Kosin Medical Journal 2015;30:13-22
http://dx.doi.org/10.7180/kmj.2015.30.1.13

KMJ
Review Article

Uterine leiomyoma research

Tae Hee Kim, Hae Hyeog Lee*
Department of Obstetrics and Gynecology, College of Medicine, Soonchunhyang University Bucheon Hospital Gyeonggi-do, Korea

자궁평활근종 연구

김태희, 이해혁*
순천향대학교 의과대학 산부인과학교실 순천향대학교 부천병원

Uterine leiomyoma is the most common type of benign tumor in women of reproductive age. This disease is rare before menarche, and its incidence decreases after menopause. Uterine leiomyoma is known to be related to hormonal changes, but the precise underlying mechanism has yet to be determined. Although it is a benign disease, the most common form of management involves surgical intervention. Uterine leiomyoma is also related to infertility and obstetric complications. Here, we present a review of the literature regarding uterine leiomyoma and discuss management of this disease.

Key Words: fibroid, research, uterine leiomyoma

Uterine leiomyoma, also known as uterine leiomyoma or fibroid, is a type of benign tumor originating from the myometrium of the uterus, and is the most common type of benign tumor encountered in gynecological practice. The prevalence of this disease ranges from 60% to 80% in women of reproductive age.[1]

Although sometimes asymptomatic, uterine leiomyoma may cause menorrhagia, dysmenorrhea, abdominal distention, bloating, increased urinary frequency and constipation, and subfertility, as well as atypical symptoms such as compression symptoms, which are uncommon, cardiac symptoms, or vascular involvement.

Uterine leiomyomas are diverse in size and location, and subserosal, intramural, submucosal,

Corresponding Author : Hae Hyeog Lee, Department of Obstetrics and Gynecology, Soonchunhyang University Bucheon Hospital 170 Jomaru-ro, Wonmi-gu, Bucheon-si, Gyunggi-do, 420-767, Korea
TEL: +82-10-5273-7840 FAX: +82-2-6008-6874 E-mail: hhl22@chol.com, hhl22@schmc.ac.kr

Received : Sep. 12, 2013
Revised : Sep. 12, 2013
Accepted : Oct. 13, 2013

broad ligament, and cervical lesions have been reported. These characteristics affect the types of symptoms seen as well as the effect on fertility. The most common forms of treatment for uterine leiomyoma are gynecological operations, such as myomectomy or hysterectomy. Uterine leiomyoma is a common disease and is important in the fields of obstetrics and gynecology. Here, we used the PubMed search engine to identify articles published using the search keyword "uterine leiomyoma" and found 4671 abstracts.

We selected 1196 abstracts published between January 1, 2004, and May 31, 2013. We also performed searches on KoreaMed and the journal homepage of the Obstetrics & Gynecology Science using the same search term. We read the abstracts and determined trends of research regarding uterine leiomyoma worldwide, including in South Korea. We deleted articles about leiomyomas in other organs, such as the heart and lung, and read only abstracts in English and Korean. The articles were divided into the following categories: cause, pregnancy-related reports, case reports, surgical methods, clinical characteristics, diagnostic tools, basic research, medical management including use of intrauterine devices (IUDs), embolization, and review articles. In descending order, the numbers of articles in each category were as follows: surgical methods and complications, case reports, pregnancy-related reports, basic research, diagnostic tools, medical management, embolization, and review articles. Here, we provide the new information regarding uterine leiomyoma.

Etiology

The precise cause of uterine leiomyoma is unknown,[2] but risk factors include age, early menarche, nulliparity, increased body mass index, and ethnicity.[3] Uterine leiomyoma has a high prevalence rate among African Americans, and familial history of uterine leiomyoma is a significant risk factor.[2]

Interest is also growing in the relationship between environmental factors and gynecological disease. Exposure to environmental cadmium pollution can disturb coagulation and fibrinolysis, which are related to uterine leiomyoma and endometrial cancer.[4]

Pregnancy and uterine leiomyoma

The rates of uterine leiomyomas in pregnancy are higher now than in the past, possibly because many women now delay childbearing.

