Review Article

Scope of Medical Science on Fibriods

Swapnali A Patil*, Dr Anil Jadhav
*Sandip Institute of Pharmaceutical Sciences, Timbak Road, Mahiravani, Nashik-422213, India.
***Corresponding author's E-mail:** swapnaliap78@gmail.com

Received: 18-04-2019; **Revised:** 26-05-2019; **Accepted:** 05-06-2019.

ABSTRACT

Uterine fibroids are non-cancerous malignancy that grows from the layers of muscles in and around the womb. This benignant smooth muscle grows and the size of fibroid can vary from small pie to as big as melon. The other name for fibroid is leiomyomas and myomas. They develop usually between at the early age from 16 to 50 years. These are the reproductive years during which estrogen levels are high. Uterine Fibroid may lead to unreprodutiveness, abortion, and early labor. This article is a review of recent updates and progress to understand the organic fibroids nature, their cycle and their hereditary origin. Recent updates in surgical and interference management is studied, medical management, analysis with selective progesterone receptor modulators, are reviewed in brief. The most common effect of fibroids is on the woman's pelvic pressure pain or menstrual syndrome. The uterine fibroids are treated depends on the number, size and which part it is located. The non- surgical and surgical approaches are myomectomy by hysteroscopy, hysteroscopy by laparotomy or laparoscopy, uterine artery mobilization and interference done by radiologic or ultrasound guidance to insert thermal abscission of the fibroids. In woman this disease is fast viable diseases and symptoms are not very much clear in many cases.

Keywords: Non-cancerous, hysteroscopy, myomectomy, laparotomy, laparoscopy, embolization.

INTRODUCTION

Uterine fibroids also known as myomas or leiomyomas is the common benignant uterine tumors, and mostly 20%–40% women during their reproducing age are incident of it.[1,2]

It is a mangling tumor of the smooth muscle cells in and around uterine and consist of heavy amount of extracellular matrix which consist of collagen, fibronectin, and proteoglycan.[3,4] They are multiple, and the size ranges from a few millimeters to as massive growths of 20 cm diameter or more. The pharmacology is largely unknown, but they are oestrogen- and progesterone-dependent tumors, very rare before monarchy, common in reproductive life, and widely grow in size after menopause.[5] Symptoms of uterine fibroids are abnormal uterine bleeding, pelvic pain, and dyspareunia, obstructive effects on bladder or rectum, and fertility problem. Fibroid size cannot not determine the seriousness of clinical symptoms. The online survey was studied in eight countries with at least 2,500 nominees from each country (4000in USA), 59.8% women were diagnosed of uterine fibroids they reported of prolonged and high vaginal bleeding comparatively to 37.4% in those not suffering from fibroids[6]. Pelvic pain at many times in the menstruation or during sexual intercourse was very significant in fibroid patients. Large amount of vaginal blood loss can lead to severe weakness and anemia which can be life threatening, yet some patients do not realize the seriousness of the problem, many may consider their blood loss to be normal, and do not seek help[7].

Symptoms' of Fibroids

1) Change in menstruation
   - Heavy, long, frequent menstrual period
   - Menstrual cramps
   - Anemia
   - Vaginal bleeding instead of menstrual periods
2) Pain
   - In lower back and abdomen
   - During sex
3) Pressure
   - Difficulty during urination.
   - Constipation, rectal pain, difficulty in bowel pain.
   - Abdominal Pain
   - Miscarriage
   - Enlarged uterus and abdomen
   - Infertility

Fibroids can sometimes show no symptoms so routine pelvic checkup is the only option to detect fibroids.

