Abstract

Uterine fibroids (leiomyomas) are noncancerous growths that can have deleterious effects on the health and quality of life for millions of women. Attempts to better understand the factors that influence prevalence and disparities associated with fibroids have been made; however, significant knowledge gaps continue to persist, which hinder care for individuals living with fibroids. The Society for Women’s Health Research convened an interdisciplinary Uterine Fibroids Working Group to review the current state of knowledge about uterine fibroids and recommend areas in which to prioritize efforts to address research gaps and improve diagnosis, treatment, and access to care for patients with this chronic disease. Throughout a 2-day roundtable meeting, participants discussed updates on key literature, research, clinical practice, and public health data on uterine fibroids. Overarching themes and recommendations were identified and determined by consensus agreement of the participants at the conclusion of the meeting. Systematic studies of the etiology and pathology of uterine fibroids are needed to address important knowledge gaps and unmet clinical needs regarding the multifaceted management of fibroids and their effects on overall health and quality of life. The Working Group recommends addressing key deficits within the spheres of research, clinical care, and federal policy. Immediate needs include increasing research investment, improving fibroid assessment using pelvic imaging, implementing longitudinal study designs, addressing factors that contribute to disease disparities (especially among women of color), developing fertility-friendly treatment options, expanding awareness and education beyond gynecologic specialists, and advancing personalized patient care through shared decision-making approaches.

Keywords: gynecologic condition, heavy menstrual bleeding, hysterectomy, leiomyoma, policy, reproductive health

Introduction

Uterine fibroids, or leiomyomas, are benign neoplasms of smooth muscle tissue that arise from the myometrium. Approximately 30%–35% of women will be diagnosed with fibroids using ultrasound detection, but over 70% of women are estimated to develop them by age 50.1,2 Although fibroids are not cancerous, they deleteriously affect the quality of life for millions of women. Approximately 25% of US women with uterine fibroids will experience symptoms severe enough to require treatment.3,4 Fibroids can cause heavy and prolonged menstrual bleeding, pelvic and back pain, anemia, and bulk symptoms such as increased urination, constipation, and abdominal distention. Because symptoms overlap with other gynecologic disorders such as endometriosis and adenomyosis, the average time to diagnose fibroids can be significantly prolonged.5 Furthermore, once a patient is diagnosed, heterogeneity in the size, number, and location of the fibroids can make treatment difficult.

The spectrum of fibroid disease is substantial—with some patients developing 60 or more fibroids and with growths ranging in size from tiny seedlings to as large as a melon. Moreover, fibroid size is not directly correlated with urinary or bleeding symptoms, making it challenging to predict the impact and burden from patient to patient.6,7 Several factors have been proposed to influence an individual’s risk for developing fibroids, including age of menarche, obesity, high blood pressure, gravidity, family history...
of fibroids, and race. There are limited data across all populations of women of color; however, some studies have found that black women are twice as likely to develop fibroids than Hispanic women and up to four times more likely than white women. Black women also present with earlier age of onset, more and larger growths, and increased severity of symptoms. In 2010, direct costs associated with patient management of fibroids were estimated at $9.4 billion, with an additional $17 billion lost in work-hour costs. The epidemiology and unmet health care needs concerning fibroids warrant further investigation to better understand the factors that influence the prevalence and disparities associated with the disease and to ameliorate the financial burden on patients and the health care system.

Methods

Society for Women’s Health Research (SWHR) held a closed roundtable meeting to create an interactive dialog between researchers, clinicians, patient advocates, and policy experts. The objective of the meeting was to recommend areas in which to prioritize efforts to address research gaps and improve diagnosis, treatment, and access to care for patients with uterine fibroids, based on current state of knowledge discussed by a multidisciplinary team at the roundtable. Participants were clinicians and researchers with expertise in fibroids and gynecological diseases, patients with a history of fibroids and advocacy leadership, and professionals with experience in the policy landscape concerning this topic. Collectively, the participants in the SWHR Uterine Fibroids Working Group (UFWG) were selected to represent diversity in training, background, area of expertise, and geographic location. Table 1 provides a list of the SWHR Uterine Fibroids Roundtable participants and affiliations.

The roundtable consisted of a series of sessions that presented updates on the research, clinical practice, public health impacts, and relevant public policy concerning uterine fibroids, based on priority areas of interest defined by the experts before the meeting. An SWHR facilitator moderated the meeting, using a discussion guide to engage participants in sharing data and experiences that supported the science presented and filled knowledge gaps among the group. The Working Group reached a consensus concerning the key gaps and priority areas of need that are discussed in this report (Table 2).

