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REVIEW

Leiomyoma: genetics, assisted reproduction, pregnancy and therapeutic advances

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Abstract
Purpose Uterine leiomyomas are common, benign, reproductive tract tumors affecting a majority of reproductive aged women. They are associated with gynecologic morbidity and detrimentally affect reproductive potential. The etiology of leiomyomas is poorly understood and their diagnosis prior to treatment with Assisted Reproductive Technologies (ART) represents a management dilemma. The purpose of this paper is to review known genetic and molecular contributions to the etiologies of leiomyomas, describe their impact on ART outcomes and reproductive potential, and review alternative therapies and future directions in management.
Methods A critical review of the literature pertaining to genetic component of uterine leiomyomas, their impact on ART and pregnancy and leiomyoma therapeutics was performed.
Results Uterine leiomyomas are characterized by complex molecular mechanisms. Their location and size determines their potential detriment to ART and reproductive function and novel therapeutic modalities are being developed.
Conclusion The high prevalence of uterine leiomyomas and their potential detrimental influence on ART and reproductive function warrants continued well-designed studies to ascertain their etiology, optimal treatment and novel less morbid therapies.

Capsule Uterine leiomyomas are highly prevalent reproductive tract tumors. Their morbidity is dependent of their size and location and the detriment on ART and reproductive function warrants continued studies to investigate their etiology, optimal treatment and novel therapies.

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Introduction

Uterine leiomyomas are benign monoclonal tumors [1] afflicting up to 60 % of reproductive aged women and 80 % of women during their lifetime [2]. The majority of leiomyomas are asymptomatic, however up to 20 % cause menorrhagia, pelvic pain and genitourinary symptoms [3]. One of the main factors in leiomyoma growth is the influence of gonadal steroids. These tumors also disproportionally afflict women of African descent [4, 5]. Uterine leiomyomas are associated with 10 % of infertility cases and are a sole cause of infertility in 1 % to 3 % of patients [6]. With novel technologies, the molecular abnormalities responsible for these prevalent tumors are being identified. Familiarity with the molecular etiology of fibroid growth is becoming increasingly important as new therapies are currently being developed to target these specific abnormalities [7].

The literature regarding uterine leiomyomas and their impact on Assisted Reproductive Technologies (ART) can be confusing. Current consensus is that submucosal leiomyomas and intramural leiomyomas that distort the uterine cavity decrease implantation and pregnancy; therefore, these patients may benefit from myomectomy [8]. The effect of intramural leiomyomas not distorting the endometrial cavity is more controversial with regard to reproductive impact and their effect on assisted reproductive technologies (ART). Some authors have demonstrated a harmful impact of intramural fibroids on ART [9, 10] while others have failed to find such an association in fresh autologous [11, 12] and donor oocyte cycles [13]. Several studies and meta-analyses have been published attempting to clarify the effect of uterine leiomyomas on ART and provide clinical recommendations [8, 14–18]. However a significant

number of the published trials are retrospective, underpowered to detect a difference in the outcome variables of interest, and not controlled for critical confounders, most importantly fibroid size and location, but also age, method of diagnosis and number of lesions [19]. As a result, the evidence regarding the impact of uterine leiomyomas on reproductive function and ART outcomes may appear inconsistent or confusing to the practitioner; which has fueled debate on recommended management in women seeking fertility treatment. The objective of this narrative review is to summarize the available literature and provide recommendations to the practicing clinician. The molecular mechanisms of this disorder are reviewed and presented, and the future directions of interventional and medical therapy are described.

Genetic and molecular mechanisms involved in leiomyoma etiology

The molecular etiology of leiomyomas is incompletely understood. This is despite the public health care burden of uterine leiomyomas that is estimated to exceed 34 billion dollars annually [20] and their common prevalence, affecting up to 80 % of women during their lifetime. Family history has long been known as a risk factor for development of uterine fibroids [21, 22]. In addition, black race, age, nulliparity, and obesity are risk factors for the development of leiomyomas [4]. The reason for the racial disparity is currently unclear. A report linking a higher incidence of estrogen receptor α polymorphism [23] as an etiologic explanation for the disease disparity has not been substantiated in other studies where genomic and proteomic profiling failed to detect any racial differences. Evaluation of differential expression of steroid receptors in fibroids across racial lines has also not been consistently observed [24–26].

