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Review Article

Overview of Uterine Fibroid Treatment Procedures; Review Article

Joanna Pietras [1]*, Anna Markowska [2], Stefan Sajdak[3,4]

[1] Poznań University of Medical Sciences, Doctoral School, Department of Perinatology, Gynecological Obstetric Clinical Hospital of Poznan University of Medical Sciences, Polna 33, 60-535, Poznan, Poland.

[2] Department of Perinatology, Gynecological Obstetric Clinical Hospital of Poznan University of Medical Sciences, Polna 33, 60-535, Poznan, Poland.

[3] Poznan University of Medical Sciences, Fredry 10, 61-701 Poznan, Poland.

[4] Collegium Medicum University of Zielona Góra, Zyty 28, 65-046, Zielona Góra, Poland.

***Corresponding Author:** Joanna Pietras, Department of Perinatology, Gynecological Obstetric Clinical Hospital of Poznan University of Medical Sciences, Polna 33, 60-535, Poznan, Poland.

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Abstract:

Myomas are benign uterine tumours found in 40-70% of women of reproductive age. About 30% of them cause various ailments (bleeding, pain, infertility) that reduce the quality of women's life.

Uterine fibromas are the cause of 40-60% of hysterectomies.

Different treatment methods are used depending on the size, number, location of myomas and the patient's preferences. Conservative treatment includes nonsteroidal anti-inflammatory drugs, hormonal therapies as contraceptives, GnRH agonists or antagonists, selective progesterone receptor modulators and levonorgestrel.

Radiologic intervention types include are UAE (uterine artery embolization), high-intensity focused ultrasound (HIFU), magnetic resonance (MRgFUS), and radiofrequency ablation (RFA).

There are also more radical methods, namely surgical treatments, such as myomectomy (hysteroscopic, laparoscopic, robotic or abdominal) and hysterectomy. The oldest of methods is abdominal hysterectomy, while in some women, vaginal hysterectomy can be applied. Recently, laparoscopic or robotic hysterectomy (using the da Vinci robot) has been used. The latter procedures are associated with a better quality of life following treatment.

Key words: uterine fibroids; pharmacological treatment; interventional radiological techniques; surgical treatment

Introduction

Uterine fibroids are benign tumors composed of involuntary muscle and fibroblasts, occurring in 40-70% of women of reproductive age. Their wide incidence range depends on the studied population and diagnostic methods used. Most women do not report any symptoms; in about 30%, uterine fibroids affect the quality of life, causing: abnormal uterine bleeding, heavy menstruation, pelvic pain and pressure, and infertility [1,2,3,4,5]. Lockwood showed that aberrant angiogenesis underlines abnormal bleeding associated with myomas and endometrial polyps. As it turns out, vascular flow disorders the influence of the etiopathogenesis of uterine fibroids and many other uterine pathologies. [6,7] The term "fibroids" was first introduced in the 1860s. Hippocrates, a Greek physician (460-375 BC), termed them "uterine stones" (womb stones), and Galen (2nd century) described them as "scleromas" [5,8]. Numerous factors have been identified as playing a role in the pathogenesis and epidemiology of fibroids. Stewart et al. [9], based on 60 publications, showed that 12 factors are involved in the development of fibroids, the dominant one being African American women. The critical role of ovarian steroid hormones - estrogens and progesterone has been established in epidemiological, clinical and experimental studies. Progesterone is essential for developing and proliferating fibroid cells, while estrogens are required for sensitising fibroid cells to progesterone [10,11,12]. It has been shown that chromosomal aberrations are found in 40-50% of patients with uterine fibroids [13,14]. In their review, Yang et al. [5] described four types of molecular mutations: in MED12,

overexpression in HMGA2, deficiency in fumarate hydratase (FH), and deletions in COL4A5/COL4A6. Mutations in MED12 are the dominant type and occur more frequently in African women. They are associated with smaller fibroid sizes and subserosal locations. Studies have also shown that stem cells participate in developing fibroids using the Wnt/ßcatenin signaling pathway. Increased expression of VEGF-A has been found in the uterine fibroids of young women, which may be a sign of increased angiogenesis and intensive tumor growth. According to literature data, a close relationship has also been demonstrated between impaired VEGF gene expression and the development of ovarian tumors. [15,16] The involvement of cytokines and chemokines with pro-inflammatory and profibrinolytic features has also been suggested in developing fibroids. Vitamin D deficiency has been studied to play a role in the growth of myomas [5,17]. It turns out that vaginal dysbiosis plays a crucial role in the development of uterine fibroids and many other diseases of the uterus, including endometrial cancer [18,19] Fibroid treatment includes numerous methods, from conservative pharmacological treatment to various types of surgical procedures. The choice depends on various factors, such as the size, number, location of fibroids, symptoms, the patient's age, health condition, and individual expectations, e.g., maintaining fertility [5,20,21,22]. Conservative treatment involves regular monitoring of small asymptomatic fibroids.

