REVIEW ARTICLE

Conservative treatment of fibroids

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Introduction

Incidence

Fibroids are the most common benign uterine tumours with
an incidence range of 5.4–77% in women of reproductive
age depending on the method of diagnosis [1]. They increase
in incidence towards the end of a woman's reproductive
life. They are particularly common in black populations
with a nine-fold increase compared to Caucasian popula-
tions [2, 3]. Some familial tendencies have been identified
[4]. The aetiology of fibroids is unknown, although fibroid
growth is oestrogen dependent. It is estimated that 50%
of fibroids are asymptomatic and are an incidental finding
at the time of clinical or ultrasound examination. Approx-
imately 0.1% of fibroids present as sarcomatous fibroid
which is a rare but serious smooth-muscle malignant tumour
[5]. Submucosal fibroids or intramural fibroids in close
relation to the uterine cavity are found in 40% of patients
with heavy and/or prolonged menstrual bleeding [6–9].

The goal for therapy of fibroids and debilitating men-
orrhagia must take into consideration the needs and desires
of the patient in terms of her lifestyle (e.g., days lost from
work because of symptoms) and childbearing plans.

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Hysterectomy has been regarded as the definitive surgical
treatment for fibroids and has been a very commonly per-
formed operation [10]. However, hysterectomy continues to
be financially costly with billions of dollars spent annually,
as well as costly in more fundamental terms of morbidity and
mortality when compared with the less invasive alternatives
of myomectomy, ablation, and myolysis [11–13]. Myomec-
tomy involves the shelling out of fibroids from the
myometrium, and in the case of submucosal fibroids, these
can be removed surgically via hysteroscopic procedures
[14]. Although morbidity is reduced with endoscopic
surgery, this technique is not widely available and has
limitations.

Fibroid vascular supply

The uterus has a very rich blood supply through two
extrinsic arterial systems, the uterine and ovarian arteries.
Intrinsic uterine arteries consist of ascending uterine,
arcuate, radial, and peripheral arteries imply free flow
through the uterus. Fibroids receive their blood supply from
the intrinsic arteries, primarily from branches of arcuate
arteries, and the vessels are located in the pseudocapsule
around the fibroid. The ipsilateral uterine and ovarian
arteries are connected by a communicating branch. In
addition to its primary (uterine artery) and secondary
(ovarian artery) extrinsic blood supply, the uterus enjoys a
vast network of lesser known arterial collaterals [15]. If the
blood supply from the right or left uterine artery is
occluded, blood from the left or right artery will supply
the myometrium via communications through arcuate
arteries. Finally, if both uterine arteries are occluded, blood
flow to the myometrium will develop from anastomoses
with ovarian arteries. In addition to the primary and
secondary blood flow, the uterus has a vast network of

collateral arterial communications from the aorta external iliac and femoral artery branch [16].

To occlude primary blood flow, uterine artery occlusion must be more distal than the internal iliac artery, in case occlusion of both internal iliac arteries does not stop antegrade blood flow [17], and subsequently it does not cause uterine ischemia, and the Doppler flow remains unchanged after bilateral internal iliac artery ligation [18]. When bilateral internal iliac occlusion is performed distal to the posterior division, reverse flow in the middle hemorrhoidal artery reconstitutes antegrade flow in each uterine artery. Under these conditions, the antegrade flow in each uterine artery persists and pulse pressure is damped, resembling a venous system instead of an arterial system; consequently, it does not cause uterine ischemia.

Therapy

Medicinal

Progestational agents have been reported to have an influence on myoma growth and have a direct anti-oestrogenic effect at the cellular level [19].

In an open observational study, the effectiveness of a levonorgestrel-releasing intrauterine device (LNG-IUD) in the treatment of myoma-related menorrhagia was studied. In conclusion, this study demonstrated the clinical effectiveness of LNG-IUD in the treatment of myoma-related menorrhagia [20].

Mifepristone

A total of 166 women with symptomatic uterine myoma received 5–50 mg/day of mifepristone for 3–6 months, and daily treatment with all doses of mifepristone resulted in reductions in uterine and leiomyoma volumes ranging from 27–49% and 26–74%, respectively. Mifepristone treatment reduced the prevalence and severity of dysmenorrhea, menorrhagia, and pelvic pressure, and the rates of amenorrhea ranged from 63–100%. A notable adverse effect of mifepristone was development of endometrial hyperplasia [21].

In another study, the response of uterine leiomyomata to three daily doses of RU486 (5, 25, and 50 mg) was tested, and the effective dose to cause a clinically significant (50%) decrease in leiomyoma volume appears to be 25 mg daily [22].

