Myoma uteri – methods of treatment

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Review article

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Summary
Uterine fibroids are benign, hormone-dependent tumors deriving from the smooth muscle tissue. They occur in 20-50% women at the age of 35 and 70% at the age of 50. The most common symptoms of uterine fibroids include: heavy, prolonged menstrual bleeding, pain and the tightness in the pelvis. Methods of treatment of uterine fibroids can be divided into: pharmacological, surgical and minimally invasive, such as - uterine artery embolization, laparoscopic uterine artery coagulation. Up to date, surgical procedures (hysterectomy or myomectomy) have been the dominant managements but recently uterine artery embolization have also been taken into consideration. In connection with the late maternity there are growing need for effective pharmacological treatment of uterine fibroids (Gonadotropin Releasing Hormone, Ulipristal acetate), which can replace traditional surgical methods.
Key words: uterine fibroids; treatment

INTRODUCTION

Uterine fibroids are benign, hormone-dependent tumors that arise from the smooth muscle tissue. They occur in 20–50% of white women at the age of 35 [1,2]. This number increases to 70% at the age of 50 [3]. It is suspected, however, that their actual frequency of occurrence can be much higher since, in many cases, uterine fibroids are asymptomatic.

The mechanisms of the origin and development of fibroids are not fully explained. It has been found that the growth of these masses can be caused by a too high concentration of estrogen and progesterone receptors in the uterus [4]. The remaining risk factors include: black race, obesity, low number of pregnancies/infertility, arterial hypertension, genetic predisposition as well as differences in cytokine and their receptor induction [5–7]. Multiple labors, oral contraceptive pills, vegetarian diet and smoking reduce the risk of fibroids [5].

Symptomatic uterine fibroids considerably lower the quality of life assessed with the use of the Quality of Life test (QoL) and increase the anxiety about one's health and life [8]. They can cause, e.g. heavy and long menstruation, pelvic pain as well as dyspareunia, and frequently lead to considerable anemia [2,5,8,9]. Furthermore, they can be a reason for infertility, miscarriages, preterm labors and other obstetric complications [5,10].

The methods of treating uterine fibroids can be divided into: pharmacological (hormonal) therapy, surgery (abdominal, laparoscopic and vaginal) as well as minimally invasive procedures, such as uterine artery embolization or laparoscopic uterine artery coagulation.

SURGICAL MANAGEMENT OF UTERINE FIBROIDS

The most radical, and at the same time the most common method to treat uterine fibroids is hysterectomy.

It can be conducted by laparotomy, laparoscopy or through the vagina. The surgical approach as well as the type and extent of the surgery depend on patient's age, localization and the type of fibroids. According to Stadnicka et al., the removal of the uterus with fibroids that cause pain or discomfort in the pelvis minor improves the comfort of the patient's life in its physical and mental aspects [11]. Other authors claim that hysterectomy can lead to the deterioration of sexual life; it can lower libido, decrease the number of sexual intercourses and reduce sexual satisfaction [12,13]. It has been observed that women in whom total abdominal hysterectomy (TAH) has been conducted declare lower sexual satisfaction compared with patients after supracervical hysterectomy (SCH) [13]. Authors do not agree whether or not the simultaneous removal of the adnexa affects sexual life of women after hysterectomy.

