPA for 3 months, the uterine bleeding and anemia were controlled in more than 90% patient.[40]

However, in May 2018, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency determined that UPA might have played a role in the occurrence of certain instances of severe liver injury. In the last years, some reports of rare, albeit serious, liver injury also had been made. These reports leading to restrictions of the SPRMs. The European Medicines Agency (EMA) indicates that 5-mg UPA can be used only for intermittent treatment of moderate-to-severe symptoms of UFs in adult women who have not reached menopause, when fibroid embolization and/or surgical treatment is not a suitable option, or have failed.[41] Other SPRMs, such as vilaprisan, are currently under study, and the recent randomized controlled ASTEROID 3 trial showed promising results in efficacy and safety to control heavy menstrual bleeding caused by uterine fibroid.[40]

Aromatase Inhibitors (AIs)

Aromatase inhibitors include letrozole (2.5 or 5 mg orally once a day) and anastrozole (10 mg orally once a day), is a promising class of agents for the treatment of uterine fibroids in pre-menopausal women. The mechanism of action od aromatase inhibitors is by blocking estrogen synthesis, primarily through the inhibition or inactivation of the microsomal cytochrome P450 enzyme aromatase, which is responsible for catalyzing the synthesis of estrogens from androgens via hydroxylation. By inhibiting the aromatization of androgens to estrogens induce a hypoestrogenic state, results in thinning of the endometrial lining and reduced menstrual bleeding.[41,42] In addition, a Cochrane review in 2013 on aromatase inhibitors efficacy has shown an approximate 40%–50% reduction in fibroid size, together with an improvement in dysmenorrhea, menorrhagia, and duration of menses.[42]

Tranexamid Acid

Tranexamid acid as a synthetic lysine derivative, is an antifibrinolytic agent and promoter of blood clot formation. Tranexamid acid if one of the oldest and most globally available treatments for abnormal uterine bleeding. Its mechanism of action is by preventing fibrin degradation at the level of the plasminogen lysine receptor site, which lead to a reduction in menstrual blood flow and improvement of symptoms. It is effective in reducing menstrual blood loss by 26%–50%, surpassing the efficacy of NSAIDs alone.[41,42] Tranexamic acid is available in oral or intravenous formulations. Most commonly, it is administered at a dose of two 650 mg tablets orally three times a day for up to 5 days. It can be used independently or in conjunction with an NSAID during days 1–5 of menstruation.[41,42]

Tranexamic acid is generally well tolerated, but it is contraindicated for patients with color blindness, active bleeding, history of intravascular clotting, or hypersensitivity to the medication. Tranexamic acid is an effective treatment for heavy menstrual bleeding both in acute or chronic to improve the patient's quality of life. However, tranexamic acid has no direct effect on uterine fibroid so tranexamic acid is not providing a long-term treatment option.[41,42]

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

CONCLUSION

Women with uterine myoma can now choose from a variety of medical procedures, each having pros and cons of its own. The data currently available supports the use of selective progesterone receptor modulators (SPRMs) and gonadotrophin-releasing hormone (GnRH) agonists as medical therapy for monthly bleeding symptoms. These drugs also effectively reduce the amounts of fibroid tumors. The patient's individual treatment objectives, the therapy's effectiveness, and whether or not it requires recurrent interventions all influence the choice of care.

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COMPETING INTERESTS

Authors have declared that no competing interests exist

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