The purpose of this article is to provide a comprehensive summary of the various pharmacological and surgical options available for uterine fibroid treatment, highlighting their benefits, risks, and potential outcomes.

Pharmacological treatment

- **Nonsteroidal anti-inflammatory drugs**

It is a group of analgesic and anti-inflammatory drugs that inhibit cyclooxygenase, thereby reducing the synthesis of prostaglandins at the endometrial level. This mechanism leads to a reduction in heavy menstrual bleeding and painful menstruation [20,23,24]. Tranexamic acid reduces menstrual blood loss by inhibiting fibrinolysis via reversible plasminogen blockade. It is often used in laparoscopic or abdominal myomectomy to reduce blood loss [20,22].

- **Vitamin D and supplements**

Recent studies indicate the beneficial role of vitamin D and epigallocatechin gallate (Epicatechin-3-gallate-EGCG) - catechin belonging to polyphenols contained in green tea (Camellia sinensis) [24,25,26]. Vitamin D regulates cell proliferation and differentiation, inhibits angiogenesis and stimulates apoptosis [27]. EGCG inhibits the proliferation of myoma cells and induces apoptosis by inhibiting the COMT enzyme (catechol-O-methyl transferase) associated with the pathogenesis of myomas [28]. Both of these compounds can be used together or separately. Currently, a prospective randomized FRIEND study (from 2022-2025) is ongoing, involving 200 patients with uterine fibroids and a history of infertility, assessing the efficacy of EGCG in reducing the volume of fibroids and their impact on infertility [29].

- **Contraceptives**

Contraceptives are commonly used to treat abnormal uterine bleeding and heavy periods. Studies have shown a reduction in menstrual blood loss after six months of use by up to 72% [20]. In some cases, combined pills containing estrogen and progesterone can help with menstrual pain [12]. The role of hormonal contraception in the development of fibroids is minimal [30]. However, some studies show it is a protective factor against developing fibroids [31].

- **Levonorgestrel-releasing intrauterine system (LNG-IUS)**

LNG-IUS is a contraceptive method that is also effective in treating heavy menstrual bleeding. It affects the endometrium locally, reducing the duration and intensity of menstruation. It has also been noted that it does not impact the size of pre-existing fibroids. However, it is not recommended for women with submucous fibroids due to the possibility of expulsion of the device [20,30].

- **Selective progesterone receptor modulators (SPRM).**

SPRMs reduce fibroid cell proliferation by inducing apoptosis and reducing collagen synthesis and extracellular matrix. This results in a 20–57% reduction in fibroid volume [20,26,30]. In 2012, the European Medicines Agency (EMA) approved ulipristal acetate (Esmya) for the treatment of moderate to severe symptoms associated with fibroids in women of reproductive age [26]. Studies have shown that UPA (ulipristal acetate) causes significant changes in the expression of four genes in uterine fibroids. UPA treatment significantly reduced the expression of the *integrin subunit beta 4*, tenascin C and surviving gene. In those who did not respond to UPA treatment, the expression of delta-two catenin increased [32]. Although UPA significantly reduced bleeding, the size of fibroids and the size of the uterus and was used by over 765,000 women, this drug caused severe liver damage in 5 women, of which four required transplantation [33]. As of 2020, the EMA Risk Assessment Committee indicates that UPA may only be used for intermittent treatment in premenopausal women, especially in cases where surgical interventions, including embolization, are unsuitable or ineffective [20,26,33].