The greatest disadvantage of hysterectomy applied in uterine fibroid treatment is the permanent loss of fertility. It is reported that uterine fibroids affect 3–10% of women of child-bearing age [14]. In the light of these data and constantly delaying maternity, sparing procedures are becoming more and more popular. These procedures include: conservative myomectomy, uterine artery embolization or laparoscopic dissection of the uterine arteries as well as proper ovarian ligament coagulation. The most effective and, according to numerous authors, the best method in the management of symptomatic uterine fibroids in patients planning to get pregnant or being treated because of infertility is conservative myomectomy [15]. Its aim is to remove fibroids and preserve the reproductive function in women with simultaneous alleviation of symptom. The indications for conservative myomectomy are: symptomatic uterine fibroids (submucosal lesions are removed via hysteroscopy) and infertility (after other common causes have been ruled out). Intramural or subserous myomas can be removed either via laparoscopy or laparotomy, and the approach depends on the size and localization of lesions [16]. Laparoscopy, being a less invasive procedure, seems to be more beneficial to patients (lower postoperative pain, shorter recovery period and lower blood loss during the procedure) [17]. Neither of the methods, however, is superior in terms of the number of complications during pregnancy. Fukuda et al. presented 105 cases of pregnant patients after the procedure of myomectomy (48 after laparoscopy, 57 after laparotomy). The authors did not observe any significant differences in the occurrence of complications during pregnancy (e.g. the frequency of urgent cesarean sections, abnormalities in the position of the placenta or pregnancy-induced hypertension). Moreover, there were no instances of uterine rupture in the second half or the pregnancy or during labor [18]. Kim et al., in turn, described a group of 66 patients who got pregnant after myomectomy (54 after laparotomy and 12 after laparoscopy). In one of the patients from the laparoscopic group, an injury to the posterior uterine wall with the diameter of 5 cm was detected during a planned cesarean delivery. The site of damage corresponded with the site of a removed uterine fibroid. Due to excessive and uncontrollable hemorrhage, hysterectomy was necessary. The authors draw attention to numerous reports on uterine rupture during pregnancy and labor in patients after laparoscopic myomectomy and recommend careful consideration of the clinical situation prior to making a decision about such a procedure in women of child-bearing age [17]. Moreover, Bernardi et al. are also of the opinion that pregnancy after laparoscopic myomectomy carries a higher risk of uterine rupture and placental complications [19]. The history of myomectomy associated with the opening of the uterine cavity is considered an indication for an elective cesarean section [20].

MININALLY INVASIVE MANAGEMENT OF UTERINE FIBROIDS

Uterine artery embolization (UAE) is one of minimally invasive treatment methods of symptomatic uterine fibroids. It consists in the introduction of a catheter through the femoral artery to the uterine arteries and administration of an embolic agent, which occludes abnormal vessels that supply fibroids [21]. Proper patient selection for the procedure, based on the medical history and imaging (US, MRI), is essential for the clinical efficacy and prevention of UAE complications. The eligible candidates are women with diagnosed symptomatic uterine fibroids localized intramurally with no other pelvic pathologies [22]. Embolization is not recommended in women who plan pregnancy. Arthur et al. examined 8 women after uterine artery embolization and 5 women after laparoscopic myomectomy. They observed a considerably lower number of ovarian follicles and lower level of anti-Müllerian hormone in patients who underwent UAE [23]. Moreover, Torre et al. have observed decreased fertility in women after UAE without lower ovarian reserve [24]. Another negative aspect of this procedure can be so-called post-embolization syndrome. It is a reaction of the organism to fibroid ischemia and includes severe pain, nausea, vomiting, slightly raised body temperature and bradycardia [21]. Patients treated with the use of this method should also be informed about possible adverse effects, such as premature ovarian failure that can lead to iatrogenic menopause and difficulties in conceiving and maintaining pregnancy [22].

Another minimally invasive method to treat uterine myomas is laparoscopic dissection of the uterine arteries and coagulation of the proper ovarian ligaments. Szyłło et al. have described a group of 31 patients who have undergone this procedure. The 6-month follow-up revealed a considerable reduction of symptoms (less heavy menstruation, urinary urgency, pain reduction and decrease in the size of uterine fibroids in ultrasound).

The authors recommend this method to women who wish to retain their uterus but do not plan to have children [25]. The efficacy of laparoscopic closure of uterine vessels compared with embolization was also assessed in another study on a group of 46 women. The following effects were observed after a 6-month follow-up: lower uterine volume by 37% (+/- 18%), decrease in the size of the dominant fibroid by 36% (+/-31%) and reduced pain after the surgery requiring lower doses of analgesics than after embolization (ketobemidone 38 mg vs 18 mg in the laparoscopic group) [26]. Obturator nerve injury was a specific complication of the laparoscopic technique. It occurred in 3 patients [26].

PHARMACOLOGICAL MANAGEMENT OF UTERINE FIBROIDS

The efficacy of interventional methods is unquestionable. However, because of late maternity and fear of invasive treatment, more and more clinicians decide to institute pharmacological, mainly hormonal treatment. The fibroid tissue contains more estrogen and progesterone receptors than the uterine tissue. That is why, the therapy involves the use of GnRH analogues, two-component contraceptive pill, selective estrogen receptor modulators (SERMs) and selective progesterone receptor modulators (SPRMs) [3,28].

