NEW CONCEPTS IN THE THERAPEUTIC MANAGEMENT OF MYOMA

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ABSTRACT

The therapeutic management of symptomatic uterine fibroids is based on three pillars: surgery, pharmacotherapy, and interventional radiotherapy. Modern myoma treatment is personalised and should involve an interdisciplinary approach according to the patient's wishes and pathology.

Keywords: Myoma, uterine fibroids, ulipristal acetate (UPA), myoma enucleation, hysterectomy.

INTRODUCTION

Uterine leiomyomas or 'fibroids' (also known as myomas) are common, benign tumours of the myometrium.[1] Their growth is dependent on the female sex hormone.[2,3] Data from the USA show that up to 40% of all 35-year-old Caucasian women have myoma, whereas in African-American women it occurs even more frequently (estimated at 60% in this age class), and at the age of 50 years the prevalence of myoma reaches up to 70% in Caucasian women and >80% in African-American women.[4] More than 50% of all myomas are asymptomatic and do not require any therapy. The size of the myoma does not necessarily correlate with the severity of symptoms: even large myomas may not cause any symptoms. However, the localisation of the myoma is crucial in determining the extent and nature of symptoms. Myomas remain the predominant cause of hysterectomy for benign indications (about 50%).[4] Symptoms that require therapeutic intervention are: anaemia due to uterine bleeding, dysmenorrhoea, bulky symptoms (dyspareunia, pelvic pain, constipation, urge incontinence, pollakiuria, nocturia, symptoms of overactive bladder, compression of the ureter and subsequent hydronephrosis, and pyelonephritis leading to renal dysfunction), and acute pelvic pain in necrotic myoma. Another group of patients who should undergo appropriate therapy are patients with subjective wellbeing but with subfertility due to myoma.[5] Undiagnosed myoma can be a cause of recurrent miscarriage and sterility. Intrauterine myoma or polyps are diagnosed in 28.7% of women with recurrent miscarriage.[6]

In myoma patients suffering from bleeding-related anaemia, a submucosal localisation of the fibroid is most likely. Bleeding symptoms are due to dysregulated angiogenesis.[7] Bulky symptoms are found in patients with subserous and large intramural myoma. Bulky symptoms depend on the size and especially on the localisation of the myoma (e.g. due to the application of pressure on the intestine or bladder). In contrast to dysmenorrhoea, pelvic pain due to bulky symptoms occurs irrespective of the stage of the menstrual cycle.[8,9]

Modern myoma treatment consists of three therapeutic pillars: surgery, pharmacotherapy, and radiological interventions (high-intensity focussed ultrasound [HIFU] and myoma embolisation). The predominant therapeutic aim is to improve quality of life (QoL). Three aspects have to be taken into account in order to establish adequate therapeutic management:

- Does the patient wish to conceive?
- What is the size, number, and localisation of the myoma?
- What are the predominant symptoms?