GnRH agonists

Gonadotrophin-releasing hormone (GnRH) agonists are widely used in the treatment of women with symptomatic myomas. The effectiveness of this treatment, as far as symptoms are concerned, is well established, and in recent years many studies have contributed to defining the optimum role for GnRH agonists. Side effects and health risks prohibit the long-term use of these compounds. The combined use of high-dose agonists and steroids in the so-called add-back schedules reduces many of the disadvantages of the monotherapy. However, it is still an expensive alternative when compared with definitive surgery, and therefore should only be used in women who insist on preservation of the uterus. Low-dose agonist therapy ('draw back') has not yet been proven to be suitable for clinical application. The use of GnRH agonists and steroids in sequential schedules seems to result in a loss of both the volume reduction as well as the reduction in clinical symptoms.

The use of GnRH agonists prior to myoma surgery should not become a routine measure and should be limited to cases where the size of the uterus is >600 ml. Hysterectomy should only be preceded by GnRH agonist treatment if uterine volume decrease is expected to facilitate either the abdominal or vaginal procedure. For both operative procedures, the presence of myoma-related anaemia is an indication for pretreatment [23]. The use of GnRH agonists before endoscopic surgery is widely accepted on the basis of assumed advantages; however, definite proof of these advantages is not yet available [24]. It is, however, known that fibroids tend to return to their pretreatment size about 6 months after discontinuing treatment. GnRH agonist treatment cannot be continued indefinitely due to its potential complications and high cost. Experience with presurgical GnRH agonist use may indicate a treatment advantage, and the use of GnRH agonists as adjuncts to surgery is well established [25].

Twenty-seven women with uterine leiomyomas were treated with a standard dose of triptorelin for 8 weeks. Patients were then randomised to use 100, 20, or 5 μg of triptorelin until week 26. Uterine and myoma size, pituitary-ovarian function, bone metabolism, and bone mineral density were monitored. During standard treatment, uterine size was reduced to 67.1% of baseline. During randomised treatment, uterine size was further reduced to 57.8% of baseline. There were no differences in overall volume reduction among the groups. Bone mineral density decreased significantly in the highest-dose group at week 26. This study shows that the beneficial effects of initial high-dose agonist treatment on uterine leiomyomas can be preserved by continued low-dose treatment. Bone mineral density does not seem to change during reduced-dose agonist treatment [26].

Asoprisnil (Schering, TAP Pharmaceutical Products) is a novel, orally active, selective progesterone receptor modulator (SPRM) developed for the treatment of uterine

fibroids and is now under clinical investigation in large phase III trials.

Fibroid myolysis

Myoma coagulation or myolysis with the laparoscope or hysteroscope is a valuable addition to the armamentarium of treatments for a problem that remains pervasive among women. Likewise, surgical techniques include the use of the Nd:YAG laser as well as the bipolar needle. The addition of myolysis to earlier uterine-sparing endometrial ablation or resection markedly improves the success rate of these minimally invasive alternatives to hysterectomy [11]. Myoma coagulation, when combined with endometrial ablation among women with symptomatic fibroids and bleeding, also reduces all subsequent surgery rates compared with endometrial ablation alone [11].

Power colour-Doppler imaging was performed preoperatively and postoperatively to determine the effectiveness of cryomyolysis (a freezing probe inserted into the fibroid controlled with ultrasound) in reducing or eliminating the primary blood supply as well as regression of the myomas. Myomas regressed up to 80%, and major blood supply to the myomas was eliminated [27].

Cryomyolysis is able to maintain (or slightly reduce) the uterine fibroid at its post-GnRH agonist size, whereas all other uterine tissues return to pre-treatment size [28].

In case of pregnancy after myolysis, caution and intensive surveillance of mother and foetus must be applied, and caesarean section should be performed at earliest signs and symptoms of uterine rupture and at term before onset of labour [29].

Laparoscopic myomectomy and hysteroscopic myomectomy

In recent years, the endoscopic minimally invasive approach has significantly improved the quality and increased the options of treatment of fibroids.

Results from randomised trials and clinical series have shown that laparoscopic myomectomy provides the advantages of shorter hospitalisation, faster recovery, fewer adhesions, and less blood loss than abdominal myomectomy when performed by skilled surgeons. Improvements in surgical instruments and techniques allow for safe removal and multilayer myometrial repair of multiple large intramural myomas. Randomised trials support the use of absorbable adhesion barriers to reduce adhesions, but there is no apparent benefit of presurgical use of GnRH agonists. Pregnancy outcomes have been good, and the risk of uterine rupture is very low when the myometrium is repaired appropriately.