Risk factors

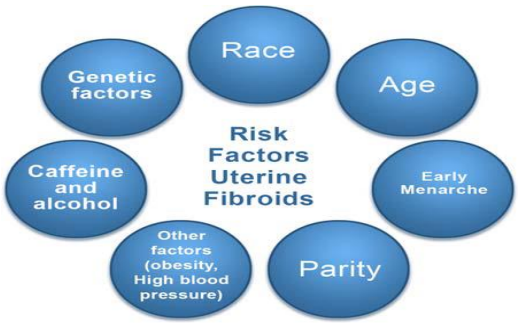

Figure 1: Risk factors of uterine fibroid. These include age, race, early menarche, delayed pregnancy parity (protective effect), caffeine, genetic alterations, such as obesity and a food rich in red meat.[8]

- Age and ethnicity are the one of the important risk factors
- It starts developing during adolescence, with increasing incidence until menopause
- There are two to three times increased chances in women of African ancestry compared with Caucasian women.
- The risk factor is also more in case of patient with hypertension and diabetes
- Possible risk factors- Nulliparity, early menarche, a history of dysmenorrhea, a family history of uterine fibroids, genetic factors and a high body mass index (BMI) [9]

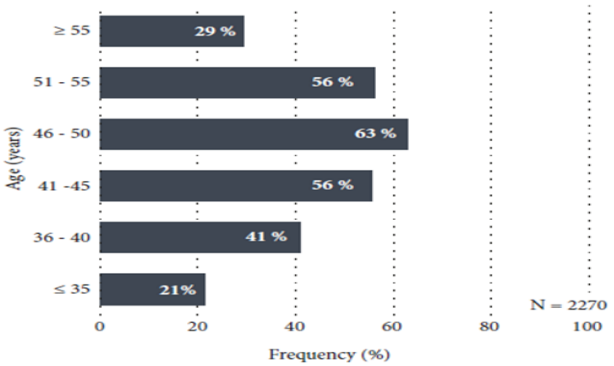

Figure 2: Prelevance of fibriod according to age factor, as percentage, according to Ahrendth et al.,[9]

Classification of fibroids is according to their site in the uterine wall:

• *Subserosal fibroids:* are located under the outer lining of the uterus, the serosa. Their growth is seen in the inner walls or completely inside the serosa and become reticulated with a thin bridge to the myometrium (Figure 2).

• *Intramural fibroids:* Is one of the most common one. They are situated in the mid layer of the uterine Muscle (Figure 2).

• *Sub mucosal fibroids: Is the* myometrium growth, the endometrium that is inner lining of the uterus. Like the sub serous fibroids, they can become pedunculated and can be seen into the uterine cavity (Figure 2).

• Ligaments are the uncommon areas of the uterus. The fibroids here are hard to surgically manage, as they are mostly near other organs such as the ureters, vessels and nerves and so can be treated by expert surgeons. This characterization of fibroids is most important as they show various different syndromes and might need a different access during surgery.

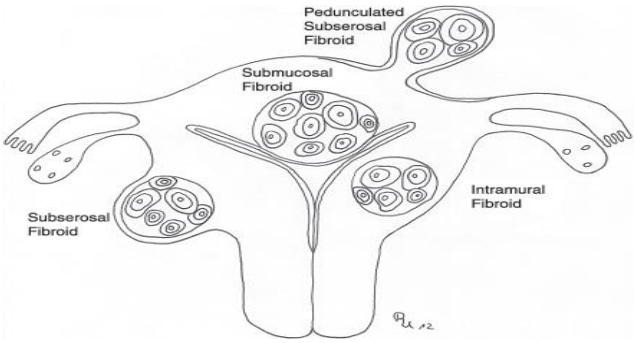

Figure 3: Locations of uterine fibroids

Pathophysiology of fibroids

Fibroids appear as circular, well circumscribed, solid nodules that are tan or whitish, and show whorled shape on homological section. The size and shape can vary, from microscopic to abrasion in size. Mostly abrasion of pie size or bigger than that can be sensitized by the patient herself by the abdominal growth of wall.[10] Microscopically, tumor cells look like normal cells (elongated, spindle-shaped, with a cigar-shaped nucleus) and form bundles which spread in direction (whorled). These cells are same in size and shape, with scarce mitoses. There are three types of benignant variants:

Bizarre (atypical);

Cellular;

Mitotically active.