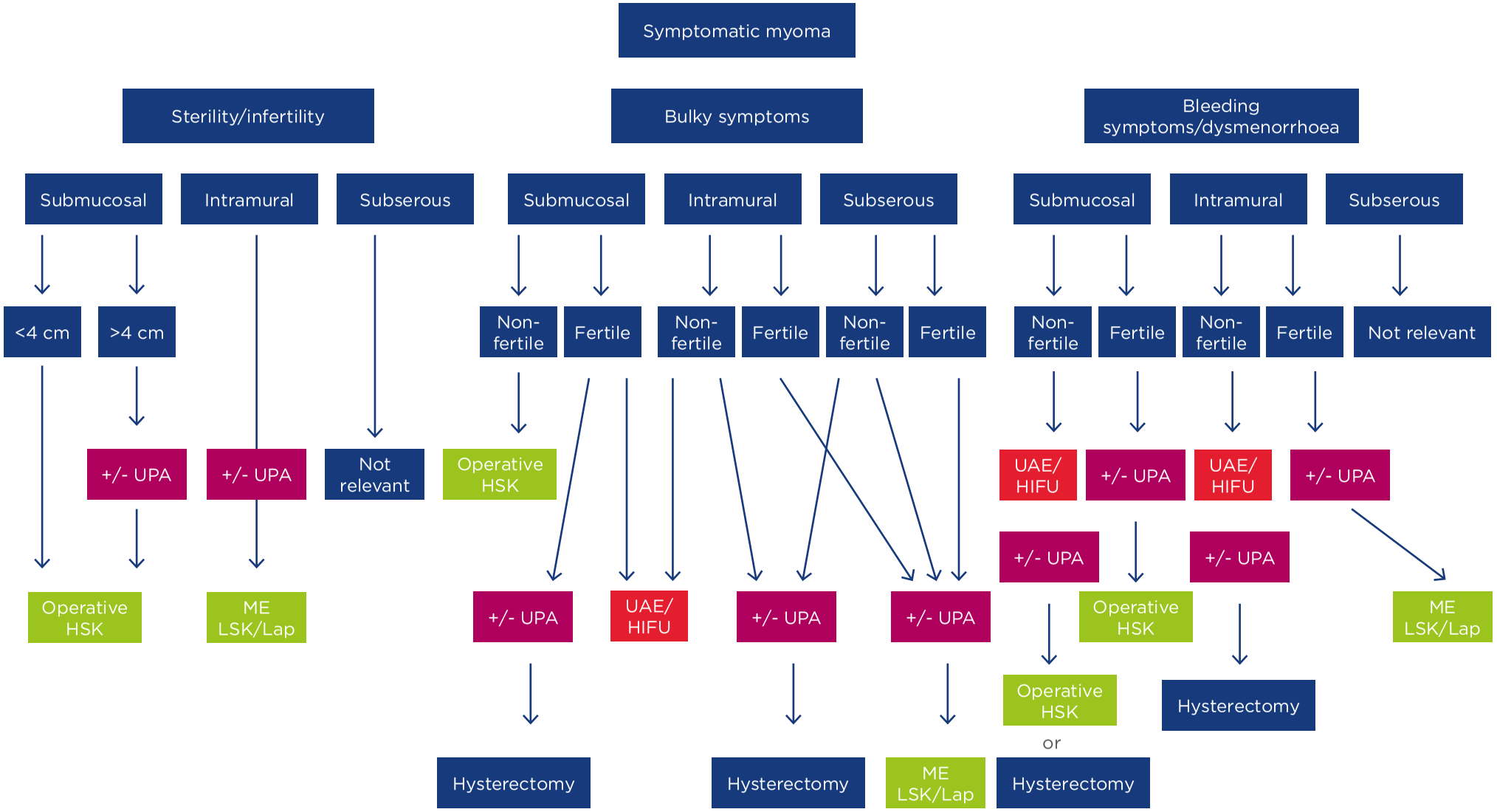

Figure 1: Algorithm for the personalised therapy of symptomatic myoma according to the patient's symptoms and respecting their wish to conceive.
ME: myoma enucleation; UPA: ulipristal acetate; UAE: uterine artery embolisation; HIFU: high-intensity focussed ultrasound; HSK: hysteroscopy; Fertile: wish to conceive; Non-fertile: no wish to conceive; LSK: laparoscopy; Lap: laparotomy.
+/- UPA refers to preoperative UPA treatment for either one or two cycles in order to achieve shrinkage and amenorrhoea.

Menopause and the expected interval until menopause have to be considered, as well as contraindications for surgery (comorbidity or if the patient refuses surgery). Modern therapeutic management of symptomatic myoma consists of personalised concepts tailored to the individual situation of the patient (Figure 1).

Surgery

An elaborate preoperative work-up is essential prior to surgical therapy for myoma. Six aspects must be clarified:

i. The symptoms must be attributed to the myoma.
ii. In uterus-preserving procedures, three groups of patients must be differentiated: asymptomatic patients who present for subfertility, symptomatic patients who wish to conceive in the future, and symptomatic patients who wish to maintain their uterus irrespective of reproduction and menopausal stage.
iii. The aim of the procedure must be clearly defined (symptom control versus fertility improvement).
iv. The ideal operative access must be defined.
v. The reasonableness of preserving the uterus in patients with completed family planning and perimenopausal patients must be estimated.
vi. The patient must be informed about alternatives to the procedure.