Laparoscopic myomectomy is an appropriate alternative to abdominal myomectomy, hysterectomy, and uterine artery embolisation for some women [30].

Interference with the blood supply to the uterus

Nonsurgical treatments interfering with the blood supply to the uterus or the fibroids include uterine artery embolisation performed by an interventional radiologist or laparoscopic/vaginal uterine artery occlusion by the gynaecologist [31].

Uterine artery embolisation

The use of transcatheter uterine artery embolisation (UAE) as a treatment for uterine fibroids represents a new approach to the management of this common problem [32, 33]. In the presence of fibroids, arteriography of the uterine arteries shows these vessels as dilated and tortuous, and laterally one can confirm the hypervascular nature of the fibroid by noting the extensive network of intrinsic arteries within the fibroid. Once identified, the uterine arteries are selectively catheterised. An embolic agent, such as polyvinyl alcohol (PVA) particles measuring 350–500 or 500–710 μm in diameter, is injected directly into the uterine arteries to induce thrombosis. Both uterine arteries should be embolised because the arcuate arteries arising from them anastomose across the midline. It has been shown that fibroids will decrease in size and symptomatology [34], and hypervascular fibroids tended to decrease in size after treatment compared to more isovascular or hypovascular fibroids [35]. Uterine artery embolisation can produce a mean reduction of 29–51% in uterine volume at the time of the 3-month review, with longer follow-up showing continued shrinkage and no regrowth [36].

This procedure is unfortunately not without complications [37]. The acute degenerative procedure can be very painful and infection can occur. Hysterectomy may again be required in the case of hemorrhage or severe tissue necrosis. Delivering fibroids or sections of fibroids may be a natural process after uterine artery embolisation, therefore it is essential to warn women about the possible risk of infectious symptoms such as heavy discharge and fever, and consequently close follow-up is essential. The spontaneous expulsion of fibroids occurs over several months resulting in a significant reduction in menstrual loss and dysmenorrhea. Adequate antibiotic cover may be necessary to prevent sepsis [38]. A long-term side effect could be premature ovarian failure secondary to interference with the ovarian blood supply. In most studies, ovarian failure after UAE was found to occur most often in women in their late 40s, with an overall incidence of 5% [34]. Although UAE

is recognised for the treatment of fibroids and associated infertility, it is currently controversial which treatment modality has the greatest efficacy with regard to post-treatment pregnancy rates and also lowest side-effect profile.

Uterine artery occlusion

Laparoscopic bipolar coagulation of uterine arteries and anastomotic sites of uterine arteries with ovarian arteries represents another modality of avoiding hysterectomy in women with symptomatic fibroids [39, 40]. The peritoneum overlying the external iliac artery is incised with a T incision between the round ligament and the infundibulopelvic ligament. The iliac vessels are identified, and the retroperitoneal space is developed. The uterine artery is occluded with an endoclip at the level of the internal iliac artery. An identical procedure is performed on the ipsilateral side. The collateral arteries between ovaries and uterus (in the utero-ovarial ligament) are coagulated using bipolar forceps.

In our institution, we studied 46 premenopausal women with symptomatic uterine fibroids undergoing radiological embolisation (n=24) or laparoscopic closure of the uterine arteries (n=22) [41, 42]. The laparoscopic technique reduced picture blood assessment score after 6 months by 50% in both groups. Uterus volume was reduced by 35–40% in both groups. We found that laparoscopic occlusion of uterine vessels is a promising new method for treating fibroid-related symptoms, with less postoperative pain than embolisation and comparable effects on symptoms.

The effect of the temporary artery uterine clamp was first demonstrated in our institution in 2004, when a 43-year-old woman with menorrhagia, dysmenorrhea and pelvic pain of several years' duration with a uterus enlarged by fibroids to the size of a 16-week pregnancy was treated [43]. Her uterine arteries were non-invasively identified transvaginally and occluded for 6 h with a clamp that was guided by audible Doppler ultrasound. Following removal of the clamp, blood flow in the uterine arteries returned immediately. Three months after treatment, the uterine volume had decreased by 49% and the dominant fibroid volume by 54%. Even though fibroid-related symptoms may effectively be relieved by interference with the blood supply to the uterus, there seems to be no substantial effect in patients with dysfunctional bleeding.