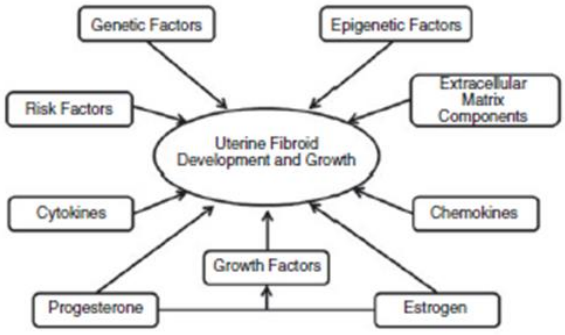

Figure 4: Factors involved in Uterine Fibroid formation and growth

Types of Fibroid Tumors

1. Sub mucosal Fibroids – It can be seen just under the lining of the uterus and can cause menstrual complication, including pain as they grow very fast. Typically, also cause large amount of bleeding during menstruation.

2. Intramural Fibroids – It occur inside the wall of which can cause enlarging of the uterus with fast growth.

3. Subserosal Fibroids – This class of fibroid mostly grows on the outer side of the uterus and usually causes no syndrome are seen and it grows larger enough and interfere with other organs.

4. Pedunculated Fibroids –They mostly develop when a subserosal fibroid grows a peduncle (stalk) with the growth and they may get twisted and cause unbearable pain in the abdomen.

5. Interligamentous Fibroids –They grows between the ligaments in sideway manner, that support uterus in the abdominal region.

Diagnosis of fibroids

- Ultra sonography
- Hysterscopy
- Hysterosalpingography
- Sonshysterography
- Laparoscopy
- Magnetic Resonance imaging
- Computer tomography scans

Treatment of uterine fibroids

Surgical treatment was one of the main medical treatments for fibroids available before the introduction of nonsurgical options. Hysterectomy was the common treatment for women suffering with fibroid related syndrome, prior to the advent of less invasive surgical options, especially for women not able to conceive. Myomectomy means extraction/removal of the fibroids while conserve the uterus, is the other surgical treatment and can be performed abdominally, laparoscopically or hysteroscopically depending on the uterine fibroid size, shape and location. Many nonsurgical medical management for the treatment of fibroids are upcoming over the last few years, with medical therapy as well as radiological interventions being invented. The traditional medical therapies used are gonadotropin-releasing hormone (GnRH) analogues and, more recent are the, selective progesterone receptor modulators (SPRMs), e.g. ulipristal acetate. Radiological interventions include uterine artery embolization (UAE) and the application of magnetic resonance-guided with high-intensity focused ultrasound (MRgFUS).

Nonsurgical Medical Management of Uterine Fibroids

Gonadotropin-releasing hormone (GnRH) analogues

GnRH analogues lead to pituitary desensitization resulting in a hypo gonadotrophic and hypoestrogenic state. The oestrogen-deficient causes reduction or shrinking in fibroid volume, size and symptomatic cause improvement. GnRH analogues result to a 40% decrease in fibroid size after 6 months of treatment,[11] It has being reported that 97% of women show improved bleeding pattern.[12] However, these drugs most commonly have specific side effects on body, including hot flushes, sleepless night, mood disorders, vaginal dryness, headaches and reducing bone mineral density.[13] These side effects are preferred for short-term use prior to surgery to shrink the fibroids size and reduce bleeding rate during surgery. Lethaby et al.[14] has discussed that uses of GnRH analogues for 3–4 months before fibroid surgery that helps in correction of iron deficiency anemia and reduced intraoperative blood loss. Additional therapy with GnRH analogues, mostly for use beyond half year, is further to lessen the side effects, mainly bone deficiency, caused by the hypoestrogenic state. A Cochrane review [15] came to conclusion that, there were low or moderate evidences that tibolone, raloxifene, estriol and ipriflavone help in preserving the bone density and that medroxyprogesterone acetate and tibolone may reduce vasomotor symptoms. Mostly, women with a larger uterine size and volume showed a less degree of fibroid shrinkage when some additional therapies were used.