Uterine leiomyoma during pregnancy increases the incidences of abortion, ectopic pregnancy, preterm labor, premature membrane rupture, placental abruption, abnormal fetal presentation, and red degeneration of uterine leiomyoma.5 Uterine leiomyoma occurs in 1.6-2% of pregnancies. During pregnancy, uterine leiomyoma is usually asymptomatic, but serious symptoms such as pain indicating serious complications have been reported.[5]

Diagnostic methods

Uterine leiomyoma is usually diagnosed by ultrasonography. Two-dimensional ultrsonography can easily detect uterine leiomyoma, and three-dimensional ultrasonography can be used to determine the volume of uterine leiomyomas.[6] Endometrial power Doppler ultrasound is helpful to differentiate between cancer and uterine leiomyomas.[7] Additionally, a number of biomarkers for use in novel diagnostic methods for rapid detection of uterine leiomyoma have been described, including prolactin, total albumin and globulin, soluble serum HLA-G, vascular endothelial growth factor, ghrelin and obestin, lactate dehydrogenase A (LDHA), hypermethylated death-associated protein kinase (DAPK), cancer antigen-125, hematopoietic growth factors, human epididymis protein 4 (HE4), and gonadal hormones and growth factors, such as plasma insulin-like growth factor I.[1] However, data regarding the utility of biomarkers in increasing the diagnostic sensitivity and specificity for uterine leiomyoma are lacking.[1]

Management of uterine leiomyoma

1. Invasive management

The most prevalent published articles regarding uterine leiomyoma in PubMed and Korea Med involved discussions of surgical methods and complications. The surgical methods included myomectomy, total abdominal hysterectomy, vaginal hysterectomy, laparoscopic- assisted myomectomy, laparoscopic total hysterectomy, laparoscopic vaginal hysterectomy, and hysteroscopy.

Twelve randomized controlled trials of myomectomy with various interventions to reduce blood loss indicated that misoprostol, vasopressin, bupivacaine plus epinephrine, tranexamic acid, gelatin thrombin matrix, pericervical tourniquet, and mesna were correlated with reduction in bleeding during myomectomy.[8] However, there is no evidence that oxytocin or morcellation reduce blood loss.[8] A number of

reports have discussed the application of minimally invasive surgery, such as laparoscopy and hysteroscopy, in the surgical treatment of uterine leiomyoma. A tendency toward uterus-preserving and minimally invasive surgery has been noted. The hysteroscopic procedure is safe for the postmenopausal atrophic uterus and is helpful to remove submucosal leiomyoma and intramural leiomyoma with intraoperative transabdominal ultrasonographic guidance.[9]

Laparoscopic myomectomy was first described by Semm in 1979.[10] There are three different types of laparoscopic myomectomy, i.e., laparoscopic-assisted abdominal myomectomy, laparoscopic-assisted vaginal myomectomy, and total laparoscopic myomectomy. Laparoscopic myomectomy is associated with spontaneous uterine rupture as a serious complication. However, the incidence of spontaneous rupture of the uterus is very rare, occurring at a rate of 1.0% among 72 patients in studies focusing on labor, pregnancy outcome, and delivery following laparoscopic myomectomy.[11] Selection of laparoscopic myomectomy depends on the skill of the gynecologist, as well as the size, location, and number of uterine leiomyomas. Contraindications for laparoscopic myomectomy include diffuse leiomyomatosis, more than three uterine leiomyomas >7 cm in size, uterine size greater than that at 20 weeks of gestation, desire for hysterectomy, uterine leiomyoma >15 cm, and conditions unsuitable for prolonged laparoscopic surgery. The current trend is toward reduction of laparoscopic port sites, and use of a single port with transumbilical gel port access was reported with no surgical or wound complications.[12] However, further multicenter trials of single-port laparoscopic myomectomy or hysterectomy are required. Laparoscopic-assisted robotic myomectomy using the Da Vinci system is a new surgical technique that provides a three-dimensional view of the operative field and allows ready approach to the suture site. Of a total of 872 women who underwent robotic myomectomy, 107 subsequently conceived, resulting in 127 pregnancies.[13] Further prospective multicenter studies of robot-assisted laparoscopic surgery are required.