Application of conservative techniques

Infertility

Myomectomy has significant associated risks to the woman and her future fertility. These include massive intra-operative hemorrhage, risk of emergency hysterectomy and disfigurement of the uterine cavity. In addition, the scar left on the uterus after myomectomy increases the chance of uterine rupture in future pregnancies. The association between fibroids and infertility has long been recognised [44]. It is accepted that there is an improved fertility outcome after myomectomy [45]. Many women do not wish to undergo an operative procedure as they may not accept the associated risks of an operation, and due to these circumstances, prefer even less invasive procedures such as UAE.

To determine the effect of myomectomy as a therapy for infertility and to define the factors that influence reproductive outcome, a retrospective study of a case series is summarised. To assess the role of leiomyomas and their surgical removal on pregnancy rates, 212 women who were investigated for infertility were studied. Patients were divided according to case control criteria as those who underwent laparoscopic removal of myomas (106) and those who did not (106); both groups were compared with 106 women with unexplained infertility without myomas. Of the 318 women, 83 (26%) became pregnant and delivered live infants. The 44 (42%) who underwent surgical removal of leiomyomas had higher delivery rates than 12 (11%) who did not undergo surgery (P<0.001) and 27 (25%) who did not have myomas (P<0.001). Patients whose myomas were not surgically treated had fewer deliveries than women who did not have myomas (12 vs. 27, P<0.002). Fifteen women had spontaneous abortions before week 12: 3 (3%) who had surgery, 10 (9%) who did not have surgery, and 2 (2%) who did not have myomas. The conclusion of this study emphasised that myomectomy improved pregnancy rates over nonsurgical management of myomas [46].

To determine the effects of hysteroscopic myomectomy on menorrhagia and infertility, the long-term outcomes of 108 women who underwent hysteroscopic resection of submucosal (n=54), sessile (n=30), or intramural (n=24) leiomyomas over 7 years were investigated [47, 48]. After a mean follow-up of 41 months, myomas recurred in 27 subjects, with a 3-year cumulative rate of 34%. Twenty women had recurrent menorrhagia, with a 3-year cumulative probability of 30%. The 3-year cumulative probability of conception was 49% in women with pedunculated lesions, 36% in those with sessile lesions, and 33% in those with intramural lesions. Hysteroscopic resection of submucosal myomas gives satisfactory menorrhagia control and limited recurrence and shows beneficial effect for infertility.

Pregnancy outcome

Another retrospective study was conducted to establish the impact of myomectomy on pregnancy outcome with particular reference to its effect on the incidence of pregnancy loss [49]. Myomectomy was performed using microsurgical procedures on 51 women who had intramural or subserosal fibroids and wished to conceive. Overall, the conception

rate following myomectomy was 57%. Multiple regression analysis showed that age was the only factor which influenced conception rate; there was no instance of premature labour or scar rupture among 25 live births. This retrospective study suggests that myomectomy for intramural and subserosal fibroids may significantly improve the reproductive performance of women presenting with infertility or pregnancy loss.

To compare pregnancy outcomes in women with fibroids who were treated with UAE with those treated with laparoscopic myomectomy, data from 53 pregnancies after UAE and 139 pregnancies after laparoscopic myomectomy were analysed. Pregnancies after UAE had higher rates of preterm delivery (odds ratio 6.2; 95% CI 1.4–27.7) and malpresentation (odds ratio 4.3; 95% CI 1.0–20.5) than did pregnancies after laparoscopic myomectomy. The risks of post-partum hemorrhage (odds ratio 6.3; 95% CI 0.6–71.8) and spontaneous abortion (odds ratio 1.7; 95% CI 0.8–3.9) after UAE were similarly higher than the risks after laparoscopic myomectomy; however, these differences were not statistically significant. Pregnancies in women with fibroids who were treated by UAE compared with pregnancies after laparoscopic myomectomy were at increased risk for preterm delivery and malpresentation [50].

Conclusions

Fibroids present with a variety of symptoms including infertility, bleeding problems, pressure and pain. They may be single or multiple, occur at different ages, and they require individualised treatment approaches.

In infertility patients, single fibroids should be removed; with multiple fibroids, medical or circulation therapy might be the only option for saving the uterus. For bleeding problems, an important issue is the location of the fibroid, in case of submucosal or type 0, hysteroscopic resection is the method of choice.

For the bigger intramural, subserosal and even multiple fibroids, uterine artery therapy with embolisation or laparoscopy seems to achieve good results for both bleeding problems and pressure symptoms.

Both radiological and laparoscopic occlusion techniques are potential treatment options. However both techniques require a high level of skill and should be confined to special centres with appropriate expertise. Complication rates are significant, but similar for the two procedures. Counselling of patients is of importance.

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