The majority of uterine fibroids (60 %) are chromosomally normal and the remainder share similar tumor-specific cytogenetic anomalies. These include translocations between chromosome 12 and 14, trisomy 12, translocations between chromosome 6 and 10 and deletions of chromosome 3 and 7 [27]. Translocation (12:14) is the most common cytogenetic abnormality, occurring in about 20 % of chromosomally abnormal lesions [27]. Analysis of the region revealed the presence of HMGA2 gene that encodes a high mobility group DNA binding protein and embryonic proliferation modulator that was not expressed in patient-matched myometrium. Subsequent studies revealed that HMGA2 was involved in other proliferation phenotypes [28, 29]. Antagonism of HMGA2 in vitro led to leiomyoma cell senescence and decreased proliferation [30].

Leiomyoma cytogenetic abnormalities correlate with tumor size and location. Chromosomally abnormal tumors are usually larger and a greater percentage of cytogenetically abnormal fibroids are located submucosally [31, 32], although the underlying reasons remain unclear.

Uterine leiomyomas may also occur as part of heritable cancer syndromes. One such syndrome is hereditary leiomyomatosis and renal cell cancer (HLRCC). This autosomal dominant syndrome predisposes patients to benign leiomyomas of skin and uterus and early-onset renal cell carcinoma. The responsible gene was identified as fumarate hydratase (FH) that encodes a Kreb's cycle enzyme responsible for conversion of fumarate to malate [33]. Another syndrome associated with leiomyomas is Alport syndrome. Alport syndrome is a progressive nephropathy and the most common mode of inheritance is X-linked transmission. This syndrome is associated with uterine leiomyomas due to defect in COL4A5 and COL 4A6 genes [34]. The occurrence of leiomyomas as part of a heritable cancer syndrome is underappreciated, and the finding of cutaneous leiomyomas (the most common finding in HLRCC) warrants familial screening [35].

Improvements in sequencing technology have allowed genome wide screening studies to identify genes associated with leiomyoma susceptibility. Cha and colleagues [36] genotyped 1607 individuals with uterine fibroids and identified 3 susceptibility loci associated with uterine fibroids: 10q24.33, 22q13.1, and 11p15.5. Chromosome 10q24.33 was found to have the most significant association with leiomyomas and the region was mapped to the 5' region of the SLK gene encoding STE20-like kinase. STE20-like kinase is expressed in proliferating myoblasts and is activated by epithelial disruption. STE20-like kinase has a role in myogenic differentiation and cell motility and is activated by scratch wounding [36]. Another gene product located in the region is A-kinase anchor protein-13 (AKAP13). A-kinase anchor protein-13 is associated with cytoskeletal filaments in leiomyoma cells. These cells abnormally respond to mechanical stress and this is accompanied by abnormal exracellular matrix deposition [37]. Dysregulation of these processes through mutation may be responsible for the fibrotic phenotype of leiomyomas.

The most common mutations occurring in uterine leiomyomas were recently described. In analysis of 225 leiomyomas, 70 % of lesions contained a series of mutations in mediator complex subunit 12 (MED12), a transcriptional regulator [38]. This coactivator complex has been shown to directly interact with estrogen receptors α and β and enhance estrogen receptor function in vitro, [39] which may explain estrogen mediated uterine fibroid growth enhancement. However, the association of MED12 with fibroids needs to be confirmed in a more sizable population.

Genome-wide screening by microarray experiments support the conclusion that uterine leiomyomas are a fibrotic disease. Genes involved in fibrosis and extracellular matrix (ECM) production and maintenance accounted for 30 % of altered gene expression between leiomyomas and myometrium [40]. The search for the etiology of abnormal ECM in

fibroids implicated transforming growth factor β (TGFβ). TGFβ is a growth factor with profibrotic activity [40–42] and TGFβ3 is the major isoform expressed in the female reproductive tract [43]. Its receptors are found in leiomyomas and normal myometrium [44, 45]. TGFβ3 and its downstream signaling molecules were overexpressed in leiomyomas compared to myometrium [46] and treatment of rats and human leiomyoma cells with TGFβ pathway inhibitors resulted in decreased production of ECM proteins and an *in vivo* reduction in the number fibroids in rats ([47], [48]). Furthermore, downregulation of the TGF-β pathway decreased messenger RNA expression of multiple ECM genes in uterine leiomyomas [49]. Therapy directed at disruption of this fibrotic process holds promise as a future therapeutic method.