To present a concise update on the science and policy that reflected the discussions of the Working Group, a thematic overview of leiomyoma literature was conducted for inclusion in this report. PubMed and Google were searched for articles published from 2016 to present and for seminal work on the following topics: fibroid pathophysiology, disease burden and epidemiological studies, clinical practice guidelines for diagnosis and treatment, and related federal policies. When appropriate, relevant review articles, position statements, clinical guidelines, and federal reports were included.

Research Gaps

Pathophysiology

Fibroid growth is dependent on estrogen and progesterone. Current medical therapies for fibroids target the production and action of these hormones and are useful for inhibiting growth. However, because fibroids have a complex pathophysiology that includes the action of growth factors, genetic mutations, changing dynamics of cellular processes, and forces from the surrounding extracellular matrix, these therapies do not eliminate fibroids or prevent new ones from developing after the treatments are discontinued.

Developing therapeutics that target earlier stages in the tumorigenic pathway may provide better treatment options. For example, in fibroid development, a specific series of genetic mutations transform myometrium cells into leiomyoma tumor-forming stem cells. Because each fibroid growth is an independent event, varying genotypes can develop in a single patient. Studies have found that the most common mutation (up to 85% of patients) occurs in the mediator complex subunit 12 (MED12) gene. Three other genetic subgroups of fibroids have been classified: high mobility group A2 (HMGA2) overexpression, fumarate hydratase (FH)
inactivation, and deletion of collagen genes COL4A5 and COL4A6. All of these mutations have been found to arise in the uterus, except FH, which can be inherited and associated with disease outside the uterus.

There is undoubtedly a genetic component to hormone regulation and processing that impacts the growth and pervasiveness of uterine fibroids. Post-transcriptional modifications to RNA have also been linked to tumor development, but the role of epitranscriptomics is still largely unknown. Determining the genetic polymorphisms in fibroid patients will not only provide insight on the ethnic disparities associated with the disease but may also contribute to the development of personalized therapies. Furthermore, estrogen and progesterone abundance, limited vitamin D, low expression of vitamin D receptor, retinoic acid, and catechol-O-methyltransferase overexpression are factors that have been shown to contribute to proliferation. These factors could also serve as potential therapeutic targets. Extracellu

Extracellular matrix accumulation and remodeling play an important role in forming the rigid structure and metabolic activity through solid-state signaling, which contribute to the abnormal bleeding and pain that women with uterine fibroids experience. Understanding the extracellular matrix, cytokines, and other factors in the tumor microenvironment could elucidate possibilities to use antifibrotic agents to control fibroid growth and provide clinical relief.

Novel risk factors

The role of environmental risk factors on uterine fibroid incidence and disparities is understudied, and the following areas are in need of further exploration. Studies have documented that black women have higher levels of exposure to endocrine-disrupting chemicals such as phthalates and bisphenol A compared to Hispanic, white, and other ethnic groups, but the influence of these chemicals on fibroids is yet to be fully understood. Researchers are also looking at early life exposure to environmental estrogens and increased occurrence of uterine fibroids. Some studies indicate a higher percentage of black women developing fibroids after self-reported diethylstilbestrol (DES) exposure compared to their white counterparts. In utero exposure to DES may be also a risk factor for fibroids, but this is not definitively demonstrated due to conflicting data. Additional research is needed to better understand the interplay between environmental risk factors and genetic predispositions in the development of fibroids throughout an individual’s life.

Another novel risk factor identified for uterine fibroids is vitamin D deficiency. The presence of vitamin D receptor in the uterus lends plausibility for diverse functions, including antiproliferative activity in the myometrium and endometrium during the menstrual cycle and in fibroids. As vitamin D insufficiency is known to be more prevalent in people of darker skin color, this may contribute to the disparity in fibroids among black women. Additional exploration is needed concerning the potentially protective effects of vitamin D in fibroid development, as well as its inverse correlation with disease burden in different ethnic groups.

Outcomes research

Large population-based epidemiologic studies, such as the Nurses’ Health Study, Black Women’s Health Study, and California Teachers Study, have provided data to examine trends associated with uterine fibroids. However, these studies rely on self-reported data from adults and often did not include assessments to measure serum toxin levels or to identify epigenetics in participants. Furthermore, these studies were not initiated with fibroids as a focus area and did not include systematic screening of women by ultrasound, which provides higher specificity and sensitivity for detecting fibroids relative to histologic evidence. As a result, relevant longitudinal data is limited and there is little to no incidence data on fibroids, especially for high-risk populations.