In any case and even in postmenopausal women, the patient's wish to preserve their uterus must be respected.

FERTILITY-PRESERVING OPERATIVE METHODS

Hysteroscopic Enucleation of Myoma

The operative method depends on the localisation of the myoma. Submucosal myomas are usually resected via hysteroscopy. Most patients present with bleeding disorders (the diagnosis of submucosal myoma is established in 59.8% of myoma patients with hypermenorrhoea),[10] or with sterility and recurrent spontaneous abortions.[6,11] Another common symptom in submucosal uterine fibroids is dysmenorrhoea. A possible pathophysiological mechanism is dysregulated uterine contractility.[12] Intrauterine fibroids or polyps are diagnosed in more than 20% of all patients presenting with infertility.[6,13] After hysteroscopic resection of intrauterine myoma, pregnancy rates reach about 50%[14] and bleeding symptoms are resolved in 70-99% of cases.[11]

The European Society for Gynaecological Endoscopy (ESGE) defines three subtypes of intrauterine myoma:

- Type 0: the myoma is located completely in the uterine cavity or pedunculated.
- Type 1: <50% of the myoma is located in the myometrium.
- Type 2: >50% of the myoma is located in the myometrium.

This classification is crucial in order to estimate the chance for complete resection of the myoma prior to the procedure. According to European Society of Hysteroscopy (ESH) in 2012, a complete hysteroscopic resection of intrauterine myoma is achieved in the following percentages:

- Type 0: 96-97%
- Type 1: 86-90%
- Type 2: 61-83%

The hysteroscopic resection should not be postponed in infertility patients with diagnosed submucosal myoma. Even small intrauterine myomas (<1.5 cm) without any symptoms should be removed, as the operability and rate of complete resection correlates inversely with the size of the myoma.[15] Hysteroscopic resection in large myomas (>4 cm) and Type 2 submucosal myomas requires special expertise. Long operating time and intraoperative injury of vessels are risk factors for symptoms of fluid overload, especially in large myomas. In some cases of very large fibroids, hysteroscopic resection might have to be performed in two procedures rather than one.[16]

Laparoscopic Enucleation of Myoma

The impact of myomectomy of non-submucosal fibroids on fertility and sterility remains controversial. In the case of intramural fibroids <4 cm that do not affect the endometrium, a possible influence on infertility has been reported but data are inconsistent. In a recent retrospective study, Yan et al.[17] reported that non-cavity-distorting intramural fibroids >2.85 cm in their largest dimension significantly impair the delivery rate of patients undergoing assisted reproduction (*in vitro* fertilisation/intracytoplasmic sperm injection). One possible pathomechanism may be abnormal uterine peristalsis in myoma patients, which can be improved by myomectomy.[18] In a prospective study of a cohort of assisted-

reproduction patients, laparoscopic enucleation of intramural fibroids correlated with improved rates of pregnancy compared with those receiving no procedure (56.5% versus 41%, respectively); however, this analysis did not reach statistical significance.[19] Strictly subserous fibroids <5 cm do not seem to have any significant impact on fertility and outcome of the pregnancy.[20,21] Nevertheless, patients wishing to conceive should be informed about the possibility of increased myoma growth during pregnancy, which may enhance myoma-related complications (necrosis, preterm birth, obstetric obstacle, etc.).

Unfavourable factors for laparoscopic enucleation of myoma are: size >5 cm in diameter, localisation in the anterior wall, deep infiltration of the uterine muscle, uterus multimyomatosus with >4 fibroids, and gonadotropin-releasing hormone (GnRH) agonist therapy prior to surgery.[22] Uterine functional integrity is mandatory, especially in patients who wish to conceive. Another important factor is the risk of uterine rupture during pregnancy and delivery following enucleation of myoma. Incidence of uterine rupture in pregnancy after enucleation of myoma is estimated to be 1%. Risk factors for uterine rupture are excessive electrocoagulation, haematoma, and fistula in the myoma scar and suture cavities.[23] For this reason primary laparotomy is advised in large myomas >8 cm in diameter when the uterus should be preserved.[24]

Hysterectomy

Hysterectomy remains an effective treatment option in peri and postmenopausal patients, as well as patients opting for a definite therapy for myoma-related symptoms and who do not wish to become pregnant. Patients who suffer from bulky symptoms (pollakiuria, constipation, meteorism, tenesmus, pain, dyspareunia, hydronephrosis, etc.) rather than bleeding symptoms, which can often be managed with drugs or radiological intervention, benefit from hysterectomy as the appropriate therapeutic regimen.