Epigenetic changes have also been implicated in leiomyoma formation. Studies directed at identifying epigenetic abnormalities in fibroids demonstrated abnormally hypomethylated estrogen receptor-α [50]. Follow up studies demonstrated globally abnormal genomic methylation in leiomyomas compared to myometrium, [51] implicating possible epigenetic contributions to genetic susceptibility of leiomyoma development.

Knowledge regarding the molecular causes of uterine leiomyomas is in its infancy. Early studies suggest common mutations that correlate with the development of leiomyomas. Further research will need to identify specific genes responsible for the development of leiomyomas that can be directly targeted as preventive therapy. Additional efforts need to be directed at investigating specific inhibitors of disrupted pathways involved in the leiomyoma growth in susceptible patients. The wide spectrum of clinical and genetic heterogeneity of uterine leiomyomas underscores the importance of continued investigation to determine the various molecular etiologies that result in leiomyoma development.

Effect of leiomyomas on ART outcomes

Submucosal leiomyomas

Submucosal leiomyomas and intramural fibroids distorting the uterine cavity negatively impact ART outcomes [52]. Numerous retrospective and small prospective studies indicated that these tumors disrupt implantation by 33–70 % [53–55] and decrease clinical pregnancy by up to 67 % [54] compared to infertile patients without fibroids. These findings were corroborated by numerous narrative and systematic reviews indicating that presence of submucosal leiomyomas correlates with a decrease in implantation by 60–70 % compared to patients without fibroids and a 70 % decrease in clinical pregnancy [12, 14, 56]. When only prospective trials are evaluated, clinical pregnancy and live birth are reduced by up to 70 % in women with submucosal leiomyomas [8].

Women undergoing ART with submucous fibroids demonstrate a worse prognosis when compared to women without leiomyomas, including a decrease in clinical pregnancy, implantation and ongoing pregnancy/live birth rate [8, 14–17, 56, 57]. The benefit of myomectomy for these patients prior to ART will be discussed in the myomectomy section.

Intramural leiomyomas

The impact of intramural leiomyomas on ART outcomes has been the subject of debate. Similar to submucosal leiomyomas, tumors that distort the uterine cavity adversely impact reproductive outcomes [8, 14–17, 58]. Studies of intramural lesions that do not impact the uterine cavity have demonstrated conflicting results. In a prospective trial evaluating the impact of intramural leiomyomas on ART outcomes Somigliana *et al.* [19] evaluated 80 cases of intramural fibroids (10–50 mm), 39 cases of subserosal fibroids and 119 controls. Uterine cavities were evaluated with hysteroscopy to exclude any uterine cavity distortion by leiomyomas. The results suggested that intramural fibroids did not negatively effect pregnancy, implantation and delivery in ART cycles (OR: 1.41 (95 % CI: 0.67–2.98); 1.75 (95 % CI: 0.90–3.39); 1.36 (95 % CI: 0.58–3.15)) [19]. This study was powered to detect a two fold greater chance of pregnancy in women without fibroids based on a 30 % success rate at the authors' center. In addition, the inclusion of subserosal fibroids and very small fibroids (1 cm) may have contributed to the failure in finding a difference in this study. Similar results were obtained in other trials with autologous IVF [55] and oocyte recipient population[12]. In the latter case, implantation, clinical/ongoing pregnancy, and spontaneous abortion was similar in patients with a single fibroid ≤5 cm, 2 fibroids ≤5 cm, three fibroids ≤5 cm, and single fibroid >5 cm compared to controls. Additionally, only 3 out of 25 genes associated with implantation were abnormally expressed in women with intramural leiomyomas. [13]

However, other studies suggest a negative effect of intramural leiomyomas that do not impact the cavity on ART outcomes. A prospective trial evaluating the impact of intramural fibroids on ART outcomes demonstrated a reduction in implantation and ongoing pregnancy compared to controls (Implantation: 11.9 % vs. 20.2 %; $p=0.018$; Ongoing pregnancy: 15.1 % vs. 28.3 %; $p=0.003$) [9]. A retrospective study of 245 women with intramural and subserosal fibroids demonstrated a reduction in clinical pregnancy in patients with fibroids >4 cm (29 % vs 52 %, $p=0.025$) [11]. Other groups have reported similar detrimental effect of intramural leiomyomas on ART outcomes. [9, 10, 54, 59]