The Study of Environment, Lifestyle, and Fibroids is the first prospective study to identify incident fibroid cases based on ultrasound screenings and is specifically designed to investigate African ancestry, vitamin D deficiency, and reproductive tract infection as risk factors for fibroid incidence. This study is relatively new and on a smaller scale than the aforementioned ones, but it is expected to fill some critical knowledge gaps in the study of fibroids.

Racial and ethnic minorities are underrepresented in fibroid studies, making it difficult to understand disease incidence and likelihood of disparities among these populations, especially among non-black women. However, a US Armed Forces study identified that Hispanic, Asian, and Pacific Islander women were at a slightly higher risk (1.1 times) than white women for fibroids, whereas Native American and Alaskan Native women had a slightly lower risk (0.9 times). A study conducted by GfK Institute reported significantly higher symptom severity scores from Hispanic women compared to white and black women, further supporting the need for more comparative studies to investigate the impacts of fibroids on this and other ethnic minority groups.

### Table 2. Priority Areas for Improving Uterine Fibroid Research, Care, and Policy

| Research |
| --- |
| Conduct longitudinal studies that include imaging data |
| Investigate factors that contribute to disease disparities, especially among women of color |
| Explore therapeutic targets beyond ovarian hormone regulation (e.g., vitamin D activity, extracellular matrix, and epitranscriptomics) |
| Develop fertility-friendly treatment options (medical and surgical) |
| **Clinical care and education** |
| Improve primary prevention strategies for fibroid assessment |
| Implement curricula to expand fibroid medical education beyond gynecologic specialists |
| Increase patient and provider awareness of the burden of disease and diversity of patient experiences |
| Incorporate shared decision-making approaches to advance personalized patient care |
| **Policy** |
| Increase policymaker awareness of the public health burden of uterine fibroids and identify policy strategies to ameliorate this burden |
| Increase targeted federal investment for uterine fibroid research |
| Address high treatment costs and insurance coverage gaps that limit patient access to sufficient and innovative treatment options |

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Clinical Needs

Diagnosis and prevention

Fibroids are easily detected by ultrasound or other imaging technologies (e.g., magnetic resonance imaging or computed axial tomography scan); however, imaging does not indicate driver mutations or symptom presentation, nor does it differentiate between fibroids and leiomyosarcoma. A standard classification system is available to describe uterine fibroids based on location—subserosal, intramural, submucosal, or intracavity—and more detailed scoring systems incorporate symptom severity and size and heterogeneity of the growths. Updating the classifications to include other measures, such as tissue stiffness, which correlate well with patient clinical profiles and responses to treatment, is urgently needed.

While prevention or treatment of early disease would be optimal approaches, this is not the current clinical practice. Small fibroids could be detected in asymptomatic patients, but ultrasounds are often only conducted after a patient’s symptoms become severe enough to consult a medical provider. Furthermore, abnormal or heavy menstrual bleeding can be a common occurrence in patients for years before other symptoms present or a fibroid is detected. Growth data have been collected to study tumor pathology, but no method exists to predict symptomatic fibroid development that would allow for a primary prevention strategy. Although it is possible that at-risk populations could be proactively screened by ultrasound to detect and treat fibroids, targeting these groups might also result in unnecessary harm by overtreating asymptomatic patients. To achieve prevention or earlier treatment for patients with symptomatic fibroids, long-term studies are needed to provide a better understanding of the predictors and genetic markers that underlie the differences between asymptomatic and symptomatic patient populations.

Medical therapy

Medical therapies for uterine fibroids are typically prescribed to patients who are preoperative and/or highly symptomatic. Hormonal therapies, such as oral contraceptives, are often used off-label for symptom management. The US Food and Drug Administration (FDA) has recently approved the use of the first oral gonadotropin-releasing hormone agonist coupled with estradiol and norethindrone for the treatment of fibroids, which has shown to effectively reduce heavy menstrual bleeding in patients. These medications produce a hormonal milieu similar to the early follicular phase and reduce associated symptoms, but a perpetual regimen is required to maintain disease management, which can become quite costly for the patient.