If cervical dysplasia can be ruled out, and if there is no history of former cervical dysplasia, hysterectomy can be performed supracervically (laparoscopic supracervical hysterectomy [LASH]). Regarding peri and postoperative complications, operating time, blood loss, and recovery, LASH shows significant advantages compared with abdominal hysterectomy and total laparoscopic hysterectomy (TLH).[25] Women undergoing LASH report significantly lower pain levels and faster resumption of normal daily activities and sexual activity in comparison with those undergoing TLH.[25,26] The patient must be informed of a 10% risk of menstrual spotting after LASH due to remaining cervical endometrioid cells.[27]

Currently, power morcellation performed during LASH is controversial due to suspected tumour cell spreading in cases of undiagnosed uterine sarcoma. The risk of tumour cell spreading of undiagnosed uterine malignancies is estimated to be <0.2%.[28,29] The prevalence of 'smooth-muscle tumours of unknown malignant potential' is even more infrequent. According to recent data, tumour cell spreading by power morcellation of undiagnosed sarcoma is associated with upstaging of the sarcoma and is suspected of worsening the prognosis.[30] However, data describing accidentally morcellated uterine sarcoma are scarce. Reporting, follow-up, and subsequent meta-analysis of as many cases as possible should be conducted.[29,31]

Preoperative risk reduction requires a careful selection of patients appropriate for LASH. Postmenopausal patients with fast-growing myoma >6 cm in diameter showing sonographic hypervascularisation and heterogeneous structure are at risk and should not undergo morcellation.[32] However, what is the alternative? As a result of the current discussion, all patients with sonographically diagnosed myoma would be considered candidates for abdominal hysterectomy, even those with the desire to conceive, in order to avoid the potential risk of morcellation of undiagnosed malignant tumours because even abdominal enucleation of myoma may cause tumour cell spreading. As a consequence, all therapeutic improvements regarding conservative or radiological interventional myoma therapy have to be questioned. While the risks of morcellation of undiagnosed uterine sarcoma may be serious, the positive aspects of LASH have been demonstrated. The advantages regarding sexual function derive from the preservation of cervical glands that play an important role in lubrication. There is a significant reduction of genital organ prolapse and dehiscence as a result of LASH,[33] with some authors reporting significant advantages regarding bladder function after LASH when compared with total hysterectomy after a 1-year follow-up.[34] However, the data concerning bladder function after LASH in comparison with total hysterectomy remain limited and controversial, and must be

interpreted with care. As a result, the patient has to be informed meticulously about the risk of power morcellation and the alternative of abdominal total hysterectomy must be discussed. Laparoscopy reaches its technical limits in very large uteri and in patients with excessive adhesions. Some patients are not appropriate for laparoscopy if pneumoperitoneum during laparoscopy is a risk due to adipositas per magna or cardiovascular problems.[35]

In perimenopausal patients suffering from bleeding rather than bulky symptoms, the indication for hysterectomy must be established with care. On the one hand, other pathologies (e.g. endometrial hyperplasia or malignancy and perimenopausal bleeding disorders) and preoperative histological diagnosis should be considered. On the other hand, myoma-related symptoms may resolve when attaining postmenopause. Consequently, in specific cases, medical therapy (e.g. ulipristal acetate [UPA], see below) may relieve symptoms until postmenopause and hysterectomy can be avoided.