GnRH analogues are used in the perimenopausal period in women who wish to avoid surgery to reduce symptoms associated with fibroids and in the pre-operative period to reduce the size of lesions thereby facilitating the procedure and lowering the risk of complications [3,27]. However, they are even more often used in an add-back therapy [27,28]. GnRH agonists suppress the pituitary gland and, in consequence, block ovarian function. They induce hypoestrogenism that leads to a decrease in fibroid and uterine size and reduces heavy vaginal bleeding [5,27]. A monotherapy with leuprolide acetate (or goserelin) cannot be long since it causes bone demineralization and other adverse effects, such as hot flushes or vaginal dryness. Moreover, fibroids tend to regrow after the discontinuation of analogues [3,5,29].

Mifepristone is a synthetic steroidal antiprogesterone. It inhibits endo- and exogenous progesterone and exhibits weak antiandrogenic effects [5,37]. Studies published in 2009 demonstrate that the outcomes of a therapy with 2.5 mg/d of mifepristone are very similar to the ones observed with a dose of 5 mg/g. Considerable pain and bleeding reduction was documented. The greatest intensity of these effects was observed in the 2nd and 3rd months of the therapy. Subsequently, pain and bleeding increased gradually but they were not higher than the baseline values. There were no serious adverse effects or cellular atypia in the endometrium [15,31]. A randomized clinical trial published in 2013 revealed that 5 mg/d of mifepristone administered for 3 months was more efficacious in reducing fibroid and uterine volume. Following the therapy, the size of fibroids decreased by 27.9% (2.5 mg/d) and 46.4% (5 mg/d). After further 9 months of observation, the reduction was 5.1% for the dose of 2.5 mg/d and 11.6% for 5 mg/d compared with the baseline values [30].

In vitro studies conducted on fibroid cell colonies have revealed that mifepristone reduces their viability in the most significant way (37.1 ±3.5%). Leuprolide acetate mentioned above exhibits weaker action (65.7±3.5%). The weakest agent in *in vitro* experiments was raloxifene (79.6±2.3%). Its efficacy increased when the cell culture had previously been exposed to a GnRH analogue [28]. Raloxifene is practically not used in the monotherapy of uterine fibroids in premenopausal women. Other studies also confirm better clinical outcomes, i.e. uterine volume reduction, following a combined therapy of leuprolide acetate with raloxifene (7% vs 4% for a monotherapy with an analogue) [32]. Raloxifene belongs to selective estrogen receptor modulators. It has agonistic effects on bones and antagonistic effects on the uterine muscle and endometrium, as well as the mammary gland. It has been shown to have antiproliferative effects and increase apoptosis of uterine fibroids in postmenopausal patients [33].

Apart from mifepristone, progesterone receptor modulators also include asoprisnil and ulipristal acetate (UA) which was registered and authorized for the European market in 2012 based on PEARL I and PEARL II trials. *In vitro* studies conducted on normal myometrial cells and fibroid cells have shown that selective progesterone receptor modulators (SPRMs) do not cause undesirable changes in normal cells [35]. Furthermore, it has been concluded that these agents exert effects on fibroid cells via several mechanisms. It has been proved that, in fibroid cultures, SPRMs induce apoptosis (by affecting caspese 3 and Bcl-2), have antiproliferative and antifibroblastic effects and downregulate tissue growth factors thus preventing neovascularization and cell proliferation. Moreover, they inhibit collagen I and III synthesis, which contributes to changes in the extracellular matrix [9,27,35–37].

The PEARL I trial has shown that 5 and 10 mg/d of ulipristal acetate combined with iron products administered for 13 weeks, compared with placebo (also administered with iron), significantly decreased uterine bleeding and reduced total fibroid size. The fibroid volume was assessed in MRI that revealed its reduction by 21% in women using 5 mg/d of the agent and by 12% in women using 10 mg/d. The volume increased by approximately 3% in the controls. Moreover, pain accompanying fibroids was alleviated (based on the simplified McGill questionnaire), hemoglobin levels increased and the quality of life index normalized. There were no significant differences in the frequency of reporting adverse effects in all three groups. The most common undesirable reactions included headache and

breast tenderness, but they were not significantly more common than in the controls [1,9,36].