Although hormone-regulating therapies are effective in treating fibroids, they also inhibit fertility. Exploration of novel nonhormonal medical therapies may lead to much needed fertility-friendly options to treat fibroids. For example, the upregulation of vitamin D as therapeutic target could have protective effects against fibroid growth without negatively affecting ovarian function. Examining the uterine microbiome or inflammatory molecules involved in fibroid growth may also help to identify alternative targets and therapies. Ultimately, there is a need for low-risk, cost-effective medical options that consider fertility when looking at the prevention or early treatment of fibroids. Furthermore, increasing engagement with pharmaceutical companies in the development and production of new drugs may also move therapies from the bench to the clinic faster.

Surgical or interventional therapy

If medical management proves insufficient, surgical or interventional procedures are the next approach to treating symptomatic fibroids. A myomectomy (laparoscopic, hysteroscopic, or abdominal) removes fibroids to address symptomatic disease, but has a high rate of recurrence, requiring sequential treatment or a second line of therapy to manage the disease. While myomectomy preserves fertility, the cumulative risk of multiple surgeries must be considered when pursuing this course of action. Hysterectomy is the only definitive cure for fibroids, but eliminates the option of pregnancy and may have long-term health impacts. In fact, fibroids account for one-third of all hysterectomies.

The short- and long-term trade-offs of these procedures vary. Hysterectomy, even with ovarian conservation, affects ovarian function and leads to early menopause, but it shows better outcomes for fibroids within 3–5 years post-surgery, compared to other medical treatments. However, in the longer term, hysterectomy (particularly when conducted with oophorectomy) is associated with increased risk of cardiovascular disease, fracture risk, pelvic floor dysfunction, and neurologic issues. These complications are not fully understood and often are not adequately discussed with patients.

Endometrial ablation and uterine artery embolization are not only less invasive procedures but they also inhibit fertility. Alternatively, magnetic resonance-guided focused ultrasound (MRg-FUS) is an emerging noninvasive treatment recommended for patients who have fewer and larger fibroids. Patients report symptom improvement within the first 2 years, but one-third of women will need another procedure to treat recurrent disease. Because this is a new treatment, many providers do not know enough about it to offer this option, and MRg-FUS is not always covered by health insurance. The FDA has also cleared a laparoscopic, ultrasound-guided radiofrequency ablation therapy, an outpatient procedure that spares the uterus and allows for more rapid recovery. Pregnancy data concerning these emerging technologies are still limited.

Although conservative methods of treatment to preserve the uterus and fertility are often preferred, the likelihood of re-intervention increases with these approaches. With this comes the added burdens of cost, risk, and compromised emotional wellness of the patient. To help guide clinical decision-making, there is a need for additional comparative data on treatment options and their outcomes, as well as evidence-based algorithms to help predict patient responses to treatments. More research is also needed to identify less invasive treatment options without fertility-related drawbacks.

Provider education

When assessing a patient’s gynecologic health, health care providers must consider objective measures (e.g., hemoglobin and hematocrit) as well as subjective factors, such as the “normalcy” of an individual’s menstrual cycle. What is viewed as normal for each patient varies widely, and is
typically defined by their background and environment. For example, a woman with an undocumented family history of fibroids or gynecologic disorder might consider soaking 7–10 feminine products per day and taking prescription pain relievers the norm, whereas this experience actually warrants gynecologic concern. Provider gynecologic screening may need to include questions that elicit quantifiable responses to help identify patients whose experiences are not within the normal range.

Health care professionals beyond gynecologic specialists should be well versed and trained to recognize key indicators of symptomatic fibroids. For example, primary care physicians and nurse practitioners conduct general wellness examinations and are often the first provider an individual visits with concerns about persistent pain or anemia. Pediatricians also need to be watchful during the early years following menarche for adolescent patients displaying menorrhagia. Most providers are aware of the concept of uterine fibroids, but many need more education and training about this and other gynecologic disorders so they are better equipped to determine whether a patient’s symptoms warrant treatment or referral to a specialist.

Patient needs

The heavy bleeding, clotting, spotting, long periods, and severe pain associated with symptomatic fibroids not only impact sexual health but they can also affect a woman’s mental health. Managing the unexpected blood stains in public settings, excessive costs for feminine products and medications, and mood instability can invoke feelings of embarrassment and shame for patients living with fibroids. Health care providers often rely on patients to initiate the conversation about symptoms. However, patients may normalize these symptoms and thus do not mention them to their provider. The social and cultural constructs that normalize gynecologic-associated pain can further prolong and complicate the process of seeking treatment. Additional racial biases continue to shape the way both providers and patients perceive expectations and management of pain and disease in different ethnic groups, further exacerbating the disparities in prevention and timely treatment of fibroid disease in women of color.