Embolization of the uterine artery is a very effective alternative to hysterectomy, and favorable outcomes have been reported for uterine volume reduction and reduction of menorrhagia and compression symptoms, but long-term data are still required.[3] Few complications after uterine artery embolization, such as premature ovarian failure, have been reported.[14]

Innovative methods such as endometrial ablation, radiofrequency myolysis by laparoscopy, and magnetic resonance-guided focused ultrasonography (MRgFUS) have also been reported. Vaginal expulsion of uterine leiomyoma was re-

ported after MRgFUS, and some rare cases of pyometra leading to increased morbidity in patients were reported after radiofrequency myolysis.[15]

Progesterone plays a role in increasing mitotic activity in uterine leiomyomas. The use of hormone (levonorgestrel)-releasing intrauterine devices was not associated with reduction in uterine leiomyoma size, but only showed effects on menorrhagia.[16]

2. Noninvasive management

Gonadotropin-releasing hormone agonists effectively reduce uterine leiomyomas by down regulation of gonadotropin-releasing hormone (GnRH) receptors. However, these agents have been associated with side effects, including hot flushes, headaches, vaginal dryness, depression, and osteoporosis. After cessation of injection of these drugs, leiomyomas returned to the original size or larger. Therefore, gonadotropin-releasing hormone agonists are recommended for use in perimenopausal patients to reduce the uterine size prior to surgery. The antiprogesterone steroidal derivative RU486 was shown to be effective in reducing uterine leiomyoma volume. The selective progesterone receptor modulator asoprisnil (J867) is an antiprogestin that binds to the progesterone receptor. However, further studies to assess the long-term risk of complications such as endometrial hyperplasia are required. Aromatase inhibitors reduce the uterine volume and urinary retention symptoms without a flare-up period, but further studies are required to determine the long-term safety of these agents. Ulipristal acetate has been shown to reduce menstrual bleeding and uterine leiomyoma volume without side effects, such as estrogen deficiency, reduced bone mineral density, or endometrial thickening.[17] Ulipristal acetate is licensed for use as a 5-mg once-a-day oral tablet for 3 months before surgery, but it may be less effective for reducing large uterine leiomyomas.[17]

Basic research

A uterine leiomyoma is a growing mass that expresses growth factors. Insulin-like growth factors (IGFs) mediate the expression of growth hormone and estrogen-related genes.[3] Hormonal variations influence IGF-1 expression, and IGFs are expressed at low levels in the pseudocapsule and uterine myometrium, which are structurally continuous areas.[18]

After preoperative treatment with GnRH analogs (GnRH-a) and tibolone, the levels of transforming growth factor-beta 3 (TGF-β3) and connective tissue growth factor (CTGF) ex-

pression remained unchanged in myometrial samples and were reduced in leiomyomas. Following preoperative treatment with GnRH-a, the border between the leiomyoma and myometrium was less evident, and the levels of proliferating cell nuclear antigen (PCNA) and CD34 expression in the pseudocapsule were lower than those in cases without such treatment.[19]

Neurotensin (NT) regulates luteinizing hormone and prolactin release and interacts with the dopaminergic system. NT, neuropeptide tyrosine (NPY), and protein gene product 9.5 (PGP 9.5) nerve fibers are present in almost equal numbers in the pseudocapsule of uterine fibroids and in the normal myometrium (NM).[20]

The effects of aldo-keto reductase 1B (AKR1B) and 1C (AKR1C) and the tumor suppressor T-cadherin on the progress of uterine disease have been investigated.[21]

Estrogen receptor alpha and beta (ERα and ERβ, respectively) show homology in the DNA-binding domain and are expressed in the myometrium and uterine leiomyoma.[3] The expression levels of ERα, ERβ, and aromatase have been evaluated along with the occurrence and development of uterine leiomyoma. However, some studies indicated that the levels of ER α, ERβ, and aromatase protein expression were similar in leiomyoma and normal myometrium, whereas others found that ERα expression was increased in uterine leiomyoma compared with the normal myometrium.[3] The levels of ERα and ERβ mRNA expression and the levels of estrogen receptors were reported to be increased on average in leiomyomas compared with the normal myometrium.