The studies in which ART outcomes were not influenced by intramural fibroids were likely underpowered as systematic reviews have begun to demonstrate a consistent negative impact of intramural leiomyomas on assisted reproduction. Benecke *et al.* [16] performed a systematic review and meta-analysis of 6 trials evaluating the effect of non-cavity distorting leiomyomas on IVF outcomes. Each trial had a control group of fibroid free patients and, and mean fibroid sizes were 2.1±0.8 through 3.7±1.2 cm. When corrected for age and the mean number of embryos transferred the authors found decreased implantation (OR 0.62; 95%CI 0.48 - 0.80), clinical pregnancy (OR 0.66; 95%CI 0.48–0.89) and live birth (OR 0.69; 95%CI 0.50–0.95) [16]. Other systematic reviews corroborated the findings of decreased implantation, clinical pregnancy and live birth in women with intramural leiomyomas when undergoing ART. [8, 16–18]

Sunkara and colleagues [18] conducted the largest review on the topic demonstrating the negative impact of intramural leiomyomas. The authors attempted to address the extensive heterogeneity of the available studies by performing multiple sensitivity analysis based on age, order of treatment cycle and study design. These sub-analyses all demonstrated a negative impact of non-cavity distorting, intramural leiomyomas on ART outcomes [18].

The detrimental impact of intramural uterine fibroids is related to the size of the myoma. The myometrium has a finite thickness, thus larger fibroids may have an impact on the endometrium involved in implantation, and it appears that fibroids larger than 3 cm have detrimental clinical impact on ART outcomes [59, 60].

Ultrasound screening during the infertility diagnostic evaluation and ART treatment may increase the incidence of women diagnosed with incidental intramural leiomyomas not affecting the uterine cavity. Despite the conflicting evidence with regard to the impact of intramural fibroids on ART outcomes, reviews encompassing 65 studies all conclude that intramural fibroids detrimentally impact implantation, clinical and ongoing pregnancy in women undergoing ART compared to fibroid free patients. This is likely related to size with lesions greater than 3 cm negatively effecting ART outcomes [8, 16–18]. The value of myomectomy for improvement of ART outcomes in women with intramural leiomyomas will be discussed later in the myomectomy section of this review.

Subserosal leiomyomas

Defined as having more than 50 % of their total volume under the uterine serosa, these lesions do not effect implantation and clinical pregnancy in women undergoing ART. [54, 60] A systematic review of 11 trials evaluating the effect of fibroids that included sub-serosal tumors demonstrated no effect on clinical pregnancy (OR 1.0; 95%CI 0.8–1.2) or delivery (OR 0.9; 95%CI 0.7–1.1). [8] There is now sufficient evidence to demonstrate that subserosal fibroids do not negatively affect clinical pregnancy with ART or pregnancy maintenance, but may influence mode of delivery.

Perinatal complications associated with uterine fibroids

Evaluation of women with first trimester ultrasounds demonstrated that the prevalence of uterine fibroids in pregnancy is approximately 10 % [61] and less than 20 % enlarged during gestation [62]. Abdominal pain has been reported as a common pregnancy complication, afflicting up to 15 % women with uterine fibroids [63]. Leiomyomas have also been implicated in both pregnancy loss and perinatal complications. Early reviews identified a 22 % increase in miscarriage in women with symptomatic fibroids [64]. This finding was corroborated by subsequent case–control studies [65, 66] and prospective trials [67, 68]. Benson and colleagues demonstrated that patients with uterine fibroids identified on first trimester sonogram were twice as likely to have a pregnancy loss compared to controls (14 % vs. 7.6 %) Studies evaluating patients undergoing ART have also demonstrated increased spontaneous abortion in patients with uterine leiomyoma. A meta-analysis of retrospective and prospective cohort trials evaluating the impact of leiomyomas on miscarriage in patients undergoing IVF found that patients with fibroids have approximately twice the loss rate of controls (15.3 % vs. 7.7 %) [56]. Furthermore, numerous uncontrolled studies report that myomectomy reduces the incidence of early spontaneous abortion 36 % −60 % [69–72].