Selective progesterone receptor modulators (SPRMs)

SPRMs are studied to stimulate and inhibit cell proliferation in fibroids. Ulipristal acetate is approved in the European Union used as preoperative treatment for mild to severe syndrome which is associated with uterine fibroids and for intermitting treatment of fibroid syndrome in women of reproducing age. However, treatment beyond four courses of 3 months of therapy has not been studied, and it is studied in the report for this product that unnecessary interference for assessment of endometrial normality may be necessary. In reverse, a diagnosis of endometrial abnormality may sometimes be missed leading.

A phase III trial of ulipristal acetate,[16] women with symptomatic fibroids and heavy bleeding during menstruation, studied the efficacy and safety of long-term treatment for symptomatic uterine fibroids. Women received 3-month courses of ulipristal acetate 10 mg daily. After the initial course of ulipristal acetate, amenorrhea, which reduces bleeding for at least 35 days, which was noted in 79% of women with median onset of 4 days and a median uterine fibroid reduction of 45%. After two, three treatment courses of ulipristal acetate, amenorrhea rates 139 were 89%, 88% and 90% and mean fibroid volume and size showed reductions of 63%, 67% and 72%, respectively. All endometrial biopsies resulted in benignant histology without hyperplasia. The study resulted that repeated trimester courses of ulipristal acetate effectively

controlled symptoms and reduces fibroid size in women with symptomatic fibroids. Another investigation[17] by the same group of authors noted the efficacy and safety of two 12-week courses of 5 mg or 10 mg daily of ulipristal acetate in women with symptomatic fibroids and heavy bleeding. In the 5 mg and 10 mg treatment groups, 62% and 73% of women, respectively achieved amenorrhea during both treatments. Some part of women where noted with controlled bleeding, stated as no complain of heavy bleeding and a maximum only 8 days of bleeding during at least 56 days of a treatment scheduled, during two treatment was greater than 80%. Menstruation resumed after each treatment schedule and was reduced comparably with baseline. After the second treatment, median reductions from baseline in fibroid volume were 54% and 58% for the women receiving 5 mg and 10 mg of ulipristal acetate, respectively. Three cases of endometrial hyperplasia were noted in this study, including one simple atypical hyperplasia which resolved into benign secretory endometrium by the end of treatment. A few cases of spontaneous pregnancies without surgery, and a number of pregnancies following myomectomy after pretreatment with ulipristal acetate have been reported.[18] Long-term reproductive outcomes following repeated intermittent ulipristal acetate is under investigation.

Radiological interventions

Uterine artery embolization (UAE)