- **Gonadotropin-releasing hormone (GnRH) analogues and antagonists**

The use of GnRH analogs (Leuproid, Goserelin) is a well-known method of treating uterine fibroids. By inhibiting the pulsatile secretion of GnRH, they reduce the production of LH and FSH, which leads to hypoestrogenism. It has also been found that GnRH analogs disrupt the production of matrix metalloproteinases and induce apoptosis. This mechanism leads to a reduction in the size of fibroids during the first months of medication use, but in some cases, a regrowth of fibroids is observed after discontinuation of the therapy. The use of GnRH analogs leading to the inhibition of ovarian hormone secretion causes undesirable menopausal symptoms. GnRH analogues should only be used for large fibroids in the short term - especially before procedures - e.g., myomectomy, which beneficially reduces blood loss during surgery [20,26,30,34]. GnRH antagonists are considered drugs for long-term use. Blocking the GnRH receptor leads to hypoestrogenism with the risk of menopause. Add-back therapy (ABT) has been used together with the use of antagonists. It involves adding estrogen-progestogen or progestogen-only therapy to GnRH antagonist treatment to alleviate menopausal symptoms without reducing the effectiveness of the treatment. So far, three drugs for symptoms associated with fibroids have been registered: Relugolix, Elagolix and Linzagolix. The first of the medications, apart from relugolix (40 mg), also contains estradiol (1 mg) and norethisterone acetate (0.5 mg). The trade name of the medication is Ryeqo. Elagolix - 300 mg contains the same amounts of estradiol and norethisterone acetate. Its trade name is Oriahnn. Linzagolix contains only linzagolix in doses of 100mg or 200mg. Its brand name is Yselty. In May 2020, the FDA approved using Elagolix in clinical practice and then, in 2021, the use of

Relugolix. The European Medicines Agency (EMA) approved Relugolix (Ryeqo) for use in 2021. Linzagolix received approval from the EMA in 2022 [35].

Interventional radiological techniques

- **Uterine artery embolization - UAE**

This is a non-invasive procedure used for the treatment of fibroids. UAE was first introduced in France in the 1990s as an alternative method of treating fibroids for women who wish to avoid traditional surgical methods or are not suitable for them [36]. UAE involves blocking the blood flow to the myomas by using various embolization agents (e.g., hydrophilic microspheres or polyvinyl alcohol (PVA)). Contraindications to UAE include pedunculated submucosal or subserosal fibroids [12,20,37].

Quality of life studies in 6 randomized clinical trials did not show any differences with other minimally invasive procedures used to treat fibroids (e.g. myomectomy) [38,39]. Conflicting data exists regarding the frequency of re-intervention after UAE. According to the aforementioned randomized studies, UAE is associated with increased re-intervention rates, while in another study of 152 women who underwent this procedure, the recurrence rate was even lower than in patients after myomectomy (14.3% vs 31.6%, respectively) [40].

- **High-intensity focused ultrasound - HIFU**

It is a non-invasive method of treating fibroids that has been used for 20 years. This method uses a precisely directed high-energy ultrasound beam within the fibroid. The procedure can be performed under MRI or ultrasound guidance [20, 30, 41, 42]. It causes an increase in temperature in the myoma and its necrosis. Patel et al. [41], based on the analysis of 14 studies, concluded that HIFU is an equivalent therapy to surgery, allowing for the preservation of fertility. The reduction of the myoma size was 68-75% after 6-12 months. The best results were associated with the submucosal location of the myoma; the effect on the subserosal myoma was slightly worse. According to other studies, repeat HIFU interventions due to fibroid growth were noted in women under 45 years of age [43]. Long-term results of HIFU presented in a meta-analysis by Dou et al. [44] in a cohort of 5216 patients showed that the re-intervention rate was lower with the US-guided procedure (USg HIFU) than with MRI (Mg FUS). However, the overall re-intervention rates after HIFU were acceptable, and this method is considered safe and effective.

- **RFA - radiofrequency ablation**

It is an effective method of reducing the size of fibroids and their accompanying symptoms. It was first used by the American gynecologist Bruce Lee [45]. The procedure is performed under general or epidural anesthesia. The frequency range of the wave generated by the generator is 400-500 KHz (most commonly used 480 KHz). It heats the needle electrode to 60-90^{o}C, which is inserted into the fibroid. This causes fibroid necrosis, manifested by a change in its echogenicity in the ultrasound image. The procedure is completed if the change occurs in 80% of the fibroid tissue. The criteria for qualifying for the procedure include FIGO type 0-4 symptomatic myomas - up to 7 cm in size. At most, three myomas are subjected to the procedure [21,46]. In myomas subjected to effective therapy, the histological image shows hydropic degeneration or necrosis, and the expression of ER and PR receptors is reduced [47]. Complications after RFA are rare, although it has been reported that in 2 cases out of 115 procedures (1.7%), severe complications (type III according to the Clavien-Dindo scale) were observed. It was bowel perforation and bleeding into the peritoneum [48].