Women with uterine leiomyomas have a higher incidence of cesarean delivery [73–76], 48.8 % among women with fibroids compared to 13.3 % in controls in studies encompassing over 3400 patients [56]. The higher risk of cesarean delivery associated with fibroids is likely a result of concern for, as well as actual fibroid associated antepartum complications, such as an increased incidence of fetal malpresentation, abnormal placentation and obstructed labor [56, 57, 76]. Because of the high incidence of cesarean delivery associated with the presence of uterine leiomyomas, the decision to proceed with a trial of labor should be individualized based on the size, location and prior obstetrical history, with lower uterine segment tumors having a higher risk for cesarean delivery [76].

The most common neonatal morbidity associated with uterine fibroids is preterm delivery [56]. Numerous studies report women with fibroids deliver at an earlier gestational age [74, 77, 78]. Large fibroids (>5 cm) have been shown to be significantly associated with earlier delivery [79]. Short cervical length (< 2.5 cm) at ≤32 weeks gestation, a marker for preterm delivery, was associated with the presence of fibroids in a retrospective analysis [79]. Other large studies have also supported the association between fibroid size and preterm delivery [73, 80].

Abnormal placentation, which can lead to placental abruption, is strongly correlated with retroplacental fibroids. A retrospective study of over 64,000 patients found an increased risk of abruption (OR 2.1; 95%CI 1.4–3.0) in women with leiomyomas along with increased risk of placenta previa (OR 2.2, 95 % CI 1.5–3.2), and intrauterine growth restriction (IUGR) (OR 2.5; 95%CI 1.2–5.0) [80]. These findings corroborated earlier reports of uterine fibroid associated consequences of abnormal placentation such as abruption, placenta previa and IUGR [73, 74, 78].

Does myomectomy improve IVF outcome?

Despite the magnitude of this clinical problem, very few prospective studies have examined the effect of myomectomy on ART outcomes. The majority of the literature examines spontaneous pregnancy rates after myomectomy. Analysis of the available prospective trials demonstrates that over 50 % of infertile patients achieve spontaneous pregnancy after open or laparoscopic myomectomy [81–84]. Available studies evaluating the effect of myomectomy on ART outcome utilized two control groups: infertile patients without fibroids and patients with known leiomyomas who did not undergo myomectomy prior to ART. Studies that utilize in situ fibroids as controls should show a statistically significant improvement in ART outcomes with myomectomy compared to non-myomectomy patients and in studies utilizing non-fibroid infertile controls, patients undergoing myomectomy need to demonstrate comparable outcomes relative to controls [17]. In a retrospective case-controlled analysis of myomectomy in 31 autologous IVF and donor oocyte recipients with submucosal fibroids, [85] patients who underwent myomectomy either via hysteroscopic route or via laparotomy demonstrated similar clinical pregnancy compared to controls in both autologous IVF and oocyte donation cycles [85]. Patients with large fibroids (>5 cm) who underwent myomectomy prior to ART demonstrated improved live birth rates (21 % vs. 10 %; $p<0.05$) compared to those who declined myomectomy [86]. The results of additional studies demonstrate a benefit of myomectomy for resection of fibroids prior to ART [87, 88] and the benefits of myomectomy on pregnancy outcomes [67, 89]. The current evidence suggests that removal of submucosal fibroids prior to ART is beneficial. Removal of intramural fibroids >5 cm may also be of benefit with up to 50 % improvement in live birth rate [86].

Alternatives to surgical therapy

Surgical procedures have been the mainstay of definitive leiomyoma management over the last century. However, novel interventions and medical therapies with significant reductions in patient morbidity have been introduced for the treatment of uterine leiomyomas.