UAE was studied in 1995 as an alternative technique for treatment fibroids [19] and provides effective short-term treatment of heavy menstrual bleeding, pressure symptoms and pelvic pain. The updated Cochrane review[20] included seven randomized controlled trials comparing uterine artery embolization UAE with hysterectomy/ myomectomy with a total of 793 women. There was slight quality evidence to suggest similar patient satisfaction rates following uterine artery embolization compared to surgical modality at 2- and 5-year follow-up. Uterine artery embolization was associated with a high rate of surgical intervention (between 15% and 32%) after 2 years. The review insisted the need for careful patient counseling and selection because of the higher risk for further surgical intervention. Overall, the data suggest less encouraging reproductive outcomes following Uterine artery embolization compared with surgery. A study[21] included women with fibroids larger than 4 cm who were randomized to uterine artery embolization or myomectomy and followed for 24 months. Compared with the surgical group, the pregnancy (50% versus 78%) and delivery rates (19% versus 48%) following uterine artery embolization was significantly low. The miscarriage rate was also significantly high in the uterine artery embolization group (64% versus 23%). A systematic review and analysis[22] showed significantly high miscarriage rates after uterine artery embolization compared with control women with untreated fibroids (35.2% versus 16.5%). Significant adverse effects of UAE on endometrium and fertility have been reported. In one study,[23] approximately 60% of women showed abnormalities at routine hysteroscopy examination 3–9 months after Uterine artery embolization, including intrauterine adhesions, protruding myomas, myometrium fistula and necrotic tissue. A follow-up study[24] involving 61 women after Uterine artery embolization found a low monthly fecund ability rate of 0.1% (95% CI 0–0.3%) and no reduction in ovarian reserve. The study concluded that uterine artery embolization might have an adverse effect on fertility and should not be routinely offered to women of childbearing age. In a retrospective analysis of pregnancy outcomes following Uterine artery embolization,[25] 32 out of 56 (58.9%) pregnancies had successful outcomes, of which six (18.2%) were premature. There were 17 (30.4%) miscarriages, three terminations, two stillbirths and one ectopic pregnancy. Of the 33 successful deliveries,[26] (72.7%) were delivered by caesarean section. There were 13 elective sections and the indication for nine was fibroids. There were six cases of postpartum hemorrhage (18.2%). The study concluded that there was a significant increase in delivery by caesarean section and an increase in preterm delivery, postpartum hemorrhage, miscarriage and lower pregnancy rates following UAE compared with the general obstetric population.

Magnetic resonance-guided high-intensity focused ultrasound (MRgFUS)

MRgFUS provides an alternative method to surgery for the treatment of uterine fibroids. This therapeutic option causes thermal coagulation of the target fibroid by methodically sonicating multiple locations to reduce volume and provide symptom relief. A long-term study [27] involving 77 women with symptomatic fibroids comparing outcomes following MRgFUS (median follow-up 60.7 months) and UAE (median follow-up 61.9 months) found the intervention rate to be significantly higher for MRgFUS compared with UAE (66.7% versus 12.2%; $P < 0.001$). The health-related quality-of-life scores were significantly better in the UAE group compared with the MRgFUS group. Although this modality is mainly offered to premenopausal woman with symptomatic fibroids who do not wish to become pregnant, there have been several reports of successful pregnancies following MRgFUS. Rabinovici et al.,[28] in their preliminary study of 51 women who conceived after undergoing MRgFUS for fibroids, found live birth, ongoing pregnancy, and miscarriage rates of 41%, 20%, and 28%, respectively.[29] Following fibroid treatment with MRgFUS found a vaginal delivery rate of 53% (19/35). The authors concluded that the MRgFUS may be one of the better options for the treatment for women who desire fertility, but further more trials are needed to validate the findings.

Some minor complications have been reported following MRgFUS, including skin burns, abdominal wall edema, febrile morbidity; major complications, such as deep vein thrombosis, bowel injury, persistent neuropathies; and the

need for emergency hysterectomies. In a follow-up study of 5years[30] women who underwent MRgFUS for symptomatic fibroids, the investigators found a high intervention rate of 58.64%. The minor complication rate was found as 3.9% and serious complication rate (e.g. persistent neuropathy, fibroid expulsion) was around 1.1%. The major side effects of MRgFUS is that many women are not eligible for the procedure due to the bowel interposition between ultrasound beam and fibroid, or as the presence of more than five fibroids, their size or shape, or the presence of adenomyosis. Fröling et al.29 found that of 783 premenopausal women, with a mean age of 44.2 years, only about 40% were eligible for MRgFUS compared with 99.2% for UAE.

Radiofrequency ablation (RFA)

RFA has been as a minimally invasive method to treat fibroids.[31] RFA energy uses volumetric ablation to destroy tissue resulting in a more controlled zone of thermal injury. Treatment of fibroids with RFA needs very accurate targeting or localization of the placement of the operative device. Currently, a various approaches are available for locating the device, including laparoscopic, ultrasound guidance, transcervical, intrauterine ultrasound guidance and transvaginal ultrasound guidance. Initial studies [32–36] have reported results in terms of symptom improvement and shrinkage of fibroid size. However, there is much to be learned about this technique, such as its long- term success rates, how to identify the appropriate surgical candidates, and its impact on subsequent fertility and pregnancy outcomes.