Surgical treatment of fibroids

Surgical procedures for myomas include myomectomy and hysterectomy. The choice of the procedure is associated with many factors: the patient's age, number of fibroids, their topography and size, clinical symptoms, history of previous treatment and desire to preserve fertility and the uterus [1,20,22,30].

- **Myomectomy**

It is a conservative procedure involving the removal of fibroids while preserving the uterus. It can be performed hysteroscopically, laparoscopically, or by laparotomy [20,30].

- **Hysteroscopic myomectomy**

It is the recommended procedure for submucosal myomas, mainly FIGO type 3 [49]. The International Society of Gynecological Endoscopy (ISGE) guidelines include ten recommendations for planning and performing hysteroscopic myomectomy (including ultrasound examination and diagnostic hysteroscopy). ISGE considers hysteroscopic myomectomy to be a very effective procedure. In a systematic review, the live birth rate after hysteroscopic myomectomy was 42.9% [50]. Other studies also emphasize the efficacy of this procedure [51].

A meta-analysis on the effectiveness of tranexamic acid in hysteroscopic myomectomy showed that it is not associated with better outcomes regarding blood transfusion requirements compared to oxytocin, but it does improve the quality of the hysteroscopic field. [52, 53].

- **Laparoscopic myomectomy**

It is a minimally invasive surgical procedure for the removal of symptomatic intramural and subserosal fibroids, allowing for the preservation of fertility. Since 1979, it has influenced the development of surgical techniques in gynecology [21,54]. There are no standardized criteria for performing laparoscopic myomectomy. According to some studies, the possibility of performing this procedure should be assessed using preoperative ultrasound and MRI. It should be avoided in cases of more than four myomas or if they are larger than 10-12 cm [55]. According to other reports, the surgical techniques used are important—such as the number of ports or the type of sutures [56]. A randomized cohort investigation of 19 studies showed that laparoscopic myomectomy appears to be the preferred method for achieving better clinical outcomes with fewer complications compared to open myomectomy [57].

- **Myomectomy by laparotomy**

Open myomectomy is a well-known method for the removal of large uterine fibroids. Giannini et al. [58] presented the results of a meta-analysis comparing the perioperative and long-term outcome of laparoscopic and abdominal (laparotomy) myomectomy. The meta-analysis included 11 articles (out of 56 analyzed) that assessed the results in 2133 women who underwent these two types of surgery. It was found that laparoscopic myomectomy is associated with less blood loss, shorter hospital stays, and fewer pain medications needed post-surgery. No statistically significant differences were observed in the rates of intraoperative and postoperative complications, pregnancy rates, or obstetric outcomes. These results suggest that laparoscopic myomectomy

offers patients greater benefits than laparotomy. One of the methods of open myomectomy is mini-laparotomy. Russo et al. [59] believe this procedure is safe, effective, and can even be performed on an outpatient basis. The authors place cellulose adhesive barriers during peritoneal closure to limit the formation of postoperative adhesions. Tsiampa et al. [60] presented a systematic review of perioperative and reproductive outcomes of laparoscopic myomectomy and mini-laparotomy in 9 studies involving 1723 women. Laparoscopic myomectomy is a safe and reliable alternative surgical procedure for fibroids treatment. A lower number of adverse events (blood loss, bowel dysfunction, febrile episodes, pregnancy rate) was reported with the laparoscopic procedure.

- **Robot-assisted myomectomy**

Robot-assisted myomectomy is the latest, minimally invasive method of treating fibroids. Arnold Advincula pioneered robotic myomectomy, describing 35 robot-assisted laparoscopic laparotomies [61]. Most fibroids were larger than 5 cm (mean 7.9 cm).

- **Robotic myomectomy**

This procedure has several advantages over laparotomic and laparoscopic myomectomy, including the possibility of a high-resolution, three-dimensional magnification of the surgical field. An analysis of 242 robotic myomectomy cases in which most myomas were intramural and 5.8% of women had >9 myomas with a median diameter of 9 cm showed that subserosal myomas were more likely to be removed. The diameter and number of myomas correlated with total blood loss and operative time. The authors suggest that the number of > 10 myomas should be considered a limitation of robotic myomectomy [62].

Another paper presented a different opinion regarding the diameter of removed myomas. During five years, 32 of 74 patients had a myoma > 10 cm in diameter. Complications after robotic myomectomy were rare; no increased blood loss was observed, only a longer operative time [63]. Chen et al. [64] conducted a systematic review and meta-analysis of three methods of myomectomy used in clinical practice: laparotomic (AMI), laparoscopic (LM), and robotic-assisted laparoscopy (RLM). It included 32 studies with 6357 patients, 1982 of whom underwent RLM. The operative time of RLM was significantly longer, but the cesarean delivery rate after this procedure was significantly lower compared to LM. There was no difference in blood loss. Therefore, developing new techniques for myomectomy provides safety and efficacy superior to laparotomic myomectomy.