The PEARL II trial compared the efficacy of ulipristal acetate (5 mg/d and 10 mg/d) and a GnRH agonist (leuprolide acetate) in a dose of 3.75 mg/month (injections). The study revealed that the size of three largest fibroids decreased in each group. The reduction at 13 weeks was 36% and 42% for ulipristal acetate, respectively, and 53% for the GnRH analogue. However, in patients who did not undergo a subsequent surgery, the effects of ulipristal acetate occurred to be longer (approximately 45% for 5 mg/d vs merely 17% for leuprorelin). The patients treated with ulipristal acetate did not report increased hypoestrogenism, which took place in the group treated with the GnRH analogue [9,27,34,36].

Ulipristal acetate (Esmya) is not reimbursed in Poland and therefore many patients cannot use this therapeutic option. Hungarian authors conducted a cost-effectiveness analysis of a 3-month therapy with ulipristal acetate prior to surgery (hysterectomy/myomectomy). The results were referred to the QALY index, and its values in women who received the pre-operative therapy and in those who underwent a surgery without the pharmacological pre-treatment were compared. The use of UA occurred to be cost-effective and improved the efficacy of the medical procedures. Ulipristal acetate is characterized by a good quality/price ratio, in accordance with Hungarian criteria [38].

PEARL III is a long-term, double-blind and placebo-controlled open phase III clinical trial in which patients were given oral progestogen (norethisterone acetate – NETA) or placebo for 10 days following the therapy with ulipristal acetate (10 mg/d). The aim of the prolonged phase of the trial was to assess the efficacy of UA by its influence on menstrual bleeding, pelvic pain, fibroid size and quality of life index in four 3-month therapy cycles. Ulipristal acts on the endometrium mainly by exerting antiprogesterone effects. That is why patients received norethisterone acetate or placebo in the second double-blinded part of the trial. The study was conducted between July 2010 and January 2013. It enrolled premenopausal women (18–48 years of age) with uterine fibroids ranging from 3 to 10 cm in diameter and with the uterus smaller than in the 16th week of pregnancy.

The efficacy and safety of the therapy were assessed after each cycle (UA used for 3 months + NETA/placebo for the subsequent 10 days) and 3 months after the last cycle. The trial demonstrated that norethisterone acetate does not affect non-physiological UA-induced changes in the endometrium in a significant way and does not affect the size of fibroids or uterine volume. The patients did not report any adverse effects during the first cycle. In further stages, 7 women reported: uterine bleeding (5), thyroid cyst (1) and chlamydia infection (1). The most commonly reported adverse effects were: headache, nasopharyngeal infection, abdominal pain, hot flushes and fatigue. After the first cycle of ulipristal acetate, no menstrual flow was reported by 79% of women. The median change in fibroid volume was - 45% (interquartile range - 66%, - 25%). The values of the lack of menstruation were as follows: 89%, 88% and 90% for 131, 119 and 107 women, who participated in the further phases of the trial. The median change in tumor volume was - 63%, - 67% and - 72%, after 2, 3 and 4 cycles, respectively [39].

The authorization of ulipristal acetate in pre-operative uterine fibroid treatment was considered a significant breakthrough by many doctors and patients. However, pharmacological treatment cannot be the only therapeutic option and is frequently supplemented with invasive methods, including hysterectomy. Nevertheless, it is a valuable tool in conservative treatment since the therapeutic effects are comparable to those caused by GnRH analogues but not accompanied by increased hypoestrogenism [9,40].

CONCLUSION

Owing to the fact that uterine fibroids are being diagnosed more and more frequently in women of childbearing age, minimally invasive surgical and radiological procedures as well as effective and safe conservative treatment methods (pharmacological therapy) are being developed intensively. In numerous cases, uterine artery embolization or myomectomy allow the most radical treatment, i.e. hysterectomy, to be avoided thus retaining fertility. The efficacy of sparing techniques can increase by applying pre-operative hormonal treatment, which decreases the size of tumors and reduces risks associated with the procedure.

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