In patients who do not wish to conceive but opt for myomectomy, their wish to preserve the uterus must be respected and informed consent is mandatory. In cases of large or multiple uterine fibroids, myomectomy may bear a higher risk of intra and postoperative complications and requirement of surgical re-intervention compared with hysterectomy. Furthermore, the risk of accidental tumour cell spreading must be mentioned when opting for myomectomy. In cases with adenomyosis, myomectomy alone is not sufficient to alleviate the symptoms.[36]

Uterine Artery Embolisation and High-Intensity Focussed Ultrasound

Uterine artery embolisation (UAE) was introduced in 1995. The procedure offers an established fertility-preserving alternative to surgery and aims to reduce myoma-related symptoms, such as bleeding symptoms and bulky symptoms. UAE results in myoma necrosis and shrinkage but not in complete eradication of the myoma. Embolisation of fibroid perfusion is performed via a transfemoral catheter and application of small (500 μm) polyvinyl particles, for example under radiological control. UAE is a valuable alternative in cases where there are contraindications for surgery, or if the patient refuses a procedure. In specific cases of very large myoma, preoperative UAE can be helpful in order to reduce intraoperative blood loss and to reduce the risk for hysterectomy in patients who want to undergo myomectomy.[37] Adverse events (AEs) are severe ischaemic pain that can persist for some days, post-embolisation syndrome, fever, endomyometritis, sepsis, and hysterectomy. In a recent meta-analysis including seven randomised controlled trials, UAE is associated with a higher rate of minor complications and an increased likelihood of requiring surgical intervention 2-5 years after UAE when compared with primary surgery (myomectomy and hysterectomy). According to the data, 15-32% of UAE patients require further surgery within 2 years.[38]

Hormone-based fibroid medication (e.g. GnRH agonists) should not be administered for at least 12 weeks prior to UAE due to the risk of uterine artery spasms that might disturb the procedure.[39] UAE should not be performed in women who wish to conceive and especially not in patients who present for infertility or sterility due to uterine fibroids. A significant risk of miscarriage following UAE was demonstrated (up to 64% in some studies), as well as risk of preterm delivery, abnormal placentation, and postpartum haemorrhage. In contrast with evidence-based enucleation of myoma, a significant reduction in ovarian function and an increased risk for amenorrhoea has been demonstrated.[40,41]

HIFU is a non-invasive thermoablation of symptomatic uterine fibroids that can be performed in an outpatient setting. Volumetric sonification induces homogenous tissue heating with subsequent necrosis of the fibroid. The sonification system is regulated via magnetic resonance imaging (MRI) feedback mechanisms, thus AEs are rare. HIFU is considered efficient and well tolerated in a selected patient cohort, and AEs like persistent pain or injury of neighbouring organs are reduced to a minimum. Myoma-related symptoms and the size of the myoma are significantly reduced. MRI offers exact therapy planning. MRI real-time observation of energy transmission ('sonification') generates a 'mapping' of the applied temperatures in fibroid tissues. Thus, applied temperatures are measured in order to regulate and optimise the therapy. In contrast to UAE, there is no radiation exposure in HIFU. Myoma volume can be reduced by 13.5-46% after 6 months. Efficiency regarding reduction of myoma-related symptoms and significant improvement in QoL can be assessed.[42]

Data regarding fertility and pregnancy after HIFU are limited.[43] Prospective data, and particularly randomised studies, comparing fertility and pregnancy outcomes with conventional, well-established myomectomy are missing. Apart from long-term effects regarding pregnancy and obstetric outcome, AEs on endometrium, tubal factor, and ovarian function can be hypothesised.[43] In UAE and HIFU, the patient's informed consent is mandatory, particularly in infertility and sterility patients. The patient should be informed about the lack of histopathological examination of the fibroid in conservative treatment options. Although the histological diagnosis of malignant tumours instead of suspected myoma is rare (0.1-0.2%), any alternative or conservative treatment involves the risk of undetected malignancy.[28]