Uterine leiomyoma produces aromatase, which catalyzes the conversion of androgens to estrogens.[3] Expression of aromatase was detected at the periphery of every leiomyoma in patients of various ages with uterine leiomyomas of a range of sizes. Aromatase p450 expression was detected more frequently in submucous or intramural leiomyomas compared with the subserous group.

Progesterone expression was shown to increase mitotic activity in uterine leiomyoma. Progesterone receptor (PR) is expressed as two isoforms, PRA and PRB, and there are differences in PR expression between uterine leiomyoma and the normal myometrium.[3]

Elevated immunostaining for Ki-67, a nuclear antigen associated with cellular proliferation, has been reported in small and large leiomyomas. Thus, determination of the expression of Ki-67, p53, and PR is promising for immunohistochemical differentiation of smooth muscle tumors of the uterus with malignant potential.

Some articles indicated a correlation between diet and the occurrence of uterine leiomyoma. Dietary supplementation with selenium was shown to reduce the size of spontaneously occurring leiomyoma of the oviduct in the Japanese quail, mediated by its antioxidant properties and reduction in heat shock protein 70 (Hsp70) expression.[22] Genistein supplementation significantly decreased the incidence of fibroid tumors in bird compared with controls.

Additionally, acetaldehyde was reported to show an inhibitory effect on cell growth in leiomyomas compared with the normal myometrium.[23] Differences in the expression of other factors between uterine leiomyoma and the normal myometrium have been investigated. HOXA-10 (a homeobox gene) mRNA and protein expression levels in endometrial stromal cells were shown to be significantly lower in infertile patients with endometriosis, uterine leiomyoma, and unexplained infertility compared with healthy fertile controls.[24] The endometrial mRNA expression levels of HOXA-10, HOXA-11, and BTEB1 were significantly decreased in patients with submucosal leiomyomas compared with healthy women. Plasminogen activator inhibitor type-1 (PAI-1) was found to be differentially expressed between leiomyomas and normal myometrium.[25] XRCC4 X-ray repair cross-complementing group 4, which is a DNA repair protein, xeroderma pigmentosum group D, and promoter-1394* T-related genotype/alleles are associated with increased susceptibility to leiomyoma, whereas XRCC4 codon 247, XRCC4 intron 3, XPD codon 312, XPD codon 751, and XPD promoter-114 polymorphisms are not correlated with the development of uterine leiomyoma.[26] The roles of leptins in the pathogenesis of uterine leiomyoma remain to be determined because the expression of leptins did not differ between uterine leiomyoma and the normal myometrium.[27] Expression of leptin genes was demonstrated in both leiomyomas and the surrounding myometrium. After treatment with GnRH-a, no changes were observed in expression of leptin genes. One recent article regarding whole-genome sequencing focused on the mechanism underlying the occurrence of uterine leiomyoma by evaluating 38 uterine leiomyomas and 30 controls. The authors described four mechanisms for the development of uterine leiomyoma, i.e., chromothripsis/CCR, simple rearrangement, MED12 mutation, and biallelic loss of FH.[28]

As mentioned above, we performed literature searches on the KoreaMed database and the homepage of the Korean Society of Obstetrics and Gynecology journal and found that the most common types of articles were those presenting details about surgery and case reports. The hedgehog (Hh) signaling pathway may be correlated with the occurrence of uterine

leiomyoma.[29] A high degree of positivity for progesterone receptor is correlated with aggravation of health-related quality of life. The roles of bFGF, EGF, IGF-1, and TGFb in the mechanism of uterine leiomyoma were investigated, and TGFb3 was shown to be overexpressed in uterine leiomyoma.[30]

Uterine leiomyoma is a common benign tumor encountered in gynecological practice. No confirmatory biomarkers for uterine leiomyoma have been reported, and publications regarding this disease tend to focus mainly on management and surgical methods. The mechanisms underlying the pathogenesis and development of uterine leiomyoma are also unclear. The roles of structural integrity-related pathways or factors, hormonal receptors, growth factors, and growth-related factors in uterine leiomyoma have been investigated, but we found no reports in the literature regarding comprehensive full-spectrum studies encompassing genetics, signaling pathways, protein expression, and biomarkers. However, methods for noninvasive management have been developed.