Uterine artery embolization

Uterine artery embolization (UAE) is a radiologic, uterine-sparing procedure that has been a minimally invasive alternative for the treatment of fibroids since the mid 1990s. [90] In a controlled trial of 124 patients, evaluating the efficacy and safety of uterine artery embolization versus myomectomy, patients that underwent UAE had a significantly lower hospital stay, recovery time, pain scores, higher quality of life lower incidence of major complications at 6 months. However, 8 % required a repeat procedure and one patient needed to undergo a follow up myomectomy. The same authors [90] conducted the most extensive systematic review of UAE to date (13 publications) and meta-analysis showed that patients that underwent UAE had significant reductions in hospital stay and in major complications. These findings corroborated prior results regarding UAE for the treatment of fibroids that demonstrate a shorter hospital stay. However, there was an increased risk of follow up procedures, either a repeat embolization or surgery [91, 92]. Up to 30 % of patients undergoing UAE may require recurrent treatment for inadequate symptom control [92].

Fertility after UAE remains controversial [93] and its safety has not been established. Numerous trials have reported on reproductive outcomes after UAE. Goldberg *et al.* [94] reported on 23 spontaneous and one ART conceptions in a cohort of 555 women who underwent UAE. There were 4 spontaneous abortions (16.7 %) and 3 preterm births with 3 cases of abnormal placentation (one placenta accreta requiring cesarean hysterectomy) [94]. In another trial, 23 patients out of 102 who underwent UAE were actively attempting conception and 14 (61 %) succeeded spontaneously with one additional patient undergoing ART. Two patients (13 %) had spontaneous abortions and the rest of the pregnancies were uncomplicated term deliveries [95]. Furthermore, other studies have demonstrated an increased risk of obstetric complications such as first trimester pregnancy loss, fetal malpresentation, abnormal placentation, IUGR and preterm delivery [96–98]. Permanent endometrial atrophy has also been reported after UAE. [99]. Currently it is not recommended that patients attempt conception after UAE, and UAE should not be offered as an alternative therapy to patients interested in future fertility (99[93]. Myomectomy has demonstrated superior reproductive outcomes in at least one randomized controlled trial up two years after intervention [100].

High intensity focused ultrasound

Magnetic resonance imaging guided high intensity focused ultrasound (MRgFUS) has been approved by the FDA for the treatment of uterine fibroids since 2004 [101]. With MRgFUS, 80 % of patients report symptomatic improvement and size reductions can approach 20–30 % for up to two years without long-term complications [101, 102]. Rabinovici *et al.* [103]

reported on 54 pregnancies in 51 women with a mean time to conception of 8 months. The live birthrate was 41 %, with a 28 % spontaneous abortion rate. Of the patients that did not miscarry or terminate their pregnancy, twenty patients delivered at term, and there was one preterm birth at 36 weeks of gestation. Fifty-seven percent of these pregnancies had no maternal or neonatal complications [103].

The safety of this procedure for future fertility has not been established and minimal data exist regarding the effect of these newer therapies on future reproductive function. If further studies demonstrate reproductive safety, the utilization of these efficacious therapies in the mainstream practice could provide the patient with safer, fertility sparing options for management of uterine leiomyomas.

Medical management of uterine fibroids

The only FDA-approved medical fibroid therapeutic currently on the market in the US is the gonadotropin releasing hormone (GnRH) agonist, leuprolide acetate. It is approved as a preoperative adjunct to control bleeding, decrease fibroid size and improve pre -operative anemia. GnRH agonists induce a hypogonadal state that limits their duration of therapy. Fibroids rapidly re-grow after cessation of therapy [104]. GnRH agonists are currently used as preoperative adjuncts to minimize perioperative morbidity associated with fibroid surgery. A Cochrane review reported the preoperative use of GnRH agonists for up to 120 days prior to fibroid surgery reduces fibroid size, corrects pre-operative anemia, and reduces intra-operative blood loss. This treatment may potentially avoid midline vertical incisions and may offer alternative surgical routes to abdominal hysterectomy [105]. One limitation of the GnRH agonists is the initial flare effect, which is avoided with GnRH antagonists, now widely available. While an off-label use of the medication, there are reports that rapid (14 days) significant shrinkage (30–40 %) may be obtained with GnRH antagonists, which may be of clinical use for some ART patients.