Therapeutic Drugs

A higher concentration of the progesterone receptor has been found in fibroid tissue compared with normal myometrium.[44] Classical therapeutic drugs administered to myoma patients are progestins and GnRH agonists. Progesterone receptor modulators inhibit proliferation and induce apoptosis of myoma cells.[45] The cyclic use of progestins[46] can be administered to patients with bleeding symptoms. Oral contraceptive intake reduces the risk of developing myoma.[47] However, progestins do not reduce myoma growth and may even promote myoma cell growth.[7] Therefore, a clear differentiation in the treatment of myoma-induced bleedings must be made between mere symptom control, inducing amenorrhoea, and a causal therapy, reducing myoma volume.[1] In rural settings in developing countries, symptom relief achieved by the administration of progestins may, in contrast to GnRH analogues, offer a cost-effective therapeutic option. Until 2012, GnRH agonists were the only therapeutic drugs approved for the treatment of myoma. The use of GnRH analogues reduces fibroid size and bleeding symptoms.[48] GnRH agonists act by reducing serum oestrogen concentrations to a postmenopausal level.[49] However, these drugs show severe climacteric side-effect profiles, e.g. hot flushes, mood swings, loss of libido, vaginosis, depression, and bone loss. GnRH agonists should be administered 3-4 months prior to surgery and they are not recommended for long-term use.[50] Main indications are hysteroscopic resections of large submucosal and intramural fibroids. However, some authors claim that there are difficulties in fibroid preparations in myoma laparoscopy after GnRH agonist treatment.[27]

Therapeutic effects cease after stopping the medication and a high recurrence rate of fibroid growth has been observed.[51] The selective progesterone receptor modulator (SPRM) UPA was introduced in 2012.

Two large, randomised, double-blind, Phase III trials (PEARL I and PEARL II) demonstrated the effect of UPA administration for 13 weeks. A cessation of bleeding symptoms after 7 days and a 51% reduction in fibroid size were achieved.[52,53] After cessation of UPA treatment, the reduced fibroid size persists for up to 6 months. Preoperative UPA administration offers a positive effect via 'auto-transfusion' and may enable laparoscopic surgery of large myomas by preoperative shrinkage. SPRMs induce amenorrhoea while maintaining endogeneous oestrogen secretion.[7] With a daily administration of SPRMs, serum levels of oestrogen range in the low follicular phase and climacteric side-effects, such as thromboembolic effects and bone loss, do not occur.[53] The most frequent side-effects reported in women receiving multiple treatment courses are headaches, nasopharyngitis, abdominal pain, and hot flushes.[45,54]

Long-term treatment with UPA may cause sonographic endometrial thickening and progesterone receptor modulator-associated endometrial changes (PAEC). PAEC occurs in approximately 50% of all patients and is reversible 1-2 months[55,56] after cessation of UPA treatment. In cases of persistent endometrial changes 3 months after ending the UPA treatment, targeted hysteroscopic biopsy of the endometrium must be performed. These sonographic signs are generally not associated with endometrial hyperplasia but rather represent cystic glandular dilatation. Although conception during UPA intake is improbable due to suppression of ovulation, alternative contraception (especially barrier methods) must be additionally advised. The menstrual cycle also recovers quickly after ending UPA administration.[45,52] The benefits of UPA, particularly in myoma patients suffering from bleeding symptoms, are an integral part of routine myoma therapy. Future concepts of UPA administration include long-term use in order to bridge the time gap until menopause and to avoid hysterectomy. Currently, two cycles of UPA for 13 weeks with a therapy-free interval are approved.

The PEARL III study investigated the administration of up to four 3-month courses of UPA. The off-treatment period between each UPA course included one menstrual bleed and the beginning of a second bleed. In order to explore any effect on the reversibility of PAEC or timing and magnitude of the next menstruation off-treatment, 10 days of treatment with the progestin norethisterone acetate or placebo were administered after each cycle of UPA. There were improvements in amenorrhoea rates and fibroid volume reduction with successive treatment courses, while the incidence of side-effects showed a tendency to decrease after several courses. No cases of endometrial hyperplasia or adenocarcinoma were reported, although there was an increase in non-physiological pathological features in endometrial biopsies.[54]

CONCLUSION

Modern myoma therapy aims at individual patient-tailored concepts. New drugs and radiological therapies offer interesting alternatives to surgery. Therapeutic management of symptomatic myoma is based on interdisciplinary concepts involving gynaecologists, gynaecological surgeons, fertility specialists, and interventional radiologists. Patients should therefore be referred to specialised centres. Future therapeutic concepts include long-term medication without side-effects, resolving bleeding and bulky symptoms, and innovation in minimally invasive surgery and radiological interventional therapies.

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