This literature review had some limitations in that we performed searches only in PubMed, KoreaMed, and the journal homepage of the Obstetrics & Gynecology Science and did not search on other sites. Further large-scale intensive basic research regarding uterine leiomyoma is needed.

Acknowledgement

This work was supported in part by the Soonchunhyang University Research Fund.

REFERENCES

1. Levy G, Hill MJ, Plowden TC, Catherino WH, Armstrong AY. Biomarkers in uterine leiomyoma. Fertil Steril 2013;99:1146-52.
2. Parker WH. Chapter 15: Uterine fibroids. In: Berek JS, editor. Berek & Novak's gynecology. 15th ed. Philadelphia: Lippincott Williams & Wilkiins; 2012. p. 438-69.
3. Brahma PK, Martel KM, Christman GM. Future directions in myoma research. Obstet Gynecol Clin North Am 2006;33:199-224.
4. Nasiadek M, Kilanowicz A, Darago A, Lazarenkow A, Michalska M. The effect of cadmium on the coagulation and fibrinolytic system in women with uterine endometrial cancer and myoma. Int J Occup Med Environ Health 2003;26:291-301.
5. Kim TH, Lee HH. How should painful cystic degeneration of myomas be managed during pregnancy? a case report and review of the literature. Iranian J Reprod Med 2011;9:243-6.
6. Zivkovič N, Zivkovič K, Despot A, Paič J, Zelič A. Measuring the volume of uterine fibroids using 2- and 3-dimensional ultrasound and comparison with histopathology. Acta Clin Croat 2012;51:579-89.
7. Kabil KS, Temizkan O, Atis A, Gozukara I, Uludag EU, Agar S, et al. Role of endometrial power Doppler ultrasound using the international endometrial tumor analysis group classification in