Gene therapy

Fibroids have been a target for gene therapy in recent years. Gene therapy involves of introducing of genetic material into a patient's cells to achieve a therapeutic benefit. Study include: mutation compensation of deregulated genes; replacement of defective tumor-suppressor genes; inactivation of oncogenes; introduction of suicide genes; immunogenic therapy and anti-angiogenesis-based approaches. Preclinical studies [37] of gene therapy have shown best results in uterine fibroids and the researchers involved are of the view that this approach is not far from becoming a medical reality.

CONCLUSION

For a woman suffering with symptomatic fibroids who wishes to retain her uterus, a variety of nonsurgical options are available. However, patient selection is important and women should be properly guided regarding the potential benefits and adverse effects of options available. In women seeking to remain fertile, medical treatments are not a long-term option, and the place of ulipristal acetate for women with fibroids prior to fertility treatment has yet to be totally explored all around. Current data suggest reduced fecundity and high risk of pregnancy complications following UAE administration, and long-term data are needed to validate the safety and reproductive and obstetric outcomes of MRgFUS.

REFERENCES

1. Ryan GL, Syrop CH, Van Voorhis BJ, Role, epidemiology, and natural history of benign uterinemasslesions', ClinObstet Gynecol, 48, 2005, 312–324**.** DOI:10.1097/01.
2. Wallach EE, Vlahos NF. Uterine myomas: an overview of development, clinical features, and management. *Obstet Gynecol.* 104, 2004, 393–406, DOI:10.1097/01, PMID:15292018.
3. Sankaran S, Manyonda IT. Medical management of fibroids. *Best Practice Research Clin Obstet Gynaecol.,* 22(4), 2008, 655–676. DOI: 10.1016/j.bpobgyn.2008.03.001. EPUB 18468953.
4. Parker WH. Etiology, Symptomatology, and Diagnosis of uterine myomas. *Fertility and Sterililty, volume 87, April 2007, 725-736,* DOI:10.1016/j.fertnstert.2007.01.093, PMID:17430732.
5. Cramer SF, Patel A: The frequency of uterine leiomyomas. *Am J Clin Pathol.,* 94(4), 1990, 435–8. PubMed Abstract | Publisher Full Text, DOI:10.1093/ajcp/94.4.435, PMID:2220671.
6. Zimmermann A, Bernuit D, Gerlinger C, *et al.*: Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of21, 746 women. *BMC Womens Health.* 2012, 12, PubMed Abstract, DOI:10.1186/1472-6874-12-6, PMID:22448610.
7. Nelson AL, Ritchie JJ: Severe anemia from heavy menstrual bleeding requires heightened attention. *Am J Obstet Gynecol.* 213(1), 2015, 97.e1–6. PubMed Abstract, DOI:10.1016/j.ajog.2015.04.023,PMID:25935784.
8. Marshall et al., 1997, Wise et al., 2004, Stewart et al., 2013, ElToukhi et al. Uterine fibroid management: from the present to the future,Research gate, 22(6), 2016 Nov, 665–686,DOI: 10.1093/humupd/dmw023PMID:27466209.
9. Thomas R, Nicole S, Andreas E, Selective Progesterone Receptor Modulators for the Medical Treatment of Uterine Fibroids with a Focus on Ulipristal Acetate. BioMed research International volume 2018, Article ID 1374821, 12 Pages, DOI:10.11.1122/2018,PMID-1374821.
10. "Uterine fibroids fact sheet". *Office on Women's Health. January 15, 2015.* Archived *from the original on* from Wikipedia, the free encyclopedia *7July2015.*
11. Bozzini N, Messina ML, Borsari R, Hilário SG, Pinotti JA. Comparative study of different dosages of goserelin in size reduction of myomatous uterine leiomyomata structure, Obesity andgynacology, 11, 2003, 462–3, https://doi.org/10.1034/j.1600-0412.2003.00049.x.
12. Friedman AJ, Hoffman DI, Comite F, Browneller RW, Miller JD. Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. The Obstet Gynecol, 77, 1991, 720–5, DOI.org/10.11481.
13. Perry CM, Brogden RN. Goserelin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in benign gynecological disorders. Researchgate, 51, 1996, 319–46.
14. Lethaby A, Vollenhoven B, Sowter M. Pre-operative GnRH analogue therapy before hysterectomyormyomectomy foruterinefibroids, https://reference.medscape.com/viewpublication/11284, 2001, PMID:10796723.
15. Moroni RM, Martins WP, Ferriani RA, Vieira CS, Nastri CO, Candido Dos Reis FJ, et al. Add-back therapy with GnRH analogues for uterine fibroids, Cochrane Database of Systememic Review, (3), 2013, 320, https://doi.org/10.1002/14651858.CD010854.
16. Donnez J, Vázquez F, Tomaszewski J, Nouri K, Bouchard P, Fauser BC, et al., PEARL III and PEARL III Extension Study Group. Long-term