The societal norms around the experiences and priorities of women at various life stages have shifted from previous generations. Traditionally, women in their 20s and 30s were assumed to prioritize childbearing and were recommended fertility-friendly treatments for fibroids, whereas women in their 40s were more likely to be urged toward hysterectomy because menopause was soon approaching. However, recent advances in fertility are allowing women to extend their timeline to pursue pregnancy through their 40s. Conversations between providers and patients need to expand beyond traditional frameworks toward interventions that are driven by individual patient experiences and needs. The motherhood-centric focus on decision-making potentially devalues the desires of a woman who may not have fertility as a priority or future consideration. Health care providers need to consider the impact of treatments beyond fertility, focusing across the lifespan to include broader sexual health, disease management, financial impacts, mental wellness, mitigating risk factors, and quality of life.

Following the patient-centered care model of shared decision-making, treatment of a chronic condition such as fibroids needs to incorporate counseling and/or support for a patient’s emotional wellness. Fibroids generally impact women in their mid-life years, during which they are likely responsible for their own household, serving as caregivers for parents and children, and pursuing a career. Maintaining work-life-health balance can be especially difficult when battling the productivity loss experienced by women who are managing fibroid symptoms and treatment. Because fibroids impact the entire family, there is a need to mobilize men and others within and outside the household to support their loved ones with fibroids.

Policy Implications

Policy change will be required to comprehensively address the unmet needs outlined in the aforementioned priority areas for fibroid research, clinical care, and education. The Uterine Fibroid Research and Education Act of 2020 (H.R. 6383/S. 4397), most recently introduced by Representative Yvette Clarke (D-NY-9) and then-Senator Kamala Harris (D-CA), represents a possible step forward in this arena. The bill would establish new federal research funding geared toward fibroids, totaling $150 million over a 5-year period. In addition, the proposed legislation would (1) expand a Centers for Medicare and Medicaid Services database on chronic conditions to include information on services for individuals with fibroids, (2) create a public education program through the Centers for Disease Control and Prevention, and (3) direct the Health Resources and Services Administration to develop and disseminate fibroids care information to health care providers. The bill also highlights the need for improved patient and provider education surrounding the heightened risk for fibroids faced by women of color. With plans for the bill’s update and re-introduction in 2021, there is an urgent need for increased lawmaker attention to the significant economic and public health impacts of uterine fibroids.

Expanded and targeted research funding is crucial for progress in fibroid research and care. In 2019, the National Institutes of Health budget funded $17 million in fibroid research. This represents a 70% increase over the previous 5 years, but fibroids remain dramatically underfunded compared with the actual patient disease burden. Without dedicated federal funding for fibroids, research investment relies primarily on investigator-driven proposals. However, scientists tend to direct proposals to areas of public attention they perceive grant reviewers will deem worthy of immediate response. Providing fibroid-specific federal research funding would be a significant step toward elevating fibroids as an area in need of attention for future investigators.

As science progresses and care improves for fibroids, the conversation around insurance coverage and access to care must expand as well. Medical costs for patients with fibroids are relatively high (ranging from $2,200 to $16,000 more than unaffected individuals), and surgical intervention poses a significant financial burden for patients regardless of insurance status. Less invasive, cost-effective treatments, including nonmedical options (e.g., vitamin D supplementation, green tea extract, or behavioral therapy), are worth investigating and would help reduce barriers to therapy for a wider range of patients. While patients are waiting for innovation,
health coverage issues must be addressed across both private and public insurance sectors, given that high costs of treatment may limit access for those facing undue economic burden.

Conclusion

The impact of uterine fibroids on health and quality of life can be severe. The research community has made important advances identifying risk factors of the disease and genetic mutations to characterize these tumors. However, there are significant gaps in our knowledge and understanding of how these factors influence symptomatic fibroids and the increased incidence in women of color. Elucidating these areas of disease pathology could unlock novel therapeutic targets and treatments for patients, which could serve as more curative solutions short of hysterectomy. In addition, the call to action surrounding uterine fibroids should not be limited to the academic and clinical communities. Fibroids are a public health issue that will benefit from general awareness and policy intervention. Concerted efforts to increase awareness, reduce bias, and promote provider and patient education are fundamental to empower patients throughout their life-course journey as they live with and manage symptomatic uterine fibroid disease.

Authors’ Contributions

This article was developed through meetings of the SWHR UFWG. I.O.A. led the literature/data collection, article writing, and revisions. M.H.L. participated in article writing. SWHR UFWG participated in critical discussion and article review and editing. All authors have read and approved the final article.

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