predicting intrauterine pathology. Arch Gynecol Obstet 2013;288;649-54.
8. Kongnyuy EJ, Wiysonge CS. Interventions to reduce haemorrhage during myomectomy for fibroids. Cochrane Database Syst Rev 2011;11:CD005355
9. Uy K, Kim TH, Lee HH, Chung SH, Lee BI. Clinical Applications of hysteroscopic surgery in postmenopausal women. J Korean Soc Menopause 2010;16:46-51.
10. Semm K. New methods of pelviscopy (gynecologic laparoscopy) for myomectomy, ovariectomy, tubectomy and adnectomy. Endoscopy 1979;11:85-93.
11. Dubuisson JB, Fauconnier A, Deffarges JV, Norgaard C, Kreiker G, Chapron C. Pregnancy outcome and deliveries following laparoscopic myomectomy. Hum Reprod 2000;15:869-73.
12. Lee JH, Choi JS, Jeon SW, Son CE, Lee SJ, Lee YS. Single-port laparoscopic myomectomy using transumbilical GelPort access. Eur J Obstet Gynecol Reprod Biol 2010;153:81-4.
13. Pitter MC, Gargiulo AR, Bonaventura LM, Lehman JS, Srouji SS. Pregnancy outcomes following robot-assisted myomectomy. Hum Reprod 2013;28:99-108.
14. Pisal P, Kim T, Lee H, Lee W, Chung S. Premature Ovarian Failure After uterine artery embolization. WebmedCentral Obstet Gynecol 2013; 4(7):WMC004231.
15. Kim TH, Lee HH, Chung SH. Presenting Features of Pyometra including an increase in iatrogenic causes. J Low Genit Tract Dis 2011;15:316-7.
16. Kang BM, Jeong U, Ju WD , Kwon HE, Kim SH, Chae HD, et al. Clinical effect of levonorgestrel-releasing intrauterine system (Mirena®) on uterine myoma and other benign gynecologic diseases. J Korean Soc Menopause 2003;9:163-70.
17. Talaulikar VS, Manyonda IT. Ulipristal acetate: a novel option for the medical management of symptomatic uterine fibroids. Adv Ther 2012;29: 655-63.
18. Di Tommaso S, Massari S, Malvasi A, Bozzetti MP, Tinelli A. Gene expression analysis reveals an angiogenic profile in uterine leiomyoma pseudocapsule. Mol Hum Reprod 2013;19:380-7.
19. De Falco M, Staibano S, Mascolo M, Mignogna C, Improda L, Ciociola F, et al. Leiomyoma pseudocapsule after pre-surgical treatment with gonadotropin-releasing hormone agonists: Relationship between clinical features and immunohistochemical changes. Eur J Obstet Gynecol Reprod Biol 2009; 144:44-7.
20. Malvasi A, Cavallotti C, Nicolardi G, Pellegrino M, Dell'Edera D, Vergara D, et al. NT, NPY and PGP 9.5 presence in myomeytrium and in fibroid pseudocapsule and their possible impact on muscular physiology. Gynecol Endocrinol 2013; 29: 177-81.
21. Wang L, Mou X, Xiao L, Tang L. T-cadherin expression in uterine leiomyoma. Arch Gynecol Obstet 2013;288:607-14.
22. Tuzcu M, Sahin N, Ozercan I, Seren S, Sahin K, Kucuk O. The effects of selenium supplementation on the spontaneously occurring fibroid tumors of oviduct, 8-Hydroxy-2′-Deoxyguanosine levels, and heat shock protein 70 response in Japanese quail. Nutr Cancer 2010;62:495-500.
23. Shveiky D, Shushan A, Ben Bassat H, Klein BY, Ben Meir A, Levitzky R, et al. Acetaldehyde differentially affects the growth of uterine leiomyomata and myometrial cells in tissue cultures. Fertil Steril 2009;91:575-9.
24. Matsuzaki S, Canis M, Darcha C, Pouly JL, Mage G. HOXA-10 expression in the mid-secretory endometrium of infertile patients with either endometriosis, uterine fibromas or unexplained infertility. Hum Reprod 2009;24:3180-7.
25. Cheng Z, Xie Y, Dai H, Hu L, Zhu Y, Gong J. Unequal tissue expression of proteins from the PA/PAI system, myoma necrosis, and uterus survival after uterine artery occlusion. Int J Gynecol Obstet 2008;102:55-9.
26. Hsieh YY, Chang CC, Bau DT, Yeh LS, Tsai FJ, Tsai CH. X-ray repair cross-complementing group 4 (XRCC4) promoter -1394(*) T-related genotype, but not XRCC4 codon 247/intron 3 or xeroderma pigmentosum group D codon 312, 751/promoter -114, polymorphisms are correlated with higher susceptibility to myoma. Fertil Steril 2008;90: 1417-23.

27. Dingiloglu BS, Gungor T, Ozdal B, Cavkaytar S, Bilge U, Mollamahmutoglu L. Serum leptin levels in women with uterine leiomyomas. Taiwan J Obstet Gynecol 2007;46:33-7.
28. Mehine M, Kaasinen E, Mäkinen N, Katainen R, Kämpjärvi K, Pitkänen E, et al. Characterization of uterine leiomyomas by whole-genome sequencing. N Engl J Med 2013;369:43-53.
29. Choi TY, Ahn BM, Ju BS, Song SJ, Gim SG, Reproductive endocrinology : Overexpression of Hedgehog(Hh) signaling pathway system in leiomyoma tissue. Proceedings of the 96th Korean Society of Obstetrics and Gynecology; September 30-October 2; Seoul: Korean Society of Obstetrics and Gynecology; 2010. p. 212.
30. Lee BS, Jeong CJ, Bai SW, Park KH, Cho DJ, Lee K, et al. Oncology 2, general gynecology and pelviscopy: The effect of transforming growth factor-β1 and β3 on cell division of myometrium and uterine leiomyoma. Proceedings of the 78th Korean Society of Obstetrics and Gynecology; Seoul: Korean Society of Obstetrics and Gynecology; 1996. p. 94.

Peer Reviewers' Commentary

Uterine leiomyoma is the most common type of benign tumor in women of reproductive age. Uterine leiomyoma is known to be related to hormonal changes, but the precise underlying mechanism has yet to be determined. In this review, regarding uterine leiomyoma and discuss management of this disease.

(편집위원회)