treatment of uterine fibroids with ulipristal acetate. Fertil Steril, 101, 2014, 1565–73, https://doi.org/10.1016/j.fertnstert.2015.09.032.

17. Donnez J, Vázquez F, Tomaszewski J, Nouri K, Bouchard P, Fauser BC, et al., PEARL III and PEARL III Extension of long-term treatment of uterine fibroids with ulipristal acetate. Fertility and Sterility, 101, 2014, 1565-1573.
18. Donnez J, Hudecek R, Donnez O, Matule D, Arhendt HJ, Zatik J, et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertil Steril, 103, 2015, 519-27, DOI: 10.1016/j.fertnstert.2014.10.038. Epub 2014 Dec 24.
19. Ravina JH, Herbreteau D, Ciraru-Vigneron N, Bouret JM, Houdart E, Aymard A, et al. Arterial embolisation to treat uterine myomata, 346, 1995, 671–2, https://doi.org/10.1016/S0140-6736(95)92282-2.
20. Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. Cochrane Database Syst Rev, 12, 2014: CD005073. https://doi.org/10.1002/14651858.CD005073.pub4.
21. Mara M, Maskova J, Fucikova Z, Kuzel D, Belsan T, Sosna O. Midterm clinical and first reproductive results of a randomized controlled trial comparing uterine fibroid embolization and myomectomy. 31, 2008, 73–85, PMID: 17943348. https://reference.medscape.com/medline/abstract
22. Homer H, Saridogan E. Uterine artery embolization for fibroids is associated with an increased risk of miscarriage. Fertil Steril, 94, 2010, 30, DOI: 10.1016/j.fe rtnstert.2009.02.069. Epub 2009 Apr 9.
23. Mara M, Horak P, Kubinova K, Dundr P, Belsan T, Kuzel D. Hysteroscopy after uterine fibroid embolization: evaluation of intrauterine findings in 127 patients. J Obstet Gynaecol Res, 38, 2012, 823–31, DOI /10.1111/**j**.1447-0756.2007.00530.x
24. Torre A, Paillusson B, Fain V, Labauge P, Pelage JP, Fauconnier A. Uterine artery embolization for severe symptomatic fibroids: effects on fertility and symptoms. Human Reproduction, Volume 29, 2015, 490–501, https://DOI.org/10.1093/humrep/det459.
25. 25. Walker WJ, McDowell SJ. Pregnancy after uterine artery embolization. Am J Obstet Gynecol, Volume 192, Number 6, 195, June 2009, 1266–71, https://dx.doi.org/10.1590/2FS1807-59322011000500016, PMID: 21789384.
26. Froeling V, Meckelburg K, Schreiter NF, Scheurig-Muenkler C, Kamp J, Maurer MH, et al. Outcome of uterine artery embolization versus MR-guided high-intensity focused ultrasound treatment for uterine fibroids: long-term results, Eur J Radiol, 82, 2013, 2265–9, PMID: 24075785
27. Froeling V, Meckelburg K, Schreiter NF, Scheurig-Muenkler C, Kamp J, Maurer MH, et al. Outcome 345 of uterine artery embolization versus MR-guided high-intensity focused ultrasound treatment for 346 uterine fibroids: long-term results. Eur J Radiol, 82, 2013, 2265–9.