Removal of the uterus - hysterectomy

Hysterectomy is one of the oldest surgical procedures for women, dating back to ancient times [65,66,67]. It is the second most common operation for women after cesarean section. An analysis of 5279 hysterectomies in Finland showed that uterine fibroids were the indicator for hysterectomy in 33% of cases [68]. Depending on clinical symptoms, the size of uterine fibroids, their location and number, pelvic organ prolapse, dysplastic changes in the cervix, the surgeon's experience and patient acceptance, there are three ways of performing this procedure. These include total or subtotal abdominal hysterectomy (AH), laparoscopic hysterectomy (LH), and vaginal hysterectomy (VH) [20,30,68]. The pioneers of these operations were: Ellis Burnham, who performed a successful abdominal hysterectomy in 1853 [65]; in 1822, the first vaginal hysterectomy was performed by Sauter [69]. In 1988, Harry Reich performed a total laparoscopic hysterectomy [66]. The most common of these operations is abdominal hysterectomy (AH). A cohort study of 2094 women in the USA lasting an average of 21.9 years (with ovaries left intact) showed an increase in cardiovascular disease and metabolic disorders after this type of surgery. In women ≤ 35 years, the risk of congestive heart failure and coronary artery disease increased significantly (4.6-fold and 2.5-fold, respectively) [70]. A review by Agarwal et al. [71] covering 300 patients undergoing AH and laparoscopic hysterectomy (LH) indicates that laparoscopic hysterectomy is an effective and safer procedure. LH is associated with a lower rate of postoperative wound infection, lower blood loss during surgery, and a shorter hospital stay. Similar data indicating the superiority of LH over AH were reported in another data analysis [72]. Picket et al. [73] presented the results of 63 studies covering 6811 women undergoing different types of hysterectomy (AH, vaginal hysterectomy – VH, LH). The authors believe that VH is preferable to LH due to a lower incidence of postoperative wound infections or abdominal wall infections. According to another meta-analysis [74], VH is a favorable procedure associated with shorter recovery time, less blood loss, and shorter operative time, although it is associated with more pain on the day of surgery compared to LH. In recent decades, the da Vinci robotic hysterectomy procedure has evolved. This system received FDA approval in 2005 and is currently used worldwide. The advantage is an excellent visualization of the surgical field. The procedure is a safe alternative to traditional abdominal or laparoscopic hysterectomy [75,76]. Technology in the field of surgical devices is continually developing. Komatsu et al. [77] were the first to publish a report on performing a total hysterectomy in a woman with a uterine fibroid using the HUGO™ RAS system, comparing it to the already established da Vinci system. The availability of new surgical methods for women worldwide is not uniform. According to multivariate analyses of health care for women with fibroids, especially the possibility of participating in minimally invasive hysterectomies (including laparoscopic and robotic) is diverse. This applies to women of different races, ethnicities, and geographic locations [78].

Future prospectives and limitations

In the future, treatment for uterine fibroids may advance towards more personalized and less invasive therapies, such as gene therapies or novel hormonal treatments. Progress in imaging techniques and minimally invasive interventions could improve diagnostic accuracy and treatment outcomes. However, limitations include the high cost of modern therapies and the lack of long-term studies assessing the safety and efficacy of new approaches. Additionally, current challenges include the risk of recurrence after treatment and the potential side effects of both surgical and pharmacological therapies.

Conclusions

In recent years, methods for treating uterine fibroids have developed. This applies to pharmacological treatment, interventional radiological techniques, and minimally invasive surgical procedures. This progress is associated with improving the quality of life of treated women and possibly preserving fertility. Nevertheless, there is still a lack of an ideal method that minimizes risk, has no side effects, and is highly effective.

Author Contribution: Author 1: Joanna Pietras led the conceptualization of the review, conducted the literature search, and drafted the initial manuscript.

Author 2: Anna Markowska contributed to the selection and analysis of key articles, organized the structure of the review, and critically revised the manuscript.

Author 3: Stefan Sajdak provided expertise in the subject matter, reviewed the content for accuracy, and oversaw the final editing and approval of the manuscript.

Conflict of Interests

The authors declare no conflict of interests.

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