Other medical treatments have shown promise in treating uterine leiomyomas. Selective progesterone receptor modulators (SPRM) have been evaluated for the management of uterine fibroids since the late 2000s. Mifepristone was efficacious in treating fibroid size and fibroid associated symptoms [106–108]. Treatment with the progesterone receptor modulator asoprisnil also demonstrated a dose dependent decrease in fibroid size and uterine bleeding in patients with leiomyomas [109]. In follow up studies, after six months of therapy with mifepristone, treatment effects persisted up to one year [110]. Ulipristal acetate (CDB-2914) is currently approved in the US as an emergency contraceptive and has been shown to decrease fibroid volume, induced amenorrhea and improved quality of life scores after 12 weeks of therapy in randomized controlled trials [111, 112]. In a double blind non-inferiority trial compared to leuprolide acetate, ulipristal acetate was shown to control bleeding in 98 % of women taking 10 mg daily [113]. Additionally, women achieved amenorrhea 2 weeks faster on ulipristal compared to leuprolide acetate and had a significantly lower incidence of side effects [113]. Furthermore, treatment with ulipristal was able to decrease leiomyoma volume by 24 % compared to placebo [114]. A benefit of SPRMs compared to GnRH analogues is the absence of hypo-estrogenic side effects such as a decrease in bone mineral density and hot flushes, as SPRMS maintain mid-follicular estradiol levels for the duration of therapy [115].

The main concern with SPRMs is the long-term effect on the endometrium. This is due to the theoretical SPRM blockade of progesterone action on the endometrium and the inhibition of ovulation, providing continued unopposed estrogen exposure [116]. Initial data demonstrated an increased risk for endometrial changes [117, 118]. Follow up analyses have demonstrated that the endometrial findings associated with SPRM therapy are a separate clinical entity than endometrial hyperplasia and have been termed progesterone associated endometrial changes (PAEC) [119]. These changes are now believed to be histologically distinct from endometrial hyperplasia [120, 121]. Newer studies have not detected complex or atypical hyperplasia and PAEC regresses after 3–6 months after cessation of therapy [114, 122]. However, the natural history of PAEC while on SPRM therapy or the long-term safety of PAEC has not been established.

Aromatase inhibitors have also been shown to be efficacious in treating uterine leiomyomas. In a randomized controlled trial of seventy patients with fibroids >5 cm, 2.5 mg of letrozole was found to be superior to a GnRH analogue (triptorelin) in decreasing leiomyoma volume (45.6 % vs 33.2 %) after 12 weeks of therapy[123]. Due to the encouraging results of aromatase inhibitors in treating uterine fibroids and their favorable side effect profile more studies are needed to determine the length of the treatment effect, long-term safety and reproductive function after treatment.

Future directions in leiomyoma management

Future medical therapies can be targeted at leiomyoma cellular differentiation pathways. Leiomyomas are tumors with overproduction of abnormal extracellular matrix and modulation of this process provides a novel way to manage this disease. Different investigators demonstrated that leiomyomas possess a disrupted retinoic acid pathway [124, 125]. Retinoids also modulate pathways responsible for proliferation, apoptosis and survival in leiomyomas [126]. The decreased endogenous retinoic acid and the abnormal ECM production appear to be linked in uterine leiomyomas, and treatment of leiomyoma cells with retinoic acid transformed their ECM phenotype to closely resemble myometrium by decreasing expression of ECM collagens and proteoglycans [49, 124]. Compounds that increase endogenous retinoic acid in fibroids, such as liarozole

(a retinoic acid metabolism blocking agent) have therapeutic potential as they inhibit abnormal ECM formation through the retinoic acid pathway without significant side effects.

Other promising therapeutic agents are nutritional supplements. Curcumin, a dietary spice with anti-neoplastic activity, inhibited leiomyoma cellular proliferation and decreased ECM proteoglycan expression in fibroids [127]. Green tea extract also inhibited the proliferation of leiomyoma cells in vitro [128]. The benefit of these newer agents is their low side effect profile and potential therapeutic effectiveness as a long term preventative treatment. Since prevention of disease is superior and more cost effective than treatment, identification of patients at high risk for leiomyomas through family history and follow up loci screening would identify good candidates for preventive therapy. Low risk compounds such as curcumin or green tea extract may then be initiated to these patients as prevention, to stop abnormal cellular proliferation and ECM secretion leading to fibroid tumors.

Uterine leiomyomas are a heterogeneous disease and recent breakthroughs have shed light on the molecular environment responsible for the etiology and pathophysiology of uterine leiomyomas. The process of their discovery and confirmation will eventually allow the practicing clinician to tailor care to the specific mechanism responsible for the patient's tumor.

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