28. Clark NA, Mumford SL, Segars JH. Reproductive impact of MRI-guided focused ultrasound surgery for fibroids: a systematic review of the evidence. Curr Opin Obstet Gynecol, 26, 2014, 151.
29. Quinn SD, Vedelago J, Gedroyc W, Regan L. Safety and five-year re-intervention following magnetic resonance-guided focused ultrasound (MRgFUS) for uterine fibroids. European Journal of Obstetrics & Gynecology and Reproductive Biology, Volume 182, November 2014, Pages 247-251, https://doi.org/10.1016/j.ejogrb.2014.09.039.
30. Fröling V, Kröncke TJ, Schreiter NF, Scheurig-Muenkler C, Collettini F, Hamm B, et al. Technical eligibility for treatment of magnetic resonance-guided focused ultrasound surgery, Cardiovascular Intervention Radiology, 2014, 37, 445–50. https://link.springer.com/journal/270.
31. Lee BB. Radiofrequency ablation of uterine leiomyomata: a new minimally invasive hysterectomy alternative. *Obstet Gynecol,* 2002, 99 Suppl 4, 9S, DOI: 10.1007/s13669-016-0183-x.
32. Berman JM, Guido RS, Garz Leal JG, Pemueller RR, Whaley FS, Chudnoff SG, Halt Study Group. Three-year outcome of the Halt trial: a prospective analysis of radiofrequency volumetric thermal ablation of myomas. *J Minim Invasive Gynecol,* 21, 2014, 767–74. PMID: 24613404.
33. Brucker SY, Hahn M, Kraemer D, Taran FA, Isaacson KB, Krämer B. Laparoscopic radiofrequency volumetric thermal ablation of fibroids versus laparoscopic myomectomy. *Int J Gynecol Obstet,* 125, 2014, 261–5, DOI: 10.2147/IJWH.S105955, PMID: 27274313.
34. Galen DI, Pemueller RR, Garza-Leal JG, Abbott KR, Falls JL, Macer J. Laparoscopic radiofrequency fibroid ablation: phase II and phase III results. *JSLS,* 18, 2014, 182–90, https://doi.org/10.1007/978-3-319-58780-6_5.
35. Bongers M, Brölmann H, Gupta J, Garza-Leal JG, Toub D. Transcervical, intrauterine ultrasound-guided radiofrequency ablation of uterine fibroids with the VizAblate System: *Gynecol Surg,* 12, 2015, 61-70, DOI: 10.1007/s10397-014-0873-1.
36. Brölmann H, Bongers M, Garza-Leal JG, Gupta J, Veersema S, Quartero R, et al. The Fast-EU trial: 12-month clinical outcomes of women after intrauterine sonography-guided trans cervical radiofrequency ablation of uterine fibroids. *Gynecological Surgery,* 13, 2016, 27–35, https://doi.org/10.1007/s10397-015-0915-3.
37. Markowski DN, Holzmann C, Bullerdiek J. Genetic alterations in uterine fibroids – a new direction for pharmacological intervention, European PMC, *Expert Opinion There Targets,* 19, 2015, 1485–94, DOI: 10.1517/14728222.2015.1075510.

Source of Support: Nil, **Conflict of Interest:** None.